

“Multidimensional Molecular Biomarkers In Advanced Heart Failure – Reviewing the MyLeukoMAP™ Hypothesis Rationale”

Galyna Bondar Ph.D.¹, Martin Cadeiras M.D.^{1*}, Nicholas Wisniewski Ph.D.¹, Azadeh Esmaceli, Giovanni Godoy[?], Eleanor Chang¹, Maral Bakir¹, Sophie Kupiec-Weglinski[?], Tra-Mi Bao[?], Josephine Hai[?], Robin Yee[?], Amy Li, Miki Rai[?], Desai Chu[?], Dan Tran[?], Liliana Madrigal[?], Ryan Togashi[?], Peipei Ping Ph.D.¹, Elaine Reed Ph.D.¹, Mario Deng M.D.^{1,2}

Author affiliations:

¹University of California Los Angeles, Los Angeles, CA, United States

Address for correspondence:

Mario Deng, MD FACC FESC
Professor of Medicine
Advanced Heart Failure/Mechanical Support/Heart Transplant
David Geffen School of Medicine at UCLA
Ronald Reagan UCLA Medical Center, 100 Medical Plaza Drive, Suite 630
Los Angeles, CA 90095
Email: mdeng@mednet.ucla.edu
Phone (Patients/Clinic): 310 825 9011; Phone (Research/Academic/Admin): 310 825 3035, Fax: 310 825 9013.

ABSTRACT

This review develops the hypothesis that in patients with advanced heart failure (AdHF) accurate longitudinal clinical phenotype assessment and leukocyte transcriptome/phenome modeling allows the development of a multidimensional molecular biomarker (MMB)-predictor of “progression/death on optimal medical management (OMM) in heart failure with reduced ejection fraction (HFrEF)” termed MyLeukoMAP™ which provides a better comparative survival benefit prediction of AdHF treatment options than by clinical predictors alone.

Key Words: heart failure, mechanical circulatory support device, multiorgan dysfunction, whole blood, peripheral blood mononuclear cells, gene expression profiling

Funding: Funding for the MyLeukoMAP™ pilot study phase was obtained by Columbia University NIH SCCOR Grant (PI Rose, Co-PI Deng), UCLA NIH R21 (PI Deng), UCLA R01 (PI Weiss, Joint PI Deng), UCLA R01 (PI Ping, Co-I Deng), UCLA DOM and Columbia University (Geier, Milo, Tocco) and UCLA patient philanthropy (Mulder).

Comment [Av1]: Kindly add affiliation details for author 2 and also add details for the authors where (?) is assigned.

THE GROWING EPIDEMIC OF HEART FAILURE

In the United States, heart failure (HF) affects 6 million persons (**Yancy 2013**). HF with reduced ejection fraction (HFrEF) affects 3 million people. The lifetime risk of developing HF is 1 in 5 for men and women older than 40 years of age. The death rate remains unacceptably high at approximately 50% within 5 years from the time of index diagnosis. In the US, an annually estimated 300,000 persons are diagnosed with Stage D heart failure, also classified as AdHF (**Hunt 2009**). Patients with this etiology may benefit from therapies such as long-term, lifetime or destination therapy such as mechanical circulatory support (MCS, approx. 30,000) or heart transplantation (HTx, approx. 3,000) **in lieu of** optimal medical management (OMM) or palliative/hospice care (PC). HF is a major public health concern due to its tremendous societal and economic burden, with an estimated direct and indirect costs in the U.S. of \$37.2 billion in 2009, which is expected to increase to \$97 billion by 2030 (**Roger 2012**). While 25% of all spending occurs during the last year of life (**Orszag 2008, Zhang 2009**), in patients hospitalized with HF, more resource spending is associated with lower mortality rates (**Ong 2009**). A key question is: Which of these therapies does a healthcare provider recommend to the individual AdHF-patient in order to tailor personal benefits in the most cost-effective way?

PREDICTION OF DISEASE PROGRESSION IN ADHF

While in Stage C HF guideline-based

medical therapy is well established, the **comparative** benefit of OMM, MCS, HTx or PC in Stage D HF is not as well defined. This ambiguity suggests unpredictability of clinical trajectories, even with current clinical prediction tools tailored to the progressive clinical **trajectory** of HF severity and HF-related organ dysfunction (OD). Such models include Brain Natriuretic Peptide (BNP) measurements (**Troughton 2000, Gardner 2003, Doust 2003**), the Heart Failure Survival Score (HFSS) (**Aaronson 1997**), Seattle Heart Failure Model (**Levy 2006, Ketchum 2010**), MAGGIC score (**Sartipy 2014**), Frailty Scores (**Martinez-Selles 2009, Flint 2012**), INTERMACS Score (**Smits 2013, Kirklin 2014**), UCLA score (**Chyu 2014**), Sequential Organ Failure Assessment (SOFA) Score (**Vincent 1996**), HeartMate II risk score (**Cowger 2013**), Model of End-stage Liver Disease (**Matthews 2010**), Model of End-stage Liver Disease Except INR (MELD-XI) Score (**Abe 2014**) and right ventricular failure score (**Kormos 2010**). However, most validated prediction tools have the tendency to underestimate risk among the most severely ill patients. (**Sartipy 2014**). Due to the uncertainty of predicting Stage D HF progression, what is the impact of this lack of accuracy on individual patients' health and healthcare costs? Can adding leukocyte biomarkers to clinical predictors alone achieve an improved prediction of risk associated with each treatment option and ultimately an improved prediction of risk reduction when choosing one treatment option over another treatment option, i.e. an improved prediction of comparative survival benefit from

Comment [Av3]: It seems that the noun benefit might better combine with other adjectives than comparative.

Consider using one of the following relative similar

Comment [Av4]: The word trajectory appears repeatedly in this text.

Consider using a synonym in its place. path

Comment [Av2]: The phrase in lieu of may be wordy. Consider changing the wording. in lieu of → instead of in place of

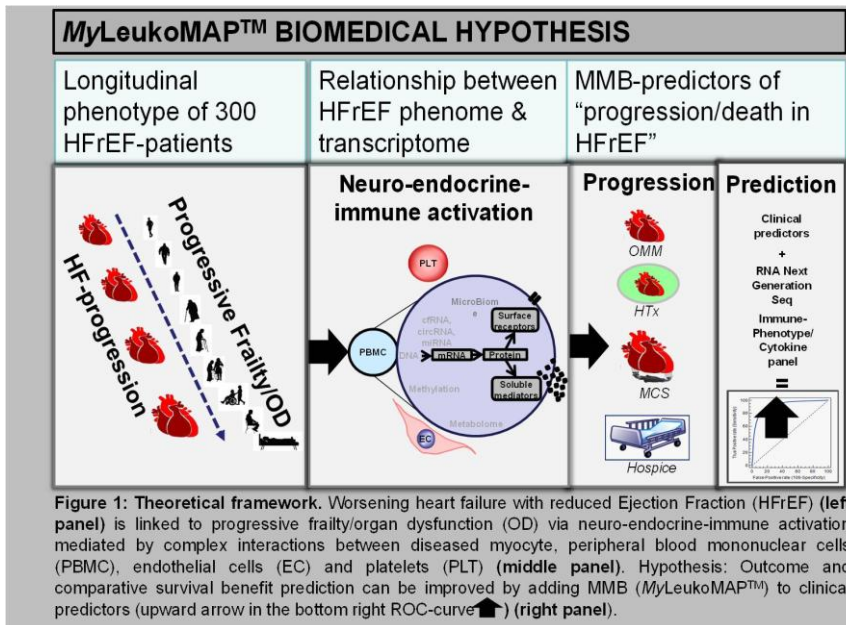
interventions in AdHF-patients suffering from HFrEF?

THE LINK BETWEEN THE DISEASED HEART MUSCLE IN ADHF, NEURO-ENDOCRINE ACTIVATION, AND INFLAMMATORY LEUKOCYTE BIOLOGY

For more than 25 years, the associations between diseased heart muscle, neuro-endocrine activation, and inflammatory leukocyte biology have been well-established (**Levine 1990, Deng 1996, Deng 1996, Deng 1997, Caruso 2010, Caruso 2012, Kaur 2009, Soejima**). For example, higher levels of the proinflammatory and cachectogenic cytokine tumor necrosis factor (TNF) correlate with more severe AdHF, as indicated by extreme weight loss and cachexia. Since TNF is produced by leukocytes called monocytes which mediate innate immunity, this suggests involvement of innate immunity in the pathophysiology of HF (**Levine 1990**). A more pronounced inflammatory response after HF-related surgery is linked to worse outcomes in HF (**Mann 2002, Braunwald 2012**) and other heart disease conditions (**Deng 1996, Caruso 2010, Deng 1995**). Additionally, more pronounced degrees of OD mediate the severity of such disease (**Caruso 2010**). In critical illness and injury situations, immunological activation is characterized by virtually global leukocyte transcriptome changes and aberrant leukocyte activation or suppression (**Rittirsch 2008**).

THE ROLE OF SERIAL PERIPHERAL BLOOD MONONUCLEAR CELL GENE EXPRESSION PROFILING IN ADHF

Circulating peripheral blood leukocyte populations continuously survey tissues and blood (**Matzinger 2007**) and thus sense the functional state of the heart under various conditions of HF (**Yndestad2002, Cappuzzello 2009, Sinha 2010, Bondar 2014**), coronary artery disease with in-stent restenosis (**Ganesh 2011**), hypertensive heart disease (**Gerling 2013**) and other organs in a coordinated manner. Blood leukocytes can be easily monitored to assess the state of various tissues and can provide diagnostic information. Gene expression profiling (GEP) of peripheral blood mononuclear cells (PBMC) has been used to understand the underlying physiology and improve diagnostic tools (**Deng 2014, Deng 2014**). PBMC GEP has been helpful to characterize the systemic inflammatory response syndrome (SIRS) following intravenous endotoxin administration in healthy individuals. Since this experiment is not replicable on animals or human cell lines, it had to be conducted in human subjects. In one study, healthy individuals injected with endotoxin showed significant gene expression changes as opposed to healthy control subjects injected with placebo. Over half of injected subjects' gene transcripts were immediately down-regulated, while a smaller number of genes showed a delayed response. All these genes returned to baseline after 24 hours (**Calvano 2005**).



Inflammation is also prevalent in many other diseases such as AdHF, heart transplant rejection, and in MOD following trauma (Laudanski 2006). The factors that are involved in the establishment and regulation of the PBMC phenotype in critical illness are complex and regulation of gene expression occurs at multiple levels, including transcriptome, proteome and metabolome (Ping 2009, Singer 2007).

The Deng UCLA research lab has a longstanding interest, in the context of the expanding global epidemic of heart failure, in translational systems biology, systems medicine, health systems development, and Personalized Medicine and is positioned at the intersection of the immune and cardiovascular systems. The MyLeukoMAP™ project focusses on a translational research question: How can one

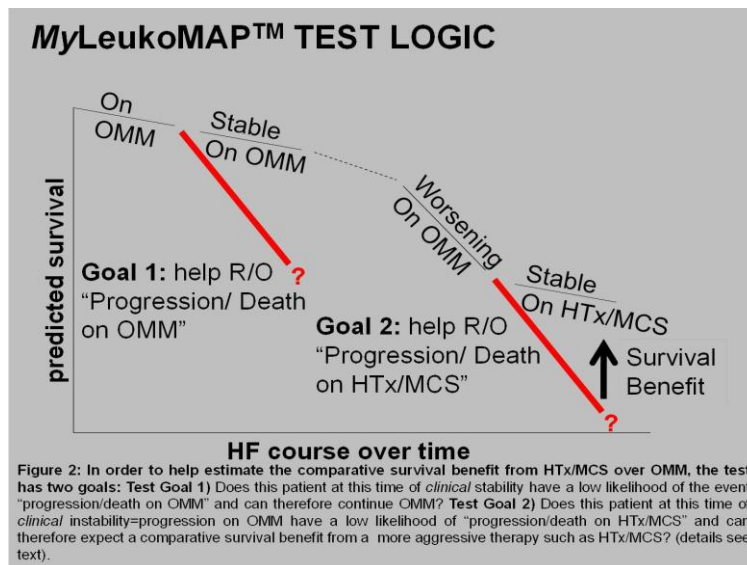
better understand the mechanisms of HF while incorporating current scientific knowledge and interpretive abilities to predict the best treatment option for a given heart failure patient at a particular timepoint (Figure 1) Over the last 20 years, from past contributions at Stanford University, Muenster University and Columbia University, the Deng Lab has co-developed the conceptual translational framework and first diagnostic and prognostic leukocyte (PBMC-GEP) biomarker test in transplantation medicine. This test gained US-FDA-regulatory clearance and international evidence-based medicine guideline acceptance to rule out rejection without invasive biopsies (Deng 1995, Deng 1995, Deng 1998, Deng 2006, Pham 2010, Deng 2014).

COMPARATIVE SURVIVAL BENEFIT RATIONALE FOR *MyLeukoMAP*TM TEST DEVELOPMENT

Based on this success, the NIH-United States Critical Illness and Injury Trials (USCIIT) Group invited the Deng lab in 2008 to expand this work to develop a similar PBMC-GEP biomarker test to better understand HF-related frailty and OD, diagnose and predict outcomes, and treat HF-related OD which was named *MyLeukoMAP*TM. This test is expected to predict more precisely comparative survival

benefit (**Deng 2000**) of HTx/MCS over OMM than current clinical tests alone.

As a long-term vision, this new genomic blood test will assist the HF-specialist in recommending the best treatment option (OMM vs. HTx/MCS) to an individual patient for the best outcome. Following the path of the successful AlloMapTM heart transplant rejection rule-out test, it is expected that *MyLeukoMAP*TM addresses two test goals of clinical utility (**Figure 2**).



Goal 1: Is OMM for a patient at a particular timepoint best recommended because of a low likelihood of progression/death on OMM? To assist in the clinical decision-making, a rule-out test with a high negative predictive value would be helpful to achieve this goal. If *MyLeukoMAP*TM confirms the clinical impression of a low likelihood of

progression/death on OMM, and, therefore, no expected survival benefit from HTx/MCS, then OMM continues until the next encounter and the test is repeated.

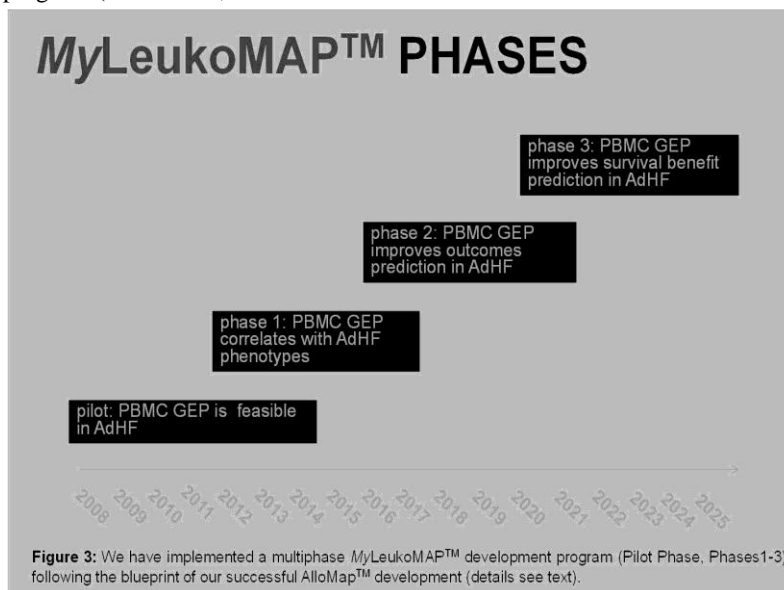
Goal 2: If either the clinical data or *MyLeukoMAP*TM suggest an elevated likelihood of progression/death on OMM, more aggressive therapies such as HTx/MCS are considered over PC. Next, the

following question must be answered: Is HTx/MCS for a patient at a particular timepoint best recommended because of a low likelihood of progression/death on HTx/MCS? To assist in the clinical decision-making, a rule-out test with a high negative predictive value would again be helpful. **If the test confirms a low likelihood of progression/death on HTx/MCS in contrast to OMM, HTx/MCS is recommended.** However, if either the clinical data or test suggests a high likelihood of progression/death on HTx/MCS and no sign of risk reduction under OMM (no survival benefit expected), PC is recommended.

MyLeukoMAP™ TRANSCRIPTOMIC BIOMARKER DEVELOPMENT PHASES

A multiphase MyLeukoMAP™ development program (Pilot Phase, Phases1-

3) (**Figure 3**) achieves this long-term goal. The MyLeukoMAP™ Pilot study, completed in 2014, tested the hypothesis that PBMC GEP is feasible in AdHF patients (**Sinha 2010, Bondar 2014**). MyLeukoMAP™ phase 1 that is currently testing the hypothesis that PBMC GEP correlates with AdHF phenotypes is expected to conclude in 2017. MyLeukoMAP™ phase 2 that will be testing the hypothesis that PBMC GEP is improving outcome prediction precision over clinical predictors alone in AdHF patients suffering from HFrEF is currently being organized. MyLeukoMAP™ phase 3, based on the multidimensional molecular biomarkers (MMB) generated in phase 2, will be testing the hypothesis that PBMC GEP is improving survival comparative benefit prediction over clinical predictors alone in AdHF patients suffering from HFrEF.



MYLEUKOMAP™ PILOT STUDY PHASE HYPOTHESIS: PBMC-GEP IN ADHF IS FEASIBLE

The MyLeukoMAP™ Pilot study, completed in 2014, tested the hypothesis that **PBMC GEP is feasible in AdHF patients**. In preparation to develop the MyLeukoMAP™ test based on the overall project hypothesis that the interaction between altered leukocyte and endothelial cell biology in hypoperfused organs and tissues has the potential to worsen organ dysfunction and further activate the immune system, leading to uncontrolled systemic inflammatory response, MOD and death, it has been demonstrated that this approach of multiparametric immune monitoring to elucidate this conundrum is feasible (**Deng 1995, Deng 1996, Deng 1999, Plenz 2001, Li 2006, Cadeiras 2011**).

Implementation of genome-wide molecular diagnostics was made possible by microarray technologies. Integrative genomics and systems biological methodologies provided the basis for the development of a new generation of molecular tools as reliable biomarkers. Flow cytometry is a robust methodology that allows for the characterization of many subsets of cells in a complex mixture such as blood by identifying cell-surface proteins, intracellular phosphoproteins and cytokines, as well as other functional readouts. Research has demonstrated the feasibility of PBMC GEP in AdHF patients undergoing longterm/destination MCS surgery and identified patterns of inflammatory response after MCS assessed by PBMC gene expression that are directly and specifically related to increasing degrees of OD

(**Shahzad 2008, Shahzad 2009, Sinha 2010**). The MyLeukoMAP™ pilot phase (**Figure 3**) has also demonstrated the feasibility of using the clinically-translationally more applicable whole-blood approach by PAX tubes instead of CPT tubes in AdHF patients (**Bondar 2014**).

MYLEUKOMAP™ PHASE 1 HYPOTHESIS: PBMC GEP CORRELATES WITH ADHF PHENOTYPES

Phase 1 of the MyLeukoMAP™ project currently tests the hypothesis that **MMB correlate with AdHF phenotypes (Figures 1, 3)**. MMBs incorporate genome-wide transcriptome analysis using RNA Sequencing and multi-parameter immune cell flow cytometry analysis of PBMC, evaluated in a time-dependent design, using systems-based computational analysis. To test the hypothesis, the study is conducting a prospective time-dependent study designed to characterize (1) temporal patterns of PBMC gene expression and PBMC immune phenotypes in AdHF to (2) reconstruct the temporal PBMC gene expression and immunophenotype program in AdHF.

PBMC GEP is correlated with early manifestations of frailty and organ dysfunction in HF-patients at the time of HTx/MCS-evaluation. The study plans to complete an analysis with 100 AdHF patients on OMM (Heart Failure Controls, HFC), after HTx and after MCS as well as 10 healthy volunteers (HV). Preliminary data shows that the organ dysfunction effects are mediated by PBMC mitochondrial energy metabolism changes (**Chang 2014**) and that the mathematical

modeling of these high dimensional datasets faces optimization challenges (**Wisniewski 2015**).

MYLEUKOMAP™ PHASE 2 HYPOTHESIS: PBMC GEP IMPROVES OUTCOME

PREDICTON/PREDICTION IN ADHF

Phase 2 (**Figure 3**), aims to develop an MMB test that improves risk prediction of “progression/death on OMM in heart failure with reduced ejection fraction (HFrEF)” over current clinical predictors alone and has the potential, by conducting phase 3, to increase the precision of prediction of comparative survival benefit in patients with HFrEF. The MyLeukoMAP™ phase 2 that will be testing the hypothesis that **PBMC GEP is improving outcome prediction in AdHF patients suffering from HFrEF over current clinical predictors alone** is currently being organized.

The study will enroll 300 HFrEF patients (150 UCLA, 150 UC San Diego/UC Irvine/UC Davis/VA WEST-Los Angeles, hereafter called Consortium) over three years and follow them ≥ 1.5 years. All consecutive adult HF patients with reduced EF (HFrEF) undergoing formal evaluation for HTx/MCS surgery providing consent will be included. Patients with preserved EF (HFpEF), patients with complex congenital HF will not be included because of their heterogeneous clinical phenotype. Based on the UCLA experience, up to the end of the follow-up period (estimated median follow-up: 3.0 years), 170 patients are expected to continue OMM or PC (expected deaths 20), 30 patients are expected undergo MCS, and

100 patients are expected to be listed United Network for Organ Sharing (UNOS) status 1 for HTx. In summary, a total of 150 patients are expected to have reached the primary endpoint of “progression/death on OMM in HFrEF” (HTx Status 1, MCS, death on OMM) by the end of the follow-up period. 26/130 (20%) patients reach the secondary endpoint of “progression/death on HTx/MCS” by this time. For the primary analysis, –the study will use the baseline samples of all co-accrued 300 patients (300 samples). A second sample will be analyzed in the 100 patients who are expected to experience “progression/death on OMM in HFrEF” (100 samples) in the MMB development cohort of 200 patients. For the 20 patients in this cohort expected to die on OMM/PC, the sample closest to death will be analyzed. The study will use a stratified randomization based on outcome to ensure that the model building (training) (200) and validation (testing) (100) cohorts have the same proportion of progressors and have similar distributions of patient level characteristics.

The study is interested in predicting the likelihood of HF-progression and comparative survival benefit from HTx/MCS over OMM. The time point of initiation of evaluation for HTx/MCS represents a milestone in the patient trajectory because it is based on a consensus clinical impression of progression of HF-severity between patient and cardiologist. As a clinically meaningful, measurable and temporally well-defined primary outcome measure of HF-progression on OMM (**Hicks 2015**), the study uses either of three first events after initial evaluation including

death from any cause while on OMM or PC, MCS implantation, or listing for HTx in the UNOS status 1 category. These events can be combined to a composite endpoint of “progression/death on OMM in HFrEF”. Since the decision about the cardiologist’s recommendation of MCS-implantation or listing for HTx in the UNOS status 1 category requires the patient to make the ultimate decision, the ~~perposed~~proposed study includes modeling under different primary endpoint assumptions. A secondary outcome measure is “progression/death on HTx/MCS” to identify patients with too high risk for MCS or HTx. Primary and secondary outcome measures combine to “progression/death in HFrEF”.

Decision-making in HF is shared between patient and physician (Allen 2012). Various primary endpoint scenarios will be modeled since preferences of patients and, therefore, the number of accrued primary endpoint events may differ from recommendations made by the treating cardiologists. This will consist of the construction of an alternate study outcome based on the clinician recommendation rather than the observed study outcome. The subjects in which there will be a difference between the observed study outcome and this alternate outcome will be cases when the cardiologist recommends that the subjects undergo MCS or UNOS 1 listing, but the subject chooses against this recommendation. The various clinical models will be applied in the 200 subjects in the model building cohort. The study will compare the model-based predictions with the observed progression endpoint the cardiologist recommendation-based

progression endpoint. A comparison of the area under the curve (AUC) for the model predictions versus the two endpoints will also be made to evaluate if the models better predict observed vs. recommended endpoints. This alternate endpoint will also be evaluated in the model building and validation. The complexity of AdHF patients requires a highly individualized shared decision-making. If the iterative 3-monthly data review suggests that higher granularity of understanding of the shared decision-making information is required for the endpoint analyses, all recruited patients will be offered participation in the ongoing UCLA Encounter Research Project. ~~This~~The research model that has been published (Raia 2014) proceeds iteratively in three stages of data collection and analysis.

The study is interested in predicting progression at the time of AdHF-evaluation, utilizing the combined information from the PBMC eigengene network, immune-phenotyping, and clinical phenotyping. The study will use the network based strategy previously discussed to assign gene significance scores based on network connectivity, pathway connectivity, and log p-value from the corresponding univariate predictive model. Next, researchers will create a predictive model using 200 HFrEF-etiology-stratified (non-ischemic versus ischemic dilated cardiomyopathy) and outcome-stratified patient samples randomly selected from the total sample pool of 300 of the Consortium population. The model structure will be multivariable Cox model that will be built on the baseline data. We will use Least Absolute Shrinkage and Selection Operator (LASSO) penalization

and k-fold cross-validation to perform variable selection and model building. Selection of the optimal model without overfitting occurs by using the results of k-fold cross-validation to minimize the mean squared prediction error while minimizing the number of predictor variables. As in the process of the AllomapTM-development (G6b-B expression in PBMC during acute cellular cardiac allograft rejection) (Li 2007), it is planned that equivalent validation studies during the MMB development in this MyLeukoMAPTM phase 2 are tailored to the reproducibility of those biomarkers incorporated into the MMB classifier.

After completion of model development using the 200 samples, researchers will be able to determine the improvement of prediction precision of progression adding the MMB-model on top of the clinically established prediction models. After the GEP MMB model is built using a co-accrued 200 randomly selected patient samples (expected HF progression event rate 100), the MMB model is fixed and applied to the validation subjects (100), at the same time as predictions from key clinical prediction tools are calculated, including HFSS (Aaronson 1997), Seattle HF (Levy 2006), UCLA (Chyu 2014), and MELD-XI (Abe 2014) scores as stand-alone models. Each model alone, the standard model and the new combined model provides a score for an individual patient from the validation cohort. This study will use AUC (area under the ROC curve) to obtain a measure of performance. Next, models will be compared using the change in AUC (delta AUC) and Net

Reclassification Improvement (NRI) (Pencina 2008) algorithms to measure the increase in performance precision predicting progression/death on OMM in HFrEF.

MYLEUKOMAPTM PHASE 3 HYPOTHESIS: PBMC GEP IMPROVES SURVIVAL BENEFIT PREDICTION IN ADHF

The MyLeukoMAPTM phase 3, based on the MMB generated in phase 2, will be testing the hypothesis that **PBMC GEP is improving survival benefit prediction over current clinical predictors alone in AdHF**. Phase 3 (Figure 3) plans to evaluate the predictive utility of the MMB predictors on comparative survival benefit. The phase 3 multicenter study will test the following hypothesis: If the MMB developed in the proposed project will allow better prediction of HF-progression than current clinical prediction models alone, AdHF-therapies guided by incorporation of this MMB on top of the clinical prediction tools into the decision-making process will yield a better comparative survival benefit prediction than by clinical predictors alone. For example, an AdHF-patient whose likelihood of HF-progression is low, would benefit from continuation of OMM and deferral of HTx or MCS. In contrast, an AdHF-patient whose likelihood of HF-progression is high, would benefit from more urgent HTx-listing or more urgent DT-MCS-surgery before HF-related OD ensues and before PC is indicated. The optimal study design for phase 3 is an appropriately powered randomized clinical trial in which one arm is allowing the MMB to be incorporated into the clinical-decision-making process.

**PERSONALIZED
MEDICINE
INFRASTRUCTURE****PRECISION
RESEARCH**

The study is innovative because it proposes the integration of a multi-system-level approach into a single predictive test towards the goal of *Personalized Precision Medicine* (Dzau 2015, Mensah 2015, Collins 2015). There is currently no molecular classifier of AdHF that incorporates a multidimensional pattern into its prediction algorithm. It will follow strict methodologies and robust information platforms characteristic of the new era of “Big Data” (Committee 2012). This information is captured at a high-dimensional multi-omic level, embedded in a comprehensive distilled set of clinical characteristics facilitated by the UCLA electronic medical record (CareConnect) and a Big Data infrastructure developed by the investigators with the UCLA Clinical-Translational Science Institute (CTSI), UCLA-Research Theme “Immunity, Infection, Inflammation & Transplantation” (I3T) and University of California Biomedical Research Acceleration, Innovation and Development (UC-BRAID). We will use the UC-BRAID mechanism (<http://www.ucbraid.org>) to optimize patient population identification, representing a population of 12 million Californians, patient recruitment & IRB-consent, shared

sampling logistics & repository, shared data analysis & publication, and integrated product development & regulatory approval.

SUMMARY

Based on the hypothesis for the MyLeukoMAP™ project ~~reviewed~~reviewed here, it is anticipated that discoveries made by the MyLeukoMAP™ project will lead to novel molecular biomarkers for the improved evaluation of complex phenotypes, risk prediction and ultimately survival benefit prediction in AdHF patients. The discoveries will improve the understanding of mechanisms, detection, prediction and treatment of AdHF across the disease spectrum. The clinical decision-making challenge at the time of evaluation may culminate in the differential recommendation between “all that high-tech modern medicine has to offer” to “compassionate care at the end of life”. The clinical situations leading up to this ultimate – medically, ethically and economically challenging - scenario requires a humanistically sound practice of high-tech modern medicine (which is termed “Relational Medicine™”) and deserves the best evidence-based decision-making support that post-genomic bioscientific translational research has to offer to enable a practice that lives up to the highest humanistic expectations that society has entrusted us with.

REFERENCES

1. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95(12):2660-7. PMID: 9193435.
2. Abe S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, Iwaya S, Owada T, Miyata M, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S, Takeishi Y. Liver dysfunction assessed by model for end-stage liver disease excluding INR (MELD-XI) scoring system predicts adverse prognosis in heart failure. *PloS one*. 2014;9(6):e100618. PMID: 24955578. Pmc4067358
3. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, Cook NR, Felker GM, Francis GS, Hauptman PJ, Havranek EP, Krumholz HM, Mancini D, Riegel B, Spertus JA. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*. 2012;125(15):1928-52. PMID: 22392529. PMC3893703
4. Bondar G, Cadeiras M, Wisniewski N, Maque J, Chittoor J, Chang E, Bakir M, Starling C, Shahzad K, Ping P, Reed E, Deng M. Comparison of whole blood and peripheral blood mononuclear cell gene expression for evaluation of the perioperative inflammatory response in patients with advanced heart failure. *PloS one*. 2014;9(12):e115097. PMID: 25517110. Pmc4269402
5. Bondar G, M. Cadeiras, N. Wisniewski, E. Chang, M. Bakir, J. Chittoor, J. Maque, K. Dong, C. Y. Chan, Y. D. Korin, P. Ping, E. F. Reed, M. Deng. NGS PBMC Transcriptome Analysis Identifies More Pronounced Activation of the Inflammatory Response in Advanced INTERMACS Class Before MCS D Implantation (abstr). *J Heart Lung Transplant* 2014;33:S39
6. Braunwald E, Bonow RO. Braunwald's heart disease : a textbook of cardiovascular medicine. 9th ed: Saunders; 2012.
7. Cadeiras M, von Bayern M, Sinha A, Shahzad K, Lim WK, Grenett H, Tabak E, Klingler T, Califano A, Deng MC. Drawing Networks of Rejection - A Systems Biological Approach to the Identification of Candidate Genes in Heart Transplantation. *J Cell Mol Med* 2011;15:949-56
8. Calvano SE, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, Chen RO, Brownstein BH, Cobb JP, Tschoeke SK, Miller-Graziano C, Moldawer LL, Mindrinos MN, Davis RW, Tompkins RG, Lowry SF, Inflamm, Host Response to Injury Large Scale Collab. *Res P. A*

Formatted: Numbered + Level: 1 + Numbering Style: 1, 2, 3, ... + Start at: 1 + Alignment: Left + Aligned at: 0.25" + Indent at: 0.5"

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman, Font color: Text 1

- network-based analysis of systemic inflammation in humans. *Nature*. 2005;437(7061):1032-7. PMID: 16136080.
- 9. Cappuzzello C, Napolitano M, Arcelli D, Melillo G, Melchionna R, Di Vito L, Carlini D, Silvestri L, Brugaletta S, Liuzzo G, Crea F, Capogrossi MC. Gene expression profiles in peripheral blood mononuclear cells of chronic heart failure patients. *Physiological genomics*. 2009;38(3):233-40. PMID: 19336532.
- 10. Caruso R, Trunfio S, Milazzo F, Campolo J, De Maria R, Colombo T, Parolini M, Cannata A, Russo C, Paino R, Frigerio M, Martinelli L, Parodi O. Early expression of pro- and anti-inflammatory cytokines in left ventricular assist device recipients with multiple organ failure syndrome. *ASAIO J*. 2010;56(4):313-8. PMID: 20445439.
- 11. Caruso R, Verde A, Cabiati M, Milazzo F, Boroni C, Del Ry S, Parolini M, Vittori C, Paino R, Martinelli L, Giannessi D, Frigerio M, Parodi O. Association of pre-operative interleukin-6 levels with Interagency Registry for Mechanically Assisted Circulatory Support profiles and intensive care unit stay in left ventricular assist device patients. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2012;31(6):625-33. PMID: 22386451.
- 12. Chang E, M. Cadeiras, C. Chan, G. Bondar, N. Wisniewski, M. Bakir, J. Chittoor, T. Khuu, M. Deng. Differential Mitochondrial Gene Expression in Patients Undergoing MCS D Implantation (abstr). *J Heart Lung Transplant* 2014;33:S234
- 13. Chyu J, Fonarow GC, Tseng CH, Horwich TB. Four-variable risk model in men and women with heart failure. *Circulation Heart failure*. 2014;7(1):88-95. PMID: 24281135.
- 14. Collins FS, Varmus H. A new initiative on precision medicine. *The New England journal of medicine*. 2015;372(9):793-5. PMID: 25635347.
- 15. Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical T, Board on Health Care S, Board on Health Sciences P, Institute of M. In: Micheel CM, Nass SJ, Omenn GS, editors. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. Washington (DC): National Academies Press (US) Copyright 2012 by the National Academy of Sciences. All rights reserved.; 2012.
- 16. Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G, Jaski B, Farrar DJ, Slaughter MS. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. *Journal of the American College of Cardiology*.

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman

- 2013;61(3):313-21. PMID: 23265328.
- 17. Deng MC, Bell S, Huie P, Pinto F, St. Goar F, Hunt SA, Stinson EB, Sibley R, Hall BM, Valentine HA. Cardiac Allograft Vasculopathy: Relationship to Microvascular Cell Surface Markers and Inflammatory Cell Phenotypes on Endomyocardial Biopsy. *Circulation* 1995;91:1647-1654
- 18. Deng MC, Dasch B, Erren M, Mollhoff T, Scheld HH. Impact of left ventricular dysfunction on cytokines, hemodynamics, and outcome in bypass grafting. *Ann Thorac Surg*. 1996;62(1):184-90. PMID: 8678641.
- 19. Deng MC, Dasch B, Erren M, Wiedner M, Möllhoff T, Assmann G, Scheld HH. Impact of left ventricular dysfunction on cytokines, hemodynamics and outcome in bypass surgery. *Ann Thor Surg* 1996;62:184-90
- 20. Deng MC, De Meester JM, Smits JM, Heinecke J, Scheld HH. Effect of receiving a heart transplant: analysis of a national cohort entered on to a waiting list, stratified by heart failure severity. Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study Group. *BMJ (Clinical research ed)*. 2000;321(7260):540-5. PMID: 10968814. PMC27468
- 21. Deng MC, Eisen HJ, Mehra RM, Billingham M, Marboe CC, Berry G, Kobashigawa J, Johnson FL, Starling RC, Murali S, Pauly DF, Baron H, Wohlgemuth JG, Woodward RN, Klingler TM, Walther D, Lal PG, Rosenberg S, Hunt SA, for the CARGO Investigators. Non-invasive detection of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant* 2006;6:150-160
- 22. Deng MC, Elashoff B, Pham MX, Teuteberg JJ, Kfoury AG, Starling RC, Cappola TP, Kao A, Anderson AS, Cotts WG, Ewald GA, Baran DA, Bogaev RC, Shahzad K, Hiller D, Yee J, Valentine HA; for the IMAGE Study Group. Utility of Gene Expression Profiling Score Variability to Predict Clinical Events in Heart Transplant Recipients. *Transplantation*. 2014 Mar 27;97(6):708-14.
- 23. Deng MC, Elashoff B, Pham MX, Teuteberg JJ, Kfoury AG, Starling RC, Cappola TP, Kao A, Anderson AS, Cotts WG, Ewald GA, Baran DA, Bogaev RC, Shahzad K, Hiller D, Yee J, Valentine HA, for the ISG. Utility of Gene Expression Profiling Score Variability to Predict Clinical Events in Heart Transplant Recipients. *Transplantation*. 2014. PMID: 24492465.
- 24. Deng MC, Elashoff B, Pham MX, Teuteberg JJ, Kfoury AG, Starling RC, Cappola TP, Kao A, Anderson AS, Cotts WG, Ewald GA, Baran DA, Bogaev RC, Shahzad K, Hiller D, Yee J, Valentine HA, for the ISG. Utility of Gene Expression Profiling Score Variability to Predict

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman, Font color: Gray-80%

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman

Clinical Events in Heart Transplant Recipients. *Transplantation*. 2014. PMID: 24492465.

- 25. Deng MC, Erren M, Kammerling L, Gunther F, Kerber S, Fahrenkamp A, Assmann G, Breithardt G, Scheld HH. The relation of interleukin-6, tumor necrosis factor-alpha, IL-2, and IL-2 receptor levels to cellular rejection, allograft dysfunction, and clinical events early after cardiac transplantation. *Transplantation*. 1995;60(10):1118-24. PMID: 7482719.
- 26. Deng MC, Erren M, Lutgen A, Zimmermann P, Brisse B, Schmitz W, Assmann G, Breithardt G, Scheld HH. Interleukin-6 correlates with hemodynamic impairment during dobutamine administration in chronic heart failure. *Int J Cardiol*. 1996;57(2):129-34. PMID: 9013264.
- 27. Deng MC, Erren M, Roeder N, Dreimann V, Günther F, Kerber S, Baba HA, Schmidt C, Breithardt G, Scheld HH. T-Cell and monocyte subsets, inflammatory molecules, rejection and hemodynamics early after cardiac transplantation. *Transplantation* 1998;65:1255-1261
- 28. Deng MC, Erren M, Tamminga N, Tjan TDT, Wertz B, Zimmermann P, Weyand M, Hammel D, Möllhoff T, Scheld HH. Left ventricular assist system support is associated with persistent inflammation and temporary immunosuppression. *Thorac*

Cardiovasc Surgeon 1999;47 (Supplement):326-331

- 29. Deng MC, Kämmerling L, Erren M, Günther F, Kerber S, Assmann G, Breithardt G, Fahrenkamp A, Scheld HH. Relation of interleukin(IL)-6, tumor-necrosis factor- α , IL-2, and IL-2-receptor-levels to cellular rejection, allograft dysfunction and mortality early after cardiac transplantation. *Transplantation* 1995;60:1118-1124
- 30. Deng MC, Roeder N, Plenz G, Erren M, Brisse B, Soeparwata R, Scheld HH. [Proinflammatory cytokines and cardiac pump function]. *Z Kardiol*. 1997;86(10):788-802. PMID: 9454446.
- 31. Deng MC, Wiedner M, Erren M, Möllhoff T, Assmann G, Scheld HH. Arterial and venous cytokine response to cardiopulmonary bypass for low risk CABG and relation to hemodynamics. *Eur J Cardiothor Surg* 1995;9:22-29
- 32. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ (Clinical research ed)*. 2005;330(7492):625. PMID: 15774989. PMC554905
- 33. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfil the promise of personalised medicine. *Lancet (London, England)*.

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman, Font color: Text 1

- 2015;385(9982):2118-9. PMID: 25957453.
- 34. Flint KM, Matlock DD, Lindenfeld J, Allen LA. Frailty and the selection of patients for destination therapy left ventricular assist device. *Circulation Heart failure*. 2012;5(2):286-93. PMID: 22438521. PMC3869992
- 35. Ganesh SK, Joo J, Skelding K, Mehta L, Zheng G, O'Neill K, Billings EM, Helgadottir A, Andersen K, Thorgeirsson G, Gudnason T, Geller NL, Simari RD, Holmes DR, O'Neill WW, Nabel EG. Time course analysis of gene expression identifies multiple genes with differential expression in patients with in-stent restenosis. *BMC medical genomics*. 2011;4:20. PMID: 21356094. PMC3053213
- 36. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *European heart journal*. 2003;24(19):1735-43. PMID: 14522568.
- 37. Gerling IC, Ahokas RA, Kamalov G, Zhao W, Bhattacharya SK, Sun Y, Weber KT. Gene expression profiles of peripheral blood mononuclear cells reveal transcriptional signatures as novel biomarkers of cardiac remodeling in rats with aldosteronism and hypertensive heart disease. *JACC Heart failure*. 2013;1(6):469-76. PMID: 24622010.
- 38. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Journal of the American College of Cardiology*. 2015;66(4):403-69. PMID: 25553722.
- 39. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119(14):e391-479. PMID: 19324966.
- 40. Kaur K, Dhingra S, Slezak J, Sharma AK, Bajaj A, Singal PK. Biology of TNFalpha and IL-10, and

Formatted: Font: Times New Roman

their imbalance in heart failure. *Heart Fail Rev.* 2009;14(2):113-23. PMID: 18712475.

- 41. Ketchum ES, Moorman AJ, Fishbein DP, Mokadam NA, Verrier ED, Aldea GS, Andrus S, Kenyon KW, Levy WC. Predictive value of the Seattle Heart Failure Model in patients undergoing left ventricular assist device placement. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2010;29(9):1021-5. PMID: 20558086.
- 42. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Miller MA, Timothy Baldwin J, Young JB. Sixth INTERMACS annual report: a 10,000-patient database. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2014;33(6):555-64. PMID: 24856259.
- 43. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, Massey T, Milano CA, Moazami N, Sundaeswaran KS, Farrar DJ. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. *The Journal of thoracic and cardiovascular surgery.* 2010;139(5):1316-24. PMID: 20132950.
- 44. Laudanski K, Miller-Graziano C, Xiao W, Mindrinos MN,

Richards DR, De A, Moldawer LL, Maier RV, Bankey P, Baker HV, Brownstein BH, Cobb JP, Calvano SE, Davis RW, Tompkins RG. Cell-specific expression and pathway analyses reveal alterations in trauma-related human T cell and monocyte pathways. *Proc Natl Acad Sci U S A.* 2006;103(42):15564-9. PMID: 17032758. PMC1592643

- 45. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *The New England journal of medicine.* 1990;323(4):236-41. PMID: 2195340.
- 46. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation.* 2006;113(11):1424-33. PMID: 16534009.
- 47. Li J, Cadeiras M, Prinz von Bayern M, Zhang L, Colovai AI, Dedrick R, Jaffe EA, Suci-Foca N, Deng MC. G6b-B cell surface inhibitory receptor expression is highly restricted to CD4+ T-cells and induced by interleukin-4-activated STAT6 pathway. *Hum Immunol* 2007;68:708-14
- 48. Li J, Cadeiras M, Prinz von Bayern M, Zhang L, Colovai AI, Dedrick R, Jaffe EA, Suci-Foca N, Deng MC. G6b-B cell surface inhibitory receptor expression is

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman

- highly restricted to CD4+ T-cells and induced by interleukin-4-activated STAT6 pathway. Human immunology. 2007;68(8):708-14. PMID: 17678728.
- 49. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res. 2002;91(11):988-98. PMID: 12456484.
- 50. Martinez-Selles M, Vidan MT, Lopez-Palop R, Rexach L, Sanchez E, Datino T, Cornide M, Carrillo P, Ribera JM, Diaz-Castro O, Banuelos C, Spanish Society of Cardiology Section on Geriatric Cardiology "Endstage heart disease in the elderly" working g. End-stage heart disease in the elderly. Rev Esp Cardiol. 2009;62(4):409-21. PMID: 19401126.
- 51. Matthews JC, Pagani FD, Haft JW, Koelling TM, Naftel DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. Circulation. 2010;121(2):214-20. PMID: 20048215. PMC2824259
- 52. Matzinger P. Friendly and dangerous signals: is the tissue in control? Nat Immunol. 2007;8(1):11-3. PMID: 17179963.
- 53. Mensah GA, Kiley J, Mockrin SC, Lauer M, Hoots WK, Patel Y, Cook NL, Patterson AP, Gibbons GH. National Heart, Lung, and Blood Institute Strategic Visioning: setting an agenda together for the NHLBI of 2025. American journal of public health. 2015;105(5):e25-8. PMID: 25723452.
- 54. Ong MK, Mangione CM, Romano PS, Zhou Q, Auerbach AD, Chun A, Davidson B, Ganiats TG, Greenfield S, Gropper MA, Malik S, Rosenthal JT, Escarce JJ. Looking forward, looking back: assessing variations in hospital resource use and outcomes for elderly patients with heart failure. Circ Cardiovasc Qual Outcomes. 2009;2(6):548-57. PMID: 20031892. PMC2951887
- 55. Orszag PR. Increasing the Value of Federal Spending on Health Care. Committee on the Budget. WASHINGTON, D.C.: U.S. House of Representatives; 2008.
- 56. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27(2):157-72; discussion 207-12. PMID: 17569110.
- 57. Pham MX, Teuteberg JJ, Kfoury AG, Starling RC, Deng MC, Cappola TP, Kao A, Anderson AS, Cotts WG, Ewald GA, Baran DA, Bogaev RC, Elashoff B, Baron H, Yee J, Valantine HA, for the IMAGE Study Group. Gene Expression Profiling for Rejection Surveillance After Cardiac Transplantation. N Engl J Med 2010;362:1890-1900
- 58. Ping P. Getting to the heart of proteomics. The New England

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman, Font color: Text 1

- journal of medicine. 2009;360(5):532-4. PMID: 19179323. PMC2692588
- 59. Plenz G, Song ZF, Tjan TDT, Koenig C, Baba HA, Erren M, Flesch MD, Wichter T, Scheld HH, Deng MC. Activation of the cardiac interleukin-6 system in advanced heart failure. *Eur J Heart Fail* 2001;3:415-421
- 60. Raia F, Deng M. *Relational Medicine – Personalizing Modern Healthcare: The Practice of High-Tech Medicine As A Relational Act*. 1 ed: World Scientific Publishing Company; 2014 December 18.
- 61. Raia F, Deng MC. *Relational Medicine – Personalizing Modern Healthcare: The Practice of High-Tech Medicine As A Relational Act*. World Scientific Publishing/Imperial College Press, London/Singapore 2014
- 62. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nat Rev Immunol*. 2008;8(10):776-87. PMID: 18802444. PMC2786961
- 63. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):e2-e220. PMID: 22179539.
- 64. Sartipy U, Dahlstrom U, Edner M, Lund LH. Predicting survival in heart failure: validation of the MAGGIC heart failure risk score in 51,043 patients from the Swedish heart failure registry. *Eur J Heart Fail*. 2014;16(2):173-9. PMID: 24464911.
- 65. Sartipy U, Goda A, Mancini DM, Lund LH. Assessment of a University of California, Los Angeles 4-variable risk score for advanced heart failure. *J Am Heart Assoc*. 2014;3(3):e000998. PMID: 24906370.
- 66. Shahzad K*, Latif F*, Sinha A*, Cadeiras M, von Bayern M, Oz S, Deng MC. Gene Set Enrichment Analysis of hyperbilirubinemia-associated leukocyte expression profiles following Mechanical Circulatory Support Device Implantation (abstr). *J Card Fail* 2008
- 67. Shahzad K, Fatima A, Cadeiras M, Wisniewski N, Bondar G, Cheng R, Reed E, Deng M. Challenges and solutions in the development of genomic biomarker panels: a systematic phased approach. *Curr Genomics*. 2012 Jun;13(4):334-41

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman

- 68. [Shahzad K, Latif F, Sinha A, Cadeiras M, Bayern M, Oz S, Deng MC. Whole Transcriptome Analysis of Changes in Immune Function Early after Mechanical Circulatory Support Device Implantation in End Stage Heart Failure Patients \(abstr\). J Heart Lung Transplant 2009;28: S183](#)
- 69. [Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. Crit Care Med. 2007;35\(9 Suppl\):S441-8. PMID: 17713391.](#)
- 70. [Sinha A, Shahzad K, Latif F, Cadeiras M, von Bayern M, Oz S, Naka Y, Deng MC. Peripheral Blood Mononuclear Cell Transcriptome Profiles Suggest T-cell Immunosuppression after Uncomplicated Mechanical Circulatory Support Device Surgery. Hum Immunol 2010;:71:164-9](#)
- 71. [Sinha A, Shahzad K, Latif F, Cadeiras M, Von Bayern MP, Oz S, Naka Y, Deng MC. Peripheral blood mononuclear cell transcriptome profiles suggest T-cell immunosuppression after uncomplicated mechanical circulatory support device surgery. Human immunology. 2010;71\(2\):164-9. PMID: 19879911.](#)
- 72. [Smits JM, de Vries E, De Pauw M, Zuckermann A, Rahmel A, Meiser B, Laufer G, Reichenspurner H, Strueber M. Is it time for a cardiac allocation score? First results from the Eurotransplant pilot study on a survival benefit-based heart allocation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2013;32\(9\):873-80. PMID: 23628111.](#)
- 73. [Soejima H, Irie A, Fukunaga T, Oe Y, Kojima S, Kaikita K, Kawano H, Sugiyama S, Yoshimura M, Kishikawa H, Nishimura Y, Ogawa H. Osteopontin expression of circulating T cells and plasma osteopontin levels are increased in relation to severity of heart failure. Circ J. 2007;71\(12\):1879-84. PMID: 18037740.](#)
- 74. [Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide \(N-BNP\) concentrations. Lancet \(London, England\). 2000;355\(9210\):1126-30. PMID: 10791374.](#)
- 75. [Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA \(Sepsis-related Organ Failure Assessment\) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine. 1996;22\(7\):707-10. PMID: 8844239.](#)
- 76. [Wisniewski N, Cadeiras M, Bondar G, Cheng RK, Shahzad K, Onat D, Latif F, Korin Y, Reed E,](#)

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman, Font color: Text 1

Formatted: Font: Times New Roman

Formatted: Font: Times New Roman, Font color: Text 1

- Fakhro R, Deng MC. Weighted Gene Coexpression Network Analysis (WGCNA) Modeling of Multiorgan Dysfunction Syndrome after Mechanical Circulatory Support Therapy (abstr). *J Heart Lung Transplantation* 2013;32:223
- 77. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-327. PMID: 23741058.
- 78. Yndestad A, Damas JK, Geir Eiken H, Holm T, Haug T, Simonsen S, Froland SS, Gullestad L, Aukrust P. Increased gene expression of tumor necrosis factor superfamily ligands in peripheral blood mononuclear cells during chronic heart failure. *Cardiovascular research*. 2002;54(1):175-82. PMID: 12062373.
- 79. Zhang B, Wright AA, Huskamp HA, Nilsson ME, Maciejewski ML, Earle CC, Block SD, Maciejewski PK, Prigerson HG. Health care costs in the last week of life: associations with end-of-life conversations. *Arch Intern Med*. 2009;169(5):480-8. PMID: 19273778.PMC2862687

Formatted: Font: Times New Roman