Accelerating Medicines Partnership® in Heart Failure (AMP HF) / HeartShare (HS) Program
Overview of AMPHF/HeartShare(HS)

Vandana Sachdev, NHLBI
William Chutkow, Novartis
AMP HF/HS aims to deconstruct the syndrome of HFpEF and classify potential disease subtypes, ideally by molecular classification.

**Component 1:**
Aggregate and analyze existing datasets with omics on existing samples.

**Component 2:**
Create a new cohort of deeply phenotyped HFpEF patients with analysis of cardiac, skeletal muscle, and adipose tissue.
**HFpEF is a growing CV health problem marked by racial disparities in incidence, prevalence, and outcomes**

Lifetime risk for heart failure by gender

- **24%**
  - 6 out of 25 Women with HF

- **28%**
  - 7 out of 25 Men with HF

Heart failure prevalence is shifting to HFpEF

Heart Failure in 1000 person (years)

- Median follow-up 4 years
  - (log rank test $P=0.01$)

Bozkurt B, *J Cardiac Failure*, 2023

Savarese & Lund, *CRF* 2017

Bozkurt B, *J Cardiac Failure*, 2023
HFpEF morbidity and mortality is considerable and there are few evidence-based therapies

5 year heart failure hospital readmission

- HFpEF (EF ≥ 50%)
- HFmrEF (EF 41-49%)
- HFrEF (EF ≤ 40%)

5 year composite of mortality and heart failure hospital readmission

SGLT2 inhibitors and mortality?

Shah KS, J Am Coll Cardiol 2017
HFpEF is a heterogenous syndrome of myocardial-intrinsic and systemic pathologic mechanisms.

Adapted from Pandey AK, Eur Heart J 2024

**Systemic Risk Factors**
- Aging
- Hypertension
- Diabetes mellitus
- Obesity
- Metabolic Syndrome
- OSA
- Renal dysfunction
- Smoking

Neurohumoral RAAS activation and NP insufficiency

Atrial remodeling & arrhythmias

Chronotropic incompetence

Arterial stiffening, endothelial dysfunction & myocardial ischemia

Extracellular fibrosis, inflammation & oxidative stress

Intrinsic cardiomyocyte stiffness: Titan-dependent; impaired NO-sGC-cGMP-PKG signaling

Intracellular Na\(^+\) and Ca\(^{2+}\) overload

Altered energetics & metabolism

Adapted from Pandey AK, Eur Heart J 2024
Previous insights from HFpEF phenomapping reveal multiple overlapping phenotypes

Traditional clinical trial design & enrollment

Initial assessment of ‘HFpEF’ cohorts

Traditional risk stratification

Phenomapping

- Age
- Sex
- HTN
- DM
- CAD
- BNP
- BMI
- AF
- EI
- GFP
- LAVI
- PASP
- LVH

Mutually exclusive phenogroups by study

- Study 1
  - Cluster 1
  - Cluster 2
  - Cluster 3

- Study 2
  - Cluster 1
  - Cluster 3

- Study 3
  - Cluster 2
  - Cluster 1
  - Cluster 3

Aggregate overlapping phenotypes across studies

- Older, Vascular Aging Phenotype
- Metabolic Obese Phenotype
- Younger, Low BNP Phenotype

Peters AE, Cardiovascular Research, 2022
Transcriptional profiling of endomyocardial biopsies supports HFpEF is distinct from HFrEF, and HFpEF hearts cluster into distinct clinical groups.

HFpEF heart transcript profiles are distinct from HFrEF.

Transcriptome-based HFpEF patient clusters show distinct clinical trajectories.

Hahn V et al. Circulation 2021
HFpEF endomyocardial biopsy metabolomics reveal myocardial metabolism ≠ peripheral metabolism

Hahn V et al. Circulation 2023
Overview of AMP HF Design

Retrospective (Y1-2)
- Existing datasets (cohort studies, trials)
  - Data aggregation, harmonization
  - Image repository
  - New biospecimen multi-omics
- Advanced analytics (e.g. multi-omics, ML) for HFpEF sub-classification

Prospective (Y1-5)
- Deep phenotyping protocol (baseline + longitudinal)
  - EHR data + image collection
    - N=100K HF, 100K controls
  - HeartShare Registry via Eureka app
    - N=10K HF + controls
- HeartShare Deep Phenotyping Cohort
  - N=1000

HeartShare Clinical Centers

Future (Y5+)
- Master Protocol to test precision Rx in HFpEF
  - Clinically actionable sub-groups and biologic targets

Screening protocol

Data Translational Center (NWU)

Learnings from retrospective component
AMP HF Project Timeline and Progress

Sept 2021: NHLBI RFAs awarded HeartShare - 6 clinical sites and DTC

Sept 2022: AMP HF launched

Oct 2023: AMP RFA awarded 7th site with expertise in cardiac tissue

Dec 2023: AMP SC approves support for EMB tissue & site coordinators

March 2025: Go/No Go Milestone

2021

Develop deep phenotyping protocol

2022

AMP SC/HeartShare PIs prepare for EMB

Applications for partner data access

2023

Harmonization/analysis of extant data

DTC awarded TOPMed funding for omics, sample prep ongoing

2024

Patient Enrollment into virtual registry and deep phenotyping cohort

2025

2026

2027
# Acknowledgements

## NHLBI
- Gary Gibbons
- David Goff
- Vandana Sachdev
- Renee Wong
- Jackie Wright
- Patrice Desvigne-Nickens
- Emily Tinsley
- Sweta Ladwa

## HeartShare Clinical Centers
- Barry Borlaug (Mayo)
- Maggie Redfield (Mayo)
- Dalane Kitzman (WFU)
- Oguz Akbilgic (WFU, ancillary study)
- Greg Lewis (MGB)
- Akshay Desai (MGB)
- Michael Givertz (MGB)
- Scott Solomon (MGB)
- Sadiya Khan (NWU)
- Laura Rasmussen-Torvik (NWU)
- Julio Chirinos (UPenn)
- Ken Margulies (UPenn tissue repository)
- Nipavan Chiamvimonvat (UC Davis)
- Martin Cadeiras (UC Davis)
- Javier Lopez (UC Davis)
- Kavita Sharma (JHU)
- David Kass (JHU)

## HeartShare Data Translation Center (NWU)
- Sanjiv Shah
- Laura Alagna
- Denise Scholtens
- Abel Kho
- Yuan Luo
- Ambarish Pandey (UT Southwestern, consultant)

## FNIH
- Tania Kamphaus
- Melissa Reyes
- Harina Raja
- Aimee Ahmed
- David Wholley
- Lynette Nguyen

## Industry Partners
- Will Chutkow (Novartis)
- Mariell Jessup (AHA)
- Jen Hall (AHA)
- Judy Hung (ASE)
- Lothar Roessig (Bayer)
- Maria Borentain (Bayer)
- Steffen Schaper (Bayer)
- Karen Paraschin (Bayer)
- Steve Heitner (Cytokinetics)
- Fady Malik (Cytokinetics)
- Jason Duran (Ionis)
- Adam Mullick (Ionis)
- Sam Tsimikas (Ionis)

## Strategic Partners
- Mike Mendelson (Novartis)
- Claudio Gimpelewicz (Novartis)
- Ross Upton (Ultromics)
- Ashley Akerman (Ultromics)
- Hania Piotrwoska (Ultromics)

## Patient Representative:
- Cynthia Chauhan

## HeartShare Co-Chairs:
- Svati Shah (Duke)
- Javed Butler (Baylor)

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## Strategic Partners
- Norman Stockbridge
- Mary Ross Southworth

Still welcoming new partners!
AMP HF/HeartShare Data Repository and Cross-Portal Integration: Opportunities for Collaboration

Sanjiv J. Shah, MD
Principal Investigator, HeartShare Data Translation Center
Stone Endowed Professor of Medicine
Northwestern University Feinberg School of Medicine
sanjiv.shah@northwestern.edu — https://www.HeartShareStudy.org
AMP-HF and the NHLBI HeartShare Study

• Leadership/governance:
  → Industry co-chair: Will Chutkow, MD, PhD (Novartis)
  → NHLBI scientific lead: Vandana Sachdev, MD
  → HeartShare co-chairs: Svati Shah, MD (Duke), Javed Butler, MD (Baylor Scott White)
  → HeartShare DTC PI: Sanjiv Shah, MD (Northwestern)

• Current private partners represented on AMP-HF steering committee:
  → AHA, American Society of Echocardiography, Bayer, Cytokinetics, Ionis, Novartis, Ultromics

• Strategic partners:
  → Heart Failure Society of America, US Food and Drug Administration

Public funding (NHLBI)

Private funding

$25M committed to HeartShare with additional funding for multi-omics

AMP Heart Failure

HEARTSHARE (launched in 2021)

Additional HF-AMP initiatives independent of HeartShare
HeartShare Scientific Approach

CVD cohorts  
HFrEF trials  
HFpEF trials

Data harmonization

Hypothesis-driven approach
Pre-defined HFpEF subtypes, molecular pathways

Multi-omics  
Machine learning  
Deep learning

Prospective HeartShare component

Unbiased approach

Novel HFpEF subtypes, molecular pathways

Precision medicine
- Precision therapeutics
- Enrichment for clinical trial selection
- Automated deep learning-based identification
- Biomarker discovery
- Targeted behavioral interventions
- Prognostication

HeartShare Data Portal

NIH  
BioData

NHLBI secure cloud-based data  
+ image repository

NIH  
National Heart, Lung, and Blood Institute

FNIH  
AMP® HF  
HEARTSHARE
HeartShare Data Repository

Additional independent datasets (including industry studies)

Data, images

Data, images, ±omics

De-identification
Harmonization

Data, omics

EHR data, images, registry data
Deep phenotyping data, images, omics

NHLBI secure cloud-based data + image repository

Data requestors

HeartShare investigators

AMP-HF partners

External collaborators

AMP collaborators

Cohort generation
### HeartShare Extant Datasets → BioData Catalyst

<table>
<thead>
<tr>
<th>Observational Studies</th>
<th>Clinical trials</th>
<th>Clinical trials (cont’d)</th>
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<tbody>
<tr>
<td>WHI</td>
<td>ACCORD</td>
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<td>ARIC</td>
<td>ALLHAT</td>
<td>RELAX</td>
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<td>CARDIA</td>
<td>BEST</td>
<td>ROSE</td>
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<td>CHS</td>
<td>ESCAPE</td>
<td>SCD-HeFT</td>
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<td>Framingham</td>
<td>GUIDE-IT</td>
<td>SOLVD</td>
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<td>FHS-Cohort</td>
<td>HF-ACTION</td>
<td>SPRINT</td>
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<td>FHS-Gen III</td>
<td>ATHENA-HF</td>
<td>STICH</td>
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<tr>
<td>FHS-Offspring</td>
<td>CARRESS</td>
<td>TOPCAT</td>
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<tr>
<td>HCHS-SOL</td>
<td>DOSE-AHF</td>
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<tr>
<td>JHS</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>PVDOMICS</td>
<td>INDIE</td>
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</tr>
<tr>
<td>SPIROMICS</td>
<td>IRONOUT</td>
<td></td>
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</table>
Extant datasets summary

• HF clinical trial dataset harmonization is complete
  → Included trials (18): ATHENA, CARRESS, DOSE, ESCAPE, EXACT, FIGHT, GUIDE-IT, HF-ACTION, INDIE, NEAT, RELAX, ROSE, SCD-HeFT, SOLVD Prevent, SOLVD Registry, SOLVD Treat, STITCH, TOPCAT
  → Total number of variables: 257
  → Total N=27,313 study participants, 26% female (54% female in HFpEF)
  → Race/ethnicity: 1.5% Asian, 14.4% Black, 2.7% Hispanic, 78.5% White
  → LVEF <40%: n=19,860; LVEF 40-50%: n=2,562; LVEF >50%: n=3,370
  → There are 2 harmonized datasets: baseline data (wide format) and longitudinal data (long format)

• Cohort study dataset harmonization is in progress
• Next up: dbGaP dataset harmonization: phenotypes and omics
Extant datasets summary

- Harmonized HF clinical trial dataset domains:
  - Demographics
  - Comorbidities
  - Medications
  - Physical exam findings
  - Laboratory values: BNP (n~3900), NTproBNP (n~3100), both (n~500)
  - Surveys: KCCQ (n~9300), MLWHF (n~3200), NYHA, EQ5D, CESD, VAS
  - Echocardiography parameters (n~2200-5100)
  - 6MWD (n~5800)
  - CPET parameters (n~2600)
  - Cardiac MRI (n~540)
  - Invasive hemodynamics
HeartShare: Extant Datasets from dbGaP

Datasets from dbGaP are currently being uploaded to BioData Catalyst:

<table>
<thead>
<tr>
<th>Dataset Description</th>
<th>Dataset Details</th>
</tr>
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<tr>
<td>NHLBI's Collection of Datasets for General Research Use</td>
<td>NHLBI TOPMed: The Jackson Heart Study (JHS)</td>
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<tr>
<td>NHLBI TOPMed: Coronary Artery Risk Development in Young Adults (CARDIA)</td>
<td>PAGE: CALiCo: Strong Heart Study (SHS)</td>
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<tr>
<td>NHLBI TOPMed: MESA and MESA Family AA-CAC</td>
<td>CARDIA Cohort</td>
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<td>NHLBI Big Data Analysis Heart Failure Challenge Data Collection</td>
<td>Women's Health Initiative</td>
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<td>Genetic Epidemiology Network of Arteriopathy (GENOA)</td>
<td>Framingham Cohort</td>
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<td>Diabetes Heart Study</td>
<td>The Jackson Heart Study (JHS)</td>
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<td>NHLBI TOPMed - NHGRI CCDG: Hispanic Community Health Study/Study of Latinos (HCHS/SOL)</td>
<td>Cardiovascular Health Study (CHS) Cohort</td>
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<td>Disease-Specific (Diabetes and Heart Disease in in NIDDM-Atherosclerosis Study (NIDDM-Athero))</td>
<td>Atherosclerosis Risk in Communities (ARIC) Cohort</td>
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<td>Hispanic Community Health Study / Study of Latinos (HCHS/SOL)</td>
<td>MESA Cohort</td>
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<td>NHLBI TOPMed: Women's Health Initiative (WHI)</td>
<td>Immunosenescence: Immunity in the Young and Aged</td>
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<td>Veterans Administration (VA) Million Veteran Program (MVP) Summary Results from Omics Studies</td>
<td>A Comprehensive Platform for Analyzing Longitudinal Multi-Omics Data</td>
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<td>Genetic Epidemiology Network of Salt Sensitivity (GenSalt)</td>
<td>VESPA Cohort: Vanderbilt Electronic Systems for Pharmacogenomic Assessment</td>
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<td>NHLBI TOPMed: Genomic Activities such as Whole Genome Sequencing and Related Phenotypes in the Framingham Heart Study</td>
<td>eMERGE: A Multi-Center Pilot of Pharmacogenetic Sequencing in Clinical Practice</td>
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<tr>
<td>NHLBI TOPMed: Trans-Omics for Precision Medicine (TOPMed) Whole Genome Sequencing Project: Cardiovascular Health Study</td>
<td>eMERGE Phase III: Clinical Center at Partners HealthCare</td>
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<tr>
<td>NHLBI TOPMed: Genetic Study of Atherosclerosis Risk (GeneSTAR)</td>
<td>A Genomic Atlas of Systemic Interindividual Epigenetic Variation in Humans (GTEx)</td>
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<td>GENEVA: Lung Health Study</td>
<td>eMERGE: Northwestern (NUgene) WGS</td>
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<td>Common Fund (CF) Genotype-Tissue Expression Project (GTEx)</td>
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<td></td>
<td>NHLBI GO-ESP: Lung Cohorts Exome Sequencing Project (Lung Health Study of Chronic Obstructive Pulmonary Disease)</td>
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MAP-HF: Multi-omics to Advance Precision medicine in Heart Failure

Funded TOPMed X01 application to create a comprehensive HeartShare TOPMed multi-omics resource, including whole genome sequencing, DNA methylomics, proteomics, metabolomics, PBMC transcriptomics.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study type</th>
<th>Total (N)</th>
<th>HFrEF (N)</th>
<th>HFrEF (N)</th>
<th>Control (N)</th>
<th>Sample availability</th>
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<td>DNA</td>
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<td>4875</td>
<td>3065</td>
<td>999</td>
<td>811</td>
<td>— — —</td>
</tr>
</tbody>
</table>
Demographics
Age, Sex, Race, Ethnicity

Encounters
Outpatient Hospitalizations

Electrocardiogram
PR interval, QRS duration, QTc interval, QRS axis, T wave axis, QRS-T angle

Echocardiogram
LV heart structure, LV systolic function, LV diastolic function, RH structure, RV function, Hemodynamics, Pressure-volume analysis

Co-morbidities
Coronary artery disease, Hypertension, Hyperlipidemia, Diabetes mellitus, Obesity, Chronic kidney disease, Atrial fibrillation, Chronic obstructive pulmonary disease, Obstructive sleep apnea

Vital Signs
Body-mass index, heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure

Medications
ACE-inhibitor or ARB, β-blocker, Calcium channel blocker, Nitrate, Loop diuretic, Thiazide diuretic, Statin, Aspirin

Laboratory Data
Sodium, potassium, bicarbonate, blood urea nitrogen, creatinine, estimated GFR, fasting glucose, white blood cell count, hemoglobin, red cell distribution width, platelet count, B- type natriuretic peptide

Invasive Hemodynamics
Right atrial pressure, Pulmonary artery systolic pressure, Pulmonary artery diastolic pressure, Mean pulmonary artery pressure, PCWP, PVR, Cardiac Output

H2FPEF Score
MAGGIC Risk Score

NYHA Functional Class
HF Duration

Future: CT, PFTs, CPET, Coronary Angiography

HeartShare EHR data + imaging repository
ECGs, echos, CT scans, MRIs, pathology images
Deep Phenotyping Cohort: Baseline Visit

<table>
<thead>
<tr>
<th>Duration</th>
<th>Study component</th>
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</thead>
<tbody>
<tr>
<td><strong>Prior to baseline visit</strong></td>
<td></td>
</tr>
<tr>
<td>20 minutes</td>
<td>eConsent (to be done in person for participants who request it)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Telephone survey for medication reconciliation and medical history (in person if no prior eConsent)</td>
</tr>
<tr>
<td><strong>Day 1 (begin fasted)</strong></td>
<td></td>
</tr>
<tr>
<td>15 minutes</td>
<td>Blood &amp; urine</td>
</tr>
<tr>
<td>30 minutes</td>
<td>EndoPAT (peripheral arterial tonometry)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>12 lead ECG, vitals, waist and hip circumference</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Snack</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Pulmonary function tests</td>
</tr>
<tr>
<td>20 minutes</td>
<td>Arterial tonometry (for arterial stiffness and pulsatile hemodynamics assessments)</td>
</tr>
<tr>
<td>90 minutes</td>
<td>Cardiopulmonary exercise testing + echo (rest + exercise)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Eureka questionnaires (if not done prior the study visit)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Education on Eureka, Kardia, and 24-hour BP devices and remote study procedures and geolocation + light lunch</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
</tr>
<tr>
<td>15 minutes</td>
<td>6-minute walk test</td>
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<tr>
<td>60 minutes (scan time 15 minutes)</td>
<td>CT (chest, abdomen, thigh)</td>
</tr>
<tr>
<td>120 minutes (scan time 60 minutes)</td>
<td>Cardiac MRI</td>
</tr>
<tr>
<td>25 minutes</td>
<td>Cognitive testing</td>
</tr>
<tr>
<td>10 minutes</td>
<td>Short Performance Physical Battery</td>
</tr>
<tr>
<td>60 minutes</td>
<td>Lunch</td>
</tr>
<tr>
<td>90 minutes</td>
<td>Skeletal muscle biopsy (optional), adipose biopsy (optional)</td>
</tr>
</tbody>
</table>

Opportunist myocardial tissue procurement for research use (endomyocardial biopsy, autopsy, cardiac surgery) has been added to HeartShare
HeartShare Prospective Study Data Flow

Data Types
- Echo
- ECG
- CT
- MRI
- Mixed

Core Lab Locations
- Brigham
- Cedars Sinai
- Northwestern
- Mayo
- JHMI
- U Miss
- Wake Forest
- Others

Data Ingestion, Controlled Access, Analysis
- Ambra
  - De-ID, ingestion
- Flywheel
  - Viewing, processing
- Azure

Linking Clinical Data and Images
- Index imaging data and provide access/linkage to relevant data from BDC

Image / Multi-Omics Analysis
- BioData Catalyst
  - Clinical, Lab, Omics
- Seven Bridges
  - Exploration, Visualization, Analytics, AI/ML

NIH
National Heart, Lung, and Blood Institute
FNIH
AMP® HF
HEARTSHARE
Deep learning + multi-omics

Deep learning autoencoder

OMICS data

Data dimension reduction (e.g., PCAs, clusters)

HFpEF phenotypes

Echo A4c view

Case study: Immunometabolic HFpEF

Comorbidities
- Obesity
- Type 2 diabetes
- Hypertension
- CKD
- COPD
- Anemia
- Sleep apnea

Systemic Inflammation
- Pulmonary HTN
- ↑Na+ retention
- ↓Exercise O2 uptake

Multi-organ endothelial dysfunction

Deranged endothelium-cardiomyocyte signaling
- Coronary microvascular dysfunction

Abnormal titin

ONOO− → ROS
↓NO
Leukocytes
TGF-β
Fibroblasts
Myofibroblasts
Collagen

↓sGC
↓cGMP
↓PKG
Hypertrophy

NIH National Heart, Lung, and Blood Institute
FNHI AMP® HF
HEARTSHARE
Myeloperoxidase (MPO) in HFpEF

**Mechanism**

- Systemic inflammation via sterile and/or microbial triggers of innate immunity
- MPO secreted by neutrophils
- MPO electrostatically bound to proteoglycans in the vascular wall
- MPO + H₂O₂ → reactive oxygen and nitrogen species

**Pathophysiology**

- **Vascular smooth muscle cells**
  - NO oxidation ⇒ impaired vascular relaxation and reduced perfusion
- **Cardiomyocytes**
  - Hypertrophy and impaired relaxation due to local ROS production
- **Fibroblasts**
  - Fibrosis as a result of ROS-driven activation and increased collagen secretion

**Clinical picture**

- Reduced CFR (and FMD)
- Impaired filling (diastolic dysfunction)
- Reduced exercise tolerance

The adverse effect of MPO in HFpEF is due to MPO deposited in the systemic microvasculature rather than MPO in neutrophil intracellular granules.
Mitiperstat: MPO inhibitor for HFpEF

**SATELLITE: Phase 2A RCT of mitiperstat (MPO Inhibitor) vs. placebo in HFpEF**

**Baseline to end-of-treatment change (%) in MPO activity**

**SATELLITE: Proteomic analysis**

3 independent observational HFpEF cohorts and 1 randomized controlled HFpEF trial

- PROMIS-HFpEF
- KaRen
- SHOP

**Multivariate projection (OPLS)** to identify and rank associated patient features

- All patient features
- Associated Olink biomarker patterns

**Mechanisms inferred from annotated findings in the literature**

**Associated inflammatory pathways**

- Increased risk for heart failure hospitalization or death
- Lower functional capacity (6MWD)
- Lower quality of life (KCCQ score)

**3-month Placebo**
**3-month AZD4831**

**KAREN outcomes**
**SHOP outcomes**
**PROMIS KCCQ**
**PROMIS 6MWD**
**SATELLITE**

Michaelsson E, et al. JACC Heart Fail 2023
Take home points

• AMP-HF and HeartShare are building a massive data repository that includes images and omics from multiple extant datasets, EHR datasets, prospective multi-omics, and prospective deep phenotyping studies
• Although data, omics, and images are from CVD epidemiology, CVD risk factor, and heart failure studies, the rich datasets can be used for other medical conditions
• HFpEF is a systemic, multi-organ, reserve-dysfunction syndrome that will likely benefit from cardiovascular and non-cardiovascular therapeutics and treatment paradigms
• HeartShare / BioDataCatalyst: Platform for AI/ML studies
Thank you!

HeartShare@northwestern.edu • http://www.AMPHF.org • Twitter: @HeartShareStudy
HFpEF
Uncovered

Ross Upton PhD
Founder, CEO and Chief Scientific Officer
Ultromics
Improving HFpEF diagnosis and outcomes is critical

Heart failure affects 64 million worldwide and 6 million in the U.S.\(^1,2\)

HFpEF constitutes approximately 50% of all heart failure.\(^3\)

“Understanding what HFpEF is, when it happens, and how to treat it remains the single largest unmet need in cardiovascular health.”

HF #1 cost of hospitalization\(^4\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>$43B</td>
</tr>
<tr>
<td>2030</td>
<td>$69B</td>
</tr>
</tbody>
</table>

Severe hospital burden and high mortality rates\(^5\)

- Readmission: 84%
- Mortality: 75.7%

Characterizing and diagnosing HFpEF remains challenging

Unclear patient presentation

Underlying CV conditions present with similar signs and symptoms\(^1\)

~50% of patients have 5+ major co-morbidities, often sharing common signs and symptoms\(^2\)

Confounding disease characteristics

Lack of uniformity in disease definition\(^1\)

Wide variation in diagnostic criteria across society guidelines\(^1\)

Co-morbid conditions often affect diagnostic measurements\(^1\)

Limited access to specialized care

Inconsistent access to HF cardiologists and clinics

Shortage of sonographers to measure diastolic function

up to 64% of HFpEF patients may be undiagnosed\(^3\)

\(^1\) Ho JE et al., Circ 2020;142:1770-1780. \(^2\) Dunlay, Roger, Redfield et al., Nat Rev Cardiol 2017;14:591-602. \(^3\) Borlaug et al., J Am Coll Cardiol 2023;81:1810–1834.
The novel AI technology behind EchoGo

1. CNN applied for view classification
2. CNN applied for auto contouring
3. Supervise ML algorithm for cardiac cycle detection and frame extraction
4. Automated feature extraction and quantification output
5. If EF preserved, 3D CNN model applied to detect if HFpEF is present
HFpEF Uncovered

Detects HFpEF with 88% sensitivity¹

Patients identified with EchoGo had 90% higher 5-year mortality risk¹

EchoGo HEART FAILURE

Detects HFpEF from a single 4-chamber view, giving you critical information to confidently diagnose and treat HFpEF.

Powered by AI

EchoGo Heart Failure - Training and validation

Rigorous methodology
Robust, objective definition of HFpEF to create distinct groups and to ensure accurate identification of patterns associated with HFpEF

- HF diagnosis documented through ICD 9 or 10 codes
- EF > 50% measured by echo
- Increased filling pressure documented through TTE

Large and representative data set
Designed to ensure exposure to a wide variety of cardiac physiologies and to minimize bias

- Over 6,500 patients across 8 sites
- Diverse pool of demographics across age, sex and ethnicity
- Range of co-morbidities: AF, hypertension, structural heart disease, CAD, pulmonary disease
- Data collected from both tertiary and community-based centers

“This novel solution applies AI to cardiovascular imaging to greatly simplify identification of HFpEF patients, a diagnosis that can be challenging, and allow more expeditious treatment.”

Patricia A. Pellikka, M.D.
Vice Chair, Department of Cardiovascular Medicine at Mayo Clinic
EchoGo Heart Failure - Diagnostic performance

Sensitivity
- 88% (95% CI: 84.5, 90.9)
  - Positive predictive value (80.2, 87.0)

Specificity
- 82% (95% CI: 78.2, 85.6)
  - Negative predictive value (83.0, 90.0)

EchoGo demonstrated excellent ability to differentiate between patients with HFrEF and those without.

8 sites
6,756 patients training & validation
1,284 testing

EchoGo Heart Failure vs clinical scores

EchoGo successfully reclassified 515 patients (73.5%)

EchoGo successfully reclassified 571 patients (73.6%)

Non-diagnostic by HFA-PEFF¹
701 / 1284 patients
54.5%

Non-diagnostic by H2FPEF¹
776 / 1284 patients
60.4%

EchoGo reclassified >73% of patients who had returned non-diagnostic results using the HFA-PEFF and H2FPEF scores.

EchoGo Heart Failure - Improved Outcomes

The diagnostic positive (HFpEF) and uncertain group all had poorer 5-year outcomes.

The diagnostic positive (HFpEF) had a 90% higher probability of dying over the 5 years. These cases have the opportunity for therapeutic intervention.

EchoGo was able to identify patients with worse survival, demonstrating its capacity to meaningfully improve patient outcomes.

Amyloidosis Uncovered

Under development as part of FDA TAP Program

EchoGo
AMYLOIDOSIS

Detects Cardiac Amyloidosis (CA) from a single 4-chamber view

funded by

Powered by AI

Release: Q2 2024
*Pending FDA Submission

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EchoGo Amyloidosis pending 510(k) clearance
Seamless and Scalable - Software-as-a-Service

- Secure cloud archive
- Data anonymization
- Cloud-based: Cloud native - optimal resource saving
- On-premise infrastructure
- Secure VPN connection
- QC + secured: CyberEssentials, ISO 27001, and ISO 13485 HIPAA Compliant
- Real-time access to data and reports with smart analytics
- Vendor neutral: Standard interfaces into all PACS – via secure, encrypted VPN.
- Seamless: Simple + easy integration that fits your workflow
- No training: No new software to learn or train on

<30mins: Turnaround from image sent to report received

EchoGo® cloud platform

Echo Study
EchoGo® Report
PACS or CVIS integration

Cloud-based

Dashboard

Secure VPN

© Ultromics Limited 2023
Reimbursement and clinical impact

Assigned New Reimbursement Codes by CMS

NTAP Code for EchoGo HF (Inpatient)
- ICD-10: XXE2X19
- $1000 per analysis
- Covered by Medicare

HCPCS Code for EchoGo HF (Outpatient)
- C9786
- Clinical APC 5743
- $284.88 per analysis
- Covered by Medicare and some commercial payers

→ Reduce the number of patients with HFpEF that go undiagnosed (up to 64%)¹

→ Start patients on new treatments, earlier, which reduce HF admissions (up to 29% risk reduction)²

→ Reduce the overspend on HF admissions which is often in excess of $15k per admission

¹ Borlaug, Sharma, Shah et al. JACC 2023;329:801-809
Ultromics has partnered with FNIH to tackle HFpEF

“Understanding what HFpEF is, when it happens, and how to treat it remains the single largest unmet need in cardiovascular health.”

FNIH launched a $37 million, 5-year initiative in 2022 to improve HFpEF classification and treatment.

**Ultromics will support with groundbreaking AI technology for precision HFpEF detection.**
Thank you

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Importance of myocardial tissue molecular profiling

Maggie Redfield, Mayo Clinic (prerecorded)
Importance of Myocardial Tissue Molecular Profiling in HFpEF

Maggie Redfield, MD
Mayo Heart Share Center
Co-Chair HS Cardiac Tissue Working Group
• **Myocardial Mechanisms in HFpEF: A HS Clinical Study**
  - Multiomics in Cardiac Tissue from HFpEF and Controls
    - Tissue prospectively obtained via research EMB in HFpEF
    - Tissue in Controls from Penn Cardiac Tissue Repository
  - Approved by the HS OSMB: Funded by FNIH-AMP
  - Protocol start up at sites underway

• **Myocardial Mechanisms in HFpEF: Insight from Historical EMB**
  - Protocol Draft - Ongoing pilot studies to prove feasibility
  - Finalizing study design
HS Cardiac Tissue Working Group

Leadership

Jason Duran, Ionis
Maggie Redfield, Mayo Clinic

Members

Matt Feinstein, Northwestern
Ravi Patel, Northwestern
Sanjiv Shah, DTC/Northwestern
David Liem, UC Davis
Ken Margulies, Penn
Julio Chirinos, Penn
Eliot Peyster, Penn
Dalane Kitzman, WF
Olivia Gilbert, WF
Akshay Desai, MGH/BW
Joe Maleszewski, Mayo
Ahmed Fayyaz, Mayo
Barry Borlaug, Mayo

Members

Akhilesh Pandey, Mayo
Surendra Dasari, Mayo
Kavita Sharma, JH
David Kass, JH
Virginia Hahn, JH
Will Chutkow, Novartis
Vandana Sachdev, NHLBI
Svati Shah, Heart Share Cochair, Duke
Why heart tissue?
Cardiac abnormality causes HFpEF

Defining cardiac pathophysiology drive Rx development

Symptoms and/or Signs of HF caused by a structural or functional cardiac abnormality

Animal models can help but may not replicate human pathophysiology.
Pathophysiologic Insight from Human Cardiac Tissue in HFpEF
A scoping review

Entry Criteria
• Original Investigation
• Human Cardiac Tissue
• HFpEF or LV Diastolic Dysfunction

56 papers
Human Cardiac Tissue - HFpEF

HF + pEF + HCM, AS or CAD

Surgical Biopsy

Epicardial  Endocardial

Transvenous RV Endomyocardial Biopsy (EMB)

Autopsy Full Thickness RV or LV Sections
A. Structural, Metabolic, and Functional Alterations in Human HFP EF Myocardium

Myocardial Fibrosis → Cardiomyocyte Hypertrophy → Microvascular Rarefaction → T-tubule Dilatation + Proliferation

Titin Hypophosphorylation
Impaired Ca++ cycling

Impaired Metabolism:
- Lower mitochondrial area
- Fragmentation, cristae destruction and vacuolar degeneration
- Decreased mitochondrial to sarcomere distance

Prolonged Relaxation

↑ Passive Force

Fayyaz AU, …Redfield MM; In Review
B. Underlying Pathophysiologic Pathways Tested in Human HFpEF Myocardium

- **cGMP-PKG Pathway Myocardial Effects**
  - ↓ Hypertrophy
  - ↓ Fibrosis
  - ↓ Stiffness
  - ↓ Autophagy

- **Inflammation Myocardial Effects**
  - ↓ eNOS (NOS3) but ↑ iNOS (NOS2)
  - ↓ Oxidative stress
  - ↑ Fibrosis
  - ↑ Hypertrophy
  - ↓ Mitochondrial Dysfunction

- **Unfolded Protein Response Myocardial Effects**
  - ↑ Protein Quality Control
  - ↓ Cardiomyocyte Function

- **DNA Damage Response Myocardial Effects**
  - ↑ DNA Repair
  - ↓ Cardiomyocyte Function

Directional Changes (↑ vs. ↓) in Pathway Component Activity or Concentration Demonstrated in Human HFpEF Myocardium vs Non-Failing Control
Hypothesis Driven Research

• Precious cardiac samples
• One pathway investigated
  • PCR, IHC, Westerns, Enzyme activity, etc
Discovery Omics for Drug Development

RNA and Protein Crucial (Examples of ↑RNA but ↓Protein)

Approx 13 K Genes

60% DEG

5% DEG

RV EMB; HFpEF (41), HFrEF (30), NF Con (24)

Autopsy LV; HFpEF (13), NF Con (10)

Surg LV Bx CABG; HFpEF (5), NF Con (1)

LV EMB Mix Con; HFpEF (16), NF Con (12)
• Myocardial Mechanisms in HFpEF: A Heart Share Clinical Study
  • Molecular Profiling of Cardiac Tissue
    • Prospectively obtained via EMB in HFpEF
    • Biobanked Tissue from Relevant Controls
  • Approved by the HS OSMB: Funded by FNIH-AMP
  • Protocol start up at sites underway

• Myocardial Mechanisms in HFpEF: Insight from Historical EMB
Evaluation of HFpEF

- Genetic
- Infiltrative
- Constrictive vs Restrictive
- Inflammatory

Redfield MM and Borlaug BA, JAMA, 2023
Exclude transplant patients
Different phenotypes remain

- Each site has tens to thousands of historical EMB (all FFPE):
  - HFpEF
  - HFrEF
  - Controls
- Myocardial Mechanisms in HFP EF: A Heart Share Clinical Study
  - Molecular Profiling of Cardiac Tissue
    - Prospectively obtained via EMB in HFP EF
    - Biobanked Tissue from Relevant Controls
  - Approved by the HS OSMB: Funded by FNIH-AMP
  - Protocol start up at sites underway

- Myocardial Mechanisms in HFP EF: Insight from Historical EMB
  - Protocol draft
  - Pilot studies
    - Patient characterization
    - Tissue microarrays, digital histopathology, Spatial Transcriptomics and Spatial Proteomics on FFPE +/- MS Proteomics
Highlights of AMP HF/HeartShare Clinical Centers

Svati H. Shah, Duke University
Javed Butler, Baylor Scott and White Health (BWS), University of Mississippi
NHLBI’s foundational investment of $25M in AMP HF, via two RFAs, to support deep phenotyping of HFpEF in Sep 2021

RFA-HL-21-015 HeartShare: Next-Generation Phenomics to Define Heart Failure Subtypes and Treatment Targets - Clinical Centers

- Supports 6 Clinical Centers to create a large registry of participants from EHR data and recruit ~1,000 HFpEF participants for deep phenotyping

RFA-HL-21-016 HeartShare: Next Generation Phenomics to Define Heart Failure Subtypes and Treatment Targets Data Translation Center

- Supports a Data Translation Center that will coordinate the HeartShare program, develop a new cohort of HFpEF subjects for deep phenotyping, and curate and analyze existing data and images from cohorts and trials
HeartShare Data Translation Center (DTC) and Clinical Centers

**Data Translation Center**
Extant data collection from many NHLBI cohorts and trials

Sanjiv Shah  
Northwestern University

**HeartShare Co-chairs**

Javed Butler  
BWS, University of Mississippi

Svati Shah  
Duke University

**Clinical Centers**
Prospective data collection at 6 HeartShare clinical sites. EHR data and all research data and images will be cleaned, curated and deposited into BioData Catalyst

Barry Borlaug  
Mayo Clinic

Julio Chirinos  
University of Pennsylvania

Nipavan Chiamvimonvat  
UC, Davis

Dalane Kitzman  
Wake Forest University

Sadiya Khan  
Northwestern University

Greg Lewis  
Massachusetts General-BWH
FNIH RFP announced in Feb 2023 to identify a 7th Clinical Center with expertise in endomyocardial biopsy acquisition

**Aim 1.** Join HeartShare as a 7th Site with a focus on myocardial biopsy procurement and analysis, to help establish such protocols in other Centers and coordinate analytics.

**Aim 2.** Pursue studies of myocardial tissue to better elucidate underlying pathobiology of HFpEF, provide molecular roadmaps for animal models, and define targetable abnormalities for novel therapies.

Kavita Sharma
Johns Hopkins University
IRB approval is established at 6 of 7 sites and EHR data collection and recruitment has begun

- EHR Data
  - ~50K HF pts per site, 56% HFpEF
  - Phase 1: Demographics, encounters
  - Phase 2: Vitals, meds, labs, comorbidities
  - Define HeartShare-specific tables, fields, and inclusion criteria in OMOP CDM

- Virtual Registry
  - 675 enrolled

- Deep Phenotyping Cohort
  - 65 enrolled

- Eureka Platform e-consent
Deep Phenotyping Protocol

Cohort: 750 HFpEF patients & 250 age, sex, and BMI-matched controls

- Exercise capacity
- Cardiac structure & function
- Body composition & biology
- Lung structure & function
- Biomarkers/omics
- Vascular
- Frailty

Subset with endomyocardial and/or skeletal muscle biopsy
Participant demographics data (As of 1/26/2024)

HeartShare Registry

- Male: 50%
- Female: 50%
- Combined: 82%

Deep phenotyping cohort

- Male: 39%
- Female: 61%
- Combined: 78%

- Hispanic or Latino: 4%
- Native Hawaiian/Pacific Islander: 5%
- Black or African American: 7%
- American Indian/Alaska Native: 1%
- Asian: 1%
- Non-Hispanic White: 6%
- More than one race: 2%
- Other: 1%
Clinical Site Recruitment Strategies

- Clinic-based enrollment
  - Dyspnea evaluation clinic
  - Virtual HFpEF clinics
  - Partnerships with community clinics
  - High risk pre-HFpEF

- Innovative enrollment strategies
  - EHR-based identification
  - MyChart invites
  - QR codes with links to study websites
  - Social media engagement
  - Weekly calls with all HF investigators

- Participant centric approach
  - Provide transportation
  - HFpEF education to participants (HF summit, community education)

- Personal contacts with participants
  - Clinicians approaching potential participants
  - Meeting potential participant in the lobby
Diversity, Equity, Inclusion and Accessibility (DEIA) is an important goal of the study.

Geographic Distribution of 7 sites

Estimated Gender, Racial, and Ethnic Diversity

- Female: 46%
- Male: 54%

- Non-Hispanic White: 58%
- Black or African American: 20%
- Hispanic or Latino: 10%
- More than One Race: 4%
- Asian: 4%
- American Indian/Alaska Native: 1%
- Native Hawaiian/Pacific Islander: 2%
Recruitment Strategies to Ensure Diversity

- Partnerships with faith-based groups
- Partnerships with community health programs and clinics
- Partnerships with health equity programs
- Partnerships with community health workers
- Rural outreach
- Diverse recruitment teams
AMP HF/HeartShare Study
Key Research Questions
Innovative Imaging Based Research

- 4-dimensional flow MRI
- AI for pulmonary vascular characteristics
- Whole body PET

Mitochondrial Function: Interplay Between Muscle & Heart

Figure. Associations of Maximal Capacity With Exercise Capacity and Physical Ability

A. PCA of Myocardial Tissue Metabolome
B. PCA of Plasma Metabolome
C. Myocardial Tissue
D. Plasma
Novel Molecular and Cellular Pathways of HFpEF

Artificial Intelligence/Machine Learning Approaches

- ML phenomapping
- AI ECG algorithms for HFpEF identification
- AI for pulmonary vasculature/heart interactions
- AI digital microscopy
The patient perspective

Cynthia Chauhan, Stage III HFpEF patient (prerecorded)