HeartShare Deep Phenotyping Study

HEARTSHARE

Study Protocol
Version 2.0

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1. INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a major public health problem that is growing in prevalence, associated with poor quality of life and outcomes, and has few clearly proven treatment options.[1,2] A major barrier to the advancement of HFpEF therapeutics is the heterogeneity of the HFpEF syndrome.[3-8] It is now well recognized that a "one-size-fits-all" approach is unlikely to work in HFpEF. The heterogeneity and poor understanding of HFpEF was the rationale for the creation of dedicated HFpEF clinical programs.[9] A number of studies over the past decade have identified specific phenotypes of HFpEF *a priori*, based upon characteristic features related to cardiac structure and function, hemodynamics, and comorbidities, with examples including obesity-related HFpEF, pulmonary vascular disease, and left atrial myopathy. In 2015, phenomapping (unsupervised machine learning) of HFpEF was first described and demonstrated both the heterogeneity of the HFpEF syndrome and the feasibility of identifying novel HFpEF subgroups via a data science approach.[10] Since that initial study, several additional studies that have used machine learning to classify the HFpEF syndrome have been published.[11-13]

In 2017, the NHLBI convened a working group on research priorities in HFpEF to address the lack of progress in identifying effective treatments in HFpEF.[5] A key conclusion of that meeting was the need to develop a network of collaborative centers to accelerate translational and clinical research of pathobiological mechanisms underlying specific HFpEF subtypes, based on prior research in the field.[14-21] The NHLBI Working Group envisioned that this resource would facilitate comprehensive, deep phenotyping of a multicenter HFpEF patient cohort with standardized protocols and a robust biorepository, which is a critical unmet need to advance subtyping of HFpEF.[5] To address this unmet need, NHLBI released a request for applications for the HeartShare Program, which was funded in September, 2021.

Although prior studies have highlighted the heterogeneous nature of the HFpEF syndrome, additional, prospective, multi-center resources such as HeartShare are needed to advance the science of HFpEF subtyping. Identifying and understanding biologically distinct HFpEF subtypes will lead to innovative, targeted HFpEF clinical trials.[22] An important unanswered question is whether prior machine learning- and omics-based subtyping of HFpEF truly represents biologically distinct subsets of HFpEF or simply subgroups based on disease progression or severity. Although both are important, the identification of biologically, mechanistically distinct HFpEF subtypes is more likely to advance HFpEF therapeutics. A multi-omics, deep phenotyping approach using both retrospective and prospective analyses, such as HeartShare, will allow us to better identify pathobiological HFpEF subtypes.

Although several studies on HFpEF phenotyping, using both conventional (e.g., pathophysiological characterization) and novel (e.g., machine learning) techniques have been published, most of these have been single center, retrospective (i.e., secondary data analyses), and/or limited in their phenotypic approach (i.e., not multi-omics).[7,11,12] The comprehensive deep phenotyping, multi-omics approach utilized by HeartShare allows for the advancement of the scientific knowledge of HFpEF subtypes by integrating a large amount of orthogonal data over multiple centers to increase confidence in that the identified subtypes are generalizable, which will help inform future targeted HFpEF clinical trials.

Here we describe the protocol for the HeartShare Deep Phenotyping Study. This component of HeartShare is a prospective, observational, longitudinal cohort study that consists of 2 parts: (1) a HeartShare Registry, which aims to enroll up to 10,000 individuals with HF and age- and sex-matched comparators, and the HeartShare Deep Phenotyping Cohort, which aims to enroll up to 2000 participants (75% individuals with HFpEF and 25% age- and sex-matched individuals without HFpEF). Both parts of the study will enroll participants from at least 6 HeartShare

Clinical Centers. **The overall goal of the HeartShare Deep Phenotyping Study is to create a rich repository of data (e.g., demographic, social determinants of health, clinical, physiological, laboratory), images, and multi-omics (blood and tissue samples) that will serve as a resource for investigators to identify novel HFpEF subtypes and mechanisms (biological and pathophysiological) to inform future strategies for enhanced diagnosis and treatment of HFpEF.**

2. OBJECTIVES

2.1. Specific Aims

- **Overall Aim:** To establish both a HF registry and a HFpEF cohort with deep phenotyping and a biorepository to facilitate mechanistic studies and unbiased discovery approaches to HFpEF.
- **Aim 1:** To identify novel diagnostic, physiologic, imaging, and molecular markers that differentiate individuals with and without HFpEF to characterize the pathophysiology and mechanistic basis of the overall HFpEF syndrome.
- **Aim 2:** To investigate the underlying pathophysiological and biological determinants of previously identified HFpEF subtypes, including, but not limited to: (1) obesity with natriuretic peptide deficient phenotype; (2) cardiometabolic-comorbidity-inflammation phenotype; (3) myocardial-predominant phenotype; (4) left atrial myopathy phenotype; (5) supranormal ejection fraction phenotype; (6) pulmonary vascular disease, right heart failure phenotype; (7) chronotropic incompetence predominant phenotype; and (8) peripheral extraction impairment predominant phenotype.
- **Aim 3:** To identify and enable external validation of novel HFpEF subtypes using unsupervised machine learning of deep phenotyping data, images, and multi-omics, followed by further investigation to determine the underlying pathophysiological and biological determinants of these novel HFpEF subtypes.

2.2. Study Design

The HeartShare Deep Phenotyping Study is composed of 2 prospective, multicenter, longitudinal components: (1) the HeartShare Registry and (2) the HeartShare Deep Phenotyping Cohort study involving up to 10,000 and 2,000 participants, respectively, enrolled from at least 6 HeartShare Clinical Centers.

2.2.1. Organizational Structure of the Study

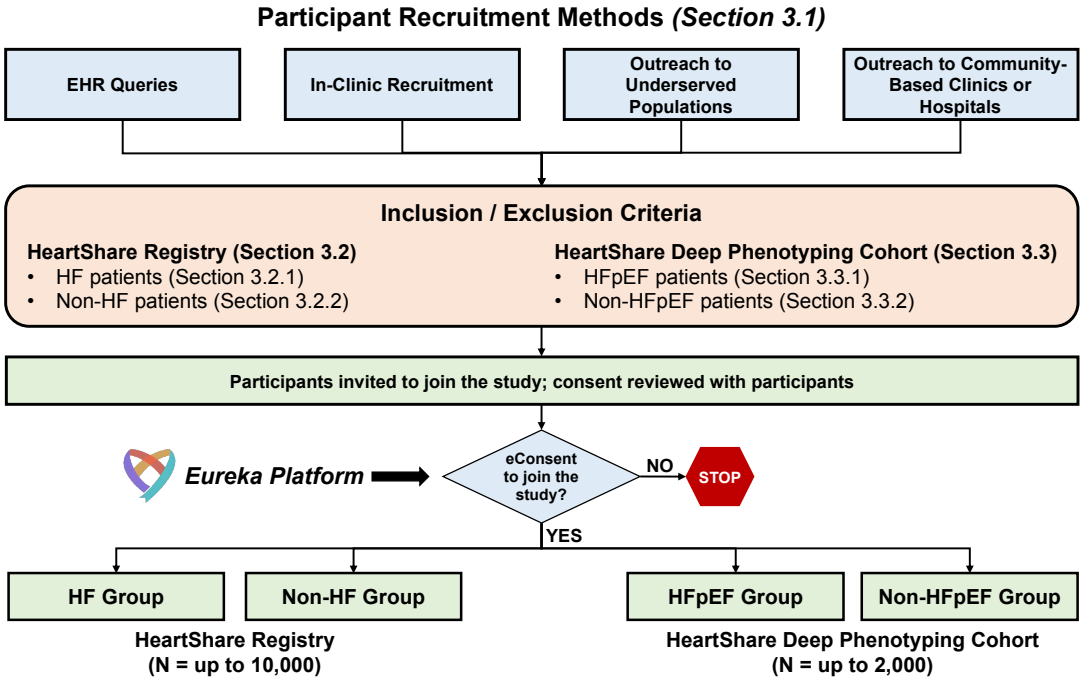
HeartShare is governed by a Steering Committee composed of the Principal Investigators (PIs) of the HeartShare Data Translation Center and the HeartShare Clinical Centers, NHLBI Project Scientists and Program Officers participating in HeartShare, and the Steering Committee Co-Chairs of HeartShare. The Steering Committee has the primary responsibility for the study protocol, monitoring study conduct, and reviewing data prior to reporting study results. It is also responsible for determining policies in areas such as access to participant data, ancillary studies, publications, and presentations. Study oversight is also provided by an Observational Safety and Monitoring Board (OSMB) appointed by the NHLBI. Ancillary study proposals of high scientific merit are encouraged to further enhance the scientific value of the main study and to optimize the yield from collected data, images, and biospecimens. A key aspect of HeartShare is the continuous deposit of all data, images, and omics into the NHLBI BioData Catalyst cloud computing resource so all aspects of study will be archived and shared according to NHLBI policies.

There will be several core laboratories for HeartShare, including ones for cardiopulmonary exercise testing, echocardiography, cardiac magnetic resonance imaging (MRI), arterial

stiffness/pulsatile hemodynamics assessments, pulmonary function testing, electrocardiography, tissue biopsies, multi-omics, microbiome, and clinical events. These core labs will provide central direction, personnel training, and supervision of the deep phenotyping protocol components, while supporting ascertainment of high-quality, standardized data. Study coordination, centralized data management, biospecimen management, and statistical analytic support will be provided by the HeartShare Data Translation Center at Northwestern University. All omics (i.e., genomics, proteomics, microbiome, metabolomics, epigenetics, and transcriptomics) will be conducted using the core laboratories and facilities involved in the NHLBI Trans-Omic for Precision Medicine (TOPMed).[23-25]

3. STUDY PARTICIPANTS

3.1. Participant Recruitment Methods (Figure 1)



Participants (HFpEF patients and age- and sex-matched individuals without HFpEF) for both the HeartShare Registry and the HeartShare Deep Phenotyping Cohort will be recruited at the HeartShare Clinical Centers using a variety of methods, including but not limited to: (1) a standardized electronic health record (EHR) query at each of the Clinical Centers; patients who meet the query criteria will be contacted by the study team on the phone or via electronic communication such as email or MyChart; (2) recruitment of patients who present to the Clinical Centers or clinical facilities affiliated within their health systems for evaluation of possible HFpEF, and from existing patients managed in primary care, internal medicine, cardiology, HF, and HFpEF clinics at each of the Clinical Centers; (3) outreach by the Clinical Centers to underserved populations who may not have access to healthcare at the Clinical Centers or smartphones or computers (and therefore cannot be recruited via the HeartShare Eureka app)—we will do this by specifically targeting identified HFpEF and comparator patients who reside in zip codes with lower socioeconomic status, such as the National Neighborhood Data Archive (NaNDA) and Common Ground Health; and (4) outreach by the Clinical Centers to community-based clinics and hospitals to increase the race/ethnic/socioeconomic diversity and generalizability of the HeartShare study—we will do this by giving presentations about the

HeartShare study to healthcare providers at these community-based clinics and hospitals to drive referrals for the study.

Written informed consent will be obtained from the participants by the research team prior to entry into the research study and will be performed in accordance with the guidelines and under the supervision of the Northwestern University Institutional Review Board (IRB), which will serve as the central IRB for the entire HeartShare Deep Phenotyping Study. The study procedures and the associated risks will be explained to the participants during the informed consent process. Only IRB-approved consent forms and related materials will be used for recruitment of study participants.

For the HeartShare Deep Phenotyping Cohort, our goal is to recruit a broad variety of HFpEF patients who represent HFpEF in the general population and to recruit age- and sex-matched individuals without HFpEF who have a broad spectrum of comorbidity burden ranging from healthy aged individuals to those with multiple comorbidities who do not have the HF syndrome. Age, sex, race/ethnicity, and individual comorbidities (e.g., obesity, hypertension, diabetes, chronic kidney disease, coronary artery disease, etc) will be tracked continuously in all participants of both the HeartShare Registry and the HeartShare Deep Phenotyping Cohort. The HeartShare Steering Committee, composed of PIs from the Data Translation Center and Clinical Centers and NHLBI staff, will review these metrics monthly and ensure that the enrolled participants have demographic and clinical characteristics that match epidemiological studies of HFpEF and that the comparator group has a wide range of comorbidity burden.

3.2. Inclusion/Exclusion Criteria for the HeartShare Registry

3.2.1. HF Inclusion Criteria (HeartShare Registry)

1. Age ≥30 years.
2. Prior diagnosis of HF in the EHR (any left ventricular ejection fraction).

3.2.2. Non-HF Group Inclusion Criteria (HeartShare Registry)

1. Age ≥30 years.
2. No known prior diagnosis of HF or use of loop diuretics.
3. No known prior history of BNP >100 pg/ml or NTproBNP >300 pg/ml, if prior laboratory tests are available in the EHR.

3.2.3. Exclusion Criteria (HeartShare Registry)

The following exclusion criteria apply to both HF and non-HF group participants, unless otherwise indicated.

1. For non-HF group: any prior known left ventricular ejection fraction <50%.
2. Prior history of solid organ transplantation.
3. Prior history of mechanical circulatory support.
4. Prior history of non-cardiac cirrhosis.
5. Inability to provide written consent to the study.

3.3. Inclusion/Exclusion Criteria for the HeartShare Deep Phenotyping Cohort

3.3.1. HFpEF Inclusion Criteria (HeartShare Deep Phenotyping Cohort)

1. Age ≥30 years.
2. Left ventricular ejection fraction ≥50% measured by echocardiography.
3. Definition of HFpEF: signs and symptoms of HF, NYHA functional class II-IV, and <u>at least one</u> of the following:
    a. Elevated BNP (≥75 pg/ml in sinus rhythm or ≥225 pg/ml in atrial fibrillation/flutter) or NTproBNP (≥225 pg/ml in sinus rhythm or ≥675 in atrial

fibrillation/flutter) at baseline. Choice of BNP or NTproBNP is based on availability at each clinical center.

b. Prior HF hospitalization (primary reason for the hospitalization is HF with elevated natriuretic peptide levels [using the thresholds listed above], requiring IV diuresis for HF, or pulmonary edema or pulmonary vascular congestion on chest radiography).
c. Elevated pulmonary capillary wedge pressure (PCWP) at rest (≥15 mmHg) or during exercise (≥25 mmHg for supine exercise or PCWP/cardiac output ratio ≥2 mmHg/L/min for upright exercise).
d. Elevated H_2FPEF score[26] (≥5) or HFA-PEFF[27] score (≥5).

3.3.2. Non-HFpEF Group Inclusion Criteria (HeartShare Deep Phenotyping Cohort)

1. Age ≥30 years.
2. Left ventricular ejection fraction ≥50% measured by echocardiography.
3. No known prior diagnosis of HF or use of diuretics for fluid management.
4. No known prior history of BNP ≥75 pg/ml or NTproBNP ≥225 pg/ml, if prior laboratory tests are available in the EHR.
5. BNP <75 pg/ml or NTproBNP <225 pg/ml at the time of screening. Choice of BNP or NTproBNP is based on availability at each clinical center.

3.3.3. Exclusion Criteria (HeartShare Deep Phenotyping Cohort)

The following exclusion criteria apply to both HFpEF and non-HFpEF group participants, unless otherwise indicated.

1. Life expectancy estimated to be < 1 year.
2. Primary cardiomyopathy (including amyloid, hypertrophic cardiomyopathy, cardiac sarcoidosis, hemochromatosis, or other infiltrative cardiomyopathies) or pulmonary arterial hypertension (WHO Group I, III, or IV pulmonary hypertension).
3. Any prior known left ventricular ejection fraction <40%, except if this occurred only in the setting of an acute tachycardia episode (e.g., acute atrial fibrillation).
4. Clinically significant valvular heart disease defined as:
    a. Moderate to greater aortic stenosis, pulmonic stenosis, or tricuspid stenosis.
    b. Any mitral stenosis.
    c. Moderate or greater aortic regurgitation.
    d. Greater than moderate mitral regurgitation.
5. Any planned cardiac surgery or cardiac intervention in the next 3 months.
6. Alternative primary reason for symptoms of shortness of breath and exercise intolerance in HFpEF participants in the opinion of the enrolling investigator.
7. Cardiac surgery, acute coronary syndrome, percutaneous coronary intervention, stroke, transient ischemic attack, or carotid intervention in the preceding 6 months prior to enrollment.
8. Known symptomatic epicardial coronary artery disease that is not revascularized.
9. Any non-elective hospitalization in the preceding 2 weeks.
10. Prior history of solid organ transplantation.
11. Prior history of chronic infection (HIV, hepatitis C, hepatitis B, tuberculosis) unless treated and not clinically active in the opinion of the enrolling investigator.
12. Prior history of mechanical circulatory support.
13. Prior history of non-cardiac cirrhosis.
14. Estimated GFR <20 ml/min/1.73m^2 or currently on dialysis.
15. Any condition that may preclude participation or adherence to the study protocol, in the opinion of the enrolling investigator.
16. Inability to provide written consent to the study.

17. Current acute decompensated heart failure.
18. Currently pregnant.
19. Uncontrolled heart rate (>110 bpm) at the time of screening.

3.4. Participant Timeline and Burden

Study participants will be enrolled during years 2-5 of the overall HeartShare program (which started in September 2021). **Table 1** lists the duration for each of the in-person deep phenotyping components (see below). Baseline, follow-up, and outcome data to be collected in the HeartShare Deep Phenotyping Study are provided in **Table 2** (schedule of events, see below).

3.5. Consenting Participants

The informed consent process will afford the opportunity for the patients and their family members to ask questions and express any concerns about participating in the study. Potential study participants will also be given the opportunity to consider the requirements of participation and the option of not participating in the study. Efforts will be always made to confirm that patients understand the information and are making an informed voluntary decision to participate in the study. Patients will also be encouraged to have family members and other trusted individuals assist with their decision to participate in the study and address any questions or concerns about participation in the study. Patients will be given adequate time to review the consent.

IRB-approved electronic informed consent (eConsent) will be completed before any patient undergoes any study activity via Eureka. Participants who are consenting electronically through Eureka will receive an invitation link to register with Eureka sent to their email. This link contains a unique identifier linked to the participant's email. This link can only be used for a participant to register for Eureka once and verifies the unique ID with the email used during registration. At this point, the participant has registered for Eureka and has gone through a verification step. Participants will be asked to install the Eureka smart phone app, if the participant has a smart phone and agrees to install the app. Participants will log in and verify their phone number used during registration. After logging in with their registered Eureka account, in both the smart phone app and web browser, participants will then be able to access the consent form. At the end of the consent form, the participants are asked if they agree to participate by providing their signature. If the participant is using the mobile device, they will be able to provide the signature with using their touchscreen by signing with their finger, or be prompted to adopt an eSignature using their typed name via DocuSign. Optional study elements will be displayed to the participant immediately following the main consent. This is due to limitations within the Eureka infrastructure that only allows participants to agree/decline to participate in one item at a time. Each of the items consented to/declined participation will include the response from the participant, the participants name, and the version of the consent embedded into the consent form.

A copy of the consent will be given physically or electronically to the participant and a copy will be saved electronically and maintained according to the policies of each Clinical Center's IRB.

There will be an option for in-person eConsent using tablets and/or computers, whereby a study coordinator can obtain eConsent from the participant. Formal consent for the study will be verified in-person for participants who signed eConsent prior to their in-person study visit. Patients will have the option of including family members or trusted advisors in their decision process. Consent forms in languages other than English can be used according to the policies

of each Clinical Center's IRB. Patients who cannot read will be read the entire consent form and will consent in the presence of a witness.

3.6. Meeting Recruitment Goals

The Data Translation Center will train study coordinators and investigators at each site on optimal recruitment practices prior to the start of each site's recruitment. The Data Translation Center will also keep track of the cumulative running total number of HFpEF and non-HFpEF comparator participants, and recruitment metrics (including age, sex, race/ethnicity, and comorbidities) will be reviewed by the Steering Committee on a monthly basis. The Data Translation Center will conduct ad-hoc meetings with any site that is not meeting monthly recruitment goals in order to troubleshoot recruitment obstacles.

3.7. Participant Compensation

Participants will receive financial compensation in the amount of $500 total for participating in this study. An additional $125 will be provided in compensation for each tissue biopsy procedure. Participants may choose to decline financial compensation. Participants may also receive reimbursement for travel and accommodations necessary for study visits, at the discretion of each Clinical Center.

3.8. Participant Withdrawal / Early Termination

Participants may voluntarily withdraw from the study at any time and for any reason. Investigators may also withdraw a patient from the study due to protocol non-compliance, incorrect enrollment, or for any other reasons related to participant safety. The reason for study discontinuation will be recorded on the source documents.

4. DATA COLLECTION

4.1. Eureka Platform

4.1.1. Overview of Eureka

The Eureka Research Platform is a direct-to-participant digital platform developed in part with NIH funding (U2CEB021881) at UCSF as a resource for enabling efficient clinical health research that utilizes mobile and digital technology. Eureka is available on the web and via native mobile apps (iOS and Android). Eureka is a custom-built, HIPAA-compliant platform that runs on Amazon Web Services (AWS), and is able to scale for users, and provides for redundancy, security and data integrity. While the Eureka platform is optimized for remote study participation, Eureka is also equipped for hybrid studies with both remote and in-person components such as HeartShare.

4.1.2. Survey Tools and eVisits

The Eureka platform has a highly configurable and robust survey engine that will deliver the surveys to the participants, including complex triggering and skip logic within surveys and between surveys as well as real-time data validation during data entry. Eureka also includes an eVisit capability; the eVisit is a collection of study activities that can open and close with time windows or can be triggered by events or previous activities. A list of surveys and frequency of the surveys are listed in the **Appendix**.

4.2. Data Collection Instruments

The HeartShare Data Translation Center will work with the HeartShare investigators to prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each study participant. Study personnel at each site will enter data from

source documents corresponding to a participant's visit into the protocol-specific electronic case report form (eCRF) or paper CRF when the information corresponding to that visit is available. Participants will not be identified by name in the study database or on any study documents to be collected by the Data Translation Center, but will be identified by a site number and participant number.

For eCRFs, if a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change. The site PI at each Clinical Center is responsible for all information collected on enrolled participants. All data collected during the study must be reviewed and verified for completeness and accuracy by the investigator. A copy of the CRF will remain at the Clinical Center where the patient is enrolled at the completion of the study.

4.3. Data Management Procedures

The data will be entered into the study database in Eureka. The Data Management Core will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

4.4. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries will be directly entered, tracked, and resolved through the Eureka electronic data capture (EDC) system. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented. The Eureka database will be routinely exported by the HeartShare Data Management Core. The data will undergo another set of data quality checks by the Data Management Core. From here, it will be staged for upload into BioData Catalyst.

4.5. BioData Catalyst

NHLBI BioData Catalyst is a cloud-based ecosystem providing tools, applications, and workflows in secure workspaces. By increasing access to NHLBI datasets and innovative data analysis capabilities, BioData Catalyst accelerates efficient biomedical research that drives discovery and scientific advancement, leading to novel diagnostic tools, therapeutics, and prevention strategies for heart, lung, blood, and sleep disorders, and is therefore directly applicable and designed for studies such as HeartShare. BioData Catalyst allows researchers to find, access, share, store, and compute on large scale datasets and images that will be collected in HeartShare and will serve as the HeartShare data ecosystem. Only users authorized by the Data Translation Center can access the HeartShare data and images, only de-identified data and images can be uploaded, and no data or images can be downloaded.

5. STUDY PROCEDURES

5.1. Study Visits

Once consented, all study participants will undergo a 2-day baseline visit. Depending on the scheduling systems, physical location, and availability of the various tests required for the study, centers may split each of these visits into more than 2 days or rearrange the order of procedures, but in all cases, the duration of testing will closely approximate the details in **Table 1**. The in-person and remote data collection components of the baseline visit must occur within

a 30-day window. Thereafter, participants will receive two short surveys monthly and several longer surveys evey 6 months via Eureka (see Supplementary Tables 2 and 3).. Participants will return to the Clinical Center for an in-person follow-up visit one year after the baseline visit. The one-year follow-up visit will be much shorter than the baseline visit. **2** lists the schedule of events (all components of the deep phenotyping study visits and and remote data collection instruments).

Table 1. Duration of Deep Phenotyping Study Components

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

Total time for Day 1: ~5 hours
Total time for Day 2: ~3 hours, 45 min (total time = ~5 hours, 15 min with optional biopsies)

Table 2. Schedule of Events

Assessment/Activity	Baseline	Monthly surveys via Eureka	6-month surveys via Eureka	12-month Follow-up visit* (In-Person)
In Person Visits				
eConsent	(X)			
Medical history	(X)			X
Medications	X			X
Vital signs and physical exam	X			X
Weight and weight history	X			X
Family history	X			
Pregnancy history (in females)	X			

Laboratory tests	X			X
Blood collection	X			X
Urine collection	X			X
Stool and saliva collection (take home)	X			
EndoPAT testing	X			
12-lead electrocardiogram	X			X
6-minute walk test	X			X
Short Performance Physical Battery (SPPB)	X			X
Pulmonary function testing	X			
Arterial tonometry	X			
Cardiopulmonary exercise test	X			
Rest and exercise echocardiography	X			
Cardiac / liver MRI with contrast	X			
CT chest, abdomen, upper thighs	X			
Cognitive assessment (MoCA)	X			
Skeletal muscle biopsy (optional)	X			
Adipose tissue biopsy (optional)	X			

Remote data collection				
24-hour ambulatory blood pressure (take home)	X			
AliveCor at-home Kardia 6-lead ECG**	X		X	X
Current weight**	X		X	X
Medication inventory	X		X	X
Eureka social demographics	X			
Kansas City Cardiomyopathy Questionnaire-12	X		X	X
NYHA class self-assessment	X		X	X
TAPS-1 and TAPS-2 (habits)	X		X	X
Epworth Sleep Quality Survey	X		X	X
FRAIL Questionnaire	X		X	X
CES-D (10-question format)	X		X	X
Symptom Overview Survey (includes MMRC Dyspnea Scale and Rose Angina survey)	X		X	X
STOP-BANG Questionnaire	X		X	X
CPAP survey (if applicable)	X		X	X
Seattle Angina Questionnaire (if applicable)	X		X	X
Palpitations survey (if applicable)	X		X	X
Calgary Syncope Survey (if applicable)	X		X	X
Atrial Fibrillation Severity Scale (if applicable)	X		X	X
3-Question Monthly Survey		X	X	
Hospitalizations survey	X	X	X	X
Outcomes assessment (hospitalizations, death)			X	X

*Note: after the initial 12-month visit, the monthly and 6-month surveys repeat until the end of the study (maximum participation = 5 years).

5.2. Baseline Evaluation and Data Collection

All participants in the Deep Phenotyping Cohort (with and without HFpEF) will undergo the same phenotyping protocol (listed in **Table 2**, above).

5.2.1. Demographics and History

Birth date, sex assigned at birth, gender identity, self-reported race, self-reported ethnicity, and zip code of most frequent domicile will be recorded. Family and social history data (Eureka Social Demographics, General Family History, TAPS-1, and TAPS-2 questionnaires) will be recorded using the Eureka platform.

5.2.2. Health Status Questionnaires

A series of health status and symptom questionnaires, including the Kansas City Cardiomyopathy Questionnaire (KCCQ-12), NYHA heart failure scale, MMRC Dyspnea Scale, Epworth Sleep Quality Survey, FRAIL Questionnaire, Symptom Overview Survey (with subsequent Rose and Seattle Angina surveys, palpitations, and Calgary Syncope Survey, and Atrial Fibrillation Severity Scale [if applicable]), and CES-D will be recorded via the Eureka platform.

5.2.3. Comorbid Conditions

Medical history will be recorded based on self-report in the Eureka app, EHR diagnosis codes, and chart review by study coordinators. Any discrepancies will be resolved at the time of enrollment.

5.2.4. Medications

Medication inventory will be collected using the Eureka platform and will be reviewed with the patient in person to ensure accuracy. A complete list of prescribed medications, over-the-counter medications, and herbal medications/supplements will be collected for each participant. For each medication, dose and frequency will be recorded.

5.2.5. Physical Examination

- **Anthropometry:** Height and weight will be measured to the nearest 0.1 cm and 0.5 kg respectively. Body mass index (kg/m^2) will be used a measure of overall obesity. Girths (waist at the umbilicus and hips at the maximal circumference of buttocks) will be measured to the nearest 0.1 cm using a flexible measuring tape.
- **Blood Pressure:** Resting blood pressure will be measured in the right arm after five minutes in the seated position. An automated oscillometric method and appropriate cuff size will be used. Three readings will be taken; the second and third readings will be averaged to obtain the blood pressure levels used in analyses.
- **Pulse Oximetry:** Resting oxygen saturation will be measured in the seated position after 30 seconds of recording (to allow for stabilization of the photoplethysmography signal). A pulse oximeter with a finger probe will be used. Nail-polish will be removed, if necessary. Oximetry will be measured off supplemental oxygen, if used. For participants who use supplemental oxygen, supplemental oxygen will be restarted immediately if they are short of breath or if their oxygen saturation drops below 82%.
- **Heart Rate:** Resting heart rate will be documented during from the pulse oximetry monitor at the time of oxygen saturation reading.
- **Auscultation:** A digital stethoscope (EKO Duo) with built-in single-lead ECG will be utilized to record heart and lung sounds.

5.2.6. Laboratory Measurements

- **Blood:** All consented participants continuing to meet the screening criteria will undergo baseline blood draws after an overnight fast. Cells, serum, and plasma will be collected. Laboratory tests will include (but not limited to): complete blood count (CBC), complete chemistry panel (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, ALT, AST, alkaline phosphatase, and total bilirubin), cystatin C, NT-proBNP (or BNP, based on local lab availability), and hemoglobin A1c. HeartShare biorepository and genetics samples with also be obtained. Whole blood samples for DNA and blood stored in RNA stabilization tubes (e.g., PaxGene) will be collected at the baseline examination and stored for future genetic analyses. Whole genome sequencing, proteomics, metabolomics, DNA methylomics, and peripheral blood mononuclear cell transcriptomics will be performed. Blood for RNA will be collected at the baseline examination and stored for future analyses in PAXgene tubes. RNA sequencing will be performed to study gene expression.
- **Urine:** We will obtain a urine sample from each participant. Urine tests will include (but not limited to): urinalysis and urine albumin to creatinine ratio. Urine will be aliquoted into 3 ml samples and frozen for future batched assays. We will check a urine pregnancy test on all pre-menopausal female participants before performing any radiographic procedures in order to exclude the possibility of radiation exposure to a fetus.

- **Stool:** Stool will be collected at home by the patient using a standardized microbiome collection kit. The sample will then be sent by the patient in a prepaid shipping container to the microbiome core laboratory.
- **Saliva:** Saliva will be collected at home by the patient using a standardized microbiome collection kit. The sample will then be sent by the patient in a prepaid shipping container to the microbiome core laboratory.

5.2.7. Peripheral Arterial Tonometry (EndoPAT)

EndoPAT is a medical device that tests the reactivity of blood vessels in the fingertips to determine whether systemic endothelial dysfunction is present. The EndoPAT procedure involves sensors at the fingertips in both hands and brachial blood pressure cuffs that transiently occlude upper extremity arterial flow (similar to blood pressure measurement). EndoPAT measurements include reactive hyperemia index and arterial augmentation index. The EndoPAT procedure requires at least 4 hours of fasting.

5.2.8. Electrocardiography

A standard 12-lead electrocardiogram will be obtained in all participants. All electrocardiograms will be stored in XML format for analytic purposes.

5.2.9. Arterial Tonometry

Brachial pressures will be measured using a BP+ device (Uscom Medical). We will use a high-fidelity Millar applanation tonometer (SphygmoCor, AtCor Medical) to record carotid pressure waveforms. Radial waveforms will also be acquired, which will be calibrated using brachial artery pressures. Carotid waveforms will be calibrated using the radial diastolic and mean pressures. Central arterial pressure waveforms will be analyzed for central aortic augmentation index, pulse pressure, and forward and backwards components of aortic pulse waves. Carotid-femoral pulse wave velocity (PWV), an index of large artery stiffness, will also be measured. We will also measure carotid-radial PWV using the SphygmoCor device. Various additional physiologic parameters will be obtained from pressure-flow analyses, in which central aortic pressure is modeled along with left ventricular outflow, as measured by echocardiography.[28,29]

5.2.10. Six-Minute Walk Test (6MWT)

The 6MWT, a practical and simple exercise test that requires a 100-ft hallway, will be performed by trained study coordinators according to American Thoracic Society guidelines.[30] The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWT distance may better reflect the functional exercise level for daily physical activities and is often performed clinically in the assessment of HF patients and is a frequent endpoint in HF clinical trials. Oxygen saturation, blood pressure, heart rate, and the Borg dyspnea score and fatigue scores will be obtained at rest and immediately upon completion of the 6MWT.

5.2.11. Short Physical Performance Battery (SPPB)

The SPPB is an objective assessment tool developed by the National Institute on Aging for evaluating lower extremity functioning in older persons. The SPPB consists of three assessments: (1) repeated chair stands; (2) balance tests (side-by-side, semi-tandem and tandem balance tests); and (3) an eight-foot walk test. The assessments will be performed by trained study coordinators using the “SPPB Guide” administration app.

5.2.12. Pulmonary Function Test

Spirometry, lung volumes, and diffusion capacity of carbon monoxide (DLCO) will be performed in all participants. Total lung capacity will be done by body plethysmography.

5.2.13. Cardiopulmonary Exercise Test

All participants will undergo cardiopulmonary exercise testing unless they meet one of the following exclusion criteria: (1) unstable angina; (2) history of exertional syncope (unless the underlying cause has been treated); (3) history of exercise-induced sustained ventricular arrhythmia; (4) resting systolic blood pressure ≥200 mmHg.

We will use a semi-recumbent exercise protocol in conjunction with expired gas analysis to assess oxygen consumption uptake (VO_2) during exercise. Exercise acquisitions may be modified depending on equipment availability at each site. Participants will perform a maximal exertion-limited exercise test using a graded-exercise protocol. The protocol will consist of resting assessment of metabolic rate for 4 minutes, followed by exercise with zero (or equipment-minimal) resistance for a period of 3 minutes. Resistance will then begin at 20W for 3 minutes, increasing by 20W every 3 minutes thereafter to the endpoint of exhaustion. Breath-by-breath information will be recorded. Total work performed will be computed and exercise efficiency will be defined as total work/total oxygen consumed starting at 1-minute into the incremental ramp portion of exercise. The total length of the bicycle exercise test will depend on the participant and how long they are able to exercise. We will also continuously monitor each participant's heart rate and rhythm with electrocardiography, and blood pressure will be checked during each stage of exercise. We will also monitor the oxygen levels in their blood using a pulse oximeter. The cardiopulmonary test will be performed by trained and qualified personnel.

5.2.14. Cognitive Test

Cognitive testing will be performed using the Montreal Cognitive Assessment (MoCA). The MoCA test is a highly sensitive tool for early detection of mild cognitive impairment. It quickly and accurately assesses short term memory, visuospatial abilities, executive functions, attention, concentration, and working memory, language, and orientation to time and place. The MoCA test takes about 15 minutes to administer.

5.2.15. Cardiac Magnetic Resonance Imaging

Cardiac and limited liver MRI with gadolinium contrast will be performed on all participants unless contraindicated for assessment of cardiac structure and function, focal and diffuse myocardial fibrosis, aorta and pulmonary artery measurements, and liver fat. Non-contrast MRI will be performed in participants with eGFR <45 ml/min/1.73 m^2, and those with gadolinium allergy (or any other contraindication to gadolinium). Participants with pacemakers or defibrillators will be eligible for MRI if allowed by each site's institutional protocols for MRIs with such devices.

All scanning will be carried out on a 1.5T MRI scanner. Upon arrival, participants will undergo standard MRI safety screening. An intravenous catheter will be placed in the arm and a small amount of blood (approximately 5 mL) will be collected to test renal function (creatinine; for calculation of eGFR) and hematocrit if no recent value is available, or as indicated at each Clinical Center's cardiac MRI protocol. Participants will then be placed on the MRI scanner, ECG electrodes will be placed on the chest to allow cardiac gating, ear plugs will be inserted into or headphones will be placed over the participants' ears to protect the participants' hearing and allow communication between the patient and MRI technologist, and the participant will be provided a squeeze ball that alerts the technologist if the participant wishes to discontinue the test at any time. The participant will be advanced, head-first, into the bore of the scanner. Localizers/scouts will be performed, and the table will be withdrawn from the scanner bore

temporarily. The participant will be advanced back into the scanner bore and IV administration of a gadolinium-based contrast agent will occur: Gadobutrol (Gadavist) at 0.10 mmol/kg total dose. This is the approved dose by the FDA. There are risks associated with use of the contrast agent, which are detailed in the consent form for the participant, and in the participant risk section below. The participant will be advanced back into the scanner bore and images will be acquired. Once imaging has been completed, the IV catheter will be removed, and a temporary bandage will be placed at the site of venipuncture.

5.2.16. Resting and Exercise Echocardiography

All study participants will undergo comprehensive 2- dimensional (2D) echocardiography with Doppler and tissue Doppler imaging (TDI) at rest in the supine and left lateral decubitus positions. A cardiac ultrasound system with harmonic imaging will be used for all echocardiographic examinations. A limited vascular (carotid and femoral) 2D and Doppler interrogation may be performed at sites that have the ability and equipment (i.e., vascular linear probes). During the cardiopulmonary exercise test (see above, section 5.2.12), exercise echocardiography will be performed during semi-recumbent bicycle exercise. Images will be obtained at each stage of exercise. Cardiac structure/function will be quantified at rest and during each stage of exercise as recommended by the American Society of Echocardiography. LV and RV structure/function, LV diastolic function, atrial size/function, hemodynamics, and speckle-tracking strain parameters will be measured at rest and at each stage of exercise. Exercise acquisitions may be modified depending on equipment availability at each site. Blood pressure will be measured using a digital BP monitor. BP at rest and at each stage, and total exercise capacity, will be recorded.

5.2.17. Computed Tomography

Participants will undergo non-contrast CT scanning of the chest, abdomen, pelvis, and upper thighs. Experienced and trained technologists will perform CT scans in each consenting participant in order to obtain an accurate and reproducible assessment of body composition (visceral fat, subcutaneous fat, and lean body mass), aortic and coronary calcium, aortic geometry, and parenchymal lung disease.

5.2.18. Tissue Biopsies (optional)

Patients who take blood thinners (for example, warfarin or novel oral anticoagulants) may be asked to stop or reduce these medications during the week leading up to a tissue biopsy procedure. For both muscle and adipose tissue collection, participants will be given printed instructions on how to prepare for the day of the tissue collection and how to care for the collection sites after the procedure. Follow-up phone calls will be made approximately a week after the procedures to assess healing of the collection sites.

5.2.18.1. Skeletal Muscle Biopsy

Skeletal muscle biopsy, which will take approximately 1 hour, will be used to sample muscle cells from the Vastus Lateralis (thigh) muscles. Skeletal muscle biopsy will be done on a subset of participants. After cleaning the skin on the front of the thigh with iodine, a local anesthetic will be injected under the skin to reduce feeling and pain in the area of the biopsy. The doctor or a trained/certified designee will make a small incision in the skin and insert a needle under the skin to remove muscle cells from the thigh. Approximately 600 milligrams of muscle will be removed. After the tissue sample is completed, the skin will be held closed with sterile adhesive strips, an antibiotic ointment will be applied, and the area will be covered. An ACE bandage wrap will be applied securely for 1 hour. After 1 hour, the ACE bandage may be loosened, and then removed after 4 hours.

5.2.18.2. Adipose Tissue Biopsy

Adipose tissue biopsy, which will take approximately 1 hour, will be used to sample fat cells from the abdomen (belly). Adipose tissue biopsy will be done on a subset of participants. After cleaning the skin on the front of your abdomen with iodine, a local anesthetic will be injected under the skin to reduce feeling and pain in the area of the biopsy. The doctor or a trained/certified designee will make a small incision in the skin and insert a needle under the skin to remove fat cells from the abdomen. Approximately 3 grams of adipose tissue will be removed. After the fat sample is completed, the skin will be held closed with sterile adhesive strips, an antibiotic ointment will be applied, and the area will be covered.

5.2.18.3. Tissue Processing and Assays

Muscle and adipose samples will be processed locally at the clinical centers using appropriate methods for archiving that will allow for a variety of future measures. Some lab measurements will be collected on fresh tissue locally at the clinical centers at the time of collection or on frozen samples. Muscle and adipose tissue remaining after local analyses will be de-identified and shipped for storing at the biopsy core laboratory in secure and monitored -80°C or liquid nitrogen freezers. Archived samples that remain after planned assays will be made available to investigators through an ancillary proposal process.

5.2.19. Wearable Sensor Validation Studies

In some circumstances, wearable sensors (e.g., smartwatches, chest straps, smart rings, accelerometers, or other sensors) may be placed on participants during the above-mentioned assessments to obtain simultaneous measures for validation purposes. It is anticipated that this would not substantially increase the time spent in the visit or the test but would allow for collection of simultaneous wearable data during other phenotyping studies (e.g., exercise testing).

5.3. Longitudinal Follow-up

All participants, or their designated contacts, will be contacted using the Eureka app (or by telephone) every 6 months for up to 5 years after enrollment. Vital status, hospitalizations, and any urgent outpatient or emergency department (ED) visits for intravenous diuretics for heart failure exacerbation will be recorded. Participation dates in clinical trials and types of interventions will also be captured. Cause of hospitalizations and deaths will be ascertained by the site investigators and further adjudicated by a central Clinical Events Committee (CEC).

5.3.1. Clinical Events Ascertainment

The CEC will adjudicate all deaths, cardiovascular hospitalizations, HF hospitalizations, and unplanned outpatient/ED visits for intravenous diuretics. CEC adjudication will be done centrally by trained staff according to systematic criteria.

5.3.2. Ambulatory Blood Pressure Monitoring

5.3.3. Ambulatory blood pressure monitory will be performed in all participants. Participants will receive an upper arm blood pressure monitor to wear for 24 consecutive hours. The device will record blood pressure at 15-minute intervals during the 24-hour monitoring period. After the collection periods concludes, the participant will return the blood pressure monitor in a pre-paid, pre-addressed mailer to their local study center.At-home and Wearable Sensors

Participants may also be asked to use other physiologic consumer-grade wearable or at-home sensors. These may include smartwatches, smart rings, sensor patches (worn on chest), under-mattress monitors, polysomnography devices, or on-demand ECG monitors. These devices are meant to monitor a variety of physiologic parameters such as activity, heart rate and rhythm, temperature, pulse oximetry, sleep, respiratory rate, and ballistocardiography to name a few.

The precise devices will be determined by availability and may be utilized in specific subgroups. All data from these devices will be transmitted to the Data Translation Center either via the HeartShare Eureka app or stored in the device for data download upon return.

6. STATISTICAL CONSIDERATIONS

6.1. Statistical Power Overview

We plan to enroll at least 1000 participants (and up to 2000 participants) in the HeartShare Deep Phenotyping Cohort (75% HFpEF, 25% age- and sex-matched individuals without HFpEF). The power calculations below are based on a sample size of 1000 participants. The power calculations below demonstrate that based on the minimal sample size of 1000 participants, we will have ample power to detect clinically significant differences between individuals with and without HFpEF and, additionally, among HFpEF subgroups.

6.2. Power Considerations

Assumptions: 80% Power, two-sided alpha (0.0005-0.01) accounting for multiplicity. Effect size = standardized mean difference. HFpEF subgroup analysis assumes equally sized subgroups (Table 3b, 4b). Sample size considerations accounting for multivariable modeling (i.e., control for confounders) incorporated an adjustment in sample size upward by a factor of $1/(1-R^2)$ – where R^2 is an estimate of the multiple correlation coefficient of group regressed on all other variables likely to be included in the model (i.e., how much of the variability between groups is explained by the confounding factors) (Table 4a, 4b).

Table 3a. Comparisons between HFpEF and non-HFpEF – no control for confounders

Power	HFpEF N	Control N	Effect Size	Alpha
0.8	750	250	0.316	0.0005
0.8	750	250	0.302	0.001
0.8	750	250	0.250	0.01

Table 3b. Comparisons between subgroups within HFpEF – no control for confounders

Power	HFpEF Total N	Number of Subgroups	Subgroup N*	Effect Size	Alpha
0.8	750	4	187	0.451	0.0005
0.8	750	4	187	0.430	0.001
0.8	750	4	187	0.355	0.01

Table 4a. Comparisons between HFpEF and nonHFpEF – assuming multivariable modeling (controlling for confounders)

Power	HFpEF N	Control N	R-squared	HFpEF N Inflated for Multivariable Modeling	Control N Inflated for Multivariable Modeling	Effect Size	Alpha
0.8	600	200	0.2	750	250	0.353	0.0005
0.8	600	200	0.2	750	250	0.338	0.001
0.8	600	200	0.2	750	250	0.279	0.01
0.8	490	175	0.3	750	250	0.381	0.0005
0.8	490	175	0.3	750	250	0.364	0.001
0.8	490	175	0.3	750	250	0.301	0.01

Table 4b. Comparisons between subgroups within HFpEF – assuming multivariable modeling (controlling for confounders)

Power	Sub-group N	R-squared	HFpEF Total N Inflated for Multivariable modeling	Number of Subgroups	Subgroup N Inflated for Multivariable modeling	Effect Size	Alpha
0.8	150	0.2	750	4	187	0.504	0.0005
0.8	150	0.2	750	4	187	0.482	0.001
0.8	150	0.2	750	4	187	0.397	0.01
0.8	131	0.3	750	4	187	0.540	0.0005
0.8	131	0.3	750	4	187	0.516	0.001
0.8	131	0.3	750	4	187	0.425	0.01

6.3. Overview of Statistical Methods

An overview of the statistical methods for the HeartShare Deep Phenotyping Study are presented here. Full details of the statistical methods are available in the HeartShare Manual of Procedures.

- **Aim 1:** To identify novel diagnostic, physiologic, imaging, and molecular markers that differentiate HFpEF from non-HFpEF. We will use standard methods for evaluating differences between cases (HFpEF) and comparators without HFpEF, including t-tests (or non-parametric equivalent, when indicated) for continuous variables and Chi-squared tests (or Fisher exact tests, when indicated) for categorical variables. We will also use linear, logistic, and Cox regression analyses (as indicated), adjusting for potential confounders including multiple hypothesis testing, to examine for statistically significant differences between cases and comparators.
- **Aim 2:** To investigate the underlying pathophysiological and biological determinants of previously identified HFpEF subtypes. Here we will use standard statistical approaches, comparing the previously identified HFpEF subtype to all other HFpEF patients using approaches similar to Aim 1 above. We will follow-up these analyses by bioinformatics analysis including clustering of multi-omic data to determine whether specific molecules and biological pathways are over-represented in the previously identified HFpEF subgroup vs. other types of HFpEF patients and comparators.
- **Aim 3:** To identify and enable external validation of novel HFpEF subtypes using unsupervised machine learning of deep phenotyping data, images, and multi-omics. Several types of unsupervised machine learning (unbiased pattern recognition) approaches, alone or in combination, can be used in a variety of ways in HeartShare to identify and validate novel HFpEF subtypes. For example, unsupervised ML (e.g., Bayesian model-based clustering) can be performed on deep phenotyping data, followed-up by identification of molecular pathways underlying each HFpEF subtype using multi-omics approaches. Alternatively, unsupervised ML can be applied directly to multi-omics data, and differences in deep phenotyping indices among the identified HFpEF subtypes can be evaluated. We will test whether a multimodal precision medicine approach could identify distinct HFpEF subtypes using both deep phenotyping and multi-omics data simultaneously using innovative machine learning approaches that integrate a multiple data types, such as dual autoencoders for meta-embedding (Dual-GAME) and hybrid nonnegative matrix factorization (HNMF), as described previously.[11,31-33]

6.4. Missing Data

Maximum efforts will be made to minimize missing data. When necessary, multiple imputation will be used to impute missing values in all variables included in the analyses.

7. PROTECTION OF HUMAN SUBJECTS

7.1. Potential Benefits

Participants may benefit from participation in the study as they will receive assessment of cardiovascular function and other organ function and information about their physical activity levels. With permission, these results can be shared with the participant's health care provider. Referrals to health care providers will be made, at the request of participants, in situations where participants do not have access to appropriate primary or specialty care. Study staff and if appropriate, physicians will respond to telephone calls from participants and their physicians regarding interpretation of the results provided.

7.2. Importance of Knowledge to be Gained

Understanding novel heart failure subtypes may result in advancements in precision medicine and targeted therapeutics for patients with heart failure.

7.3. Risks to Study Participants

7.3.1. Loss of Confidentiality

Only de-identified participant data are distributed for use in analyses. Participants will be distinguished by unique ID numbers that encode for clinic site. The key linking the participants' identifying information to their study number will be kept in protected files that require usernames, passwords and filenames and will exist only at the study site on a secure, encrypted computer.

7.3.2. Physical Examination

The physical examination procedures used in this study are low risk.

7.3.3. Questionnaires, Surveys, and Cognitive Testing

Questions may be sensitive in nature and may cause mental or emotional discomfort. Participants may refuse to answer any question that makes them feel uncomfortable.

7.3.4. Blood, Urine, Stool, and Saliva Sample Collection

Blood is drawn only by trained and experienced personnel via venipuncture and/or intravenous cannulation to minimize the discomfort and risks. Risks of drawing a blood sample are discomfort at the site of needle insertion, bruising, or inflammation at the site, and rarely, faintness or infection. Bruising, if it occurs, is usually painless and disappears within a few days. There are no known risks of urine, stool, or saliva sample collection.

7.3.5. Peripheral Arterial Tonometry

This procedure has no known risks other than a risk that during the 5 minutes when the blood pressure cuff is inflated, the participant may feel temporary discomfort.

7.3.6. Electrocardiography

The risks of electrocardiography can include skin irritation and a rash from the gel that is used or from wearing or removing patches that are used to conduct the measurements.

7.3.7. Arterial Tonometry

This procedure has no known risks other than temporary discomfort at the time of blood pressure cuff inflation.

7.3.8. Six-Minute Walk Test

Risks of this test include shortness of breath and chest tightness, and rarely, faintness or palpitations due to arrhythmias. We will guard against these by asking the participants questions before the test to determine whether it is safe for them to have this test. During the test, participants are closely monitored by study staff and the participant can stop and rest at any point during the test.

7.3.9. Short Physical Performance Battery (SPPB)

Risks of the SPPB include shortness of breath and rarely, lightheadedness or loss of balance. We will guard against these by asking the participants questions before the test to determine whether it is safe for them to perform this test. During the test, participants are closely monitored by study staff, and the participant can stop and rest at any point during the test.

7.3.10. Pulmonary Function Test

Participants may experience dizziness during the tests, coughing, feeling short of breath or feel lightheaded. These symptoms typically resolve shortly after the test is finished.

7.3.11. Cardiopulmonary Exercise Test

During exercise test, the patient may feel muscle soreness or fatigue, shortness of breath, abnormal blood pressure, or fainting. Rarely exercise can cause irregular heart rhythms, heart attack, stroke, or sudden cardiac death. Participants may become uncomfortable during the exercise test. It is expected that they will become tired and short of breath, and that the patient's blood pressure, heart rate, and other vital signs will change as a result of exercise. The risk of an adverse event occurring is the same or lower in the exercise laboratory as it would be if they exerted themselves elsewhere. Monitoring during exercise permits supervising staff to stop tests prior to when a patient may stop, which lowers the likelihood of an adverse event compared to the participants exercising at home on their own. Participants will be closely monitored throughout the entire period by individuals who are trained to respond if the aforementioned situations that might develop.

7.3.12. Cardiac MRI

During this test, participants will lie in a small, enclosed area inside a large magnetic tube. Some participants may be scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise. Participants who self-report claustrophobia will be excluded. Should a participant develop new claustrophobia or want the scan to be stopped for any reason, the technician will do so and remove the participant from the scanner.

The use of gadolinium-based contrast agents in patients who already have severely reduced kidney function (i.e., stage 4 or worse chronic kidney disease) is uncommonly (<0.07%) associated with a possibly fatal disease involving the skin, muscles, and internal organs. This disorder is called nephrogenic systemic fibrosis (NSF). Participants will have blood drawn to test their kidney function prior to the MRI and will be asked if they have any history of kidney problems. Deposits of gadolinium remain in the brain of some patients who have undergone MRI scans with gadolinium for a prolonged time after the last administration. Deposits of gadolinium have also been reported in skin and bone. The FDA determined that there is no evidence of long-term safety risk.

Metallic taste in the mouth, tingling in the arm, nausea, or headache occurs in less the 1% (less than 1 in 100) people. Insertion of the needle may also cause minor pain, bruising and/or infection at the injection site.

The dose and frequency of the contrast agent given to participants will be standardized. We do not expect any additional risk to be posed beyond those already described above. Participants

should avoid receiving additional gadolinium within 24 hours before or after the dose given in this research study.

7.3.13. Echocardiography

There are no known risks associated with using ultrasound waves to image the heart. Some individuals may experience some mild pressure, discomfort, and/or irritation from the transducer on the chest. The patient may also experience a cool or wet feeling from the gel applied to the chest. The risks of the exercise portion of the test are listed above in section 7.3.10.

7.3.14. Computed Tomography

The cumulative radiation exposure from the CT scan is considered small and is not likely to adversely affect the patient. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to a participant's risk of injury or disease. Before a participant decides to enter this study, patients will be asked about their past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment. The radiation exposure from one CT scan is approximately equal to 1.8 years of background radiation. The scan will be reviewed for findings that may have a major impact on the patient's health, such as cancer. These findings may cause worry, additional medical testing, and, potentially, cost.

7.3.15. Skeletal Muscle and Adipose Tissue Biopsies

The potential risks of the muscle tissue and fat tissue collection is a risk of pain from the local anesthesia, bruising and bleeding (hematoma), infection, cutaneous anesthesia from cutting a subcutaneous sensory nerve for the muscle tissue collection (<1%); the latter is almost always temporary but occasionally can become permanent. The procedures are well tolerated when performed by properly trained staff, which will be required for this study. Participants may be asked to stop or reduce their blood thinner(s) if they take them (for example, anti-platelet therapy or anticoagulation therapy) during the week leading up to a study muscle biopsy procedure. Stopping or reducing anti-platelet therapy or anti-coagulation therapy during this week may increase risk of a heart attack or stroke. These requests will be reviewed with the caring physician to minimize any risk. If risk is considered clinically unacceptable, the biopsy will be cancelled for medical reason.

7.3.16. Ambulatory Blood Pressure Monitoring

Wearing an ambulatory blood pressure monitor is considered to be low risk. The participant may feel some pressure when the blood pressure cuff inflates and may experience some discomfort while trying to sleep while wearing the cuff.

7.3.17. Genetic Research

The genetic research risks to participants are loss of confidentiality and re-identification. Prior to being included in any genetic research analysis, participants will have given written informed consent. To maintain participant confidentiality and to prevent genetic data from being linked to the identity of the participant, biospecimens will be deidentified prior to any genetic analysis. Only the collecting site will have the link between associated PHI and the genetic samples. Each site will store this linking information in a secured environment with restricted access.

7.4. Adequacy of Protection Against Risks

Approval to proceed with the HeartShare deep phenotyping protocol will be sought from the Institutional Review Board (IRB) at each study site. We anticipate this to be a low to moderate risk observational study. Participants for this study will be provided with an Informed Consent document, and written consent will be obtained from each participant prior to enrollment. We will follow existing Health Insurance Portability and Accountability Act (HIPAA) privacy regulations

with regards to personal health information. The investigators of this project will not utilize study data to identify specific persons.

8. REGULATORY CONSIDERATIONS

8.1. Institutional Review Boards (IRBs)

After approval by the HeartShare Steering Committee (comprised of the HeartShare Steering Committee Co-chairs, NHLBI program staff, and principal investigators of the HeartShare Data Translation Center and Clinical Centers) and the HeartShare Observational Study Monitoring Board, the Principal Investigator of the HeartShare Data Translation Center will submit this protocol to the IRB of record and will forward to the NHLBI a copy of the written and dated approval by the IRB. Clinical Center PIs will submit reliance agreements at their sites to their local IRBs to get approval for the study. The study (study number, protocol title and version number), the documents reviewed (protocol, informed consent form, and other study-related materials such as recruitment tools) and the date of the review will be clearly stated on the written IRB approval letter. During the study, any amendment or modification to the protocol will be sent to the IRB for approval. The IRB will also be informed of any event likely to affect the safety of participants or the continued conduct of the study, in particular any change in safety and all updates to the protocol will be sent to IRB.

8.2. Data Management, Confidentiality, and Ownership of Data and Biospecimens

All data and biospecimens will be maintained in secure locations. Data and biospecimens collected from study evaluations will be identified by study identification codes. Identifying features, including names and addresses will be known to the clinical center, but will not be provided to the Data Translation Center at Northwestern University. The study will be conducted in compliance with applicable International Council for Harmonization (ICH) guidelines, the ICH E6 Good Clinical Practice guideline, and regulations, guidelines, and applicable laws of the local site where the study is conducted. The study will be conducted with the approval of a duly constituted IRB in accordance with the requirement of US regulation Title 21 Code of Federal Regulations (CFR) Part 56-Institutional Reviews Boards. The nature and risks of the study will be fully explained to each participant, and written consent obtained in accordance with the requirements of 21 CFR 50-Protection of Human Subjects. Participants will be informed of their rights, including the right to withdraw from the study at any time.

Use of study data and biospecimens, and resulting findings, during the HeartShare study are subject to approval of the HeartShare Steering Committee and must follow guidelines of the HeartShare Publications and Ancillary Study Committee. The data and biospecimens from participants at the HeartShare Clinical Centers are the property of the HeartShare study and are under the custody of the enrolling center.

8.2.1. Data Security

The consent form signed by the participant will provide written assurance that all individual data collected in the study will be kept confidential to the extent provided by the Privacy Act of 1974 and by the Health Insurance Portability and Accountability Act (HIPAA). Each center which has data with personal identifiers will provide file security so that confidential data are not released. Specifically, participants will be informed that: (1) the only people who will know that they are research participants are members of the research team, authorized members of the workforce at the clinical center and, if appropriate, their physicians or health care providers; (2) no individual identifying information about them will be disclosed to others, except as part of ascertainment of events information, as permitted by the consent form, or if required by law; and (3) when the results of the study are published or discussed in conferences, no information will be included that would reveal their identity. All research staff at the Data Translation Center and

at each site will be required to provide proof of biomedical research training (e.g., CITI certification) prior to conducting any study-related procedures. All data will be password protected and encrypted at each site, and at the Data Translation Center. Authorization of access to all study-related data will be provided by each site principal investigator (for data that resides at the site) and by the Data Translation Center (for all data that resides centrally.

8.2.2. Quality Control

All study procedures and data will undergo quality control and quality assurance as outlined in the central core laboratory Manual of Procedures for each central core laboratory for each study procedure. In general, steps to ensure quality control include (1) central training of site staff conducting each procedure; (2) a checklist to ensure study procedure completeness that each core laboratory completes upon receipt of studies; (3) feedback to sites when quality of submitted studies is sub-optimal; (4) corrective action plan for sites who do not meet quality control metrics; and (5) assessment of inter- and intraobserver variability, and measurement drift, at regular intervals throughout the study at each core laboratory.

Quality assessment of data transmitted from sites to the Data Translation Center HeartShare REDCap database will be conducted using multiple methods. Sites will be asked to confirm whether the summaries provided are consistent with summaries they generate using their native data sets. Discrepancies will be resolved in monthly phone calls and formally tracked in a change log for each cohort and variable. These summaries and graphical displays will also be used to identify outliers and potential errant values. Range, logic and consistency checks will also be programmed, run and reviewed for all harmonized variables. The second approach to quality assessment of harmonized data will be via upload to an internal quality assessment REDCap database established expressly for purposes of harmonization. Data dictionaries will be independently constructed in the REDCap environment to complement the developed CDEs. When data harmonization for a subset of variables has been completed by the HeartShare Data Management Core and reviewed by contributing sites, bulk upload of the data for these variables to REDCap will be attempted. If values remain in the harmonized data set that do not comply with the data dictionary, e.g. if a categorical variable has values that are not included in the REDCap data dictionary, data upload will fail and errors will be noted. This approach will provide an independent check of successful harmonization across all cohorts. Furthermore, the REDCap data dictionary will provide a straightforward approach to streamlining CDM/CDEs for distribution through the HeartShare Data Portal.

8.2.3. Data/Specimen Handling

The data and biospecimens are transmitted to the HeartShare Data Translation Center (or designee) and cannot be moved to another institution unless approved by the HeartShare Steering Committee; for example, if the Principal Investigator of the center moves to another institution. At the conclusion of the HeartShare study, the data and remaining biospecimens will be transferred to a HeartShare-specified biobank and/or to the NHLBI Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) biobank and will become the property of one of these organizations. Future researchers may request data or biospecimens from a biobank with approval following the guidelines of the biobank. Only study identifiers (and no personal health information) will be included with deposited data and specimens. Data will be stored at the Data Translation Center and in BioData Catalyst. Specimens will be stored at the HeartShare biospecimen core laboratory at the University of Vermont. Data and specimens will be stored indefinitely. Only investigators approved by the Data Translation Center will have access to data and specimens. Site staff are responsible for transmission of data and specimens; the Data Translation Center staff (or designee) will be responsible for receipt of data and specimens. Data will only be transported electronically using secure, encrypted methods. Specimens will be shipped by standard shipping service providers.

Very detailed (de-identified) information about participants' genetic information will be stored centrally in the secure NHLBI BioData Catalyst computing resource, where it will be shared with other investigators for research. This information and all of participants' other data will be used by researchers to look for genes that provide better understanding of why heart failure develops and how it can be better treated. The stored information is de-identified, which means that identifying information such as the participant's name, date of birth, address, etc., is removed. The HeartShare Data Translation Center will control access to this stored information. The Data Translation Center is committed to protecting the confidentiality of all the information it receives, but will also comply with relevant laws, which might include Freedom of Information Act (FOIA) requests for deidentified information. Other researchers that are not part of HeartShare may request access to these de-identified samples or data. This access is handled by the Data Translation Center according to approved policies and procedures.

8.3. Informed Consent

See Section 3.4 above for details about the informed consent process. The site investigator, or a person designated by the site investigator, will fully inform the participant of all pertinent aspects of the study including the review of the IRB-approved informed consent form. All study procedures and potential risks will be discussed in detail with each participant. The Informed Consent Form (eConsent) will be signed and personally dated by the participant prior to the commencement of any study procedures. All participants will receive a copy of the informed consent form. Non-English speaking consent forms will be made available as needed. Electronic copies of the signed eConsent forms will be retained at each study site.

8.4. Adverse Events

All adverse events occurring within the HeartShare study evaluations (baseline or other visits) will be recorded and reported, starting at the beginning of the Deep Phenotyping baseline visit, and continuing for a 48 hour period after the in person testing has been completed. For patients participating in multiple in person study visits (e.g., for optional biopsy procedures or annual follow up visits), adverse events occurring during the 48 hours following each testing epoch will also be evaluated for and reported.

- **Adverse event:** An adverse event (AE) shall be considered any detrimental change in the patient's condition.
- **Anticipated adverse event:** Anticipated adverse events are defined for each of the protocol procedures in the sections specifically written for those procedures.
- **Unanticipated adverse event:** Any adverse event that results in risk or harm to the participant or others that differs from the known, predicted possible effects of the research protocol. An unanticipated adverse event is one that varies in nature, intensity, or frequency from information in the informed consent document.
- **Serious adverse event:** Any event that results in death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- **Monitoring of adverse events related to the study:** The occurrence of an AE may come to the attention of study personnel during study visits or telephone interviews or by a patient presenting for medical care. The AEs that are expected from participation in the study are given in the consent form.

8.5. Notification and Referral for Study Findings

One of the benefits of the study to the participants will be the provision of an extensive battery of medical tests at no cost to them. This information will be made available to the participant and their health care provider if desired. An initial report will summarize results available at the completion of the study visit, such as height, weight, and blood pressure. This report will be given to the participant at the end of the examination or mailed to the participant 1-2 weeks after the examination. A second report will be mailed within one month after the clinic visit and will include routine laboratory results (e.g., plasma glucose, lipids, and serum creatinine). A third report will be mailed 1-2 months after the completion of the examination and will include results of additional tests or procedures. Participants and their physicians (or health care providers) will be immediately notified as soon as potentially serious medical problems are identified during any of the examinations. A referral system will be established based on the urgency of the need for medical attention, as defined in section 8.6.

8.6. Incidental Findings

All study-related procedures, in particular the imaging studies described above, may reveal clinically important incidental findings. Guidelines for handling incidental findings are outlined by the central core laboratory for each study-related procedure in the core laboratory's Manual of Operations. In general, each central core laboratory will have a pre-defined list of incidental findings that require (or may require) clinical follow-up. Each site principal investigator will be responsible for clinical follow-up of incidental findings that may require medical attention. All site staff conducting study-related procedures will be notified of the list of actionable incidental findings. Incidental findings will be categorized as immediate referrals (medical emergencies which require immediate notification of both the participant and his/her primary physician due to the life-threatening nature of the incidental finding); urgent referrals (abnormalities which may require medical attention, but not on an emergency basis); and alerts (medical findings that may have adverse health consequences to the participant if left untreated, but do not qualify as immediate or urgent referrals).

8.7. Observational Safety and Monitoring Board (OSMB)

The OSMB was established by the NHLBI in accordance with NIH policies and is responsible for monitoring of patient safety and review of study performance. The OSMB consists of a chair, clinicians or scientists with expertise in heart failure, bioethics, and biostatistics. An NHLBI scientist other than the NHLBI's Project Scientist serves as the Executive Secretary to the OSMB. The OSMB meets at regular intervals (at least twice per year) and at other times as necessary, as described in the HeartShare OSMB charter. The purpose of monitoring is to (1) verify that the rights and well-being of human participants are protected; (2) ensure that the reported study data are accurate, complete, and verifiable from source documents; and (3) ensure that the conduct of the study is in compliance with the currently approved protocol/amendment, with Good Clinical Practices, and with applicable regulatory requirements. We do not anticipate more than minimal to moderate risk for all study procedures, and there is no intervention involved in the HeartShare study.

8.8. Conflict of Interest Management

All HeartShare Steering Committee co-chairs, Principal Investigators, committee members, working group members, and key personnel are required to submit written Conflict of Interest (COI) Disclosures to the HeartShare Data Translation Center. COI will be reviewed and updated annually and whenever new protocols, products, or services are considered or relationships with new entities are considered by the HeartShare study. A record of all COI forms will be kept on file at the Data Translation Center.

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APPENDIX

Surveys administered via Eureka

Supplementary Table 1. Surveys to be completed by participants using Eureka (or study coordinator phone call) prior to or at the baseline visit.

Survey	Notes
Basic demographics	
Height and weight	
Medical conditions	
Medication inventory	
Social demographics	
Family history	
Pregnancy history	In females only
Hospitalization survey	
KCCQ-12	KCCQ = Kansas City Cardiomyopathy Questionnaire (health status survey)
Self-assessed NYHA class	NYHA = New York Heart Association
FRAIL scale	Frailty screening survey
PROMIS Cognitive Survey	
Epworth Sleep Quality Survey	
TAPS-1 and TAPS-2	Tobacco, Alcohol, Prescription Medication, and Other Substance Use surveys
CES-D (10-question version)	CES-D = Center for Epidemiologic Studies Depression Scale
STOP-BANG	Obstructive sleep apnea screening survey participants who do not have a history of obstructive sleep apnea
CPAP survey	In participants who use CPAP (continuous positive airway pressure device)
Symptom survey	Includes Rose Angina survey and Modified Medical Research Council (MMRC) Dyspnea survey
Seattle Angina Questionnaire	In participants with a history of coronary artery disease or those who report chest pain
AF Severity Scale	In participants with a history of atrial arrhythmias or those who report palpitations (AF = atrial fibrillation)
Palpitations Survey	In participants who report palpitations
Calgary Syncope Survey	In participants who report syncope

Supplementary Table 2. Surveys to be completed monthly using Eureka or by phone (study coordinator interview).

Survey	Notes
3-question HF survey	Weight, MMRC dyspnea scale, and edema
Hospitalizations survey	Includes Eureka geolocation-based query of hospitalization

Supplementary Table 3. Surveys to be completed every 6 months (or annually, as indicated) by participants using Eureka or by phone (study coordinator interview).

Survey	Notes
Weight	
Medical conditions*	
Medication inventory	
Hospitalization survey	
KCCQ-12	KCCQ = Kansas City Cardiomyopathy Questionnaire (health status survey)
Self-assessed NYHA class	NYHA = New York Heart Association
FRAIL scale*	Frailty screening survey, only done annually
PROMIS Cognitive Survey*	
Epworth Sleep Quality Survey*	
TAPS-1 and TAPS-2*	Tobacco, Alcohol, Prescription Medication, and Other Substance Use surveys
CES-D (10-question version)*	CES-D = Center for Epidemiologic Studies Depression Scale
STOP-BANG*	Obstructive sleep apnea screening survey participants who do not have a history of obstructive sleep apnea
CPAP survey*	In participants who use CPAP (continuous positive airway pressure device)
Symptom survey	Includes Rose Angina survey and Modified Medical Research Council (MMRC) Dyspnea survey
Seattle Angina Questionnaire*	In participants with a history of coronary artery disease or those who report chest pain
AF Severity Scale	In participants with a history of atrial arrhythmias or those who report palpitations (AF = atrial fibrillation)
Palpitations Survey	In participants who report palpitations**
Calgary Syncope Survey	In participants who report syncope**

*Only done annually
*Only triggered once, not repeated if already previously triggered