Heart failure (HF) remains among the most common and morbid cardiovascular conditions, with high prevalence (~6 million people in the United States), mortality (40% mortality within 5 years of initial diagnosis), and cost (estimated to reach 70 billion dollars in the United States by 2030). In recognition of the clinical and economic burden of HF, the American Heart Association funded the Heart Failure Strategically Focused Research Networks (AHA HF SFRN) in 2016. This program funded 4 centers in the United States—University of Colorado, Duke University, Massachusetts General Hospital/University of Massachusetts, and the University of Utah—and was designed to fund high-impact research in HF across the basic, clinical, and population domains. The principal investigators and titles for each center project are listed in Table 1, and an overview of the HF SFRN is shown in Figure 1. Additionally, the HF SFRN was designed to facilitate collaboration and synergy both within and between SFRN sites, and support training of future scientific leaders in HF. In this report, we will summarize the major scientific output of each AHA HF SFRN center, the training opportunities and outcomes, and potential lessons learned for the future of such networks in cardiovascular science.

**Center Findings Duke University**

HF and diabetes result in substantial morbidity, mortality, and health care costs, and the prevalence of both conditions has dramatically increased in the US population. The Duke Center sought to address critical knowledge gaps related to the intersection of HF and diabetes. An overview of the framework for the Duke Center is shown in Figure 2.
To adapt to changing physiologic and nutritional conditions, the heart exhibits remarkable metabolic flexibility. Although it prefers fatty acids (FA), the heart can generate energy from multiple fuels including carbohydrates, ketones, and amino acids in order to maintain the constant supply of energy required for contractile function, and remodeling of cardiac metabolic pathways often precedes structural remodeling. During metabolic remodeling, the failing heart switches from FA as a primary energy source to glucose utilization, thus becoming more metabolically inflexible. This metabolic switch recapitulates the fetal pattern of cardiac energy utilization. While adaptive in the short term, prolonged reliance on glucose utilization leads to an inadequate supply of ATP, resulting in a state of bioenergetic starvation that is common to most cardiac diseases. Using metabolomic profiling in human cohorts, we and others have made seminal discoveries linking circulating branched chain amino acids (BCAA) with obesity, insulin resistance, and diabetes. In the basic project, we leveraged clinical trials and human myocardial samples to study the role of BCAA in the molecular intersection of diabetes and HF, as well as to identify potential novel molecular pathways and related biomarkers for this intersection.

Analyzing data from the HF-ACTION study, we found that while BCAA were associated with diabetes and functional outcomes at baseline, BCAA levels were not prognostic. Analyzing a broader set of metabolites, we found that long-chain acylcarnitine metabolites were prognostic overall and were also associated with exercise capacity. Impaired FA substrate utilization and mitochondrial dysfunction both at the level of the skeletal muscle and the myocardium may explain the decreased exercise capacity, attenuated response to exercise training, and poor clinical outcomes seen in patients with HF and diabetes.

We also sought to explore known and novel molecular pathways in myocardium, leveraging samples from explanted and donor hearts as well as left ventricular (LV) assist device implantation cores. We found that BCAA levels were higher in diabetes nonfailing as compared with nondiabetes nonfailing and were even higher in failing hearts. Furthermore, analyzing paired samples from the same individuals, we found that plasma BCAA are correlated with myocardial BCAA, and also, skeletal muscle BCAA are correlated with plasma BCAA. These results could suggest that BCAA are taken up to a greater extent by the failing myocardium.

### Table 1. Summary of Heart Failure Strategically Focused Research Network Principal Investigators and Projects

<table>
<thead>
<tr>
<th>Project/Principal investigator</th>
<th>Center/Project focus</th>
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<td><strong>Duke</strong></td>
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<tr>
<td>Center Director: G. Michael Felker, MD, MHS</td>
<td>HF and diabetes</td>
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<tr>
<td>Basic Project: Svati Shah, MD</td>
<td>Metabolic regulation in HF and diabetes</td>
</tr>
<tr>
<td>Clinical Project: G. Michael Felker, MD, MHS</td>
<td>Physical activity and medication adherence in HF and diabetes</td>
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<td>Population Project: Adam DeVore, MD</td>
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<td><strong>Colorado</strong></td>
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<td>Center Director: Peter Buttrick, MD</td>
<td>Personalized therapy for HF</td>
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<tr>
<td>Basic Project: Timothy A. McKinsey, PhD</td>
<td>Epigenetics regulators of HF progression</td>
</tr>
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<td>Clinical Project: Michael Bristow, MD, PhD</td>
<td>Ivabradine in DCM unresponsive to β-blockers</td>
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<td>Population Project: Larry A. Allen, MD, MHS</td>
<td>Patients-centered approach to improving compliance</td>
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<td><strong>MGH/UMass</strong></td>
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<tr>
<td>Center Director: Anthony Rosenzweig, MD</td>
<td>Noncoding RNAs in HF</td>
</tr>
<tr>
<td>Basic Project: Anthony Rosenzweig, MD</td>
<td>Noncoding RNAs and cardiac hypertrophy</td>
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<tr>
<td>Clinical Project: Saumya Das, MD, PhD</td>
<td>Noncoding RNAs in acute heart failure</td>
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<td>Population Project: Jane E. Freedman, MD</td>
<td>Population studies of noncoding RNAs</td>
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<td><strong>Utah</strong></td>
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<tr>
<td>Center Director: Craig H. Selzman, MD</td>
<td>Cardiac metabolism and HF</td>
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<td>Basic Project: E. Dale Abel, MD, PhD</td>
<td>Predictors of myocardial recovery in HF</td>
</tr>
<tr>
<td>Clinical Project: Stavros Drakos, MD, PhD</td>
<td>Implementation of PRO instruments in HF care</td>
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Nonstandard Abbreviations and Acronyms

| AHA SFRN | American Heart Association Strategically Focused Research Networks |
| BCAA | branched chain amino acids |
| IncRNAs | long noncoding RNAs |
heart, potentially as an alternative fuel substrate in an
adaptive response, but that they do not undergo full
catabolism and feeding into the tricarboxylic acid cycle
and instead lead to generation of branched chain α-
ketoacids. With regard to FA mitochondrial β- oxidation,
we found higher levels of long-chain acylcarnitine in
nonfailing hearts without diabetes and lowest levels in
patients with failing hearts and diabetes. These data
in human myocardium suggest that the failing heart is
not generating long-chain acylcarnitine, perhaps re-
peating impairments in FA uptake seen in the failing
heart, or FA oxidation defects that are upstream from
long-chain acylcarnitine.

Clinical Projects
HF and diabetes share common behavioral risk fac-
tors (sedentary lifestyle, poor medication adherence)
for poor outcomes. Interventions to improve health
behaviors in patients with either HF or diabetes have
generally been resource-intensive and have delivered
inconsistent results.17,18 The clinical project tested a
personalized mobile health (mHealth) intervention
in a randomized controlled trial of an at-risk popu-
lation with concomitant HF and diabetes. The TARGET-
HF-DM was a pragmatic, multicenter, rand-
omized controlled clinical trial in ambulatory patients
with both symptomatic HF and diabetes. Participants
were randomized to either usual care or an mHealth
intervention focused on (1) increasing physical activ-
ity using weekly personalized text messages and step
count targets, and (2) an educational and behavioral
intervention focused on medication adherence. The
primary end point was change in mean daily step
count from baseline through 3 months using a com-
mercial wrist-worn device. Other end points of inter-
est included change in quality of life (as assessed by
the Kansas City Cardiomyopathy Questionnaire and
change in relevant physiologic measure of disease
status [NT-proBNP [N-terminal-pro-B-type natriuretic
depot]], hemoglobin A1c). Exploratory end points in-
cluding change in metabolomic profiling from baseline
through 3 months.

The primary results of TARGET-HF-DM demon-
strated improvement in mean daily step count (be-
tween group difference of 313 steps/d) in the mHealth
intervention group compared with usual care, as well
as improvements in quality of life as measured by the
Kansas City Cardiomyopathy Questionnaire Overall
Summary Score.20 Metabolomic profiling showed
differential levels of medium and long-chain acylcar-
nitines, suggesting that the mHealth intervention had

Figure 1. Overview of the AHA heart failure strategically focused research network.
AHA indicates American Heart Association; HFREF, heart failure with reduced ejection fraction; MGH, Massachusetts General Hospital; and UCD, University of Colorado.
measurable metabolic effects. We did not identify a significant impact of the adherence intervention on measures of adherence or physiologic markers. These data have important implications for more effective lifestyle interventions in patients with HF.

**Population Projects**

The population projects leveraged data from the American Heart Association’s Get With The Guidelines-HF registry linked to Medicare claims to characterize patients with HF and diabetes. A key finding of this work is that diabetes is one of many noncardiovascular conditions that is increasing over time among patients hospitalized with acute HF. Patients with a greater number of noncardiovascular comorbidities, compared with those without, had an increased risk of poor outcomes in the hospital and early after discharge.

We also specifically considered long-term outcomes out to 3 years for patients hospitalized with HF with and without diabetes and stratified by left ventricular ejection fraction (LVEF) subtype. Among 89,659 patients from 417 hospitals in the United States, we observed that diabetes was independently associated with an additional mortality and readmission risk for patients with HF with reduced LVEF (HFrEF, LVEF ≤40%). Among patients with HF with mildly reduced LVEF (LVEF 41% to 49%), diabetes had no appreciable association with all-cause mortality but was associated with a higher risk for rehospitalization. In contrast, for patients with HF with preserved LVEF (HFpEF, LVEF ≥50%) diabetes was not associated with additional mortality risk but was associated with a higher risk of cardiovascular readmission. Taken together, these data suggest that newer therapies approved for both HFrEF and type 2 diabetes represent a unique opportunity to improve outcomes for patients discharged from the hospital with acute HF, though current use remains very low.

An important consideration before widespread adoption of therapies is that there is limited real-world evidence on the comparative effectiveness and safety of anti-hyperglycemic medications and HF therapies for patients with HF and diabetes. We attempted to address this gap in knowledge by again using data from the Get With The Guidelines-HF registry linked to Medicare claims to evaluate the effectiveness of both devices and medications in patients with HF and diabetes. Current HF guidelines recommend use of primary prevention implantable cardioverter-defibrillators (ICD) among eligible patients with HFrEF and comorbidities, including diabetes. However, prior data suggested that patients with diabetes may not benefit from ICDs, possibly because of a competing risk of other medical complications. We used propensity matching for an ICD and observed that patients receiving a primary prevention ICD versus those without an ICD had a lower rate of all-cause mortality regardless of...
history of diabetes. Although observational, this suggested effectiveness of primary prevention ICDs in this population and reinforced current guidelines. In a similar analysis, we examined the effectiveness of metformin and sulfonylurea among patients with both HF and diabetes. We performed parallel analyses for metformin and sulfonylurea in patients newly prescribed these medications within 90 days of discharge from the hospital for acute HF. We observed that metformin initiation was independently associated with improvements in 12-month outcomes in patients with HFrEF (mortality or HF rehospitalization hazard ratio [HR], 0.68 [95% CI, 0.52–0.90]), but sulfonylurea initiation was associated with increased risk of mortality and HF rehospitalization (HR, 1.24 [95% CI, 1.00–1.52]; \(P=0.045\)), regardless of LVEF (all \(P\) for interaction >0.11).

**University of Colorado**

The University of Colorado center was premised broadly on the desire to personalize therapy for HF. In the basic realm we sought to identify novel and drugable therapeutic targets, in the clinical realm we attempted to improve therapy for the challenging subpopulation of patients with dilated cardiomyopathy who are unresponsive to \(\beta\)-adrenergic blockade, and in the population science domain we developed communication strategies to augment bi-directional conversations between patients and providers with the goal of improving intensification and adherence to guideline-directed medical therapy. An overview of the structure of the Colorado center is shown in Figure 3.

**Basic Project**

Epigenetics refers to modifications at the level of chromatin, the basic unit of which is the nucleosome or histone octamer wrapped in DNA, which culminate in alterations in gene expression independent of changes to nucleotide sequence.

Prior work by the Colorado HF SFRN Basic Research Group established that inhibitors of 2 classes of epigenetic regulatory factors, histone deacetylases, which are “erasers” of histone acetylation, and bromodomain and extraterminal proteins, which “read” acetyl-histones, block pathological cardiac hypertrophy and fibrosis and improve ventricular function in murine models. During the project, we were able to delve further into the mechanistic basis by which histone deacetylases and bromodomain and extraterminal proteins promote HF, with the ultimate goal of advancing inhibitors of these epigenetic regulators into clinical testing. Furthermore, we were able to develop new methods to quantify pathological cardiac fibrosis, which, among other things, increases passive stiffness of the heart and contributes to the development of diastolic dysfunction, a key component of HFrEF.

ITF2357/Givinostat, a histone deacetylation inhibitor that is being developed for Duchenne muscular dystrophy, reversed preexisting diastolic dysfunction in a mouse model of hypertension. Surprisingly, inhibition of cardiac fibrosis initially appeared to be an unlikely culprit since traditional histological methods failed to reveal induction of LV fibrosis in control and hypertensive mice. However, mass spectrometry–based evaluation of decellularized LV samples uncovered increased expression of a large number of extracellular matrix proteins in mice with diastolic dysfunction, which correlated with elevated stiffening of the ventricle based on atomic force microscopy measurements. We refer to this as “hidden fibrosis,” and remarkably, ITF2357/Givinostat completely blocked hidden cardiac fibrosis, which was consistent with our prior work demonstrating that the bromodomain and extraternal protein, BRD4, is dynamically targeted to specific regulatory elements that control profibrotic gene expression.

Among other discoveries made by the team, bromodomain and extraterminal protein inhibition, delivered in a therapeutic mode after the heart had remodeled, was shown to attenuate cardiac dysfunction in both the murine TAC model, as well as in postmyocardial infarction cardiac remodeling in mice, by suppressing transactivation of a broad profibrotic and pro-inflammatory gene program in the heart.

**Clinical Project**

The clinical arm of the research program was premised on developing therapeutic strategies that could improve the clinical course of patients with dilated cardiomyopathy (DCM) and potentially other patients with HFrEF, specifically those who are unresponsive to current guideline-directed drug therapy. Currently,
there are 7 US Food and Drug Administration approved classes of compounds available for treatment of DCM. Each of these has a response rate of <50%. The β-adrenergic blocker class produces arguably the largest reduction in HF mortality and major morbidity of any drug class, through mechanisms of action that include changes in myocardial and cardiac myocyte gene expression resulting in “reverse remodeling” of the eccentrically hypertrophied, dysfunctional LV, implying that this reflects a true biologic improvement in failing, damaged myocardial tissue. However, a substantial proportion of patients with HFrEF treated with β-blocking agents do not reverse remodel.

In a recent study of molecular and structural/functional reverse remodeling in response to β-blocking agents in patients with DCM, we identified the inability to lower heart rate as a possible factor in nonresponsiveness, which became the hypothesis tested in this clinical project. The study, PROBE-IT (NCT02973594) (Pulse reduction on Beta-blocker and ivabradine therapy), aimed to recruit patients with DCM who do not respond to β-blocker therapy with LVEF improvement, and also who have a heart rate (HR) higher than should be the case on maximal doses of a β-blocker (≥70 bpm). The qualifying patients were randomized to concurrent treatment with the HCN channel blocking agent, ivabradine, which disrupts I\textsubscript{if} ion current flow and slows firing in the SA node. Before receiving study medication, the patients with DCM underwent endomyocardial biopsy for RNA extraction, coronary sinus norepinephrine sampling during right heart catheterization, and LVEF measurement by 3D-echocardiogram to measure remodeling and systolic function. These procedures are then repeated after 24 weeks of therapy. Candidate genes (N=58) and global gene expression profiles are measured by microarray and RNA-sequencing. The primary statistical analysis is a comparison of the half of patients with the greatest degree of HR reduction to the 50% with the least, and the secondary analysis is ivabradine treatment versus placebo.

Although the study is not yet competed, since HR change is unblinded we can analyze LVEF, gene expression, degree of β-blockade, and level of cardiac adrenergic drive data as a function of HR response in these subjects. While the results are still preliminary, some trends are evident: First, it is unlikely that inadequate β-blockade or ultra-high circulating norepinephrine overcoming competitive antagonism is responsible for the lack of clinical response, based on exercise HR response and coronary sinus norepinephrine levels. Second, HR response appears to convert the reverse remodeling nonresponders to responders. For LVEF change (Δ) in the 2 HR groups, the greater HR reduction group improved their LVEF by 17.3±1.7 (SEM) absolute % compared with −2.3±2.0 in the no-change HR group (P<0.001). And finally, the limited RNA data that have been analyzed strongly suggest that the improved LV function in the HR responsive group is associated with molecular remodeling. The expression of multiple candidate genes linked to reverse remodeling gene families evidenced altered patterns of expression in the HR responsive group with a conditional power of ≥80% for achieving a P<0.05 between the 2 groups.

**Population Project**

Therapeutic advances for HFrEF have been a double-edged sword: multiple medications (and devices) have been developed that, in combination and at high doses, are highly effective at improving cardiac remodeling, reducing hospitalization, and prolonging survival; unfortunately, this results in complex treatment regimens that can take weeks to months of intensification to achieve the goal. Real-world data show that most patients with HFrEF are not prescribed many of these beneficial treatments at goal dosing. To address this gap, we tested a patient-centered approach to improve use of these medications: the “Electronically delivered, patient-activation tool for intensification of chronic medications for heart failure with reduced ejection fraction”, or EPIC-HF (https://www.clinicaltrials.gov). Initially we developed a 3-minute video and 1-page checklist (the EPIC-HF tools, https://patientdecisionaid.org/heart-failure-medication-epic) to be texted or emailed to patients before a clinic visit with a cardiology provider. These tools were designed to engage and empower patients to discuss their heart medications with their doctor, using “direct-to-consumer” and “flipped classroom” concepts to transform clinic visits that too often involve no change in treatment. The video encouraged patients to ask for options to improve their medication regimen coupled with the checklist to help identify gaps and opportunities. These tools were then tested in a clinical trial in a large health system with prospective randomization of ambulatory patients with HFrEF. Of enrolled patients, 290 attended a clinic visit during the study period: 145 were sent the patient activation tools and 145 were controls. The median age of patients was 65 years; 29% were female, 11% were Black, 7% were Hispanic, and the median ejection fraction was 32%. From immediately preceding the study cardiology clinic visit to 30 days after, 49.0% in the intervention and 29.7% in the control experienced an intensification of their guideline-directed medical therapy (P=0.001). Most of these changes were made at the clinic encounter itself and involved dose increases, most commonly of β-blockers. There were no deaths and no significant differences in hospitalization or emergency department visits at 30 days between groups. Thus, EPIC-HF showed that a patient activation tool delivered electronically before a cardiology clinic visit improved clinician intensification of guideline-directed medical therapy, thereby...
documenting the existence of and the ability to overcome therapeutic inertia through patient engagement.

**Massachusetts General Hospital-University of Massachusetts**

The MGH-UMASS SFRN Heart Failure (HF) Center sought to address 2 fundamental unmet needs in HF by identifying better predictors of HF phenotype, progression, and prognosis, as well as by implicating new targets for therapeutic intervention. In this context, our focus was noncoding RNAs (ncRNAs), because of their central roles in cardiac development and pathophysiology.38–43 ncRNAs were once thought only to exist inside cells. However, more recent work has identified circulating, extracellular RNAs (exRNAs), most of which are ncRNAs. These exRNAs are relatively stable in biofluids and may play important roles in intercellular communication, mediating target-organ epigenetic effects relevant to myocardial biology.44–46

The overarching hypothesis of our Center was that in patients with HF, circulating exRNAs are both clinically useful biomarkers and biologically active modulators of cardiac hypertrophy and dysfunction. This hypothesis was investigated in 3 interrelated projects, with the overarching goal of identifying new clinically relevant exRNA biomarkers and investigating their functional roles. An overview of the structure of the MGH/UMass center is shown in Figure 4.

**Basic Project**

This project provided in vitro and in vivo models for complementary discovery efforts and evaluation of the functional roles of ncRNAs. Since not all patients with cardiac hypertrophy develop HF, one of our Center’s hypotheses was that there are distinct forms of hypertrophy with dramatically different outcomes. This model was supported by our prior work documenting largely distinct transcriptional networks in physiological and pathological hypertrophy.47 These observations were substantively expanded under the AHA to demonstrate similar findings with ncRNAs, particularly lncRNAs, and their implications for clinically relevant phenotypes. Using multiphoton ionization mass spectrometry imaging with 15N-thymidine, we found that exercise induces a substantial (4.6-fold) increase in cardiomyogenesis,48 making it the only known physiological enhancer of cardiomyogenesis in the adult mammalian heart. Moreover, we found that the exercise-induced microRNA, miR-222, is necessary for exercise-induced cardiac growth41 and pathological hypertrophy. In work currently under revision, we evaluated cardiac lncRNAs dynamically regulated by exercise or aortic constriction. These sets were largely distinct and each of the small number of lncRNAs that changed in both the physiological and pathological models changed in opposite directions. These findings further reinforce the concept that these 2 forms of hypertrophy, while superficially similar, reflect very different molecular underpinnings that likely contribute to their distinct clinical outcomes.

**Clinical Project**

Acute decompensated HF (ADHF) is a predictor of poor clinical outcomes, but the mechanistic basis for this trajectory is not well understood. We examined whether long RNAs (both coding mRNAs and IncRNAs)
are dynamically regulated in ADHF and could provide insights into ADHF molecular mechanisms and/or the differences between HFrEF and HfP EF ejection fraction. RNA sequencing of cell-free plasma revealed long RNAs (lncRNA and mRNA) that were differentially expressed between HfP EF with ADHF, HFrEF with ADHF, and healthy controls. These included lncRNAs previously shown to be involved in cardiac regulation such as H19,49,50 and MALAT1,51–53 as well as RNAs not previously described in this context. Pathways involved implicated mitochondrial dysfunction, RAS activation, fibrosis, inflammation, and congestion. After decongestion, RNA expression significantly changed between both types of HF, thus providing a molecular signature of ADHF in both HfP EF and HFrEF. Ongoing studies seek to validate these findings in a large independent cohort and determine associations with ventricular remodeling and clinical outcomes. A second ongoing study seeks to determine the effect of cardiac rehabilitation and exercise training on exRNAs in patients with HFrEF compared with patients without HF. Finally, given the presence of these RNAs in extracellular vesicles (EVs),54,55 we examined whether EVs contribute to phenotypes seen in ADHF. For example, investigators found that EVs in ADHF plasma from patients with renal dysfunction and subsequent cardiorenal syndrome had a toxic effect on renal tubular and endothelial cells in a novel kidney-on-chip model, suggesting a functional role for EVs and their contents in HF-associated renal dysfunction. Taken together, these studies reveal an important role for EVs and their RNA cargoes as potential functional biomarkers in HF phenotypes and ADHF.

**Population Project**

This project used RNA sequencing of exRNA in population studies to correlate the levels of circulating exRNAs with important cardiac phenotypes, such as LV remodeling and incident HF. Among other notable findings, in >2000 participants of the FHS (Framingham Heart Study), 12 exRNAs were identified that were associated with LV mass and at least 1 other echocardiographic phenotype (LV end-diastolic volume or left atrial dimension). Of these 12 ex-RNAs, 3 (miR-17, miR-20a, and miR-106b) were associated with a 15% reduction in long-term incident HF per 2-fold increase in circulating level after adjustment over a median 7.7 years follow-up and implicated central pathways of myocardial remodeling and apoptosis signaling.56 These findings were extended by examining obesity, a systemic disease marked by visceral adiposity and hepatic steatosis that is associated with oxidative stress, inflammation, and glucose intolerance, all contributors to HF development. We hypothesized that exRNAs, such as those derived from platelets, might reflect cardiometabolic phenotypes and contribute to cardiovascular disease and HF pathogenesis. We investigated differential gene expression in platelets from 21 individuals with massive (>100 lb) weight loss both before (baseline) and 23 months after bariatric surgery. Ninety-three differentially expressed genes identified using RNA sequencing were also measured by high-throughput quantitative reverse transcription polymerase chain reaction in platelet RNA from 2244 participants of the Framingham Offspring cohort. Pathway analysis implicated transcripts related to nonalcoholic fatty liver disease as the predominant pathway altered in these individuals after the surgery.57 Since nonalcoholic fatty liver disease is known to decrease dramatically with weight loss, it appears the platelet transcriptome mirrors changes in the overall improvement of liver function during weight loss interventional surgery.

**University of Utah**

The Utah center focused on the functional, metabolic, and patient-centered determinants of recovery in HF. The fundamental observation that certain patients with advanced HF supported with LV assist devices can recover significant myocardial function led to our efforts to better define the clinical and biologic factors associated with reverse remodeling and enhanced patient health. An overview of the structure of the Utah center is shown in Figure 5.

**Basic Project**

The basic project premised that HF is associated with a mismatch in glycolysis and glucose oxidation that is mediated in part by reduced expression or activity of the mitochondrial pyruvate transporters (MPC1 and MPC2). To test this hypothesis, we developed mice with cardiomyocyte-restricted deletion of MPC1. These mice developed age-dependent pathological LV hypertrophy that advanced to dilated cardiomyopathy and premature death. Detailed analysis of glucose metabolism in these hearts using tracer perfusions revealed that impaired mitochondrial pyruvate utilization led to increased flux of glucose carbons into metabolic pathways branching from glycolysis such as the hexosamine biosynthetic pathway, glycogen synthesis, the pentose phosphate pathway, and 1 carbon metabolism pathway. These diversion pathways ultimately led to the accumulation of metabolic intermediates that activated signaling pathways, which accelerated LV remodeling. Importantly, suppression of aberrant glycolytic metabolism by feeding mice either a high-fat diet or a ketogenic diet either prevented HF in this model or reversed established HF, when the diet was initiated later in life. Subsequently, mice with HF secondary to pressure overload were exposed to a ketogenic...
diet and it was observed that this intervention partially attenuated but did not completely reverse LV remodeling.\(^5^8\) Importantly, the work was confirmed by 2 independent groups in companion manuscripts underscoring the rigor and reproducibility of these findings.\(^5^9,6^0\) Moreover, another study performed within the Utah SFRN convincingly demonstrated reduced pyruvate metabolism in failing hearts that correlated with reduced expression of MPC1. Furthermore, following ventricular unloading, hearts that recovered were characterized by augmentation of MPC expression and mitochondrial pyruvate utilization. They also independently revealed additional mechanisms by which impaired pyruvate metabolism could contribute to ventricular remodeling and the novel finding that augmenting mitochondrial pyruvate uptake by treatment with a lactate transporter inhibitor also reversed ventricular remodeling.\(^6^1\) Together, these efforts have shed new insight into the role of metabolic modulation as a viable approach to treating HF, and indeed, there has been an increase in the number of trials of ketogenic diets in patients with HF.

**Clinical Project**

The clinical project aimed to better understand and phenotype the gradient of reverse cardiac remodeling and mechanistically identify novel therapeutic targets for HF. We observed a continuum of recovery in a derivation cohort of nearly 400 patients and a validation cohort of 245 additional patients. Based on ejection fraction and other systolic function indices, we identified responders (10% of enrolled patients—median change of LVEF 27%), partial responders (31% of patients—median change of LVEF 9%), and nonresponders (59% of patients—median change of LVEF -2%).\(^6^2\) It was noteworthy that structural cardiac changes (ie, LV size) followed a different pattern with very large improvements even in patients who had minimal cardiac functional improvement. The conclusion of this work suggests that reverse cardiac remodeling associated with mechanical unloading and systemic circulatory support is a continuous spectrum. Defining 3 stages across this continuum can inform clinical management, facilitate the field of myocardial plasticity, and improve the design of future investigations. Furthermore, the use of HF drug therapy was higher in responders and partial responders, suggesting that with intensification of pharmacological therapies, there is room for further improving the favorable cardiac response rates.

Although the role of myocardial tissue biomarkers predicting LV assist devices–mediated cardiac recovery has been previously examined, the lack of predictive circulating biomarkers to facilitate patient selection for myocardial recovery is a major unmet need. Guided by myocardial tissue findings, we identified a circulating 2-cytokine model (tumor necrosis factor-\(\alpha\) and interferon-\(\gamma\)) predicting significant reverse remodeling.\(^6^3\) The clinical implications are that this circulating 2-cytokine model could serve as a practical clinical tool to identify patients with HF prone to improve cardiac structure and function and thus guide patient selection and clinical management.

At a more mechanistic level, human tissues in myocardial recovery patients exhibited a preference for glucose oxidation over lactate production through regulation of the MPC and pyruvate dehydrogenase.\(^6^1\) Guided by these human myocardial recovery tissue findings, we found in follow-up in vivo and in vitro studies that the pyruvate–lactate axis is disrupted during hypertrophy and HF. This axis was rebalanced and the hypertrophy was ameliorated after inhibiting a lactate transporter, the monocarboxylate transporter 4, which emerged as a new therapeutic target for HF.\(^6^1\) In addition, mechanical unloading resulted in a dissociation of glycolysis and mitochondrial oxidative-phosphorylation characterized by induction of glycolysis without subsequent increase in pyruvate oxidation through the tricarboxylic acid cycle.\(^6^4\) Motivated by these findings, it was hypothesized that the accumulated glycolytic intermediates are channeled into accessory pathways of glucose metabolism that are cardioprotective and may induce myocardial recovery. Indeed, it was found that the recovering hearts direct glycolytic metabolites into alternative pathways such as pentose-phosphate and 1-carbon metabolism, which contributed to cardioprotection and myocardial repair by generating reduced NADP, enhancing biosynthesis, and reducing oxidative stress.\(^6^5\) Most recently, we identified by RNA sequencing that voltage-dependent anion channel 2, an outer mitochondrial membrane porin involved with apoptosis and calcium signaling, was associated with human functional cardiac recovery. This target

**Figure 5.** Interaction between basic (P1), clinical (P2), and population (P3) projects with the University of Utah Center.
was then taken back to the bench and we found that voltage-dependent anion channel 2 plays a crucial role in cardiac function by altering both intracellular and mitochondrial calcium signaling. Through this role in cellular calcium dynamics and excitation–contraction coupling, voltage-dependent anion channel 2 emerges as a plausible HF therapeutic target.

Population Project

The main aim of the population project was to implement patient-reported outcome (PRO) assessment into routine clinical care, and to determine how this information could be best used in the care of patients with HF. During the study period, we integrated PRO capture into the flow of the HF clinic at the University of Utah, such that patients completed a set of PRO tools, either before their arrival at the clinic through a weblink, or at the clinic on tablet computers. We collected the Kansas City Cardiomyopathy Questionnaire, a visual analogue scale, and several Patient-Reported Outcomes Measurement Information System domains.

To assess the generalizability of this approach, we further conducted a qualitative study among providers participating in the different HF SFRN centers and determined the barriers and the facilitators of such implementation at different medical centers. In addition, to better understand patient experiences with PRO collection and capture their perspectives on this process, we conducted a patient semistructured interview study. This work demonstrated that patients viewed PRO assessment positively and felt it added value to their care, as long as the results were shared with them and their caregivers.

Over the study duration, we completed >4500 PRO assessments among patients with HF. We examined health-related quality of life (HRQOL) in patients with HF with recovered ejection fraction. We determined that recovery of systolic function was associated with HRQOL improvement, such that for each 10% increase in LVEF, the Kansas City Cardiomyopathy Questionnaire summary score improved by a mean 4.8 (SD 1.6) points (P<0.003). Improvements of physical function, satisfaction with social roles, and a reduction in fatigue were significant limiting factor in the potential for recovery of HF with recovered ejection fraction. In a separate analysis, we were able to quantify the impact of atrial fibrillation in HF on HRQOL.

In order to determine whether PROs could be used to build predictive models that could inform treatment, we tested several statistical approaches in design of risk models of hospital admission and mortality. We showed that HRQOL significantly modified the risk of hospitalization and mortality, and that addition of PROs to more traditional risk factors improved model performance (abstract presented at 2021 AHA Scientific Sessions, Boston, MA).

Training Programs

A key deliverable of the SFRNs was to provide training opportunities for young investigators within a multidimensional environment across research domains (basic, clinical, population) and centers. Each center selected trainees for a cross-disciplinary experience (generally 2 years) that included mentored research within the Center as well as opportunities for networking, mentoring, and collaboration across the different centers. Over the course of HF SFRN, the centers collectively trained 18 young investigators, many of whom have gone on to start careers as independent researchers. We believe that the SFRN created a unique training environment, particularly related to opportunities for “cross-talk” between different research approaches within each center (basic, translational, clinical, and population) as well as opportunities for collaboration and academic network across centers. Training outcomes for the funded participants in the training program are summarized in Table 2.

Inter-center Collaboration

An important goal of the SFRN was to catalyze novel collaborations between different centers that would lead to important research initiatives that would be unlikely to occur otherwise. Throughout the period of the HF SFRN, a variety of successful collaborative research efforts involving 2 or more of the SFRN centers were launched. Broadly speaking, these included sharing of biosamples between centers, validation of findings of 1 center in new data sets or preclinical models from other centers, and enrollment of patients into study protocols at multiple centers with the SFRN. Importantly, many of these collaborations would have been unlikely to occur without support and the infrastructure provided by the SFRN mechanism. The SFRN provided both funding for collaboration as well as structured time for collaboration within each annual SFRN meeting.

<table>
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<th>Table 2. Heart Failure Strategically Focused Research Network Training Outcomes</th>
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<td>Outcomes</td>
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<tr>
<td>Fellows trained</td>
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<td>Fellow publications</td>
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<td>Extramural grants awarded</td>
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<td>Faculty appointments</td>
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Lessons Learned and Future Directions

Overall, the SFRN model met an important goal of fostering interdisciplinary collaborations both within and across centers, while providing a platform for developing the careers of young investigators in HF. The SFRN awards underscore the unique values of collaborative and team science as summarized in a recent commentary.72 These include increasing rigor and reproducibility, resource sharing, training opportunities, and addressing large questions that are not easily achieved by a single center. That said, several lessons were learned during our funding period that could prove useful for future network initiatives:

1. Incentivizing more direct collaborations between centers by designating additional funding directly targeting collaborative activities between centers (or between SFRN Networks)

2. Increasing the breadth/number of institutions involved could be incentivized as part of a renewal or retention process. One might look, for example, to the initiatives of some National Institutes of Health networks whereby core centers had to link with affiliate centers in an application process.

3. Provide options for renewal: 4 years is a relatively short period to establish Centers and advance ambitious scientific agendas within and across these Centers. Options for renewal of highly meritorious science would provide additional mechanisms to leverage the success of the SFRNs.

ARTICLE INFORMATION

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REFERENCES


52. Cremer S, Michalik KM, Fischer A, Pfisterer L, Jae N, Winter C, Boon
50. Zhang Y, Zhang M, Xu W, Chen J, Zhou X. The long non-coding RNA
55. Rodosthenous RS, Hutchins E, Reiman R, Yeri AS, Srinivasan S,
46. Liu X, Xiao J, Zhu H, Wei X, Platt C, Damilano F, Xiao C, Bezzerides V,
J Am Heart Assoc. 2022;11:e025517. DOI: 10.1161/JAHA.122.025517
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2022;11:e025517. DOI: 10.1161/JAHA.122.025517
52. Cremer S, Michalik KM, Fischer A, Pfisterer L, Jae N, Winter C, Boon
50. Zhang Y, Zhang M, Xu W, Chen J, Zhou X. The long non-coding RNA
55. Rodosthenous RS, Hutchins E, Reiman R, Yeri AS, Srinivasan S,
46. Liu X, Xiao J, Zhu H, Wei X, Platt C, Damilano F, Xiao C, Bezzerides V,