Biomarkers in Medicine

A peripheral blood transcriptome biomarker test to diagnose functional recovery potential in advanced heart failure

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Heart failure (HF) is a complex clinical syndrome that causes systemic hypoperfusion and failure to meet the body's metabolic demands. In an attempt to compensate, chronic upregulation of the sympathetic nervous system and renin-angiotensin-aldosterone leads to further myocardial injury, HF progression and reduced O_2 delivery. This triggers progressive organ dysfunction, immune system activation and profound metabolic derangements, creating a milieu similar to other chronic systemic diseases and presenting as advanced HF with severely limited prognosis. We hypothesize that 1-year survival in advanced HF is linked to functional recovery potential (FRP), a novel clinical composite parameter that includes HF severity, secondary organ dysfunction, co-morbidities, frailty, disabilities as well as chronological age and that can be diagnosed by a molecular biomarker.

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional cardiovascular disorder that causes systemic hypoperfusion and failure to meet the body's metabolic demands. HF affects 6 million persons and is a major public health concern due to its tremendous societal and economic burden with an estimated cost in the USA of US$37 billion in 2009, expected to increase to US$97 billion by 2030 [1,2]. HF is initiated by various myocardial injury mechanisms. Despite chronic neurohormonal upregulation in order to maintain a compensated state, further myocardial injury leads to HF progression, resulting in overall catabolic/anabolic imbalance, secondary organ dysfunction (OD), cardiac cachexia, iron-deficiency anemia and frailty. This triggers immune system activation that coincides with progressive dysfunction of the kidneys, liver, bone marrow, brain and metabolism, creating a milieu similar to other chronic systemic diseases [3,4], clinically presenting as advanced HF (AdHF) with severely limited prognosis.

Outcomes are dependent on chronological age (CA) and multiple other factors jointly called the 'Personal Biological Age (PBA)'. According to the Economist Special Report on 8 July 2017 [5], "For most of history humans lived only long enough to ensure the survival of the species. Today babies born in the West can expect to see their grandchildren have children." However, at any given CA, there are great biological disparities and great heterogeneity in health outcomes [6,7].

This discrepancy relates to a difference in the potential of individual persons to recover from stressors that we termed the functional recovery potential (FRP), or in equivalent term, the probability of functional recovery. Our central postulate is that FRP integrates the clinical composite including CA as well as PBA (primary and secondary organ failure, co-morbidities, frailty, disabilities; Figure 1).

AdHF patients with low FRP may be at increased risk for death before AND after AdHF therapies such as mechanical circulatory support (MCS) or heart transplantation (HTx). Recently, we reported that preoperative differential gene expression profiles (GEP) of peripheral blood mononuclear cells (PBMC) are predictive of early
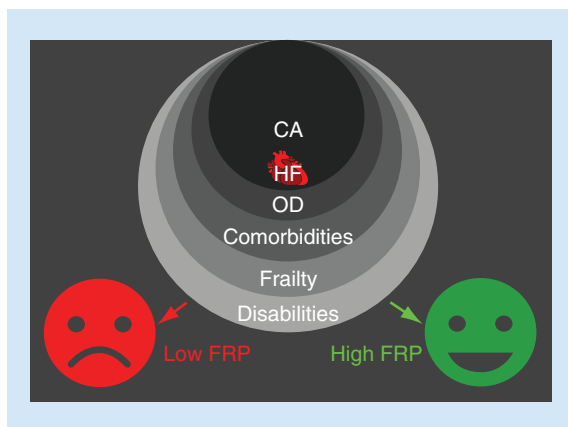
Future Medicine

Figure 1. Functional recovery potential is an novel integrated clinical parameter, defined as a clinical composite parameter that includes chronological age as well as personal biological age, measurable by established and validated heart failure, secondary organ dysfunction, co-morbidities, frailty and disability instruments. Functional recovery potential (FRP) represents the instantaneous potential of the person with advanced heart failure (AdHF) to cope with stressors such as AdHF surgical/interventional therapies and is a surrogate parameter for a long-term survival benefit. Heart failure severity tools include HFSS, Seattle Heart Failure Model and University of California Los Angeles scores. Organ dysfunction severity tools include Sequential Organ Failure Assessment and Model of Endstage Liver Disease Except INR scores. Co-morbidity burden tools include Society of Thoracic Surgeons and EuroSCORE. Frailty tools include the FRIED scale. Disabilities can be measured by the Activities-of-Daily-Living scale. A high FRP is defined as the composite score improving after AdHF interventions. A low FRP is defined as the composite score not improving after AdHF interventions. Our central postulate is that the FRP can be diagnosed, i.e. that functional recovery can be predicted, by a molecular biomarker.

postoperative outcomes in AdHF patients undergoing MCS. We defined FRP outcomes as changes of Sequential Organ Failure Assessment (SOFA) and Model of Endstage Liver Disease except INR (MELD-XI) scores from preoperatively to 8 days postoperatively, which correlate with long-term mortality [8].

Here, we hypothesize that FRP is a generalizable and clinically useful concept and can be:

- Defined as a person's potential to return to a functional life after stressor exposure;
- Modulated by long-term bio-psychosocial interventions;
- Characterized within a general clinical framework integrating CA and PBA data;
- Quantitatively described;
- Used as a surrogate for long-term outcome prediction;
- Diagnosed from prestressor molecular data.

Incorporating these molecular data in the clinical encounter can improve the quality of the decision-making in a shared decision-making process and help achieve the value-based healthcare goals of optimizing 1) patient experience, 2) morbidity and mortality outcomes and 3) health system cost–effectiveness.

In this Perspective article, we discuss the biomedical foundation and potential clinical utility of FRP in HF medicine.

AdHF outcomes in high-risk AdHF patients

During the last five decades, HF outcomes have improved with medical management [1,2,9]. However, patients with stage D, or AdHF, often cannot tolerate optimal medical management by guideline-directed medical therapy (GDMT) and do not derive the same benefit as patients with less advanced disease [10]. Older patients may not derive the same benefit as younger patients [11].

It has been suggested that biomarker-guided therapy could improve outcomes over solely GDMT [12]. We are interested in developing a biomarker to assist the clinician in predicting long-term outcomes after AdHF surgical/interventional therapies.

Table 1. Summary of advanced heart failure intervention studies with inclusion criteria, sample size and major outcomes: across the different interventions, the 1-year mortality rate is in the range of 10–30%.

Study (year)	Inclusion	Patients	Intervention	Outcome/comments	Ref.
Petrie *et al.* (2016)	LVEF <35%	1212	CABG	More than 67-year equipoise GDMT versus CABG at 10 years	[13]
Holmes *et al.* (2015)	STS 7%	12,182	TAVR	1-year mortality 23%	[17]
Leon *et al.* (2010)	STS >15–50%	2032	TAVR	1-year mortality 30%	[18]
Smith *et al.* (2011)	STS >10–15%	699	TAVR	1-year mortality 24%	[19]
Leon *et al.* (2016)	STS >4-8%	2032	TAVR	1-year mortality 12%	[20]
Whitlow *et al.* (2012)	STS ≥12	78	MitraClip	1-year mortality 24%	[21]
Chiarito *et al.* (2018)	LVEF 39–59%	2615	MitraClip	1-year mortality 16%	[22]
Tung *et al.* (2015)	LVEF 31%	2061	VT ablation	1-year mortality 12%	[23]
Vakil *et al.* (2017)	LVEF 30%, >70 years	681	VT ablation	1-year mortality 15%	[24]
Vergara *et al.* (2017)	LVEF 34%, ES	677	VT ablation	1-year mortality 20%	[25]
Kirklin *et al.* (2017)	LVEF low	17,633	MCS	1-year mortality 20%	[26]
Lund *et al.* (2017)	LVEF low	21,614	HTx	1-year mortality 10–15%	[27]

CABG: Coronary artery bypass surgery; ES: Electrical storm; GDMT: Guideline directed medical therapy; HTx: Heart transplantation; LVEF: Left ventricular ejection fraction; MCS: Mechanical circulatory support; STS: Society of Thoracic Surgeons estimated surgical mortality risk (%); TAVR: Transcatheter aortic valve replacement; VT: Ventricular tachycardia.

Outcomes in AdHF patients undergoing revascularization

AdHF patients undergoing high-risk percutaneous coronary intervention

The benefits or harms of percutaneous coronary intervention in populations with AdHF are unknown because of a lack of randomized trials date [13].

AdHF patients undergoing high-risk coronary artery bypass surgery

In the Surgical Treatment for Ischemic Heart Failure Study trial, a total of 1212 patients with an left ventricular ejection fraction (LVEF) of less than 35% were randomly assigned to undergo coronary artery bypass surgery (CABG) plus medical therapy or medical therapy alone [14,15]. In the Surgical Treatment for Ischemic Heart Failure Extended Study trial, the median duration of follow-up was 9.8 years. There was a trend toward a smaller reduction in all-cause mortality with CABG compared with GDMT in older compared with younger patients, implying that an improved understanding of the efficacy of CABG in different age groups is needed [13,16]. This result is consistent with recent HF trials [11]. Since there were few patients in the older age groups, the true long-term benefit may be even lower. In other words, there is equipoise between GDMT and CABG in patients more than 67 years with HF with reduced ejection fraction [13] (Table 1).

Outcomes in AdHF patients undergoing valve interventions

AdHF patients undergoing transcatheter aortic valve replacement

Following the initial transcatheter aortic valve replacement (TAVR) experience [18,19] (Table 1), mortality in US clinical practice at 1-year follow-up was 23.7%. It is "imperative to focus on better prediction of the overall risks and benefits of the procedure, particularly given the existing co-morbidities of the group of patients being considered for TAVR" [17]. In a systematic review on TAVR outcomes, 46.4 and 51.6% of deaths were related to noncardiovascular causes within and after the first 30 days, respectively [28]. In the intermediate-risk TAVR trial [20] (Table 1), the guideline for patient inclusion was a Society of Thoracic Surgeons (STS) risk score [29] and EuroSCORE [30], based on the presence of coexisting illnesses to predict mortality at 30 days, between 4 and 8% [31]. The main results showed that TAVR was not inferior to surgery with respect to outcomes at 2 years (death from any cause or disabling stroke).

Per 2017 recommendations, the risks of death and morbidity associated with the natural history of severe aortic valve stenosis need to be weighed against the risk related to aortic valve replacement as a basis for recommendation of treatment [32,33]. TAVR is not recommended in patients in whom existing co-morbidities would preclude the expected benefit from correction of aortic stenosis (AS) [34].

AdHF patients undergoing MitraClip

The overall mortality rate after surgical repair of functional mitral regurgitation (FMR) ranges from 20 to 50% [35–37]. MitraClip therapy is an emerging option for selected high-risk patients with FMR [38,39]. The High Risk Study, an arm of the EVEREST II trial, enrolled symptomatic patients with 3+ to 4+ mitral regurgitation (MR) for whom surgical risk for perioperative mortality rate was estimated to be ≥12%, using the STS calculator [40,41]. Potentially qualifying criteria included high-risk patients with porcelain aorta, mobile ascending aorta atheroma, postmediastinal radiation, functional MR with LVEF less than 40%, age older than 75 years with LVEF less than 40%, previous median sternotomy with patent bypass graft(s), more than two previous chest surgeries, hepatic cirrhosis or ≥3 of the following STS high-risk criteria: creatinine level more than 2.5 mg/dl, previous chest surgery, age older than 75 years or LVEF less than 35% [21] (Table 1). A significant number of patients with symptomatic MR have extensive co-morbidities or uncertain indications for surgery and are defined as high surgical risk, inoperable or not indicated for surgery, and approximately one-half of patients with symptomatic severe MR may not undergo surgery. In a recent MitraClip meta-analysis, 1-year mortality rate was 16% (408/2498) and similar among groups in patients with FMR versus degenerative mitral regurgitation. The authors conclude that better patient selection and performing percutaneous edge-to-edge repair at earlier stage could avoid treatment of those patients with advanced LV remodeling, more than severe MR and many co-morbidities, who benefit less from the procedure [22] (Table 1).

Per 2017 American College of Cardiology (ACC)/American Heart Association (AHA) recommendations, transcatheter mitral valve repair may be considered for severely symptomatic patients (New York Heart Association [NYHA] class III–IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe co-morbidities and remain severely symptomatic despite optimal GDMT for HF [32].

Outcomes in AdHF patients undergoing ventricular tachycardia interventions

AdHF patients undergoing internal cardioverter defibrillator device therapy

Patients with stage D HF are at increased risk of sudden cardiac death from ventricular tachycardia (VT), thus antiarrhythmia device therapy is an integral part of their management. Introduction of internal cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death was proven to be of great benefit with reduction in mortality of 31% in 20 months in patients with history of myocardial infarction and left ventricular ejection fraction (EF) less than 30% [42]. Furthermore, in patients with EF less than 35% regardless of etiology and mild-to-moderate symptoms, ICD implantation decreases mortality by 23% over 5 years [24].

ACC/AHA HF guidelines recommend ICD implantation in all patients with ejection fraction of less than 30% and NYHA class I symptoms and in those with EF less than 35% with NYHA Class II and III symptoms [2]. However, this therapy is reserved for patients with projected survival of more than 1 year, which precludes some of the patients with very advanced disease from receiving an ICD. In octogenarians who are due for an ICD, careful thought should be given to the current clinical status, co-morbidities and general frailty prior to considering them for the procedure [43]. Goldenberg *et al.* highlighted a U-shaped relationship between the severity of HF and mortality benefit from ICD therapy [44].

AdHF patients undergoing biventricular pacemaker device therapy

Cardiac resynchronization therapy (CRT) in patients with wide QRS complex and Left Bundle Branch Block (LBBB) pattern has led to improvement of ventricular contractility and EF, reduction in secondary mitral regurgitation, reversal of remodeling and decrease in mortality. However, around 30% of individuals receiving this therapy derive no benefit or experience worsening of their symptoms [45]. Similar to ICD, patients with stage D HF are often considered to be too sick to benefit from CRT and therefore their treatment is limited to advanced therapies (MCS and Htx) or palliative care [2].

AdHF patients undergoing VT-ablation therapy

VT-ablation therapy has increased in the USA, specifically in patients with worsening clinical risk profile including age and co-morbidity burden [46]. In a contemporary registry, catheter ablation of VT in patients with structural heart disease results in 70% freedom from VT recurrence, with an overall transplant and/or mortality rate of 15% at 1 year. Patients who died or underwent transplant were older and had higher rates of hyperlipidemia, diabetes mellitus, atrial fibrillation, chronic kidney disease, AdHF, ICD, CRT, lower EF, electrical storm (ES), shocks, amiodarone and ≥2 antiarrhythmic drugs. In the Cox multiple regression frailty analysis, transplant or

death was associated with older age, NYHA class III and IV, chronic kidney disease, ES and use of hemodynamic support devices [23] (Table 1). The International Ventricular Tachycardia Center Collaborative Study Group registry of 2061 patients who underwent VT ablation analyzed survival of patients ≥70 years with and without VT recurrence. Of 681 patients, 92% were men, 71% had ischemic VT and 42% had VT storm at presentation. LVEF was 30 ± 11%. Compared with patients less than 70 years, patients ≥70 years had higher 1-year mortality (15 vs 11%; p = 0.002) [24] (Table 1). Patients with ES are among the highest-risk VT populations because they are frailer, older, with a lower LVEF, more AdHF status and more co-morbidities. A comprehensive approach needs to include not only the arrhythmia ablation but also careful treatment of the co-morbidities, such as AdHF, hypertension, hyperlipidemia, atrial fibrillation, diabetes and chronic kidney disease [25]. A major challenge of VT ablation is hemodynamic intolerance of the induced arrhythmia, with as few as 10% of induced arrhythmias being stable. Short-term hemodynamic support such as percutaneous temporary ventricular support devices (e.g., Impella®) and extracorporeal membrane oxygenation (ECMO) will be increasingly used in this scenario [47]. The challenge is to predict a prohibitively high risk of not being able to wean the patient from veno-arterial (VA)-extracorporeal membrane oxygenation postinterventionally.

Outcomes in AdHF patients undergoing MCS/HTx
AdHF patients undergoing MCS
MCS devices, originally used for patients with AdHF as a bridge-to-transplant or bridge-to-recovery, now increasingly used as destination (lifelong) therapy, have the potential to outnumber HTx by a factor of 1:10 [26]. Because of this success, destination MCS is increasingly being offered to patients with challenging clinical profiles. There is significant patient-to-patient variability for risk of adverse events. Overall survival continues to remain more than 80% at 1 year and 70% at 2 years [26] (Table 1).

AdHF patients undergoing HTx
Since its first introduction in 1967, HTx offers an unparalleled survival benefit in select patients with stage D HF, and remains the gold standard of treatment. Stage D HF is defined as refractory HF and often accompanied by the following parameters: repeated (>2) hospitalizations or emergency department visits for HF in the past year, worsening renal function, unintentional weight loss more than 10% (cardiac cachexia), intolerance to medical therapy due to hypotension and/or worsening renal function, persistent dyspnea/fatigue, hyponatremia and escalating use of diuretics (>160 mg per day and/or use of supplemental metolazone therapy) and frequent ICD shocks.

Annually, there are approximately 3000 HTx performed in the USA and the number of donors have remained steady for decades. Current graft survival rates with advances in immunosuppressive therapy are 85–90%, 75–80% and 70–75% in adults at 1-, 3-, 5-year, respectively, and a median survival of 11–13 years. Internationally, contemporary median survival after adult HTx is 10.7 years [27] (Table 1).

ACC/AHA guidelines designate a class I indication for HTx only in carefully selected patients with stage D HF despite GDMT, device and surgical management. The leading cumulative causes of death are graft failure, infection, cancer and multiple organ failure.

Limitations of current clinical outcome prediction tools in AdHF
Outcome prediction in AdHF
The role of risk stratification of patients with stage D HF or AdHF in a value-based healthcare framework is to predict which subset might benefit from AdHF therapies to improve outcomes related to the individual patient including mortality, morbidity and patient experience as well as to optimize healthcare delivery system outcomes such as cost–effectiveness. Risk stratification and subsequent outcome prediction as well as therapeutic recommendation-making needs to be based on the comparative survival benefit rationale [48,49]. Several clinical parameters have been associated with increased mortality in HF. Risk models can be useful in predicting outcomes. A robust model needs: to have the power to discriminate (i.e., to correctly risk stratify patients); to calibrate (i.e., to show agreement between the predicted and observed risk); to be applicable to the general population; and to provide good external validation [50]. The ability to predict preoperatively this risk for the individual patient before AdHF surgical/interventional therapies and the impact of this risk on the associated long-term survival prognosis would be a very important component of clinical decision-making and management. Currently, we have our validated clinical biomarkers and algorithms [51–66] for AdHF and organ failure risk prediction.

Limitations of outcome prediction in AdHF

Peak VO$_2$ has been found to be a prognostic predictor of survival and is often used as initial screen to identify patients with AdHF [67]. Low peak VO$_2$ consumption is an indicator of poor heart function and VO$_2$ max ≤14 ml/kg per minute is a criteria for heart transplant consideration. However, Peak VO$_2$ may be influenced by several confounding factors such as age, gender, motivation, anemia, bodyweight and muscle deconditioning. Seattle Heart Failure Model (SHFM) and Heart Failure Survival Score (HFSS) are widely used risk stratification models. SHFM uses 20 convenient clinical parameters. The most important limitation of the SHFM is that it does not include the role of major co-morbidities that may independently impact prognosis [45]. HFSS utilizes only seven parameters including peak VO$_2$ measurement. A head-to-head comparison of HFSS and SHFM shows modest correlation [10]. A limitation in this comparison study was that it was a retrospective analysis of clinical and cardiopulmonary exercise data collected at a single center and that patients unable to exercise because of respiratory disorders, arrhythmias, angina, musculoskeletal disease, neurologic disorders or frailty were excluded [68]. The suitability of the UCLA HF risk model that provides simple prognostic information in both men and women with AdHF using four common clinical variables: BNP, peak VO$_2$, NYHA class and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [59] as a selection tool for MCS and HTx is limited and high-risk discrimination was poor in an external validation cohort [56].

Outcome prediction in valve diseases

The STS score [29] (http://209.220.160.181/STSWebRiskCalc261/de.aspx; www.sts.org/riskmodels) and EuroSCORE (www.euroscore.org) [30] are often used to risk-stratify patients undergoing surgical aortic valve replacement (SAVR)/TAVR in connection with research [18–20,69–72]. The EuroSCORE II and the STS score discriminate high- and low-risk surgical patients and show better calibration than EuroSCORE I to predict postoperative outcome after valvular surgery [33,73,74]. Valvular heart diseases such as aortic stenosis (AS) and mitral regurgitation (MR) are often associated with HF, which in turn increases patients' STS score. A high STS score means the patient is at high risk for perioperative 30-day mortality during SAVR and mitral valve repair/replacement.

Limitations of outcome prediction in valve diseases

It is not uncommon for the risk score and actual mortality rate to differ significantly in cohorts of TAVR patients [75]. The STS score has well-characterized limitations in predicting surgical risk in elderly patients with AS undergoing valve replacement, particularly in terms of calibration [76,77].

A multidimensional prognostic index on the basis of comprehensive geriatric assessment was shown to outperform traditional risk scores in a cohort of elderly HF patients [78] and similar indices are beginning to be tested in elderly TAVR patients [79–81]. A multidimensional score has been proposed to predict a poor clinical outcome at 6 months after TAVR defined as death, the Kansas City Cardiomyopathy Questionnaire less than 45 (comparable to NYHA functional class IV), or a decrease of 10 points in the Kansas City Cardiomyopathy Questionnaire from baseline [82].

Outcome prediction in MCS

MCS such as durable left ventricular assist device (LVAD) is an alternative AdHF therapy, which can be used as a bridge-to-transplantation (BTT) or as destination therapy (DT). If seen as a part of a continuum of AdHF therapy, the question arises if LVAD therapy needs its own separate-risk prediction model. The answer largely lies on the intrinsic nature of the device and the complications encountered with LVAD, namely the tight balance between bleeding risk and clotting risk. Several MCS predictive models have been proposed.

One of the often used risk scores was the Destination Therapy Risk Score, which was developed as part of a US FDA-mandated postmarket surveillance of the pulsatile flow HeartMate XVE. However, the Destination Therapy Risk Score provides poor discrimination for BTT patients and only modest discrimination for DT patients supported with continuous flow LVADs [83]. The Interagency Registry for Mechanically Assisted Circulatory Support classification system, while not designed as a predictive model, has been used to classify patient risk according to preoperative clinical acuity with reasonable prognostic discrimination. HeartMate Risk Score (HMRS) was derived from clinical trial patients enrolled in the HeartMate II in BTT and DT clinical trials and a simple clinical prediction rule based on patients' age, international normalized ratio, albumin, creatinine and the implant center's volume [60]. HMRS has been validated using the Interagency Registry for Mechanically Assisted Circulatory Support database. Among 10,847 patients, the HMRS exhibits moderate discrimination in both, short-term 90-day and long-term

2-year mortality. Relative risk of 90-day mortality is 2.8-times greater with patients in the highest HMRS category compared with those in the lowest HMRS category (13.0 vs 4.7%; p < 0.001).

Limitations of outcome prediction in MCS

HMRS excluded more severely ill patients who required acute MCS, other than an intra-aortic balloon pump [60]. Models that include more severely ill patients generally rely on patient demographics and various biomarkers of organ function. Although the models have shown utility in predicting which patients have a greater risk of harm from an LVAD, they do not account for sarcopenia (degenerative loss of skeletal muscle mass and a component of the frailty syndrome), cachexia (prognostically unfavorable catabolic state as consequence of advanced systemic illness and a component of the frailty syndrome) or other core components of frailty [84].

Rationale for an integrated clinical outcome parameter

Secondary OD severity & outcomes

The above outcome prediction tools center around the primary organ function (i.e., heart) status. However, AdHF is a systemic syndrome with multiorgan involvement and mandates a multidimensional risk prediction paradigm (Figure 1). Multiorgan dysfunction (MOD) syndrome is one of the leading causes of morbidity and mortality. It is associated with grossly aberrant immune activation. Preoperative HF-related immunologic impairment is a component of poor outcomes after MCS and HTx, owing to the known associations between increased age, T-cell and innate immune cell dysfunction, frailty, increased numbers of terminally differentiated T cells, immune senescence (deficient replicative ability) and immune exhaustion (impaired antigen response) [85]. The prevention and correction of OD represents a therapeutic target of interest in AdHF and strategies that specifically prevent, reduce or reverse OD remain to be identified and evaluated to determine if such interventions impact mortality, morbidity and patient-centered outcomes [86].

Co-morbidities & outcomes

The Charlson co-morbidity index is a score widely used as an adjustment variable in prognostic models in chronic diseases, since co-morbidity is an independent predictor of all-cause mortality in various cardiovascular disorders, including HF [45,87].

Frailty & outcomes

Frailty has been defined as enhanced vulnerability [84] to stressors because of impairments in multiple, interrelated systems that lead to decline in homeostatic reserve and resiliency and as a physiological decline in multiple organ systems, decreasing a patient's capacity to withstand the stresses of surgery and disease. The so-called 'eyeball test' or 'foot of the bed test' has served for decades as the mainstay of frailty assessment [84]. Important areas for further research in the frailty concept include disability, cognitive and mood disorders.

Over 20 different metrics have been developed to define and measure frailty. There is no universally accepted definition for frailty. The most extensively validated tool is the Fried Frailty Index [88]. The frailty index [89] has served as basis for a frailty-deficit index screening tool that, since it incorporates 31 components, is difficult to use [84,85]. A recent marker for sarcopenia and frailty is psoas muscle size, as assessed by computed tomography (CT) [90]. A brief 4-item scale outperformed other frailty scales in TAVR patients [91]. An intricate relationship exists between frailty and depression [92].

Numerous publications have looked at frailty longitudinally in general populations: characterizing frailty transitions [93–95], examining potential predictors of transitions, testing interventions to limit worsening frailty, and comparing static versus dynamic frailty measures to predict functional decline including in cohorts with cardiovascular disease [89,96]. Exercise training may be beneficial in frail older adults [97]. A subset of frail patients may be responsive to MCS and will continue to thrive, whereas another groups may not [58]. In patients undergoing DT-LVAD, there was a more than threefold increased risk of death in patients in the highest frailty tertile [85]. In approximately half of older adults with AdHF who were frail before LVAD implantation, frailty had decreased 6 months after implantation [98]. Fitness-associated biological age seems a more robust determinant of outcomes than CA [99]. A growing body of evidence links renal dysfunction with frailty.

Inversely related to the concept of frailty are the concepts of resilience and fitness. Resilience is defined as the ability to recover from adverse effects of a stressor [100]. A 3-month resilience training program affects neurohormonal systems by modulating gene expression [101]. It is unclear how helpful specific interventions such as nutritional

supplements are [102]. Physical fitness has been defined as 'the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies' [103].

Studies of frailty in HF have concentrated on elderly populations, including those being considered for invasive interventions, such as TAVR, ICD and DT-LVAD therapy [85,104–106]. Symptoms of AdHF overlap considerably with the manifestations of frailty, including weakness, exercise intolerance, fatigue, exhaustion and cachexia [84,105,107–109]. HF-related frailty and cardiac cachexia are similar if not the same phenotype [110,111]. In AdHF, tissue wasting and cardiac cachexia have been associated with upregulation of the inflammatory biomarkers IL-1 and IL-6, C-reactive protein and TNF-α [112], T-cell and innate immune cell dysfunction [58,85,113], increased numbers of terminally differentiated T cells [114], immunosenescence and immune exhaustion [115,116].

Frailty in the general population has been shown to be independently predictive of falls, hospitalization, institutionalization and mortality [117] and adverse outcomes in older surgical patients [118] including SAVR/TAVR [119]. TAVR, in contrast to SAVR, where frailty strongly predicts periprocedural complications, [120], may be less physiologically stressful. Nevertheless, frail patients are three- to fivefold less likely to survive up to 1 year of follow-up [79–81]. In a recent TAVR study, 1-year mortality rates were very low in nonfrail patients and steadily worsened along with increasing frailty [121,122].

Limitations of current frailty concepts

Few studies have focused on frailty as a primary outcome and described it over time in cardiovascular patients [89,96,123]. There is a compelling need for a novel frailty tool that can reliably quantify and monitor frailty over time and accurately predict outcomes in patients with AdHF [84]. In DT LVAD, the ideal frailty measures would be novel markers (patterns of sarcopenia, hormone levels or biomarkers of immune function) that could specifically measure noncardiac frailty, but currently no such measure exists [58].

Disabilities & outcomes

Disability is defined as inability or dependency to carry out activities essential for independent living, such as dressing or eating (termed activities of daily living [ADL]), taking medications or managing finances (termed instrumental ADL [IADL]). Frail patients are at risk to develop disability in later stages, although to some authors, the two entities are not interchangeable [124,125]. By other authors, impairments in the ADL have been conceptualized as manifestations of frailty [119]. Approximately half of disability in older adults develops chronically and progressively in association with underlying severity of disease, co-morbidity and frailty; the other half develops acutely or catastrophically, in association with acute clinical events, such as hip fracture or stroke [125,126].

Functional recovery potential

Based on our hypothesis that AdHF is a systemic syndrome with multiorgan involvement and mandates a multidimensional risk prediction paradigm, we define FRP (Figure 1) as a person's potential to respond to a stressor with recovery. FRP is related to all domains of predictive variables including primary organ failure, secondary OD, co-morbidities, frailty, disabilities and CA.

We postulate underlying immunological mechanisms for FRP that may constitute final common pathways. We postulate that reduced FRP is related to the age-associated decline in immune function, referred to as immunosenescence, is well-characterized within the adaptive immune system, and in particular, among T cells. Exercise might exert an anti-immunosenescence effect, perhaps delaying the onset of immunological aging or even rejuvenating aged immune profiles, based on evidence that exercise is a powerful stimulus of immune function [127,128]. It is likely that the cumulative effect of behavior over a substantial period of the lifespan influences the rate of immunosenescence [127,129].

Outcome prediction biomarker prototype
Proof-of-principle-heart failure molecular test

In our proof-of-principle outcome prediction biomarker prototype study [8], our central postulate is that OD and patient death after MCS or HTx surgery results from innate and adaptive immune cell dysfunction. Therefore, our goal was to use leukocyte immune-biology information to develop a preoperative test, which would precisely predict postoperative outcomes in the individual AdHF patient. We utilized the widely accepted SOFA [64] and MELD-XI [61,65,66] scores as quantitative assessment tools to interpret the PBMC data and to develop a predictive

leukocyte biomarker. We specifically hypothesized that one of the most significant clinical outcome parameters for AdHF patients undergoing MCS is the probability of organ function improvement from 1 day before to 8 days after surgery. Therefore, patients were grouped into two organ failure risk strata: Group I = improving (both SOFA and MELD-XI scores improve from day -1 to day 8) and Group II = not improving (SOFA and/or MELD-XI score[s] do not improve from day -1 to day 8). In other words, if the MCS surgery improves the hemodynamic situation without complications, then the patient's organ function is expected to recover by postoperative day 5 and clearly by postoperative day 8, which should be reflected in a concordant improvement of SOFA and MELD-XI score, from day -1 to day 8. On the other hand, if SOFA or MELD-XI, or both, scores do not improve from day -1 to day 8, we hypothesize that this problem may potentially impact long-term survival. We hypothesized that in AdHF patients undergoing MCS surgery, HF-related preoperative PBMC GEP correlates with and predicts changes of early postoperative organ function status as surrogates for 1-year survival. Our studies showed that the set of 28 patented genes [130] derived from preoperative PBMC GEP is predictive of early postoperative improvement or nonimprovement of SOFA and MELD-XI scores. Out of the 28 preoperative genes, 12 genes were of specific biological interest due to their overlap in differentiating not only early postoperative organ function improvement but also year-1 survivor status [8]. We interpret the hypothetical biological role of the 12 overlap genes as follows: *BATF2* activation in Group II is due to its attempts to repair the cell necrosis-mediated damage caused by OD. This hyperactivation leads to exhaustion of adaptive immunity cells, which may explain the protracted time course to death in Group II patients. For *RHBDD3*, while downregulation in patients with rheumatoid arthritis, ulcerative colitis and Crohn's disease may be beneficial in preventing autoimmune aggression, its downregulation in AdHF patients undergoing MCS surgery might exacerbate an inappropriate innate inflammatory response and inappropriate adaptive immune incompetence via a less inhibitory effect on the IL-6 pathway. Furthermore, it is interesting to note that upregulation of genes, such as *ANKRD22*, *FRMD6* and *KIR3DL2*, and downregulation of genes, such as *TIMP3*, *SAP25*, *NAPSA* and *TIMP*, are associated with a worse prognosis in cancer, and are also associated with a worse prognosis in AdHF. This raises the question about common pathways in both clinical syndromes.

Our data suggest that the preinterventional dynamic recovery potential, rather than the static parameter of 'severity of OD', is the key prognostic property to restoring equilibrium after surgery. This also presents the possibility of using a preoperative blood sample to identify AdHF patients who may have a high chance of early postoperative recovery and a potentially good long-term prognosis. If the preoperative blood test result predicts a high FRP (Group I), this data might lead to the recommendation to undergo surgery. If the preoperative blood test suggests a low FRP (Group II), the healthcare team may avoid a potentially harmful recommendation of surgery at that time. In the USA, we estimate that out of 30,000–60,000 individuals per year with AdHF and potential candidates for MCS and other AdHF-surgical/interventional therapies, at least 7500–15,000 might not benefit from undergoing the intervention based on the test results if they are too sick at the time of testing. Since HF is a major public health concern due to its tremendous societal and economic burden, with estimated costs in the USA of US$37.2 billion in 2009 and with expectations to increase to US$97.0 billion by 2030, our proposed prediction test would simultaneously allow to tailor high-tech modern medicine to the individual patient's needs, in other words, optimize personal morbidity and mortality benefits and personal experience while also enhancing cost–effectiveness in the US healthcare. This concept would contribute to the advancement of high-value healthcare and reduction of low-value healthcare.

Outcome prediction biomarker pivotal trial strategy

It is important for the patient to choose the therapeutic option with the best short-, medium- and long-term outcome. In order to do so, the doctor needs to be able to predict, from preintervention data of the patient, what the consequences of the different options are. First and foremost, this means that all available pre-intervention data need to be analyzed for their long-term outcome prediction capacity. None of the current established clinical scoring and prediction tools integrate immune function parameters [51–55,57–61,64–66,131–136]. They have the tendency to be imprecisely calibrated in estimating risk among severely ill patients [56,57], making the therapeutic recommendation with the best survival estimate for the individual patient very difficult. Therefore, we intend to develop a molecular blood test that predicts, from pre-intervention data, recovery of organ function and frailty reversal, which, in turn, predict 1-year survival. This information will help tackle the following challenge for the individual patient and doctor: we specifically hypothesize that a molecular blood test, based on a PBMC GEP sample taken 1–3 days before scheduled surgical/interventional therapies for AdHF, can assist clinicians in more precisely diagnosing FRP,

in other words, predicting functional recovery, as a surrogate marker for 1-year survival and help the patient and clinician in the shared decision-making process to choose the most meaningful treatment option.

Developmet sequence: Analytical and clinical validity study, FDA-clearance, clinical implementation, clinical utility study

We plan to complete an FDA-clearance Pivotal Trial with ≥1000 AdHF patients, stratified for four primary HF mechanisms (ischemic, overload, arrhythmia, dyscontractility). After completion of this clinical validity study of developing the test in a framework of diagnosing the potential of future organ function recovery and frailty reversal, FDA clearance and clinical implementation, we plan to conduct a clinical utility trial, testing the impact of adding the test information to the best current clinical prediction tools of net health outcomes as we did with the AlloMAP™ test development [137,138]. We plan to make this test commercially available, likely using the Nanostring platform that has already been used for an FDA-cleared *In vitro*-Diagnostic Multivariate Index Assay test.

Biomarkers in the practice of shared decision-making

It is critical to have a multidisciplinary heart team to provide expertise to make the best recommendation regarding the individual patient's anticipated benefit [139]. It is important for these teams to get comfortable with the decision to not pursue the most aggressive option available in patients for whom the anticipated benefits do not outweigh the risks. The decision not to offer specific AdHF surgical/interventional therapies should not be equated with abandoning care [140]. Shared decision-making requires both the patient and the provider to share information, work toward a consensus and reach agreement on the course of action [141] consistent with the patient's preferences [142]. As we work on technological innovations to improve the devices, we must also use it responsibly within a framework of care that enables shared decision-making and promotes patient goals and wellbeing [140].

Conclusion

One-year survival in AdHF is linked to FRP, a novel clinical composite parameter that includes HF severity, secondary organ dysfunction, co-morbidities, frailty, disabilities as well as CA and that can be diagnosed by a molecular biomarker.

Future perspective

We will tailor the molecular test precision medicine results to a high-quality relational medicine [143] encounter to maximize its humanism and effectiveness. The clinical decision-making challenge at the time of AdHF evaluation often culminates in the choice between everything modern medicine has to offer and palliative care. This ultimate scenario is medically, ethically and economically demanding. It deserves the best evidence-based decision-making support that personalized precision medicine research has to offer in order to live up to the highest humanistic expectations that society entrusts us with.

Over the next decade, this vision of a meaningful practice of modern medicine will increasingly incorporate the elements of molecular precision medicine with relational medicine, promoting high-value healthcare over low-value healthcare. We envision the development of similar biomarkers to predict FRP in sepsis, liver failure, lung failure and kidney failure. The monetary incentives have all been implemented in the US healthcare system and are already taking effect. In order to achieve these goals, future generations of healthcare professionals will be trained to pursue a practice that allows them to achieve these goals.

Executive summary

The growing heart failure epidemy & outcomes in advanced heart failure
- Heart failure (HF) affects 6 million persons and is a major public health concern in the USA.
- Advanced HF (AdHF) triggers progressive dysfunction of the kidneys, liver, bone marrow, brain and metabolism with immune system activation and severely limited prognosis.
- Across the different AdHF interventions, the 1-year mortality rate is in the range of 10–30%.

Limitations of current clinical outcome prediction tools in AdHF
- The role of risk stratification and risk prediction in AdHF in a value-based healthcare framework is to predict who might benefit from AdHF therapies to optimize patient experience, patient outcomes and health system cost–effectiveness.
- Current prediction tools have limited calibration in AdHF patients.

Rationale for an integrated clinical outcome parameter
- Outcomes are dependent on chronological age but also on multiple other factors, including severity of HF severity and secondary organ failure, co-morbidities, frailty, and disabilities.
- We jointly conceptualize these clinical factors as potential to recover from stressors termed the functional recovery potential (FRP).
- AdHF patients with low FRP may be at increased risk for death before AND after AdHF therapies.
- There is a compelling need for a novel prediction tool that can reliably quantify and monitor our novel integrated clinical FRP and accurately predict outcomes in patients with AdHF undergoing various AdHF interventions in a personalized precision medicine paradigm.
- Preintervention molecular biomarker data can assist in diagnosing FRP and improve the quality of the decision-making between the patient and healthcare team in a shared decision-making process.

Outcome prediction biomarker prototype & pivotal trial strategy
- A set of 28 patented genes derived from preoperative peripheral blood mononuclear cell gene expression profiles is predictive of early postoperative functional recovery and year-1 survivor status in AdHF patients undergoing mechanical circulatory support surgery.
- We plan to complete a US FDA clearance Pivotal Trial with ≥1000 AdHF patients, stratified for four primary HF mechanisms (ischemic, overload, arrhythmia, dyscontractility).

Biomarkers in the practice of shared decision-making
- We will implement the molecular test precision medicine results into a high-quality relational medicine encounter practice to maximize its effectiveness.
- Our proposed prediction test allows to optimize personal morbidity and mortality benefits and personal experience while also enhancing cost–effectiveness in the US/global healthcare, thereby decreasing low-value healthcare and increasing high-value healthcare.

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