PROOF
Centre of | Centre d' EXCELLENCE

Biomarker solutions for health care.

Biomarqueurs – Solutions en soins de santé.

HEART FAILURE PROGRAMS

Unmet need in the treatment and management of heart failure

Heart failure affects 14.5 million North Americans and 6 million people in Europe. The global market for biomarkers of cardiovascular disease is predicted to reach $7.2 billion by 2018.

The PROOF Centre's heart failure programs address clinical needs in the following areas:

- Chrnoic Heart Failure
- Response to HF Therapy
- Acute Heart Failure
- Advanced Heart Failure

We are developing biomarker-based blood tests that are expected to lead to better patient care through appropriate targeted therapies.

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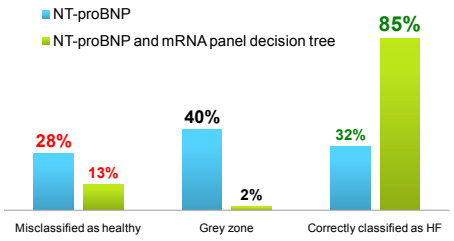
Blood tests for better manangement of heart failure

The PROOF Centre is developing prognostic and diagnostic biomarkers for better management of acute and chronic heart failure. Identifying patients early in clinical presentation will allow for more aggressive therapy and slow disease progression. For pharmaceutical companies, our markers can also be used to identify responders to medicines aimed at treating heart failure symptons.

FIGURE 1. Heart failure programs at a glance.

Diagnose Heart Failure	An 29-mRNA panel that improves on diagnostic performance of NT-proBNP	Decreases the NT-proBNP grey zone from 40% to 2%
Diagnose HFpEF vs HFrEF	An mRNA-based panel that differentiates HFpEF *versus* HFrEF in male patients	Replication AUC 0.89 when combined with NT-proBNP
Response to HF Therapy	A 17-protein panel that identifies patients who have responded to heart failure therapy	Replication AUC 0.95, with 93% sensitivity
Acute Heart Failure	Combinatorial panels (proteins, clinical variables) that predict survival from AHF and identify response to mechanical assist device	Discovery AUC 0.94-0.97
Advanced Heart Failure	A proteogenomic panel of 14 markers that predicts heart function deterioration at 1 year follow-up	Discovery AUC 0.93

FIGURE 2. Current cardiac markers (e.g. B-type naturietic peptide) misclassify a large portion of chronic heart failure patients. Our panel of molecular biomarkers significantly improves the percentage of patients correctly identified as having chronic heart failure.



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We are developing tests to identify subtypes of chronic heart failure that require different treatment regimens, as well as a test to monitor patients for recovery of heart function from drug therapy.

Medically-Managed Cohort of Recovered Patients

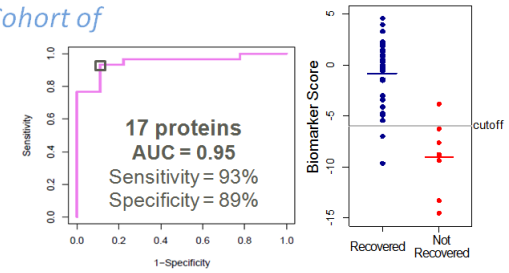

FIGURE 2. Identification of biomarkers from transplant recipients with "Recovered" heart function

	Sensitivity	Specificity	NRI	P-value
17-protein (RHF panel)	93%	89%	0.14*	0.22*
BNP	90%	78%	NA	NA
NT-proBNP	80%	89%	NA	NA
BNP + 17 proteins	97%	100%	0.29*	0.04*
NT-proBNP + 17 proteins	97%	100%	0.28**	0.02**

* relative to BNP
** relative to NT-proBNP

For acute heart failure patients, we have identified biomarkers that predict outcomes such as survival and response to mechanical circulatory assist device therapy.

FIGURE 3. Current discovery analysis of acute failure outcomes

Objective	Panel	Discovery AUC
Predict survival from AHF	Panels of **clinical variables** that predict death or VAD/Tx-free survival before day 30	0.82 (death) 0.94 (VAD/Tx-free)
Identify signature of response to mechanical circulatory assist device therapy	**Panel of proteins** that identifies response to VAD	0.94
Identify signature of response in patients not on mechanical circulatory assist device therapy	**Panel of proteins and clinical variables** that identifies response in those not on VAD	0.97
Stratify responders *versus* non-responders to device therapy	Analysis underway	

The key to PROOF Centre's work in biomarker development is our core competency in data integration and computational analysis.

FIGURE 4. Various computational and statistical methods are assessed at each step of our analysis, from data quality control to biomarker evaluation.

	PROTEOMICS	GENOMICS	CLINICAL
QC	SOP-driven quality check	MDQC, AffyPLM	Range check, data cleaning, confounder analysis
Pre-processing	PCA, clustering, standardization, imputation of missing values, log transformation	PCA, clustering, log transformation	Review of missing data
Pre-filtering	Eliminate non-informative features	ECMR, FARMS INI, PVAC	None
Univariate ranking	Fisher's Exact test, robust and non-robust LIMMA, csSAM, EDGE, GSEA		t-test, Wilcoxon test, Chi-square test
Univariate filtering	P-value and FDR cut-offs, fold change cutoffs, pathway, PPI, tissue-specific enrichment		P-value and FDR cut-offs
Classifier generation	Random GLM, SVM, LDA, elastic net, lasso, logistic regression, random forest, PAM, sPLSDA, Cox regression, Poisson		
Combinatorial biomarker generation	Classification trees, ensembles, mixOmics		
Biomarker evaluation	Deep cross-validation, performance evaluation (AUC, NRI, NB), biological plausibility (biological interpretation with pathways and networks, plausibility with disease)		

The PROOF Centre of Excellence is a not-for-profit organization that develops blood tests to better manage patients with heart, lung and kidney disease. With a cross-disciplinary team of people and organizations, including commercial partners, we can speed up the development of these tests, applying them sooner to improve lives.

To learn more, contact

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