The impact of Fontan circulatory failure, frailty, and resilience on heart failure and transplant outcomes

Short Running Title: FCF, Frailty, Resilience, and Heart Transplant

Primary Investigators:
Kurt R. Schumacher, MD MS (primary contact), kurts@med.umich.edu
University of Michigan, C.S. Mott Children’s Hospital, Congenital Heart Center and
Melissa K. Cousino, PhD, melcousi@med.umich.edu
University of Michigan, C.S. Mott Children’s Hospital, Congenital Heart Center

Organization: The Regents of the University of Michigan

Structured Technical Abstract
Rationale: Fontan circulatory failure (FCF) is a chronic disease state resulting in heart failure and widespread, multisystem, end-organ disease that often necessitate heart transplant, however, survival after transplant for FCF is worse than other types of heart disease. Neither specific FCF factors nor the influence of individual physical or psychological adaptation to FCF-induced chronic disease, specifically frailty and resilience, are characterized leading to marked deficiencies in understanding how FCF impacts post-transplant outcomes.

Aims: Aim 1: Elucidate the key FCF factors associated with HTx outcomes. Aim 2: Define the impact of frailty and resilience in modifying other FCF risk factors and influencing outcomes.

Anticipated Methods: Using modified Delphi methodology, our 16 center collaborative will design ordinal, severity stratified consensus definitions for all multisystem FCF traits. Using this framework, a retrospective cohort study will collect patient and FCF data for patients listed for heart transplant over the last 10 years. Traditional risk modeling and machine learning random forest algorithms will define associations of FCF factors on heart transplant survival and morbidities. Simultaneously, frailty and resilience testing will be prospectively collected for all new Fontan transplant evaluations, characterized across the FCF cohort, and included in repeat risk analyses.

Major Milestones: By study’s end, this collaborative research will result in published manuscripts on 1) our novel evaluation system for FCF, 2) a markedly improved understanding of FCF factors and their influence on post-HTx survival, 3) detailed characterizations of frailty and resilience in FCF patients, and 4) the impact of frailty and resilience on survival and other FCF factors.
RATIONALE

Characterizing Multisystem Fontan Circulatory Failure. For patients with single ventricle congenital heart disease, staged surgical palliation to total cavopulmonary anastomosis, or Fontan palliation, offers long-term survival but results in lifelong obligate systemic venous hypertension that is often accompanied by hypoxia, compromised cardiac output, and impaired vascular function. This unique physiology can also lead to chronic changes in other organ systems. As such, Fontan physiology may be thought of as a chronic systemic disease. When severe, these multisystem changes can result in a syndrome termed Fontan circulatory failure (FCF), which is associated with poor long term survival [1]. Beyond typical symptoms of heart failure, patients with FCF may have significant pulmonary, hepatic, renal, neurologic, immunologic, hematologic, endocrine, digestive, lymphatic, musculoskeletal, dermatologic, and psychiatric morbidities [2]. These morbidities rarely occur in isolation and often affect physical and psychological function, impair quality of life, and result in significant risk of mortality leading to consideration for heart transplant (HTx).

Heart transplant as the ultimate therapy for FCF has been performed for years, but achieving high post-HTx survival in these individuals has been a challenge. Patients with FCF have higher post-HTx mortality when compared to patients with almost all other types of heart disease. Importantly, the differential survival between FCF and non-FCF patients is seen in the early post-HTx period; when patients with FCF survive this period, their overall survival is very similar to individuals with less complex disease [3, 4]. This strongly suggests that pre-operative patient characteristics specific to FCF drive the survival differential and are of significant importance in determining outcome. While the reasons behind this difference in survival are of high interest to both the single ventricle and HTx communities, they have never been adequately described due to single center study limitations and the lack of FCF-specific, granular data in large HTx-specific datasets. As a result of these limitations, it remains unclear which FCF disease states affect outcomes. For example, Fontan-associated liver disease may be manifested by significant fibrosis or cirrhosis of the liver but does not clearly affect HTx outcomes in small cohorts [5]. Again, however, investigation has been limited by the lack of FCF-specific characterization. A potentially important but complex risk factor such as liver disease cannot be explored by simply stating whether it is present or absent; it and other risk factors must be assessed in graded fashion specific to the unique FCF condition to better characterize the full scope of disease.

Systematic characterization of multisystem complications in other chronic disease states has been achieved; we aim to develop a similar, uniform system to characterize the broad effects of FCF. Framework characterizing of adverse events and the severity of multi-organ illness is used to help predict outcome and guide therapy in other chronic disease states. For example, the Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology used in oncology to grade severity of unfavorable signs, symptoms, or diseases associated with cancer and cancer treatment [6]. The CTCAE provides standard definitions allowing harmonized characterization of complications and disease across sites and providers which in turn leads to uniform treatment practices and research. Building upon this framework, a novel, ordinal, severity-stratified classification of Fontan-related cardiac and non-cardiac end-organ complications would allow for more accurate characterization of a patient with FCF and more robust risk analyses than previously possible.

Examining Frailty and Resilience as Modifiable Risk-Reduction Targets. It is also important to highlight that individual patient response to FCF-induced risks may differ, which also likely affects outcomes. Some people may tolerate significant disease burden while maintaining relative health while others may develop significant impairment. This individual physical response can be measured and quantified by assessing frailty. Frailty is a multidimensional condition resulting in a
loss of physiologic reserve and inability to resist stressors. It has been characterized in adults with chronic disease, and individuals with frailty have increased vulnerability to adverse health outcomes in the setting of decreased physiologic reserve [7]. Importantly, increased frailty is significantly and independently associated with mortality in many chronic conditions, including heart failure in adults [8, 9]. Pediatric disease states have also been assessed for frailty, including limited investigation into heart disease [10, 11]. In children with end-stage liver disease, frailty was associated with worse outcomes. Importantly, frailty and associated outcomes are modifiable with targeted interventions [12, 13]. Our center’s pilot study of a Fontan-specific frailty measure (ongoing, unpublished) suggests a relatively wide spread in scores demonstrating variation in response to Fontan physiology in the general Fontan patient population (Figure). Based on this variation and the impact of frailty on outcomes in other populations, it may be highly valuable in predicting FCF outcomes in general and after HTx.

**Resiliency**, the process by which an individual harnesses internal, external and learned resources to maintain wellbeing amidst a stressor [14], such as chronic or critical illness, is another individual patient response that may impact FCF outcomes. Resiliency is associated with a myriad of important outcomes in pediatric chronic illness populations, including improved health-related quality of life and decreased psychological distress in pediatric cancer patients [15], better glycemic control in adolescents with diabetes [16], and decreased depressive symptoms in youth with congenital heart disease [17]. Psychological wellbeing is strongly associated with health outcomes, including hospitalization rates [18] and mortality in adults with heart failure [19]. Importantly, resiliency has also been proven to be both measurable and modifiable in pediatric populations [15], underscoring a critical need to better understand the role of resiliency in FCF and HTx populations.

**Frailty and resilience may modify the impact of other FCF risk factors.** While both frailty and resilience are often discussed independently from other patient and end-organ disease characteristics, it may be that they interact with other end-organ factors. Adding frailty and resilience scores to FCF risk assessments will achieve clear delineation of multifaceted risk imposed by FCF and guide future targeted interventions to improve the frail state and increase resilience which may result in improved patient survival and quality of life.

**ALIGNMENT WITH PEDIATRIC TRANSPLANT RISK REDUCTION INTIATIVE PRIORITIES**

The information generated from this project will be of immediate and significant value for multiple stakeholders in the Fontan community. In alignment with the stated goals of Enduring Hearts and Additional Ventures this proposal will:

1. **Improve understanding of the interplay of FCF risk factors using modeling algorithms.** Results will be used to refine referral guidelines for FCF patients to advanced heart failure care which will lead to improved heart failure and HTx outcomes. These referral guidelines may be implemented through Cardiac Networks United learning collaboratives, including ACTION, NPC-QIC/Fontan Outcomes Network, and the Pediatric Cardiac Critical Care Consortium (PC4).
2. **Identify modifiable risk factors, both physical and psychosocial, that will guide future treatment, inform and refine data collected by growing Fontan collaboratives such as ACTION and the Fontan Outcomes Network, and improve outcomes for all individuals with Fontan circulation and those referred for HTx.** Our co-cardiologist and psychologist-led team
will build upon this research with future multicenter interventions targeting modifiable FCF risk factors, specifically frailty and resilience.

**APPROACH AND SPECIFIC AIMS**

**Specific Aims:** In order to improve long-term outcomes for the single ventricle population it is critical to develop a better understanding of the factors that drive FCF and associated morbidity and mortality. Equally as critical is learning how individual physiologic and psychologic responses to FCF as manifested by frailty and resilience modify FCF risks as these may be ideal targets for intervention to improve FCF and post-HTx survival. Our proposal will leverage a large multicenter collaboration and established, advanced research infrastructure employing modern analytics to clearly identify pre-HTx risk factors in single ventricle patients that affect post-HTx outcomes. To accomplish this, we propose the following aims:

**Aim 1: Elucidate the key FCF factors associated with HTx outcomes.** We will construct a robust FCF dataset to be analyzed using traditional risk modeling and advanced machine learning methods to elucidate specific patient factors and interactions that influence FCF survival at 1 year post-HTx as well as other markers pre- and post-HTx morbidity.

**Aim 2: Define the impact of frailty and resilience in modifying FCF risk factors and influencing outcomes.** Our multicenter collaborative will prospectively collect patient frailty and resilience indices to examine their impact on FCF outcomes. We hypothesize that these factors will mitigate or intensify the impact of FCF risks using the same modeling strategies as in Aim 1.

**Approach**

**Aim 1: Elucidate the key FCF factors associated with HTx outcomes**

*Design of an FCF terminology and assessment system*

We will use the design and framework of the National Cancer Institute’s CTCAE [6] as a guide to create our FCF factor terminology and assessment system. Using the growing medical literature of systemic associations with FCF, potential complications and chronic conditions in each organ system, a core group of co-investigators including experts in each non-cardiac system will create clear definitions for each factor including a graded scale for severity (example below).

<table>
<thead>
<tr>
<th>Term</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Disabling or Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-losing enteropathy</td>
<td>Serum Albumin &lt; 3.0 mg/dl without any clinical signs symptoms</td>
<td>Low serum albumin with intermittent symptoms that resolve fully without maintenance therapies</td>
<td>Low serum albumin with intermittent or continuous symptoms requiring maintenance therapy with oral steroids or other daily treatment</td>
<td>Low serum albumin with continuous symptoms requiring hospitalization, scheduled albumin infusions, and/or vasoactive infusions</td>
</tr>
</tbody>
</table>

Collaborators from each center will then refine the definitions using modified Delphi methodology [20]. A series of surveys will seek feedback on each definition. After refinement based on feedback, a virtual meeting will facilitate active discussion and definition finalization. Additional meetings and/or surveys will occur until consensus is achieved for each definition. The conclusion of this process will yield a comprehensive, descriptive, severity-scaled terminology for FCF characteristics to use in the remainder of Aim 1 and 2. Validation and refinement of the FCF scales will be performed after completion of this project.

**Subjects**

This aim is retrospective. All patients of all ages with intact total cavopulmonary circulation *listed for HTx* since 2011 at participating centers will be included. Patients not listed for HTx are not
eligible. We anticipate based on individual center estimates and previous era cohorts approximately 250 FCF patients will be included from our 16-center collaborative.

**Data collection**
Each subject will have data collected using an electronic, online collection tool. Additionally each center is a participating member of the PC⁴ and will include each patient’s unique PC⁴ identifier allowing linkage to the extensive ICU and outcome data in the PC⁴ registry to minimize data collection burden and allow detailed characterization of ICU course [21]. PC⁴ has an established record of successful and rapid deployment of data modules for unique populations. The following (non-exhaustive) data will be collected:

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Procedural and Imaging Data</th>
<th>FCF Characteristics</th>
<th>Post-HTx Data</th>
<th>Perioperative Course Data (PC⁴)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Echo findings</td>
<td>NYHA class</td>
<td>Survival post-HTx</td>
<td>Operative course</td>
</tr>
<tr>
<td>Age</td>
<td>MRI findings</td>
<td>Growth parameters</td>
<td>Rejection episodes</td>
<td>Vasactive support</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Exercise testing</td>
<td>Hospitalizations</td>
<td>Major Infections</td>
<td>Ventilator duration</td>
</tr>
<tr>
<td>Socio-economic factors</td>
<td>Catheterization hemodynamics</td>
<td>FCF consensus factors</td>
<td>End-organ function and support needs</td>
<td>ICU and hospital length of stay</td>
</tr>
<tr>
<td></td>
<td>Cath interventions</td>
<td>Hospitalizations</td>
<td>Major morbidities</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**
The primary outcome is death within one year post-HTx. Secondary outcomes will include the following markers of both survival and morbidity: death within 3 years post-HTx, death prior to HTx (whether on the HTx waitlist or removed from the waitlist), survival without HTx, hospitalizations prior to HTx, hospital days prior to HTx, ICU days post-transplant, ventilator days post-transplant, major infections, stroke or other cerebrovascular accident, renal failure, need for temporary dialysis, need for chronic dialysis, need for ECMO, hospital days post-HTx prior to discharge, rejection episodes, and hospitalizations in the first year post-HTx.

**Analytic plan**
With advanced characterization of FCF characteristics, incrementally more sophisticated understanding of FCF factors’ impact on post-HTx survival will be possible. Using traditional parametric regression models, the independent impact of each risk factor can be characterized. However, the complex interplay of FCF factors may exceed the limits of traditional risk modeling. For example, traditional parametric modeling may fail to uncover complex combinations of risk factors, unless these are known a priori. In a complex state such as FCF, discovery of interactions between factors will be critically important. Further, traditional regression favors factors that have uniform effects over the entire patient cohort, which is also unlikely in a heterogeneous disease state like FCF. In contrast, machine learning algorithms, specifically tree based analyses [22], can define the relative importance of specific factors on outcome in relation to all other FCF factors, thereby giving a much clearer and more specific assessment of FCF factors that may truly drive risk. In addition, they can uncover factors and complex combinations of factors that may influence outcome differently in patient subgroups. These techniques will be highly useful to comprehensively exploring risk factors and advancing understanding of FCF-induced risks across this diverse, heterogenous patient cohort.

Analysis of the cohort will seek to understand the specific FCF factors that impact 1-year non-survival post-HTx. Univariate associations for each patient factor will be sought. The dataset will be analyzed using traditional logistic regression modeling with specific attention given to FCF factor interactions. We will then re-explore the data set using tree-based machine learning...
algorithms with the binary outcome of 1-year post-HTx survival. Classification tree analysis will explore subcohort differences that most influence outcomes, specifically major factors that appear to be branch points between survival and non-survival post-HTx. Random forest and other ensemble tree methods will identify the relative strength of each patient characteristic in driving outcomes and potentially detail unrecognized interactions between candidate variables. Following machine learning, any unique interactions or candidate covariates not previously identified through traditional modeling will be included in a confirmatory logistic regression model. The final product will be a detailed delineation of a wide range of FCF factors impact on outcome. Given the goal of this aim is to complete a detailed exploration and delineation of the key factors influencing FCF outcome and not necessarily achieve an accurate prediction tool, a power calculation for this aim is not justified. In addition, the suggested machine learning techniques are robust in their ability to define risk factor relative importance without the need for specific predictive coefficients, making them ideal to utilize with potential sample size limitations. The projected 250 subjects are expected to be adequate for in depth risk factor assessment including exploration of unique combinations characteristics. Planned secondary analyses include seeking factors associated with post-HTx morbidities and clinical course, as well as how post-HTx morbidities affect overall survival. We will additionally plan to describe ICU practices from PC$^4$ and analyze their influence on outcomes and examine unique subcohorts of FCF patients. The multicenter consortium will also be formally queried for ideas for additional analyses from this rich data set that align with the stated goals of the initiative.

**Aim 2: Define the impact of frailty and resilience on FCF outcomes.**

**Subjects**
This aim is prospective. All patients aged 8 and older (including adults) with intact total cavopulmonary or Fontan circulation referred for HTx evaluation at participating centers are eligible, as well as their caregivers for resilience metrics, and will be recruited. Age 8 is chosen as the lower bound of scales used for frailty and resilience. A monetary reimbursement for time and effort will be offered. Patients without intact Fontan, including those who have had their cavopulmonary connection surgically taken down, are not eligible for inclusion. Patients do not have to be listed for transplant in this aim as the data should be acquired during their formal HTx evaluation. We anticipate based on previous referral patterns up to 130 patients (4 per center per year) could be enrolled during the 2-year study period.

**Data Collection.**
Patients, and their caregivers, will be enrolled and consented following during their HTx evaluation. Each center will collect the same FCF data employing the same reporting module used in Aim 1 for each patient, as well as reporting their frailty and resilience assessments.

**Frailty testing.** Each patient will receive the Fontan-specific frailty testing battery that we have designed and piloted at our center. The testing includes the following domains (see Table below) extrapolated from the modified Fried criteria and limited non-cardiac pediatric work [7, 10]. Patient reported scales will be collected electronically via a tablet. Testing takes approximately 25 minutes in total. Scoring is included in the table below, and a score ≥ 6 indicates frail state.

<table>
<thead>
<tr>
<th>Domain Test</th>
<th>Weakness</th>
<th>Slowness</th>
<th>Wasting</th>
<th>Exhaustion</th>
<th>Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 point</td>
<td>Grip dynamometer</td>
<td>6 minute walk</td>
<td>Mid upper arm circumference</td>
<td>PedsQL Fatigue Scale [23]</td>
<td>PAQ-A and PAQ-C Scales [24]</td>
</tr>
<tr>
<td>2 points</td>
<td>&gt;2 z-scores below population mean</td>
<td>&gt;2 z-scores below population mean</td>
<td>&gt;2 z-scores below population mean</td>
<td>&gt;2 z-scores below population mean</td>
<td>&gt;2 z-scores below population mean</td>
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</tbody>
</table>
**Resilience Testing.** Patient-caregiver dyads will complete a comprehensive patient-reported outcomes battery to measure resilience, depression and anxiety (see Table below). Surveys will be collected electronically via tablet.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Construct</th>
<th>Reporter</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connor-Davidson Resilience Scale</td>
<td>Resilience</td>
<td>Patient and Caregiver (Self)</td>
<td>10</td>
</tr>
<tr>
<td>Benefit/Burden Scale for Children</td>
<td>Benefit finding and burden of illness</td>
<td>Patient</td>
<td>20</td>
</tr>
<tr>
<td>NIH PROMIS Scales [27, 28]</td>
<td>Life satisfaction, meaning and purpose, positive affect, depressive symptoms, anxiety</td>
<td>Patient and Caregiver Proxy</td>
<td>28</td>
</tr>
</tbody>
</table>

**Outcomes**

The primary outcome will be post-HTx 1-year survival. However, since this aim is prospective and each patient may not proceed to HTx, this aim will also track survival without formal listing for HTx, HTx listing, decision not to list for HTx and reasons leading to the decision, and survival while awaiting HTx in addition to all outcomes stated for Aim 1. Particular attention will also be given to post-HTx ICU morbidities documented in the PC 4 registry as surrogates for HTx success.

**Analytic Plan**

Descriptive statistics will characterize the scope of frailty and resilience. The association of frailty and resilience on 1-year post-HTx survival as well as secondary outcomes will be evaluated. Regarding power, based on our preliminary data in non-FCF Fontan subjects, assuming 1-year post-transplant mortality for the cohort of 15%, power of 80%, and significance level of 5%, N=130 will detect a 20% relative difference in mortality between patients who were frail those who were not. Additionally, the risk analyses produced in Aim 1 will be re-analyzed, including tree-based machine learning methods, now including frailty and resilience scoring, for all individuals enrolled in Aim 2 who undergo HTx to determine the relative strength of their association with outcomes and with other FCF factors.

**Timeline and Expected Major Milestones**

In addition to the knowledge acquired through this effort, we anticipate at minimum the following high-impact abstracts and manuscripts that will drive clinical care practice changes: publication of the FCF definition schema and its creation, results of the retrospective FCF risk modeling, detailed description of frailty and its impact in the FCF population, detailed description of resiliency and its impact in the FCF population, results of FCF risk analyses including the impact of frailty and resiliency, and a detailed study of operative and ICU practice impact on post-HTx outcome.

<table>
<thead>
<tr>
<th>Complete or Underway</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Post-funding</th>
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<tbody>
<tr>
<td>Study design</td>
<td>X</td>
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<tr>
<td>Protocol development</td>
<td>X</td>
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<tr>
<td>Formation of study team</td>
<td>X</td>
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<tr>
<td>IRB approval</td>
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<tr>
<td><strong>Aim 1</strong></td>
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<tr>
<td>Consensus design of FCF assessment system</td>
<td>XXXXX</td>
<td></td>
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<tr>
<td>Design of FCF data collection module</td>
<td>WWW</td>
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<tr>
<td>Data collection</td>
<td>XXXXX</td>
<td></td>
<td></td>
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<tr>
<td>Risk modelling</td>
<td>WWW</td>
<td></td>
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<tr>
<td><strong>Aim 2</strong></td>
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<td></td>
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<tr>
<td>Recruitment, Consent, Enrollment</td>
<td>XXXXXX</td>
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<tr>
<td>Data collection</td>
<td>XXXXX</td>
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<tr>
<td>Risk modelling</td>
<td>XXX</td>
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<td></td>
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<tr>
<td>Dissemination: presentations and manuscripts</td>
<td>XXXXX</td>
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INNOVATION AND SIGNIFICANCE
The complete characterization of FCF factors via a novel FCF characterization system will allow risk modeling at a level not previously achievable with any data set. The modeling will lead to complex characterization of FCF characteristics’ impact on HTx outcomes allowing markedly deeper understanding than previous efforts. Potentially of even higher significance, the addition of frailty and resilience as both independent and modifiable FCF factors will further enhance knowledge of individual adaptive response to the FCF chronic disease state and define intervention targets to improve FCF outcomes in the future. Via our strong multicenter collaboration and use of the detailed pre-existing data sets in PC^4, we are in the best possible position to delineate the risk factors, both modifiable and non-modifiable, that independently affect HTx outcomes, which will in turn guide transplant referral and improve outcomes.

Our proposed project includes several important innovations:

• Use of data-driven consensus methodologies to create the first ever FCF multisystem characterization and scoring system.
• Unique linkage of our large multicenter HTx collaboration to the highly granular and audited PC^4 database to achieve reliable and detailed outcome assessments.
• State-of-the art risk modeling using both traditional statistical approach and machine learning to explore FCF factor relationships in intense detail.
• First multi-center examination of frailty and resilience in this population, which will provide critical information for future intervention research.
• Co-PI multidisciplinary team includes both a cardiologist and a psychologist, emphasizing the significance of both physical and psychological contributors to FCF outcomes.

LAY SUMMARY
Patients with single ventricle congenital heart disease undergo a series of surgeries in early childhood with the last being the Fontan palliation. This Fontan heart circulation helps patients to survive for many years, but unfortunately, may also cause heart failure and damage to other organs. Heart failure and other organ damage following the Fontan procedure is called Fontan circulatory failure (FCF), a chronic, life-limiting disease. Patients with FCF are often referred for heart transplant, but their survival after heart transplant is not as good as others with different types of heart disease. FCF characteristics are not well defined or understood, but are likely the cause of these poorer transplant outcomes. It is also known that each patient responds to the physical and psychological stressors of chronic disease differently. Patients can be physically affected by the overall burden of disease, and this can be measured by assessing frailty. They can also be psychologically affected by disease, and this can be measured by assessing resilience. This study brings together 16 pediatric heart transplant centers to better describe and understand how FCF characteristics affect transplant outcomes and survival after transplant. This information will help us learn the best timing for transplant evaluation in patients with FCF. We will also measure frailty and resilience in patients with FCF undergoing transplant evaluation. This information will help us develop future interventions to reduce transplant risks in patients with FCF. Overall, this study aims to improve physical and psychological outcomes in patients with FCF including those who go on to heart transplant.
TEAM AND TEAM CAPABILITIES

A. SENIOR/KEY PERSONNEL

Kurt Schumacher, MD MS, Co-Principal Investigator, is a pediatric cardiology intensivist, Associate Professor at the University of Michigan (UM) and Medical Director of the Pediatric Heart Transplant Program at C.S. Mott Children’s Hospital, Associate Director for the Michigan Congenital Heart Outcomes Research and Discovery (M-CHORD) program and Director of the PC4 Data Coordinating and Analytic Center. See Biosketch. Dr. Schumacher is budgeted for 8% effort = 4.2 weeks per year but plans to provide significant non-funded effort, and this is supported by center leadership.

Melissa Cousino, PhD, Co-Principal Investigator, is a pediatric psychologist, Associate Professor at the UM and Director of Psychosocial Services and Research at the UM Congenital Heart Center. See Biosketch. Dr. Cousino is budgeted for 5% effort = 2.6 weeks per year but plans to provide significant non-funded effort with full support from center leadership.

Drs. Schumacher and Cousino have collaborated for the past 5 years on multiple externally funded research studies and publications [29-33]. As Co-PIs, Drs. Schumacher and Cousino will be responsible for all aspects and integrity of the project from start to finish. Drs. Schumacher and Cousino are committed to wide dissemination of results to quickly impact patient outcomes, and will build upon the proposed work with subsequent competitive grant applications.

B. OTHER PERSONNEL

Mousumi Banerjee, PhD, Co-investigator (Biostatistician), is the Anant M. Kshirsagar Collegiate Research Professor of Biostatistics at U-M, and the Director of Biostatistics at the U-M Center for Healthcare Outcomes & Policy. She also provides primary statistical oversight for the PC4 Registry and has extensive expertise leading outcomes analyses and advanced statistical methods, including multi-level modelling and machine learning techniques [22]. She will collaborate with Dr. Schumacher and Dr. Cousino on the design and conduct of all analyses.

Research staff. Sunkyung Yu, MS (Analyst) is the extensively experienced, lead analyst for M-CHORD. In collaboration with the investigative team, she will conduct the proposed project analyses. Garret Reichle, MS (Data Manager) is a database programmer for M-CHORD and PC4 and will design and implement the FCF consensus definition work and the FCF data collection module and manage data acquisition and uploads for the project. Janet Donohue, MS (Data manager) is the lead database programmer for PC4 who will collaborate with Mr. Reichel to assure data quality and will facilitate data linkage to PC4. Katherine Afton, BS (Lead Study Coordinator) is an experienced study coordinator with M-CHORD and will be responsible for overall and day-to-day project coordination and central IRB preparation and management at the coordinating sites. Kimberly Gonzalez, MS (Study Coordinator) is the project manager for PC4 and will be responsible for managing interactions between the study team and the PC4 registry.

In addition to the above study team, collaborators from 15 other congenital heart disease transplant programs will collaborate on this project. Letters of Support included in Appendix C. Collaborators: Sharon Chen, Stanford; Kathleen Simpson, Children’s Hospital of Colorado; Shriprasad Deshpande, Children’s National; Chad Mao, Children’s Hospital of Atlanta; Betsy Blume, Boston Children’s; Angela Lorts, Cincinnati Children’s; Matthew O’Connor, Children’s Hospital of Philadelphia; Ryan Butts, Children’s Dallas; Steven Kindel, Children’s Hospital of Wisconsin; Joshua Friedland-Little, Seattle Children’s; Lydia Wright, Nationwide Children’s; Anna Joong, Lurie Children’s; Michelle Ploutz, Primary Children’s; Justin Godown, Vanderbilt; Brian Feingold, Children’s Hospital of Pittsburgh
ENVIRONMENT
The facilities and resources available to Co-PIs at the University of Michigan’s Mott Children’s Hospital’s Congenital Heart Center provide all that is needed to successfully undertake and complete the proposed study. Please also see the included letter of support from Dr. Donna Martin, Chair of the Department of Pediatrics, and a letter of support from Dr. John Charpie, division chief of pediatric cardiology, in Appendix B.

Michigan Congenital Heart Outcomes Research and Discovery (M-CHORD) Program: The M-CHORD Program, for which Dr. Schumacher is the associate director, supports research conducted across the U-M Congenital Heart Center. This unique multidisciplinary program is composed of faculty across pediatric cardiology, cardiac surgery, critical care, genetics, nephrology, gastroenterology, neurology, and psychology, along with dedicated staff members including research nurses, study coordinators, database programmers, and statisticians. M-CHORD’s expertise spans the full spectrum of clinical investigation including translational research, clinical trials, health services and outcomes research, and collaborative quality improvement, and the group has extensive experience leading multi-center studies. Supported by M-CHORD, U-M Congenital Heart Center faculty and trainees secured over $6 million in funding and published 102 peer-reviewed manuscripts this past year alone. M-CHORD is housed in dedicated research space adjacent to C. S. Mott Children’s Hospital. M-CHORD will support the overall coordination of this project and analysis of all data, as well as the site-specific conduct of the prospective Aim 2.

Pediatric Cardiac Critical Care Consortium (PC4): PC4 is a multicenter collaborative aiming to improve congenital heart care and outcomes through research and quality improvement activities with 55 participating centers throughout North America. Dr. Schumacher directs the PC4 Data Coordinating Center housed within the M-CHORD program described above. PC4 maintains a detailed, highly audited, clinical registry capturing data on both surgical and medical pediatric cardiac patients using standard definitions. Data are submitted in real-time, and on-demand feedback is available to participating sites through a state-of-the-art web platform. PC4 infrastructure will support data collection for the entire project as well as facilitate linkage to PC4 outcome and ICU course data. All collaborating programs are PC4 members. Please see attached letter of support from Dr. Sarah Tabbutt, the executive director of PC4, in appendix B.

KEY REFERENCES

## Budget for Novel Approaches to Improve Post-Transplant longevity for Children with Complex Congenital Heart Diseases Grant Proposal

**PI Name:** Kurt Schumacher and Melissa Cousino  
**Proposal Title:** The impact of Fontan circulatory failure, frailty, and resilience on heart failure and transplant outcomes  
**Administrative Name:** Rebecca Youmans DeMoss  
**Contact Information:** including phone number and email address: 734-232-0501/ryoumans@umich.edu

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<td>2. Melissa Cousino</td>
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<td>3. Mousumi Banerjee</td>
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**TOTAL Requested Year 1:** $136,901.00  
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**TOTAL:** $300,000.00
Budget Justification

Personnel

Kurt Schumacher, MD, MS, Co-Principal Investigator (8% effort Y1 and Y2) is a pediatric cardiology intensivist, Associate Professor at the University of Michigan (UM) and Medical Director of the Pediatric Heart Transplant Program at C.S. Mott Children’s Hospital. He will co-oversee patient recruitment, data collection, and analyses, as well as and coordinate regular research team meetings and complete progress reports. Dr. Schumacher will provide content expertise specific to pediatric congenital heart disease and Fontan-associated risks and management.

Melissa Cousino, PhD, Co-Principal Investigator, (5% effort Y1 and Y2) is a pediatric psychologist, Associate Professor at the UM and Director of Psychosocial Services and Research at the UM Congenital Heart Center. She will co-oversee patient recruitment, data collection, and analyses, as well as and coordinate regular research team meetings and complete progress reports. Dr. Cousino will provide content expertise specific to psychosocial risks and modifiable intervention targets, specifically resiliency.

Mousumi Banerjee, PhD, Biostatistician, (4% effort Y1 and Y2) is a Professor of Biostatistics and Director of Biostatistics at the Center for Healthcare Outcomes & Policy at the University of Michigan and lead biostatistician for the Pediatric Cardiac Critical Care Consortium (PC4). For the proposed investigation, she will collaborate with the study team to formulate and direct the proposed analyses particularly those utilizing machine learning.

Kimberly Gonzalez MS, Project Manager (1% effort Y1 and Y2) is the Project Manager for PC4. Ms. Gonzalez will ensure the project receives appropriate PC4 review and approval, and help manage timelines and support regulatory efforts in coordination with the PC4 linkage for the study.

Garrett Reichle, MS, Database Manager (20% effort Y1 and Y2) will serve as the data manager for the FCF consensus definition generation and the FCF data module collection as well as working in conjunction with Ms. Donohue for PC4 portions of this study including linkage of datasets.

Sunkyung Yu, MS, Statistician, (0% effort Y1 and 15% Y2) has served as the lead biostatistician for the MCHORD Program for nine years. Ms. Yu, under Dr. Banerjee’s direction and guidance, will formally complete all statistical analyses, each of which is planned to occur in year 2.

Katherine Afton, BS, Lead Study Coordinator (24% effort Y1 and Y2) will serve as the lead coordinator for the study and assist all other centers with regulatory efforts, as a resource for Aim 1 and the conduct of the prospective study for Aim 2. She will also serve as site coordinator at the University of Michigan. Ms. Afton will serve as the study coordinator for the prospective portion of the study (aim 2) including ensuring completion of the consenting process for parents/patients, managing all regulatory documents, and coordinating data collection, including frailty and resilience testing data.

Janet Donohue, MPH, Database Manager (5% effort Y1 and Y2) is the Lead Database Programmer within the MCHORD Program, and is also main architect of the Pediatric Cardiac Critical Care Consortium (PC4). She will facilitate the linkage between the FCF data and the PC4
registry data, and she will assist and oversee Mr. Reichle in all aspects of data collection and management for this project.

**Lump sum start-up funds for each site, including equipment costs**

Each of the 16 sites will receive lump-sum start-up funds of $1195, for a total cost of $19,120. These funds are intended to cover regulatory fees and effort, as well as equipment including a study ipad, grip strength manometer, and 6-minute walk cones.

**Per-patient reimbursements**

Each site will receive reimbursement for every retrospective patient enrolled (n=250, $125 per patient to cover data entry) and for every prospective patient enrolled (n=130, $340 per patient, which includes $250 for coordinator effort, a $30 patient incentive, and $60 license for a written measure that is part of the study), for a total cost of $75,450. This structure was chosen to best support actual center effort and provide equitable reimbursement among centers that may have higher or lower patient volume across the collaborative.
NAME: Schumacher, Kurt

eRA COMMONS USER NAME (credential, e.g., agency login): kurts1

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

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<tr>
<td>University of Michigan Medical School, Ann Arbor, MI</td>
<td>MD</td>
<td>06/2005</td>
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<tr>
<td>University of Michigan School of Public Health, Ann Arbor, MI</td>
<td>MS</td>
<td>04/2013</td>
<td>Clinical Research Design and Statistical Analysis</td>
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<td>University of North Carolina, Dept of Pediatrics, Chapel Hill, NC</td>
<td>Resident</td>
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<td>Pediatrics Residency</td>
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A. Personal Statement

I am a heart failure trained pediatric cardiologist and have been studying the pathophysiology and treatment of Fontan-associated diseases and complications since my fellowship in pediatric cardiology at the University of Michigan Congenital Heart Center. Our institution is a leader in the care of single ventricle-type congenital heart diseases, and these individuals are the most common type of patient that I see and treat in my clinical duties. Since joining the faculty at the University of Michigan in 2011, I have been a part of a productive multidisciplinary, collaborative team that has substantially advanced knowledge of single ventricle-associated diseases. This has included specific leadership positions for me in multicenter studies of Fontan-associated protein losing enteropathy, Fontan-associated plastic bronchitis, and Fontan liver disease. Specifically, I led two multicenter retrospective studies of patients with protein losing enteropathy undergoing heart transplantation, I am the co-principal investigator of the currently enrolling FDA R01 sponsored trial of plastic bronchitis therapy, and the principal investigator for currently enrolling ancillary study of Fontan-associated liver disease within the Pediatric Heart Network's FUEL trial. I also am very interested in psychosocial outcomes of heart failure and have a very successful collaborative track record with the co-PI for this grant proposal, Dr. Cousino. Together we have successfully published 5 manuscripts on decision making and psychosocial functioning in pediatric heart failure populations, I am a mentor for her current NIH K-award, and I am a collaborator on a current NIH R21 award with her - all of which we anticipate will lead to future important publications and funded research. I have found this collaborative relationship with Dr. Cousino to be outstanding, and with our shared clinical interests, I anticipate this being extremely beneficial to the current project and throughout our careers. In addition, I have formal training in clinic research having completed a master's degree in clinical research design and statistical analysis at the University of Michigan School of Public Health. My significant clinical and clinical research experience, my previous study and understanding of Fontan pathophysiology, my formal training as a clinical research scientist, and my experience leading other multicenter and multidisciplinary research collaborations, and my track record of highly successful work with Dr. Cousino will allow us to effectively direct this research project. Together with our clinical colleagues from the many participating centers for this project, we believe this study will lead to a substantial change in the evaluation and clinical care of single ventricle patients and improve transplant outcomes.


B. Positions and Honors

Positions and Employment
2011 - 2012 Clinical Lecturer, University of Michigan Medical School, Dept of Pediatrics/Pediatric Cardiology, Ann Arbor, MI
2012 - Assistant Professor, University of Michigan Medical School, Dept of Pediatrics/Pediatric Cardiology, Ann Arbor, MI
2015 - Medical Director of Pediatric Heart Transplantation, University of Michigan Medical School, Dept of Pediatrics/Pediatric Cardiology
2018 - Associate Professor, University of Michigan Medical School, Dept of Pediatrics/Pediatric Cardiology, Ann Arbor, MI
2018 - Associate Director, Michigan Congenital Heart Research Outcomes and Discovery (M-CHORD) unit, University of Michigan Congenital Heart Center, Ann Arbor, MI
2019 - Director, Analytic Center, Pediatric Cardiac Critical Care Consortium, Ann Arbor, MI

Other Experience and Professional Memberships
2008 - Member, American College of Cardiology
2009 - Member, American Heart Association
2010 - Member, International Society for Heart and Lung Transplantation

Honors
2001 Pfizer Medical Student Research Award, University of Michigan Dept of Pediatrics
2006 Outstanding Teaching Resident, University of North Carolina Dept of Pediatrics
2006 Outstanding Teaching Resident, University of North Carolina Medical School
2008 Outstanding Teaching Resident, University of North Carolina Dept of Pediatrics
2008 Most Outstanding Resident, University of North Carolina Dept of Pediatrics
2011 Astellas Young Investigator Award, Pediatric Heart Transplant Study

C. Contribution to Science
1. Fontan circulatory failure and associated diseases Late post-Fontan diseases are universally poorly understood. Much of my research has focused on improving understanding, assessing risk, and finding treatment for these outcomes. Much of my research has focused on improving our understanding of the scope and pathophysiology of these diseases as well as understanding their impact on survival pre- and post-heart transplant, and it has furthered our fields overall knowledge of how sequelae of Fontan Circulator Failure affects patient outcome.


2. Psychosocial outcomes in pediatric heart failure. I have placed increasing importance on psychosocial outcomes research as my career has progressed. While we all want the best outcomes for our patients, a true understanding of psychological outcomes as well as the impact of our care on decision making and patient well-being has been lacking in our field despite being outcomes that amenable to intervention and improvement. Through my collaborations with Dr. Cousino, we have been able to advance our understanding of the scope and importance of these outcomes in pediatric heart failure and transplant populations.


3. Risk models and outcomes of pediatric heart failure and transplant. Through my statistical training and clinical interests, I have worked to understand specific patient factors drive clinical outcomes. I believe this knowledge is vital to improving survival both before and after heart transplantation in children. I have both led and collaborated on these efforts that have significantly contributed to the field's knowledge.


4. Collaborative research in Fontan and other congenital heart disease patients. My research has not been limited to only patients with Fontan circulatory failure, but instead has often focused on understanding both precursors to failure as well as understanding how to improve outcomes and performance of individuals with Fontan physiology. To those ends, I have been a successful and engaged leader and collaborator on multicenter studies of Fontan patients, including being a part of the core leadership group for the Pediatric Heart Network’s FUEL trial of udenafil in Fontan patients.


D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support

1R01FD005393-01A1, FDA - Schumacher, Kurt (PI) 09/16/16-07/31/20
IND119678 Phase II Safety & Efficacy of Inhaled Activase for Acute Plastic Bronchitis
This multi-center single arm trial will evaluate the safety and efficacy of inhaled tissue plasminogen activase to treat exacerbations of the rare disease plastic bronchitis. This disease occurs in patients with failing single ventricle congenital heart disease.
Role: CPI

PHN sponsored, Pediatric Heart Network - Schumacher, Kurt (PI) 02/01/18-02/01/20
Fontan Associated Liver Disease
Large multicenter study of Fontan Associated Liver Disease among patients currently enrolled in the PHN FUEL trial.
Role: PI
NAME: Cousino Hood, Melissa Kaye

eRA COMMONS USER NAME (agency login): mcousino

POSITION TITLE: Associate Professor of Pediatrics

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

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<td>Pediatric Psychology</td>
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A. Personal Statement

As the Director of Psychosocial Services and Research and attending psychologist to the pediatric heart transplant program at the University of Michigan Congenital Heart Center, my clinically-informed program of research focuses on psychosocial outcomes, healthcare communication, youth medical decision making in pediatric end stage organ disease with emphasis on pediatric advanced heart disease populations. I currently serve as PI on two NIH funded research studies which bring together the fields of pediatric psychology, medicine, bioethics, and palliative care to improve the delivery of patient-centered care to young people with critical illness. My teaching efforts are largely focused on the provision of research mentoring, primarily to physician trainees and early career faculty with interests in quality of life, mental health, and healthcare communication in pediatric medicine. I currently serve as a primary research mentor to four grant-funded early career physicians. Prior to my faculty position, I completed NIH-funded T-32 research training in pediatric psychology, providing strong foundational skills in research design, implementation, analysis and dissemination. My clinical, research, and educational work is strongly based in multidisciplinary collaborations, which has led to my involvement as the pediatric psychology representative to international and national scientific medical councils and writing groups, including the International Society for Heart and Lung Transplantation, American Heart Association, Cardiac Networks United, ACTION, and Enduring Hearts. In sum, I am well positioned to contribute as a co-PI on this exciting collaborative proposal.

B. Positions and Honors

Positions and Employment

2013-2015  Clinical Fellow, Department of Psychiatry, Harvard Medical School, Boston, MA
2015-2017  Research Affiliate, Department of Psychiatry, Harvard Medical School, Boston, MA
2015-2020  Assistant Professor, Department of Pediatrics, University of Michigan, Ann Arbor, MI
2019-      Director, Psychosocial Services and Research, C.S. Mott Children’s Hospital Congenital Heart Center
2020-      Associate Professor, Department of Pediatrics, University of Michigan, Ann Arbor, MI

Other Experience and Professional Memberships

2007-      Member, Society of Pediatric Psychology, Division 54 of American Psychological Association
2012-2015  Member, Society of Clinical Child and Adolescent Psychology, Division 53 of American Psychological Association
2014-2015  Member, American Academy of Hospice and Palliative Medicine
2014-2015  Member, Pediatric Advanced Care Team Committee, Boston Children’s Hospital
2014-        Member, Bioethics Special Interest Group, Society of Pediatric Psychology
2015-2016  Member, Society of Clinical Psychology, Division 12 of American Psychological Association
2015-2016  Member, Association of Psychologists in Academic Health Centers
2015-2017  Member, American Heart Association
2015-        Member, Cardiology Special Interest Group, Society of Pediatric Psychology
2017-        Member, Solid Organ Transplant Special Interest Group, Society of Pediatric Psychology
2017-2020  Symposium Planning Committee, International Society for Heart and Lung Transplantation
2017-        Committee Member, Nursing, Health Sciences and Allied Health Grants and Awards Workforce, International Society for Heart and Lung Transplantation
2018-        Member, International Pediatric Transplant Association
2018-        Leadership Committee, Advanced Cardiac Therapies Improving Outcomes Network
2019-        Scientific Advisory Board, Enduring Hearts
2020-        Member, Standards and Guidelines Committee, International Society for Heart and Lung Transplantation
2020-        Advisory Board, Cardiac Networks United

Honors
2004  Valedictorian Scholarship, Michigan State University
2007  Student Leader of the Year, Michigan State University
2004-2008  Psychology Honors College, Michigan State University
2004-2008  Dean’s List, Michigan State University
2009  Psychology Department Alumni Fund Travel Award, Case Western Reserve University
2011  Student Poster Award, National Conference in Pediatric Psychology
2011  Psychology Department Alumni Fund Travel Award, Case Western Reserve University
2012  Student Travel Award, American Psychological Association, Division of Pediatric Psychology
2016  International Society for Heart and Lung Transplantation Nursing, Health Sciences and Allied Health Research Award
2016  Jeanette Ferrantino Young Investigator Award, Department of Pediatrics, Michigan Medicine
2017  International Society for Heart and Lung Transplantation Leach-Abramson-Imhoff Links Award
2018  Editor’s Choice, Special Distinction Award, MedEdPORTAL
2018  Extra Mile Award, Department of Pediatrics, Michigan Medicine
2019  Faculty Award for Clinical Investigation, Pediatric Research Symposium, Michigan Medicine

C. Contribution to Science

1. Healthcare Communication and Decision Making in Pediatric Medicine. I have been actively involved in interdisciplinary team science research on healthcare communication and medical decision making in pediatric medicine for over 10 years. My work has spanned various pediatric critical illnesses, including heart disease (Cousino et al., 2019), organ failure (Cousino et al., 2019), and cancer (Cousino et al., 2012), as well as settings and types of encounters, such as end of life discussions and inpatient medical rounds (Rea et al., 2018).


2. Psychosocial and Patient-Reported Outcomes in Pediatric Heart Disease. Specific to pediatric heart disease, I published our research detailing the high rates of psychosocial risk among pediatric heart failure/transplant populations (Cousino et al., 2018). Notably, 40% of families indicated clinically significant levels of psychosocial risk. In addition, with a goal of improving health outcomes for pediatric heart failure populations through psychological interventions, I demonstrated use of variability in immunosuppressant blood trough levels, as an objective measure of adherence to medication (Cousino et al., 2017).


3. Patient and Family Adjustment to Pediatric Illness. My research has also investigated the impact of pediatric illness on family systems and aimed to identify family variables that serve as risk or protective factors with regard to child health and psychosocial outcomes. Included in this work is a meta-analysis and systematic review of the literature on parenting stress in pediatric chronic illness (Cousino & Hazen, 2013). Findings highlighted the need for intervening upon caregiver stress to improve psychological outcomes in children with chronic illness. This manuscript has been cited nearly 500 times. This line of research has been conducted across various pediatric illness populations including cancer (Cousino et al., 2017), solid organ transplantation (Cousino et al., 2017), pediatric critical illness (Yagiela et al., 2019), and diabetes.


4. Provider-Directed Communication Interventions. Utilizing findings from our communication-based research, I have participated in and led evidence-based intervention research to improve the delivery of patient-centered communication. For example, I analyzed the impact of a physician directed intervention aimed at improving informed consent discussions for pediatric clinical research trials (Cousino et al., 2011). More recently I completed the grant-funded development of a clinical tool, MyCHATT, to aide in the delivery of patient-centered communication in pediatric inpatient medical settings (Cousino, Rea, & Mednick, 2017) and co-facilitated a simulation-based intervention targeting resident communication during inpatient medical rounds (Rao et al., 2018).


Complete List of Published Work in MyBibliography:

D. Research Support

Ongoing Research Support

1 K23 HL145096-01: Melissa Cousino, PhD, (PI) 09/2019-06/2023
Palliative and End of Life Care in Adolescent and Young Adult Heart Failure NIH-DHHS-US

5 R21 NR016802-02: Melissa Cousino, PhD, (PI) 04/2018-03/2021
Advance Care Planning with Adolescents and Young Adults with Advanced Heart Disease NIH-DHHS-US-

Melissa Cousino, PhD; Elizabeth Hill, MD, Priyaka Rao, MD, (Co-PI) 07/2018-06/2021
Communication Coaches for Pediatric Residents Graduate Medical Education Innovations Program, University of Michigan

(Principal Investigator: Heang Lim, MD) 04/2018-06/2021
Quality of Life and PTSD in Pediatric Cancer Survivors with Chemotherapy-Related Cardiac Dysfunction
Children's Health Research Award, Department of Pediatrics, University of Michigan
Role: Co-I

Melissa Cousino, PhD, (PI) 04/2018-04/2021
Circumstances Surrounding End-of-Life in Pediatric Heart Transplant Recipients Palliative Care Pilot Grant, University of Michigan

Melissa Cousino, PhD; Elizabeth Blume, MD, (Co-PI) 05/2019-12/2020
Palliative and End of Life Care in Pediatric Cardiology: State of the Science and Future Directions Radcliffe Institute for Advanced Study, Harvard University

Research Support Completed During the Last Three Years

Melissa Cousino, PhD, (PI) 10/2016-09/2020
Provider Practices: Difficult Healthcare Discussions in Pediatric End-Stage Organ Disease Jeanette Ferrantino Investigator Award, Department of Pediatrics, University of Michigan

Melissa Cousino, PhD; Elizabeth Hill, MD; Priyanka Rao, MD, (Co-PI) 12/2017-12/2018
Communication Coaches for Pediatric Residents Center for Research, Learning and Teaching, University of Michigan

(Principal Investigator: Raymond Hutchinson, MD) 10/2016-09/2018
Exploring Parental Experiences, Knowledge and Perceptions of Pediatric Palliative Care after the Loss of a Child due to Malignancy Nancy Newton Loeb Pediatric Cancer Research Award, Department of Pediatrics, University of Michigan
Role: Co-I

Melissa Cousino, PhD, (PI) 04/2016-05/2018
Decision Making in Adolescents and Young Adults Pre- and Post-Heart Transplantation International Society for Heart and Lung Transplantation and Enduring Hearts-

(Principal Investigator: Emily Fredericks, PhD) 10/2015-02/2018
iSTART: Using Technology to Improve Transition Readiness Among Adolescent Transplant Recipients Charles Woodson Interdisciplinary Research Award, Department of Pediatrics, University of Michigan
Role: Co-I
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Banerjee, Mousumi

eRA COMMONS USER NAME (credential, e.g., agency login): mousumi

POSITION TITLE: Anant M. Kshirsagar Collegiate Research Professor of Biostatistics

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>Completion Date MM/YYYY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indian Statistical Institute, Calcutta</td>
<td>BA</td>
<td>07/1986</td>
<td>Statistics</td>
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<tr>
<td>Indian Statistical Institute, Calcutta</td>
<td>MS</td>
<td>07/1988</td>
<td>Statistics</td>
</tr>
<tr>
<td>University of Wisconsin, Madison</td>
<td>PhD</td>
<td>08/1994</td>
<td>Statistics</td>
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</tbody>
</table>

A. Personal Statement

As a biostatistician with 25+ years of experience, I am uniquely positioned to serve as principal investigator on this grant. I have broad interests and expertise in developing statistical methodology and applying it in biomedical research, particularly in cancer and pediatric cardiology. I have been the PI or co-investigator on numerous NIH grants over the last twenty years. My methodological research is in machine learning methods, correlated data, and survival analysis. I also serve as the Director of Biostatistics in the Center for Healthcare Outcomes & Policy (CHOP) within the Institute for Healthcare Policy & Innovation (IHPI) at Michigan. I am also a faculty in the Biostatistics Core of the Rogel Cancer Center at University of Michigan. Since 2016, I have worked closely with Dr. Michael Gaies to develop statistical methods for quality assessment to drive quality improvement initiatives within the Pediatric Cardiac Critical Care Consortium (PC4), a multi-institutional quality collaborative for children with critical cardiovascular disease. These efforts resulted in several manuscripts both published and in press in journals such as *Annals of Thoracic Surgery*, *Pediatric Critical Care Medicine*, *Circulation Cardiovascular Quality and Outcomes*, and *Critical Care Medicine*, among others. The proposed project has great potential to have a direct impact on improving real-time clinical care for critically ill children with congenital heart disease. We have unique data resources at our disposal to accomplish the aims of the project, and a track record of successful collaboration that ensures project success. Below are four specific publications that are particularly relevant to this grant application (selected from a total of 192 publications):

B. Positions and Honors

Positions and Employment
1994 – 1995 Assistant Professor, Department of Statistics, State University of New York at Buffalo, NY.
1995 – 1998 Assistant Professor, Departments of Pathology and Urology, Wayne State University, Detroit, MI.
1998 – 2001 Assistant Professor, Center for Healthcare Effectiveness Research & Department of Community Medicine, Wayne State University, Detroit, MI.
1996 – 2003 Faculty, Graduate Program in Cancer Biology, Wayne State University, Detroit, MI.
2001 – 2003 Associate Professor, Center for Healthcare Effectiveness Research & Department of Community Medicine, Wayne State University, Detroit, MI.
2003 – 2005 Associate Research Scientist, Department of Biostatistics, University of Michigan, Ann Arbor, MI.
2005 – 2010 Research Associate Professor, Department of Biostatistics, University of Michigan, Ann Arbor, MI.
2010 – Present Research Professor, Department of Biostatistics, University of Michigan, Ann Arbor, MI.

Other Experience and Professional Memberships
1990 – 1992 Consultant, Statistical Consulting Laboratory, College of Agriculture and Life Sciences, University of Wisconsin, Madison, WI.
1993 – 1994 Statistician, Department of Epidemiology and Preventive Medicine, University of Wisconsin, Madison, WI.
1994 – 1995 Director, Statistical Consulting Laboratory, Department of Statistics, State University of New York at Buffalo, NY.
1995 – 1998 Biostatistician, Prostate Cancer Initiative, Wayne State University, Detroit, MI.
2004 – Present Member, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI.
2004 – Present Member, Protocol Review Committee, University of Michigan Rogel Cancer Center.
2010 – Present Director of Biostatistics, Center for Healthcare Outcomes & Policy, University of Michigan.

Honors
1994 Best Student Paper Award, Biopharmaceutical Section, American Statistical Association
1996 NIH Study Section, Epidemiology and Disease Control
1997 Karmanos Cancer Institute Performance Recognition Award
2002 Excellence in Clinical Research Award, Blue Cross Blue Shield of Michigan
2005 McDevitt Excellence in Research Award, Blue Cross Blue Shield of Michigan Foundation
2005 Review Panel, National Institute of General Medical Sciences (NIGMS) Biomedical Research Support (MBRS)
2007 Review Panel, SPORE, National Cancer Institute
2009 Special Research Initiative Statistical Methods Review Panel, California Breast Cancer Research Program
2010 Fellow, American Statistical Association
2010 Elected Member, International Statistical Institute
2015 Review Panel, American Institute of Biological Sciences
2015 McDevitt Excellence in Health Policy Research Award, Blue Cross Blue Shield of Michigan Foundation
2016-Present Editorial Board, Circulation: Cardiovascular Quality and Outcomes
2017-Present Scientist Reviewer, Patient-Centered Outcomes Research Institute (PCORI)
2018 Anant M. Kshirsagar Collegiate Research Professor, University of Michigan
2018-Present Member, Special Emphasis Panel ZRG1 F18-Z 20 L, Fellowships: Epidemiology and Population Sciences, National Institutes of Health.
C. Contributions to Science

Contributions to correlated data analysis: One focus of my research has been on developing methodology for correlated data, specifically longitudinal and multilevel data, with particular emphasis on their application in cancer studies. In particular I have developed influence diagnostics for mixed effects models.


Contributions to survival analysis: I have been creative in developing and adapting survival analysis methods for analyzing data with competing risks. Motivated by data that frequently arise due to incompleteness in death certificates, our team has proposed strategies to handle masked competing risks data in cancer registries.


Contributions to machine learning: Motivated by problems in cancer and cardiovascular disease, I have developed machine learning methods with applications to clinical decision making.


Contributions to statistical methods for prognostication: Motivated by problems in cancer research, I have developed novel methods for prognostication in clinical studies.


Contributions to health services research: One focus of my work is developing statistical methodology for health services research, specifically to study variation in the management of diseases with an emphasis on...
the role of patients, providers, and health systems on treatment. This topic on variation in care and treatment patterns has been methodologically explored with the use of large national cancer registries such as the National Cancer Database (NCDB), Surveillance, Epidemiology and End Results (SEER) and SEER-Medicare. To obtain more granular information on decision making, we have also used physician surveys linked to the NCDB registry.


Contributions to outcomes research: I have also been involved in developing statistical methodology for studying variation in outcomes of diseases with an emphasis on the role of providers and health systems. This topic on variation in outcomes has been methodologically explored with the use of large national cancer registries such as the National Cancer Database (NCDB), Surveillance, Epidemiology and End Results (SEER) and SEER-Medicare.


D. Additional Information: Research Support and/or Scholastic Performance

**Ongoing Research Support**

1 R01 HS 024512-01A1 (PI: Haymart) 09/30/16-07/31/20
Imaging Practices and Overdiagnosis of Thyroid Cancer
The project goal is to develop a clinical strategy to minimize the overdiagnosis of thyroid cancer and to serve as a model for overdiagnosis in general.
Role: Co-Investigator

1 R01 CA201198-01A1 (PI: Haymart) 07/15/16-06/30/20
Treatment Decision Making in Low-Risk Thyroid Cancer
By using SEER-linked patient and physician surveys, we plan to understand the treatment decision making in low-risk thyroid cancer. We hypothesize that knowledge and attitudes influence decision making. Specifically, we anticipate that lack of knowledge of risks of death, recurrence and treatment complications is associated with treatment that is more intensive.
Role: Co-Investigator

1 R01 HS024698-01 (PI: Bynum) 09/30/16-07/31/21
Effects of Accountable Care Organizations on Post-Acute Care
In order to describe the impact of health reform on post-acute care delivery and outcomes, we propose the following goals: evaluate the impact of reimbursement reform on post-acute care utilization patterns and spending, evaluate the consequences of changes in post-acute care delivery on patient outcomes and evaluate heterogeneity in the impact of reimbursement reform on patient outcomes.

Role: Co-Investigator

5 P30 CA 046592 (PI: Fearon) 06/01/18 - 05/31/23
Comprehensive Cancer Center Core Grant II
Biostatistics Core (Taylor)
The core grant supports the senior leadership, programs and shared facilities of the Cancer Center. The Center provides the organizational framework to promote interdisciplinary research through the development of defined clinical, basic science and prevention programs in cancer research, and the development and support of shared resources.
Role: Co-Investigator

**Completed Research Support**

Michigan Institute for Clinical and Health Research Banerjee (PI) 01/01/19 – 12/31/19
Machine Learning Methods for Complex Designs in Pediatric Cardiac Critical Care
The goal of the project is to develop a machine learning (ML) based framework to predict extubation failure in the pediatric ICU and develop a decision-making tool that can influence real-time clinical care in this population.
Role: PI

1-R21-CA 152775-01-A1 Banerjee (PI) 10/01/11 – 09/30/14
Machine Learning Tools for Prognostication in Melanoma
The purpose of the study is to develop a well-validated tool for prognostication of stage III melanoma patients that can be used in the clinical setting.
Role: PI

1-R01-HS 018726-01-A1 Hollenbeck (PI) 12/01/10 – 11/30/14
Ambulatory Surgery Centers and Medicare Expenditures for Outpatient Procedures
The proposed research will clarify the extent to which the proliferations of ASCs, and single specialty facilities in particular is helping or hurting the efficiency of outpatient surgical specialty care.
Role: Co-Investigator.

RSG-12-269-01-CPHPS Wong (PI) 07/01/12-06/30/15
Understanding Variation in Treatment Intensity of Poor Prognosis Cancers
To provide information to help clinicians improve quality of care for patients with cancer and to help policy makers improve efficiency through changes in health care policies.
Role: Co-Investigator

1-R01-AG042340-01A1 Dimick (PI) 12/01/12-11/30/15
Understanding Variation in Failure to Rescue in the Elderly
We propose a multi-center study involving 34 hospitals participating in the Michigan Surgical Quality Collaborative (MSQC), the largest population-based collaborative quality improvement program in the United States.
Role: Co-Investigator
Curriculum Vitae

Sunkyung Yu

Michigan Congenital Heart Center
University of Michigan Medical School
Tel: 734-232-0461 (office) or 734-678-3577 (cell)
E-mail: skyu@med.umich.edu

RESEARCH INTERESTS
Repeated measures analyses using Mixed modeling approach; Longitudinal Data analysis; Categorical Data Analysis; Survival analysis; Analysis for National/International Registries/Databases; Missing data analysis using multiple imputation

EMPLOYMENT
11/2019–current  Statistician Staff Specialist, Michigan Congenital Heart Center, University of Michigan Medical School
01/2011–10/2019  Statistician Lead, Michigan Congenital Heart Center, University of Michigan Medical School
06/2007–12/2010  Senior Biostatistician, Yale Center for Analytical Sciences, Yale University School of Medicine
05/2005 –05/2007  Statistician Associate, Center for Human Growth and Development, University of Michigan
01/2004 –04/2005  Graduate Student Research Assistant, Department of Epidemiology, University of Michigan
09/2001–12/2003  Graduate Student Research Assistant, Department of Biostatistics, University of Michigan
02/2001–07/2001  Data Analyst, Department of Information Statistics, Korean National Open University, Seoul, South Korea
02/2000 –09/2000  Statistical Consultant, Statistical Consulting Services of Seoul National University School of Medicine, Seoul, South Korea

APPOINTMENT TO ADVISORY COMMITTEE
07/2013–current  Scholarly Oversight Committee (SOC) for Fellow Research, Division of Pediatric Cardiology, University of Michigan Medical School

EDUCATION
M.S. Department of Epidemiology, University of Michigan, Ann Arbor, MI, 2007
M.S. Department of Biostatistics, University of Michigan, Ann Arbor, MI, 2003
M.S. Department of Statistics, Seoul National University, Seoul, South Korea, 2001
B.S. Department of Statistics, Hankuk University of Foreign Studies, Seoul, South Korea, 1997
−Honor of Early graduation, Summa Cum Laude/Minor in Business Administration
TRAINING AND WORKSHOP

06/2007 American College of Epidemiology Workshop, Boston, MA
07/2004 Graduate Summer Session in Epidemiology, University of Michigan, Ann Arbor, MI
06/2004 GIS Symposium on Public Health, University of Pennsylvania, Philadelphia, PA
07/2000 NCI Summer Curriculum in Cancer Prevention, National Institutes of Health, Bethesda, MD

SCHOLARSHIPS / AWARDS

05/2006 Scholarship for Spatial Epidemiology Conference, London, United Kingdom
Sponsored by Center for Disease Control and Prevention (CDC) and Small Area Health
Statistics Unit (SAHSU)
03/2006 Travel grant fellowship, Rackham Graduate School, University of Michigan
01/2004 –04/2005 Graduate Student Research Assistantship, Department of Epidemiology, University of Michigan
09/2001–12/2003 Graduate Student Research Assistantship, Department of Biostatistics, University of Michigan
09/1999–02/2001 Scholarship for distinguished graduate students, Brain Korea 21 (BK21), The Korean Ministry of
Education, Seoul, South Korea
09/1997 2nd prize at the Contest Undergraduate’s Paper in memory of ‘Day of Statistics’, The Korean
Statistical Society, Seoul, South Korea
09/1994–08/1997 Scholarship for distinguished undergraduate students from alma mater, Department of Statistics,
Hankuk University of Foreign Studies, South Korea

PROFESSIONAL AFFILIATIONS

American Statistical Association, International Biometric Society, American Heart Association

COMPUTER SKILLS

SAS, SUDDAN, IVEware, StatXact PROCs, SPSS

PUBLICATIONS (including peer-reviewed journals only)

1. Ian Thomas, Naomi T Laventhal, Sunkyung Yu, Ray Lowery, Sarah Gelehrter (2020). Impact of standardized prenatal
documentation among newborns with ductal-dependent heart disease. Journal of Perinatology, 40(10);1531-1536

2. Kimberly J Watkins, Sarah Geisler, Tammy Doman, Matthew J Orringer, Paloma Tracy, Sunkyung Yu, Nicole S Wilder, Mark W
Russell (2020). Rise in Angiopoietin-2 Following Neonatal Cardiac Surgery is Associated With Adverse Clinical Outcomes. Pediatric
Critical Care Medicine, 21(9);e827-e833

3. Aparna Joshi, Weifang Kong, Sunkyung Yu, Sowmya Balasubramanian, Bhavin Jankharia, Prachi P Agarwal (2020). Female
Radiology, S1076-6332(20)30410-4

5. Karen Uzark, Sunkyung Yu, Ray Lowery, Katherine Afton, Anji T Yetman, Jonathan Cramer, Nancy Rudd, Scott Chen, Russell Gongwer, Michelle Gurvitz (2020). Transition Readiness in Teens and Young Adults with Congenital Heart Disease: Can We Make a Difference? *Journal of Pediatrics*, 212;201-206.e1


19. Adam M Lubert, Timothy B Cotts, Jeffrey D Zampi, Sunkyung Yu, Mark D Norris (2019). Echocardiographic Predictors of Elevated Left Ventricular End Diastolic Pressure in Adolescent and Adult Patients with Repaired Tetralogy of Fallot. *Cardiology in the Young*, 29(8);1020-1024


25. Katherine E Bates, Sunkyung Yu, Ray Lowery, Sara K Pasquali, David W Brown, Peter B Manning, Karen Uzark (2018). Examining Variation in Interstage Mortality rates across the National Pediatric Cardiology Quality Improvement Collaborative: Do lower mortality centers have lower risk patients?. *Cardiology in the Young*, 28(8); 1031-1036


28. Stephanie Goldstein, Martin J LaPage, Brynn Dechert-Crooks, Gerald A Serwer, Sunkyung Yu, Ray E Lowery, David J Bradley (2018). Decreased Inappropriate Shocks with New Generation ICDs in Children and Patients with Congenital Heart Disease. Congenital Heart Disease, 13(3); 413-418

29. Adam M Lubert, Jimmy C Lu, Albert P Rocchini, Mark D Norris, Sunkyung Yu, Prachi P Agarwal, Maryam Ghadimi Mahani, Adam L Dorfman (2018). Relation of Increased Epicardial Fat After Fontan Palliation to Cardiac Output and Systemic Ventricular Ejection Fraction. American Journal of Cardiology, 121(7); 862-866

30. Emefah C Loccoh, Sunkyung Yu, Janet Donohue, Ray Lowery, Jennifer Butcher, Sara Pasquali, Caren Goldberg, Karen Uzark (2018). Prevalence and Risk Factors Associated with Non-Attendance in Neurodevelopmental Follow-up Clinic among Infants with Congenital Heart Disease. Cardiology in the Young, 28(4); 554-560

31. Hayley S Hancock, Ken Pituch, Karen Uzark, Priya Bhat, Carly Fifer, Maria Silveira, Sunkyung Yu, Suzanne Welch, Janet Donohue, Ray Lowery, Ranjit Aiyagari (2018). A Randomized Trial of Early Palliative Care for Maternal Stress in Infants Prenatally Diagnosed with Single-Ventricle Heart Disease. Cardiology in the Young, 28(4); 561-570


33. H. Sonali Magdo, Joshua M Friedland-Little, Sunkyung Yu, Robert J Gajarski, Kurt R. Schumacher (2017). The impact of ischemic time on early rejection after pediatric heart transplant. Pediatric Transplantation, 21(8); e13034


37. Jimmy C Lu, Ray Lowery, Sunkyung Yu, Maryam Ghadimi Mahani, Prachi P Agarwal, Adam L Dorfman (2017). Predictors of missed appointments in patients referred for congenital or pediatric cardiac magnetic resonance. Pediatric Radiology, 47(8); 911-916
38. Michelle J White, Emefah C Loccoh, Monica M Goble, **Sunkyung Yu**, Folafoluwa O Odetola, Mark W Russell (2017). High School Cardiac Emergency Response Plans and Sudden Cardiac Death in the Young. *Prehospital and Disaster Medicine*, 32(3); 269-272


42. Brian A Boe, Jeff D Zampi, Kurt R Schumacher, **Sunkyung Yu**, Aimee K Armstrong (2016). The Use and Outcomes of Small, Medium and Large Premounted Stents in Pediatric and Congenital Heart Disease. *Pediatric Cardiology*, 37(8); 1525-1533


44. Jimmy C Lu, **Sunkyung Yu**, Ray Lowery, Janaki Sagi, Amanda Delong, Prachi P Agarwal, Maryam Ghadimi Mahani, Adam L Dorfman (2016). Predictors of Change in Functional Health Status in Adults with Repaired Tetralogy of Fallot. *Pediatric Cardiology*, 37(7); 1334-1339


46. Jeffrey D. Zampi, Darren Berman, Martin L Bocks, **Sunkyung Yu**, Evan Zahn, Jimmy C Lu, Justin A Shaya, Aimee KArmstrong (2016). Factors associated with the internal jugular venous approach for MelodyTM Transcatheter Pulmonary Valve implantation. *Cardiology in the Young*, 26(5); 948-956

47. Nicole S Wilder, **Sunkyung Yu**, Janet E. Donohue, Caren S Goldberg, Neal B Blatt (2016). Fluid Overload is Associated with Late Poor Outcomes in Neonate following Cardiac Surgery. *Pediatric Critical Care Medicine*, 17(5); 420-427


51. Nathaniel R Sznycer-Taub, Ray Lowery, Sunkyung Yu, Sonal T Owens, Jennifer C Hirsch-Romano, Gabe E Owens (2016). Hyperoxia is Associated with Poor Outcomes in Pediatric Cardiac Patients Supported on Venoarterial Extracorporeal Membrane Oxygenation. *Pediatric Critical Care Medicine*, 17 (4); 350-358


57. Karen Uzark, Cynthia Smith, Janet Donohue, Sunkyung Yu, Katherine Afton, Mark Norris, Timothy Cotts (2015). Assessment of Transition Readiness in Adolescents and Young Adults with Heart Disease. *Journal of Pediatrics*, 167 (6); 1233-1238


61. Brian Boe, Jeff D Zampi, Sunkyung Yu, Janet Donohue, Ranjit Aiyagari (2015). Transhepatic Central Venous Catheters in Pediatric Patients with Congenital Heart Disease. *Pediatric Critical Care Medicine*, 16 (8); 726-732


64. Aaron G DeWitt, Jeffery D. Zampi, Janet E. Donohue, Sunkyung Yu, Thomas R. Lloyd (2015). Fluoroscopy-guided umbilical venous catheter placement in infants with congenital heart disease. Congenital Heart Disease, 10 (4); 317-325


70. Stuart H. Covi, Wendy Whiteside, Sunkyung Yu, Jeffrey D. Zampi (2015). Pulse Fluoroscopy Radiation Reduction in a Pediatric Cardiac Catheterization Laboratory. Congenital Heart Disease, 10 (2); E43-47


74. Justin Godown, Janet Donohue, Sunkyung Yu, Joshua M Friedland-Little, Robert J Gajarski, Kurt R. Schumacher (2014). Differential effect of body mass index on pediatric heart transplant outcomes based on diagnosis. Pediatric Transplantation, 18 (7); 771-776


86. Brandon M Smith, Adam L Dorfman, Sunkyung Yu, Mark W Russell, Prachi P Agarwal, Maryam Ghadimi Mahani, Jimmy C Lu (2014). Clinical Significance of Late Gadolinium Enhancement in Patients < 20 years of age with Hypertrophic Cardiomyopathy. *American Journal of Cardiology*, 113 (7); 1234-1239

88. Jason Christensen, Jimmy C Lu, Janet E Donohue, Sunkyung Yu, Maryam Ghadimi Mahani, Prachi P Agarwal, Adam L Dorfman (2014). Relation of Aortic stiffness and Strain by Cardiovascular Magnetic Resonance Imaging to Age in Repaired Tetralogy of Fallot. American Journal of Cardiology, 113 (6); 1031-1035

89. Joshua M Friedland-Little, Ranjit Aiyagari, Sunkyung Yu, Janet Donohue, Jennifer Hirsch-Romano (2014). Survival through staged palliation: Fate of infants supported by Extracorporeal Membrane Oxygenation after the Norwood operation. Annals of Thoracic Surgery, 97 (2); 659-665


94. Wendy Whiteside, Meng Tan, Sunkyung Yu, Albert Rocchini (2013). Low total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol levels in patients with complex congenital heart disease following Fontan palliation. Journal of Pediatrics, 162 (6); 1199-1204


CURRICULUM VITAE
Janet E. Donohue, MPH

University of Michigan Health System
Division of Pediatric Cardiology
1500 E. Medical Center Drive, SPC 5202
Ann Arbor, MI 48109-5202
(T) 734-615–8149
janetdon@med.umich.edu

Education
Post-Bachelor Certification in Computer Science 1997
Wayne State University College of Liberal Arts & Science, Detroit, MI

Master of Public Health in Health Behavior and Health Education 1992
University of Michigan School of Public Health, Ann Arbor, MI

Bachelor of Arts with High Distinction in Psychology 1989
University of Michigan College of Literature, Science & Arts, Ann Arbor, MI

Continuing Education
Johns Hopkins Summer Institute of Epidemiology and Biostatistics
Oracle University
SAS Institute

Research Positions
Data Management Lead 2018 – present
Cardiac Networks United Data Coordinating Center
University of Michigan Health System, Ann Arbor, MI

Data Manager 2012 – 2018
Pediatric Cardiac Critical Care Consortium (PC4)
University of Michigan Health System, Ann Arbor, MI

Programmer/Analyst 2006 – 2012
Department of Pediatrics
University of Michigan Health System, Ann Arbor, MI

Health Statistician 2002 – 2006
Lab of Personality and Cognition
National Institute of Aging, Baltimore, MD

Honors and Awards
Alumni Association Scholarship (full tuition), UM School of Public Health 1990-1992
Select Bibliography


Gaies M, Cooper DS, Tabbutt S, Schwartz SM, Ghanayem N, Chanani NK, Costello JM, Thiagarajan RR, Laussen PC, Shekerdemian LS, **Donohue JE**, Willis GM, Gaynor JW,


DeWitt AG, Zampi JD, **Donohue JE**, Yu S & Lloyd TR (2014). Fluoroscopy-guided Umbilical Venous Catheter Placement in Infants with Congenital Heart Disease. *Congenit Heart Dis*.


Jantzen DW, Gelehrter SK, Yu S, **Donohue JE** & Fifer CG (2014). Echocardiographic factors discriminating biventricular versus univentricular approach in the foetus with borderline left ventricle. *Cardiol Young*: 1-10.


Donohue, JE


Katherine Afton, BS, CCRP
1500 E. Medical Center Drive
Ann Arbor, MI 48109
734-232-3945
kafton@med.umich.edu

Experience

May 2015-present University of Michigan – Michigan Medicine Ann Arbor, MI
M-CHORD Clinical Research Coordinator

Duties include: project coordination; IRB application submission and maintenance; patient screening and recruitment; consent; protocol implementation; data collection and instrument scoring; management of patient follow-up; ensure study protocol adherence and staff training; data entry/maintenance; organize, compile, and maintain electronic documentation and paper files; student and staff mentoring; project management as coordinating center for multi-center studies.

August 2012-May 2015 University of Michigan – Michigan Medicine Ann Arbor, MI
M-CHORD Research Assistant

Duties included: patient screening and recruitment; consent; protocol implementation; data collection and instrument scoring; track and manage patient follow-up; data entry/maintenance; organize, compile, and maintain electronic documentation and paper files; collaborate with team.

August 2011-May 2012 Institute for Social Research Ann Arbor, MI
Aggression Lab Research Assistant

Duties included: conducted research on 225 student participants looking at the effects of violent video games on aggression and the effects of ostracism on aggressive behavior in conjunction with Undergraduate Research 280 Course. Explained the study to participants, gained consent, and debriefed participants; entered and analyzed data and results; collaborated with research team; ensured the highest standards of research ethics and compliance.

Education

2019-2022 University of Michigan- Dearborn, Dearborn, MI
(Master of Business Administration (MBA)

2010-2014 University of Michigan, Ann Arbor, MI – Bachelor of Science (BS)
Biopsychology, Cognition, & Neuroscience
Spanish, minor
**Certifications and Accreditations**

Certified Clinical Research Coordinator (CCRP), August 2015  
Society of Clinical Research Associates (SOCRA)

Certification in CITI, certified through 2020  
(Collaborative Institutional Training Initiative)

Certification in PEERRS, certified through 2021  
(Program for Education and Evaluation in Responsible Research and Scholarship)

Certificate of Completion: Protection of Human Research Subjects  
Certificate of Completion: HIPAA Compliance Module for Researchers  
Certificate of Completion: Human Research During COVID-19

**Honors and Awards**

2019 - University of Michigan Congenital Heart Center- Employee of the Year

**Publications:**


Uzark, K., Afton, K., Yu, S., Lowery, R., Smith, C., Norris, M.: Transition Readiness in Adolescents and Young Adults with Heart Disease: Can We Improve Quality of Life? J Pediatr: 2019. PM31182220

**Abstracts:**

Afton, K., Yang, G., & Huesmann, R.: Role of Violent Video Games and Gender in Promoting Aggressive Behavior. Undergraduate Research Opportunity Program Research Conference, University of Michigan, Ann Arbor, Michigan, April 2012

Uzark K, Smith C, Yu S, Donohue J, Afton K, Norris M, Cotts TB.: Transition Readiness Assessment in Adolescents and Young Adults With Heart Disease: Can We Improve the Outcome?, Circulation, 2014.


**Professional Memberships**

2015- present  Society of Clinical Research Associates (SOCRA)

2016- present  Pediatric Cardiology Rewards and Recognition Committee member

2017- present  Save-A-Heart Committee – Silent Auction Chair / Social Media Marketing Chair

2018- present  Epilepsy Transition Program – Patient Advisory Committee

2018- present  Pediatrics Research Office and Children’s CTSU Committee- Pediatric Cardiology representative
Kimberly Susan (Sleater) Gonzalez
4607 North Clubview Dr. Email: gonzaleb@med.umich.edu
Adrian, MI. 49221 Cellular: (517) 231-9198

Summary of Qualifications
Extensive experience in the following:

- Facilitating communication and providing ongoing management for a large, multi-center quality improvement collaborative. Serving as liaison between participating hospitals, the data coordinating center and software vendors. Providing feedback and assistance to clinical champions, data collection personnel and administrators at participating hospitals to resolve issues and meet organizational objectives. Planning and participating in committee meetings and other events. Recruiting prospective centers, managing the contractual process, planning training/installations and audits. Preparing budget, managing financial and human resource activities.

- Managing or conducting academic and clinical research studies. Preparing study budgets and invoices, participating in the establishment of sub-contracts, facilitating contracts and negotiating result reporting timelines. Writing IRB applications and informed consent documents, screening and recruiting participants, performing consent, designing collection systems, collecting/ coordinating specimen collection and processing, coordinating sample analysis and shipping study supplies to clinical sites, maintaining Case Report Forms, preparing for inspections and monitoring visits, and participating in study conference calls.

- Managing a CAP-accredited, CLIA-certified laboratory providing quality service assays and successful research support services to academic and clinical research studies nationwide.

- Leading and maintaining the College of American Pathologists (CAP) Laboratory and Bio- Repository Accreditation as well as Clinical Laboratory Improvement Amendments (CLIA) Certification.

- Selecting, hiring and evaluating key personnel; ensuring personnel safety, training and performance.

- Representing the laboratory to regulatory agencies, sponsors, principal investigators, study coordinators, research participants, occupational safety and administrative personnel.

- Providing notable customer service and performing all administrative and financial functions for the laboratory such as time keeping approval, purchase orders, non-purchase order vouchers, contracts, travel expense reports, purchasing card reconciliation, reviewing statements of activity, preparing all recharge rates, cost studies, quotes and invoices for laboratory services as well as service unit billing clients.

- Writing, executing and reviewing an extensive manual of standard operating procedures (SOPs), document control plans, quality assurance/quality control (QA/QC) programs, progress reports and contributing to funding applications.

Education

Eastern Michigan University, College of Health & Human Services Ypsilanti MI
M.S. in Clinical Research Administration August 2015
Eastern Michigan University, College of Health & Human Services
Graduate Certificate – Clinical Research Administration
Ypsilanti MI
April 2007

Michigan State University, College of Natural Science
B.S. – Medical Technology
East Lansing, MI
1989

PROFESSIONAL DEVELOPMENT (through the University of Michigan):
Completed seminars and coursework in Project and Time Management, Foundations of Supervision, Laboratory and Radiation Safety, Research Responsibility, eResearch, PEERSS, HIPAA, MiChart, M-Pathways, and Cost Accounting/ Administration of Sponsored Projects.

Experience
THE UNIVERSITY OF MICHIGAN, Ann Arbor, MI
1991 – Present

Project Manager
January 2019-Present
Clinical Research Coordinator
January 2016-December 2018

Department of Pediatrics, Pediatric Cardiology
Responsibilities include facilitating communication and providing ongoing management for a large, multi-center quality improvement collaborative. Preparing budget, managing financial and human resource activities. Serving as liaison between participating hospitals, the data coordinating center and software vendors. Providing ongoing feedback and assistance to clinical champions, data collection personnel and administrators at participating hospital to resolve issues and meet organizational objectives. Planning and participating in committee meetings and other events. Recruiting prospective centers, managing the contractual process, planning training/installations and audits. Managing or conducting research studies, writing regulatory applications, and working with sponsors regarding contracts and billing.

Clinical Research Coordinator
November 2014- January 2016

Internal Medicine, Hematology/Oncology
Responsibilities included: coordinating multiple clinical research studies in Cancer Prevention, screening electronic medical records (MiChart), recruiting participants in the MPU, MLTCR-CC, MCRU and UMHS clinics, working with clinical teams during procedures to procure tissues, processing specimens, enrolling participants in MBECT, maintaining CRFs, preparing for and participating in monitoring visits and conference calls. Utilizing laboratory and repository expertise to research a potential biorepository initiative.

Volunteer
March 2014- November 2014

Internal Medicine- Hematology/Oncology
Responsibilities included: study coordination activities and support, biorepository/ laboratory planning and support; conducting literature searches, reviewing research protocols, entering data from source documents to electronic Case Report Forms, checking eligibility criteria and informed consent documents, and collecting specimens at participant visits and procedures at the Michigan Clinical Research Unit or the Medical Procedures Unit.

Quality Assurance Manager
July 2013- January 2014
Medical School Office of Research
(Resigned)
Responsibilities included: establishing Quality Management Systems, procedures and controls in order to ensure compliance with quality standards and best practices at the new UMHS Central Biorepository. Duties included: contributing to pilot research protocols, evaluating document control software programs, developing a business continuity plan, working towards Biorepository accreditation through the College of American Pathologists, designing audits of internal processes and systems, and coordinating or conducting staff training.
Laboratory Manager
January 2005-July 2013

Senior Research Associate, Manager
December 1999–January 2005

School of Public Health, Department of Epidemiology, CLASS Laboratory

Responsibilities included: ensuring personnel safety, training and performance; selecting, hiring, supervising and evaluating key personnel; providing service assays and research support services in an efficient, cost-effective, timely manner; supporting (and previously conducting) specimen collection kit manufacture, inventory management, sample check-in and storage, sample handling and preparation, assaying clinical research samples, and reviewing and processing assay results.

Duties included writing and executing QA/QC programs and SOPs, managing CAP Laboratory and BioRepository Accreditation as well as CLIA Certification; representing the laboratory to outside contact personnel and Investigators; writing progress reports, IRB applications, and communications; contributing to funding applications; leading the preparation for and participating in site visits/audits, overseeing and performing Service Unit Billing, M-Pathways Ordering, Non-purchase order vouchers, Travel Expense Reports and P-card Reconciliation in Concur, and preparing all recharge rates, cost studies, quotes and invoices for laboratory services.

HIGHLIGHTS:
- Laboratory five times (consecutively) awarded CAP accreditation and CLIA certification
- Laboratory awarded new CAP Bio-Repository accreditation in February 2013
- Laboratory awarded successful evaluations from NIH site visits
- Laboratory successfully served as Contract Research Organization in Phase 2, 3 Clinical Trials
- Written and implemented hundreds of SOPs for Laboratory and Bio-Repository operations
- Worked with others to consistently achieve 20,000 assay results/month
- Trained as a CAP Bio-Repository Inspector, February 2012
- Nominated for U of M School of Public Health Excellence in Staff Award, April 2012 and 2013

Manager, Research Associate II
September 1996 – December 1999

Reproductive Sciences Program, CLASS Laboratory

Responsibilities included: laboratory safety, personnel and equipment; selecting, hiring and evaluating key personnel; and all automated assay operations and all other laboratory activities (see above). Coordinated research activities with outside projects; responded to inquiries or issues, participated in project director conference calls, problem-solved, began writing SOPs and QA/QC systems, drafted IRB applications, performed consent, coordinated sample processing and participant payments. Assisted in the establishment of the CLASS Laboratory; coordinated move to a 2,700 sq.ft. North Campus facility in September 1995, procured necessary materials and supplies, electrical and plumbing work from Plant and Information Technology Central Services (ITCS). Accomplished move on time and within budget.

Research Associate I
September 1994 – September 1996

Reproductive Sciences Program, Assays & Reagents Core

Responsible for all automated assay operations, evaluating research findings and accepting/rejecting all research results; training support staff in assay methods, sample preparation, LIS operation; completing the Level III ACS-180 Proprietary and Trouble-shooting Program.

Research Assistant II
February 1992 – September 1994

Reproductive Sciences Program, Assays & Reagents Core

Duties included: performing service assays using chemiluminescent instrumentation; assisting in assay development using proprietary technology; documenting and tracking QA/QC; assisting in the development of an in-house LIS system for data capture and analysis.
Laboratory Assistant (temporary)  November 1991 – February 1992
Reproductive Sciences Program, Assays & Reagents Core

Responsibilities included: performing service assays, executing QA/QC procedures, performing inventories, and preparing reagents for distribution.

Professional Organizations/ Certifications

Society of Clinical Research Associates (SoCRA) Certification (certified through 1/1/2023)

References Available upon Request
Garrett Reichle

(248) 462-4937 · reichleg@msu.edu
2800 Windwood Dr. Apt. 129 · Ann Arbor, MI 48105

Education

**Michigan State University**
East Lansing, MI
Master of Science in Epidemiology
February 2018

**Madonna University**
Livonia, MI
Bachelor of Science in Biology
December 2014

Experience

<table>
<thead>
<tr>
<th>Database Analyst/Programmer Associate</th>
<th>Ann Arbor, MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Cardiac Critical Care Consortium (PC4)</td>
<td>June 2018 – Current</td>
</tr>
<tr>
<td>- Preparing data for clinical research and quality improvement projects, cleaning data, manipulating data, extracting project-specific data elements from large, relational datasets, and maintaining databases</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Research Assistant (Temp)</th>
<th>Ann Arbor, MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan Longitudinal Study (MLS)</td>
<td>March 2018 – June 2018</td>
</tr>
<tr>
<td>- Used SPSS and SAS to merge datasets, run descriptive statistics to clean data, handled missing data, and simplified suspect data codes to make data user friendly</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Data Analyst</th>
<th>Ann Arbor, MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan Stroke Transitions Trial (MISTT)</td>
<td>August 2016 – June 2017</td>
</tr>
<tr>
<td>- Collect and recorded data in REDCap on stroke survivors and caregivers, individual interviews, designed protocol for tracking readmissions, maintained clear and organized documentation of study files, input retrospective data and create methods to enhance the quality of data collection</td>
<td></td>
</tr>
<tr>
<td>- Accepted abstract on reliability and practicality of Patient-Reported Outcomes Measurement Information System on stroke survivors and caregivers for the Health Measures User Conference</td>
<td></td>
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<table>
<thead>
<tr>
<th>President of Graduate Epidemiologists at Michigan State</th>
<th>Ann Arbor, MI</th>
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<tbody>
<tr>
<td>May 2016 – May 2017</td>
<td></td>
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<tr>
<td>- Promoted public health and the participation of others in serving the community</td>
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<thead>
<tr>
<th>Center for Orthopedics and Sports Medicine Physical Therapy</th>
<th>West Bloomfield, MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Therapy Technician</td>
<td>January 2013 - December 2013</td>
</tr>
<tr>
<td>- Provided rehabilitation techniques to better patients with daily living activities, helped athletes regain performance abilities, managed multiple patients, organized tasks and made patient deadlines</td>
<td></td>
</tr>
</tbody>
</table>

Graduate Course Work

- Thesis: OUTPATIENT FOLLOW-UP VISITS AND THE RISK OF ALL-CAUSE 30-DAY HOSPITAL READMISSIONS FOR PATIENTS DISCHARGED FOLLOWING A CARDIOVASCULAR OR COPD RELATED EVENT: A SYSTEMATIC REVIEW AND META-ANALYSIS
  - Conducted a rigorous literature search, modified the Newcastle Ottawa scale, qualitative research through meta-analysis subgroups, evaluated data quality, and interpreted research findings
  - Downloaded and analyzed NHANES data used in SAS for cardiovascular disease research
  - Literature review explaining the public health importance of urinary tract infections by addressing descriptive and analytic epidemiology, gaps in understanding and public health interventions
  - Grant proposal: “Can Cranberry Products Prevent Urinary Tract Infections (UTIs)”
  - Grant proposal: CVD Prevention Program on a technological health intervention

Volunteering

- **Red Cross**: Promoted, helped conduct, and donated blood to the MSU vs Penn State Red Cross blood drive (2015 and 2016)
- **MSU Service Day**: Joined with the Clean Water Action to remove debris from waterways

Additional Skills

- Experience with SAS, REDCap, GIS mapping, Presentation skills, Microsoft Word, Excel, PowerPoint, Outlook, EndNote, PubMed, CINAHL, google scholar, SPSS, creating tables, graphs, and charts
APPENDIX B – INSTITUTIONAL LETTERS OF SUPPORT – UNIVERSITY OF MICHIGAN AND PC^4
Dear Additional Ventures - Enduring Hearts Review Team:

I am pleased to provide a letter in support of Dr. Kurt Schumacher and Dr. Melissa Cousino and their research proposal entitled "Defining Risks Imposed by Fontan Circulatory Failure, Frailty, and Resilience on the Outcome of Heart Transplantation: a multicenter collaboration" for an award through the Additional Ventures - Enduring Hearts partnership Novel Approaches to Improve Post-Transplant Longevity for Children with Complex Congenital Heart Diseases research fund. Drs. Schumacher and Cousino have been collaborating to advance the physical and psychosocial outcomes for children with heart failure for several years and together they have broad experience in risk modeling and assessing physical and psychosocial stressors in advanced heart disease. In addition, they have both demonstrated leadership in the field of heart failure and transplantation. The potential of this research to remarkably improve the outcomes of patients with Fontan requiring heart transplantation is truly exciting and I am pleased to support their application for your consideration.

Dr. Schumacher earned a B.S. at the University of Michigan in 2000 and his M.D. at Michigan in 2005. Dr. Schumacher next completed a Pediatric residency at the University of North Carolina followed by a fellowship in Pediatric Cardiology at the University of Michigan graduating in 2011. He subsequently earned a masters of science degree in Clinical Research and Biostatistics at the University of Michigan School of Public Health in 2013. In 2011 he was appointed to faculty at Michigan, promoted to Assistant Professor in 2012 and then Associate Professor in 2018. He is currently the Medical Director of the Pediatric Heart Failure and Transplantation, the associate director of the congenital heart center’s clinical research core MCHORD, and the director of the analytic center for the Pediatric Cardiac Critical Care Consortium.

Since joining the faculty, Dr. Schumacher has developed a productive research program spanning different areas of research. He has authored numerous manuscripts describing the pediatric heart transplant outcomes including seminal papers describing the differences in risk factors between congenital and non-congenital heart transplant patients (Circulation 2015), the outcomes of transplant in specific Fontan patients (JHLT 2015, 2019), and participated as a co-author on the scientific statement on the care of and evaluation of Fontan patients from the American Heart Association (Circulation 2019). Dr. Schumacher is also a leader on several ongoing projects that have received extramural funding including an ongoing clinical trial of inhaled therapy for patients with plastic bronchitis (FDA R01 mechanism) and the NHLBI-sponsored Pediatric Heart Network’s Fontan liver disease ancillary study to the FUEL trial. Overall his investigations and collaborations have yielded numerous publications that have helped to advance the field of single ventricle and pediatric heart failure care.

Dr. Cousino completed her doctoral training in clinical psychology at Case Western Reserve University through a NIH-funded T32 research training program in pediatric psychology. She completed her psychology internship and post-doctoral fellowship at Boston Children’s Hospital/Harvard Medical School before joining the Pediatrics faculty at the University of Michigan in 2015. She was recruited to the University of Michigan through a joint partnership between the Department of Pediatrics and the University of Michigan Transplant Center to establish a program of clinically informed research in
pediatric end-stage organ disease while also extending psychology services to pediatric solid organ transplant patients and their families.

Dr. Cousino has been very successful in these regards. In addition to the clinical services she launched with our pediatric heart failure and transplant program, she has obtained over 1 million dollars in external and intramural funding to lead novel studies in the areas of psychosocial outcomes, healthcare communication and medical decision making in pediatric and young adult advanced heart disease. As a result of her clinical acumen and research expertise, she has been named to leadership positions with various cardiac organizations, including Cardiac Networks United, ACTION, and the International Society for Heart and Lung Transplantation. Dr. Cousino is actually the first pediatric psychologist to hold high-level leadership positions for the International Society for Heart and Lung Transplantation; she currently serves on the Standards and Guidelines Committee as the only pediatric representative. She is a leading author on various consensus and clinical practice guidelines on the psychosocial care of pediatric patients with advanced heart disease. Dr. Cousino was recently promoted to Associate Professor this September and recruited to serve in a new role as the first Director of Psychosocial Services and Research for our Congenital Heart Center at the start of the year.

Together, Drs. Schumacher and Cousino have formed a remarkable and productive partnership that has resulted in several impactful publications and extramurally funded ongoing research. They serve as PI and Co-Investigator on two NIH-funded grants examining the roles of patient decision-making in pediatric advanced heart disease. To date, they have published 5 manuscripts together, with additional manuscripts currently under review/in progress. Recently, Drs. Schumacher and Cousino collaborated to quickly launch an international study of the impact of COVID-19 on pediatric cardiac care and psychological wellbeing. This research has garnered incredible interest from the heart communities. In sum, as collaborators in clinical care and research, they form an impressive team.

The Department of Pediatrics has been committed to supporting Drs. Schumacher and Cousino as they continue their research paths. The new C.S. Mott Children’s Hospital opened in 2011 creating an up to date physical environment for decades of ongoing advances in pediatric medicine. The state-of-the-art facility provides enhanced infrastructure for the accomplished pediatric clinician-scientists at Michigan who deliver life-changing care and conduct ground-breaking research. In addition, the University of Michigan Congenital Heart Center at C.S. Mott Children’s Hospital, which is annually recognized by U.S. News and World Report as one of the best heart and heart surgery programs in the country, provides diagnosis and treatment for the full spectrum of congenital heart conditions.

To complement research efforts of our investigators, the Departments of Pediatrics and Cardiothoracic Surgery have developed a highly effective and experienced clinical research program, the Michigan Congenital Heart Outcomes and Research Discovery program (M-CHORD) which is located within the Congenital Heart Center and has extensive clinical research, data management, and statistical personnel with expertise capable of guiding the development and effective completion of clinical research studies. Further, the Congenital Heart Center houses the data coordinating and analytic center for the Pediatric Cardiac Critical Care Consortium (PC4) which Dr. Schumacher directs. PC4 is a multi-center collaborative aiming to improve congenital heart care and outcomes through research and quality improvement activities with over 60 participating centers throughout North America. PC4 maintains a detailed clinical registry capturing data on both surgical and medical pediatric cardiac patients, using standardized definitions.

In summary, Dr. Schumacher and Dr. Cousino are accomplished clinician-scientists in the field of pediatric heart failure and transplant research. I believe their investigations will significantly advance clinical care for patients with Fontan requiring a heart transplant. The Department of Pediatrics and Michigan Medicine continually support their research efforts and have infrastructure in place to continue to build and support future interventions that stem from the knowledge their work will surely achieve. For all of these reasons I am particularly pleased to support their Additional Ventures - Enduring Hearts
application and feel that after completion of their proposed aims, the care and outcomes of this complex patient population will be forever improved.

Sincerely,

[Signature]

Donna M. Martin, M.D., Ph.D.
Professor & Chair, Department of Pediatrics
Ravitz Foundation Endowed Professor of Pediatrics
Professor of Human Genetics
Physician-in-Chief, Mott Children’s Hospital
University of Michigan
Dear Additional Ventures - Enduring Hearts Review Committee:

I am pleased to provide a letter in support of Dr. Kurt Schumacher and Dr. Melissa Cousino and their research proposal entitled “The Impact of Fontan Circulatory Failure, Frailty, and Resilience on Heart Failure and Transplant Outcomes” for an award through the Additional Ventures - Enduring Hearts partnership Novel Approaches to Improve Post-Transplant Longevity for Children with Complex Congenital Heart Diseases research fund. Drs. Schumacher and Cousino have been collaborating in the University of Michigan C.S. Mott Congenital Heart Center for several years to advance the physical and psychosocial outcomes for children with heart failure, and together they have broad experience in multiple domains of heart failure research. In addition, they have both demonstrated clinical, quality improvement, and research leadership in the field of heart failure and transplantation. I believe this exciting research has remarkable potential to improve the outcomes of patients with Fontan circulatory failure requiring heart transplantation, and I am pleased to support their application for your consideration.

Dr. Schumacher completed categorical fellowship in Pediatric Cardiology at the University of Michigan in 2011. He then pursued advanced training in both cardiac critical care and heart failure and transplantation. Subsequently, Dr. Schumacher earned a Master’s of Science degree in Clinical Research and Biostatistics at the University of Michigan School of Public Health in 2013. He is currently Medical Director of Pediatric Heart Failure and Transplantation, Associate Director of the Congenital Heart Center’s clinical research core, and Director of the analytic center for the Pediatric Cardiac Critical Care Consortium. Since joining the faculty, Dr. Schumacher has established a very productive research program spanning a variety of research areas, and demonstrating a strong ability to lead multicenter research efforts. Overall his investigations and collaborations have yielded numerous publications that have helped to advance the field of single ventricle and pediatric heart failure care.

Dr. Cousino completed her doctoral training in clinical psychology at Case Western Reserve University through an NIH-funded T32 research training program in pediatric psychology. She completed her psychology internship and post-doctoral fellowship at Boston Children’s Hospital/Harvard Medical School before joining the Pediatrics faculty at the University of Michigan in 2015. She was recruited to the University of Michigan through a joint partnership between the Department of Pediatrics and the University of Michigan Transplant Center to establish a program of clinically informed research in pediatric end-stage organ disease while also extending psychology services to pediatric solid organ transplant patients and their families. Recently, Dr. Cousino assumed a new leadership position as the Director of Psychosocial Services for our Congenital Heart Center. In addition to the clinical services she launched with our pediatric heart failure and transplant program, she has obtained over $1M in external and intramural funding to support her research program. Dr. Cousino also has demonstrated remarkable leadership in her relatively short career. She is the first pediatric psychologist to hold high-level leadership positions for the International Society for Heart and Lung Transplantation. She is also a leading author on various consensus and clinical practice guidelines on the psychosocial care of pediatric patients with advanced heart disease.

Together, Drs. Schumacher and Cousino have formed a remarkable and productive partnership that has resulted in several impactful publications and extramurally funded ongoing research. They serve as PI and Co-Investigator on two NIH-funded grants examining the roles of patient decision-making in pediatric advanced heart disease. To date, they have published 5 manuscripts together, with additional manuscripts currently under review or in progress.
Our program and infrastructure will support successful completion of Dr. Schumacher and Dr. Cousino’s research proposal to the fullest possible extent. The University of Michigan Congenital Heart Center at C.S. Mott Children’s Hospital, which is annually recognized by *U.S. News and World Report* as one of the best heart and heart surgery programs in the country, provides diagnosis and treatment for the full spectrum of pediatric acquired and congenital heart conditions. To complement research efforts of our investigators, the Departments of Pediatrics and Cardiothoracic Surgery have developed a highly effective and experienced clinical research program, the Michigan Congenital Heart Outcomes and Research Discovery program (M-CHORD) which is located within the Congenital Heart Center and has extensive clinical research, data management, and statistical personnel with expertise capable of guiding the development and effective completion of clinical research studies. Further, the Congenital Heart Center houses the data coordinating and analytic center for the Pediatric Cardiac Critical Care Consortium (PC4) which Dr. Schumacher directs. PC4 is a multi-center collaborative aiming to improve congenital heart care and outcomes through research and quality improvement activities with over 60 participating centers throughout North America. PC4 maintains a detailed clinical registry capturing data on both surgical and medical pediatric cardiac patients, using standardized definitions.

In summary, I believe Dr. Schumacher and Dr. Cousino’s investigations will significantly advance clinical care for Fontan patients requiring a heart transplant. This research is so important to our field and to our patients at the Congenital Heart Center that we are committed to support their effort, and that of our M-CHORD research staff, even if it should exceed that allotted by the grant.

Sincerely,

John R. Charpie, MD, PhD
Professor, Department of Pediatrics
Amnon Rosenthal Professor & Division Director of Pediatric Cardiology
Co-Director, University of Michigan Congenital Heart Center
Michigan Medicine
October 14th, 2020

Dear Additional Ventures - Enduring Hearts Review Team:

I am pleased to provide a letter in support of Dr. Kurt Schumacher and Dr. Melissa Cousino and their research proposal entitled “The Impact of Fontan circulatory failure, frailty, and resilience on heart failure and transplant outcomes” for an award through the Additional Ventures - Enduring Hearts partnership Novel Approaches to Improve Post-Transplant Longevity for Children with Complex Congenital Heart Diseases research fund. I believe this research has remarkable potential to improve the outcomes of patients with Fontan circulatory failure requiring heart transplantation and is truly exciting. I am pleased to support their application on behalf of the Pediatric Cardiac Critical Care Consortium PC4 for your consideration.

PC4 is a multicenter collaborative aiming to improve congenital heart care and outcomes through research and quality improvement activities with 55 participating centers throughout North America. PC4 maintains a detailed, highly audited, clinical registry capturing data on both surgical and medical pediatric cardiac patients using standard definitions. Data are submitted in real-time, and on-demand feedback is available to participating sites through a state of the art web platform. PC4 infrastructure will support data collection for the entire project as well as facilitate linkage to PC4 operative, outcome, and ICU course data.

Dr. Schumacher is currently the director of the analytic center for the Pediatric Cardiac Critical Care Consortium. In this role, he has developed expertise with the registry and demonstrated a significant ability to conduct complex analyses. He also has a demonstrated ability to lead and work with both a large research staff and co-investigators from other centers.

The proposed project was presented to the PC4 executive committee who approved the project to move forward with full PC4 support if funded. I believe PC4 is ideally positioned to support a highly refined examination or peri- and post-operative outcomes in this population. Further, Fontan patients after transplant are often among the most challenging to support in the ICU, and as cardiac intensivists, any project aimed at improving ICU patient outcomes aligns well with the overall goals of the PC4.

In summary, PC4 is fully supportive of this project and its use of the PC4 registry.

Sincerely,

Sarah Tabbutt, MD, PhD
Executive Director of PC4
APPENDIX C – MULTICENTER COLLABORATOR LETTERS OF SUPPORT
Dear Drs. Cousino and Schumacher,

I am writing to offer my full support in participating in the multicenter collaboration entitled “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”. This proposal will add significantly to our knowledge as well as to our ability to support patients and families with end stage heart disease. I am excited to agree that Boston Children’s Hospital Advanced Cardiac Therapies Program will participate fully in this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. This population presents unique and difficult challenges in assessing the likelihood of success with heart transplant. By elucidating key risk factors and modifying some, this study will significantly improve survival and morbidity for Fontan patients undergoing transplant evaluation.

The Department of Cardiology at Boston Children’s Hospital has the resources and infrastructure necessary for successful participation in this trial. We have a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. I have successfully completed collaborations with both Drs. Cousino and Schumacher. They are skilled clinical researchers that will be successful in leading this project.

I understand our site will receive $1,195 to cover site start-up costs (ie: study-required iPad, Grip Manometer, 6-minute walk cones). Additionally, we will receive per patient funding for both retrospective patient data ($125) and prospective patient recruitment ($340).

We fully support this important project. Please do not hesitate to contact me for further information.

Sincerely,

Elizabeth D. Blume MD
September 18, 2020

Melissa Cousino PhD  
Associate Professor  
Director, Psychosocial Services and Research  
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS  
Associate Professor  
Director, Pediatric Heart Failure and Transplantation  
Congenital Heart Center, University of Michigan  
1540 E. Hospital Dr.  
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of University of Texas Southwestern/Children’s Medical Center of Dallas as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Children’s Medical Center of Dallas has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information please do not hesitate to contact me.

Sincerely,

Ryan Butts, MD  
Medical Director of Pediatric Advanced Cardiac Care  
Associate Professor of Pediatrics
September 18, 2020

To,
Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Children's National Hospital, Washington DC as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Children's National Hospital has all the resources and infrastructure necessary for successful participation in the trial. Our transplant program has a strong history of participation in successful collaborative research including ongoing transplant related prospective trial, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success.
I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information, please do not hesitate to contact me.

Sincerely,

Shriprasad R Deshpande, MBBS MS
Medical Director,
Heart Transplant and Advanced Cardiac Therapies Program
Children's National Hospital
Associate Professor of Pediatrics
The George Washington University
111, Michigan Avenue NW
Washington, D.C. 20010-2970
Email: sdeshpan@childrensnational.org
9/21/2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of The Children’s Hospital of Philadelphia as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that The Children’s Hospital of Philadelphia has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. Our center has experience collaborating with the University of Michigan and Dr. Schumacher through
participation in the PC4 collaborative, the ACTION Network, and other collaborations through organizations such as the Pediatric Heart Network.

If you require any further information please do not hesitate to contact me.

Sincerely,

Matthew J. O’Connor, MD
Medical Director, Heart Transplant/VAD
The Children’s Hospital of Philadelphia
267-426-2882
oconnorm@email.chop.edu
9/23/20

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Seattle Children’s Hospital as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Seattle Children’s Hospital has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program have a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. As a former colleague of Dr. Schumacher’s at University of Michigan and as a collaborator with him in numerous prior research activities, I am confident that this project as designed by him and Dr. Cousino will provide data of the utmost importance in improving

Heart Center
Phone: 1-888-543-7478
Fax: (206) 987-3839

Cardiovascular Surgery
D. Michael McMullan, M.D.
Lester Permut, M.D.
Muhammad Nuri, M.D.
David Machley, M.D.

Heart Transplant and Heart Failure Service
Yuk Law, M.D.
Mariska Kemna, M.D.
Erin Albers, M.D.
Borah Hong, M.D.
Joshua Friedland-Little, M.D.
Kathryn Spencer, ARNP

Transplant Coordinators
Pam Horak, RN
Kell Morgan, RN
Jason Hopper Cruz, RN
Jennifer Stack, RN
Stephanie Church, RN
Erica Southern, RN
Katie Ayers, RN
Phone: (206) 987-3013

Clinical Psychologist
James McKeever, PhD
(206) 987-3058

Transplant Social Worker
Marcel Floresca
Phone: (206) 987-2053

Data Coordinator
Lori Iwasaki
Phone: (206) 987-3296

Program Coordinator
Carolyn Copstead
Phone: (206) 987-1417
outcomes for the growing cohort of patients with Fontan circulatory failure who will require heart transplantation.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information, please do not hesitate to contact me.

Sincerely,

Joshua Friedland-Little, MD
Associate Professor, Pediatrics
University of Washington School of Medicine
Medical Director, Mechanical Circulatory Support Program
Heart Failure and Heart Transplant Service
Seattle Children’s Hospital
September 18, 2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Lucile Packard Childrens Hospital at Stanford University as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Lucile Packard Childrens Hospital at Stanford University has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. Our previous collaboration with Dr. Schumacher on a multi-center study on Fontan-associated protein-losing enteropathy and post-heart transplant outcomes was successful published in the Journal of Heart and Lung Transplantation. We also are currently participating in a multi-center clinical drug trial with Dr. Schumacher on the safety and efficacy of inhaled tissue plasminogen activator for the treatment of acute plastic bronchitis.
I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information please do not hesitate to contact me.

Sincerely,

Sharon Chen, MD MPH
Clinical Assistant Professor, Pediatrics
Medical Director, Comprehensive Single Ventricle Program
9/16/2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Nationwide Children’s Hospital as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Nationwide Children’s Hospital has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. Several members of our transplant team, including section chief Dr. Robert Gajarski, have worked closely with the University of Michigan study team in the past.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information please do not hesitate to contact me.
Sincerely,

[Signature]

Lydia Wright, MD, MSc
Assistant Clinical Professor
Pediatric & Adult Advanced Cardiac Therapies
The Heart Center
Nationwide Children’s Hospital
700 Children's Drive, Columbus, Ohio 43205
9/17/2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I am writing to formally express my interest and enthusiasm about participating in the aforementioned multicenter collaboration, and the involvement of The Herma Heart Institute at Children’s Wisconsin as part of this important research project.

As a large volume and experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Improved understanding of the patient characteristics and profiles that indicate increased risk for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to increase our knowledge about these patients and the Fontan phenotype in general as well as provide valuable insight to improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that The Herma Heart Institute at Children’s Wisconsin has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. We have worked previously with the team at C.S. Mott and the University of Michigan on multi-center research regarding cell-free DNA monitoring of rejection after heart transplant (funded via an R01 mechanism) as well as partnering with Dr Schumacher specifically on multiple projects related to Fontan circulatory failure, listing, mechanical support and heart transplant through the ACTION learning network.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.
If you require any further information please do not hesitate to contact me.

Sincerely,

[Signature]

Steven J. Kindel, MD
Medical Director of Advanced Heart Failure and Transplantation
Herma Heart Institute/Children's Wisconsin
Associate Professor of Pediatrics
Medical College of Wisconsin
September 17, 2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Ann & Robert H. Lurie Children’s Hospital of Chicago as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Ann & Robert H. Lurie Children’s Hospital has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. As a recent example, our center is an active participant in “TEAMMATE”, the prospective multicenter randomized clinical trial in pediatric heart transplant immunosuppression regimens.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry.
We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry. If you require any further information please do not hesitate to contact me.

Sincerely,

Anna Joong, MD
Pediatric Heart Failure and Heart Transplantation
Medical Director, Ventricular Assist Device Program
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children’s Hospital of Chicago
225 East Chicago Avenue, Box 21, Chicago, IL 60611-2605
T 312.227.4100 | F 312.227.9640 | ajoong@luriechildrens.org |
September 21, 2020

Melissa Cousino PhD  
Associate Professor  
Director, Psychosocial Services and Research  
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS  
Associate Professor  
Director, Pediatric Heart Failure and Transplantation  
Congenital Heart Center, University of Michigan  
1540 E. Hospital Dr.  
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of University of Utah/Primary Children’s Hospital as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that University of Utah/Primary Children’s Hospital has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. We have been very productive partners in collaborative clinical research enterprises such as PHTS, ACTION, and the TEAMMATE trial.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information please do not hesitate to contact me.

Sincerely,

Michelle Ploutz

Assistant Clinical Professor

University of Utah
September 21, 2020

Melissa Cousino, PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher, MD, MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan

1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I am writing to express our interest and enthusiasm to participate in the above-named multicenter collaboration. I believe this is a very important and timely project and that UPMC Children’s Hospital of Pittsburgh will be able to contribute meaningfully to this work.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. This population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplantation. A significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is very much needed to improve outcomes. I believe this proposal holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

Our program has all the necessary resources and infrastructure for successful participation in the trial. We have a strong and long history of participation in successful collaborative research, including in multicenter CTOTC-4, 9, and 10 awards as well as being a founding member of and contributor to the PHTS. I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information, please do not hesitate to contact me.

Best wishes,

Brian Feingold, MD, MS, FAHA
Associate Professor, Pediatrics and Clinical and Translational Science
University of Pittsburgh School of Medicine
Medical Director, Heart Failure and Transplantation Programs
UPMC Children’s Hospital of Pittsburgh
September 16th, 2020

Melissa Cousino PhD  
Associate Professor  
Director, Psychosocial Services and Research  
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS  
Associate Professor  
Director, Pediatric Heart Failure and Transplantation  
Congenital Heart Center, University of Michigan  
1540 E. Hospital Dr.  
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I am happy to write this letter expressing our interest and enthusiasm for participating in your proposed multicenter study, “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes.” We believe that the proposed work is highly novel and will fill an important gap in the literature. Our team at Vanderbilt University Medical Center is fully supportive of this project and will play an active role to ensure successful completion of this important study.

As an experienced congenital heart center in conjunction with a large heart transplant program, we care for numerous patients with Fontan circulatory failure. This population presents highly unique and difficult challenges in assessing the impact of heart failure and understanding the risks associated with heart transplantation. Improved understanding of the factors that may contribute to poor outcomes in this group and identification of potentially modifiable factors that impact patient risk, represent critical first steps towards improving outcomes in this population. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing heart transplantation.

Vanderbilt has a wealth of available resources to ensure successful participation in this effort. Our institution and transplant program have a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. This study will build upon a number of past collaborations between our team and the providers at the University of Michigan. Past collaborative efforts have been highly successful and I fully anticipate that this project will be also.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information please do not hesitate to contact me.

Sincerely,

Justin Godown, MD
Assistant Professor, Pediatric Heart Failure and Heart Transplantation
Monroe Carell Jr. Children’s Hospital at Vanderbilt
17 September 2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Children’s Healthcare of Atlanta as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Children’s Healthcare of Atlanta has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success.

I understand our site will receive $1,195 to cover site start-up costs and the expenses associated with purchasing the study-required iPad, Grip Manometer, and 6-minute walk cones. Additionally, we will receive retrospective per patient reimbursement of $125 to cover costs of chart review and data entry. We will receive $340 per patient for each prospective patient recruited at our site to cover recruitment efforts, data collection, and data entry.

If you require any further information please do not hesitate to contact me.

Sincerely,

Chad Y. Mao, MD
Medical Director – Advanced Cardiac Therapies Program
Assistant Professor of Pediatrics
Children’s Healthcare of Atlanta – Emory University
Sibley Heart Center Cardiology
2835 Brandywine Road, Suite 300 | Atlanta, Ga | 30341
c: 404-785-6395 | c: 240-988-7742 | f: 404-256-7121
maocha@kidsheart.com | www.choa.org/cardiology
October 13, 2020

Melissa Cousino PhD  
Associate Professor  
Director, Psychosocial Services and Research  
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS  
Associate Professor  
Director, Pediatric Heart Failure and Transplantation  
Congenital Heart Center, University of Michigan  
1540 E. Hospital Dr.  
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multicenter collaboration, and the involvement of Cincinnati Children’s Hospital Medical Center as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Cincinnati Children’s Hospital Medical Center has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success.

If you require any further information, please do not hesitate to contact me.

Sincerely,

Angela Lorts, MD, MBA  
Medical Director, Ventricular Assist Device Program  
Associate Chief Quality Officer-Outcomes  
Co-executive Director ACTION
October 14, 2020

Melissa Cousino PhD
Associate Professor
Director, Psychosocial Services and Research
Congenital Heart Center, University of Michigan

Kurt Schumacher MD MS
Associate Professor
Director, Pediatric Heart Failure and Transplantation
Congenital Heart Center, University of Michigan
1540 E. Hospital Dr.
Ann Arbor, MI 48109

Re: Study “Defining Risk Factors of Fontan Circulatory Failure to Improve Heart Transplant Outcomes”

Dear Drs. Cousino and Schumacher,

I write this letter to express our interest and enthusiasm in participating in the aforementioned multi-center collaboration, and the involvement of Children’s Hospital of Denver/University of Colorado as part of this important project.

As an experienced congenital heart center and heart transplant program, we care for many patients with Fontan circulatory failure. As at other centers, this population presents unique and difficult challenges in assessing the overall impact of their heart failure as well as understanding the likelihood of success with heart transplant. Significantly improved understanding of the overall risks for poor outcome conferred by Fontan circulatory failure, as well as what factors may be modifiable, is necessary to improve these outcomes. This study holds significant promise to improve our knowledge and improve overall outcomes for Fontan patients undergoing transplant.

I can assure you that Children’s Hospital of Denver/University of Colorado has all the resources and infrastructure necessary for successful participation in the trial. Our institution and transplant program has a strong history of participation in successful collaborative research, and I am confident that we have the clinical capacity, expertise, patient volume, and academic interests necessary to aid in this study’s success. I have previously collaborated with Dr. Schumacher and the University of Michigan on several successful multi-center research endeavors which resulted in meaningful clinical outcomes and peer reviewed...
publications. I look forward to this opportunity to work again with Dr. Schumacher to advance the care of children with complex congenital heart disease and heart failure.

If you require any further information, please do not hesitate to contact me.

Sincerely,

[Signature]

Kathleen E. Simpson, MD
Associated Professor of Pediatrics
Heart failure and heart transplantation
University of Colorado Anschutz Medical Center, Children’s Hospital of Colorado
APPENDIX D

Acknowledgements and Documentation

Drs. Cousino and Schumacher offer the following statements and acknowledgements as requested:

We acknowledge the AV-EH policy that no awards will be made for projects that receive overlapping funding from other sources (unless supplementary in nature) or that duplicate other projects already funded. This project currently has no funding, and we have not applied for funding from any other source. If funding is awarded to the project, any additional funding would only be sought as supplementary.

We acknowledge that as a condition of receiving funding, we agree to the following:

- We will provide Enduring Hearts biannual scientific progress reports with an accompanying lay summary, notification of presentations and a copy of any publications to be sent to the grant’s administration office via email at grants@enduringhearts.org
- We will acknowledge Enduring Hearts/Additional Venture support in any publication or presentation resulting from this award, with logo as appropriate. Acknowledgement will read as follows: “This work was supported by an Award from Additional Venture and Enduring Hearts Transplant Risk-Reduction Initiative”
- Enduring Hearts may publish our professional titles, our project title, and our institutional affiliation except in any purchased media advertising.

We acknowledge our roles as Enduring Hearts Scientific Advisory Committee Members. We fully plan to recuse for review of this grant and any others as deemed necessary by Enduring Hearts grants leadership. Any further mitigation planning will be undertaken as deemed necessary at future time (per an email exchange between Dr. Schumacher and Ms. Carolyn Salvador).

We acknowledge and share Enduring Heart’s and Additional Venture’s commitment to safety during the COVID-19 pandemic. We do not anticipate any delays with this proposal based on COVID-19. Direct patient interaction will occur during the conduct of Aim 2, but each of these patients would already be seen in person in the hospital or clinic setting as part of their heart transplant evaluation. We will assure all study protocols minimize exposure to additional individuals as possible, include specific information on personal protective equipment, and include directives on cleaning and decontamination of all study equipment.