KEYSTONE SYMPOSIA

MASH and Fibrosis: From Molecular Phenotypes to Precision Therapeutics
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Artificial intelligence-assisted digital pathology characterizes the fibrosis phenotypes in Cardiomyopathy

Adi LIGHTSTONE[1], Junedh AMRUTE[2], Kory LAVINE[2], Li CHEN[1]

[1]PharmaNest, Princeton, NJ, USA, [2]Washington University, Center for Cardiovascular Research, St. Louis, USA

PHARMANEST DIGITAL PATHOLOGY

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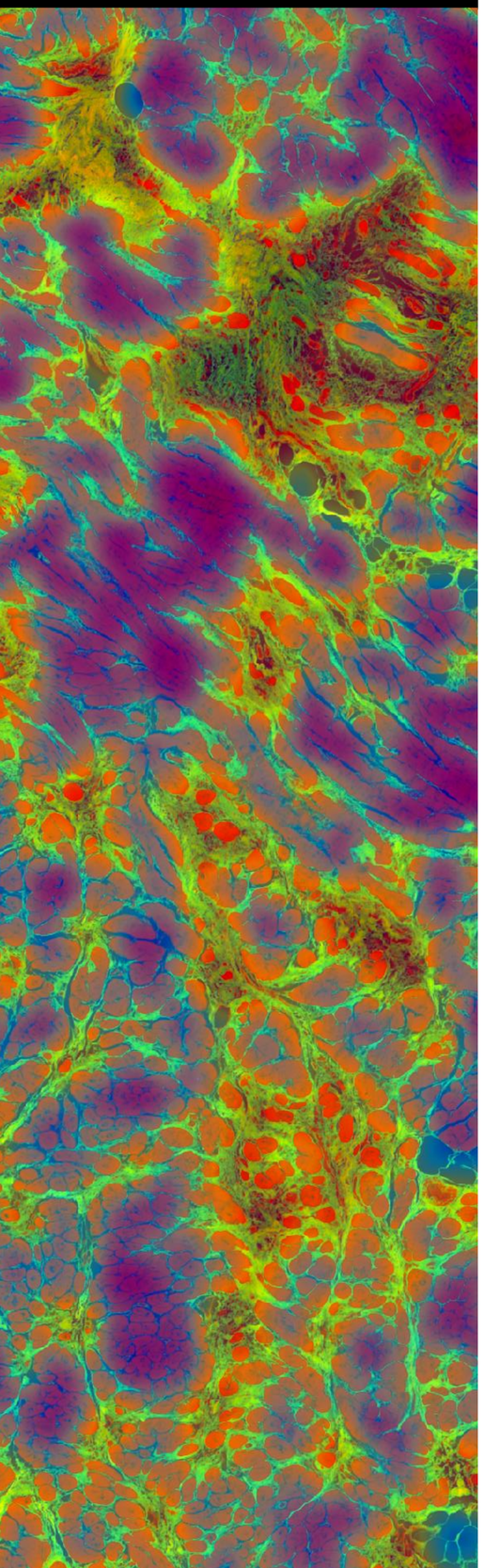


1 Introduction

Cardiomyopathy includes a wide range of heart diseases, all of which make it harder for the heart to pump blood. All forms are associated with fibrosis of the heart tissue. While they have diverse causes, treatments, and outcomes, it is not well researched if the scarring itself has different behaviors between cohorts, and what similarities or differences they may have.

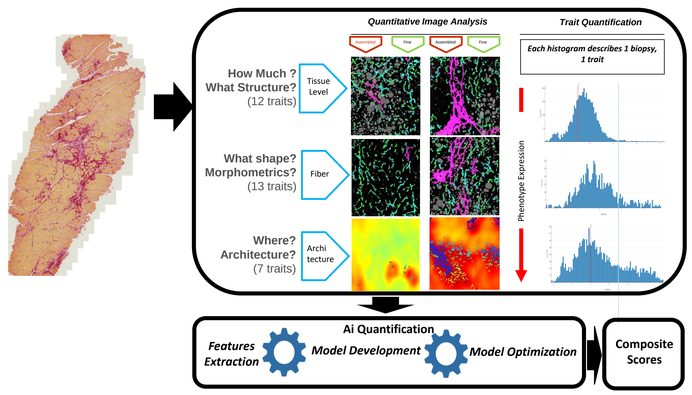
2 Aim

The aim of this study is to compare fibrosis analysis between 4 different cardiomyopathies, including **Non-Ischemic (NICM)**- disease not related to heart attack or an artery blockage, **Ischemic (ICM)**- which refers to artery blockages or heart attacks, **LMNA Dilated-** which refers to dilation of the ventricle or conduction issues due to LMNA gene mutation, and **Structural Dilated** cardiomyopathy- which refers to dilation of ventricles caused by different mutations.

We used FibroNest™ , a high-resolution single-fiber digital pathology quantification tool to describe the fibrosis phenotypes of these cardiomyopathies.

3 Method

Heart histological sections were stained with picrosirius red for collagens and imaged at 40X.



FibroNest™, a cloud-based image analysis platform, was used to quantify the fibrosis phenotype

-Including 32 traits for collagen deposition, fiber morphometry, and architecture (measures the organization and buildup of complex fibers).

-Principal quantitative fibrosis traits (up to 315 qFTs) are automatically detected and combined into a Phenotypic Fibrosis Composite Score (Ph-FCS).

-This was done individually for the 4 different cardiomyopathies,

including NICM, ICM, LMNA, and Structural groups.

-Each was compared to Donor (group rejected for heart transplant which were used as the 'Control' Group),

-qFTs from each of the studies were compared to find common traits, seen in the Veen diagram.

4 Representative Images and Results

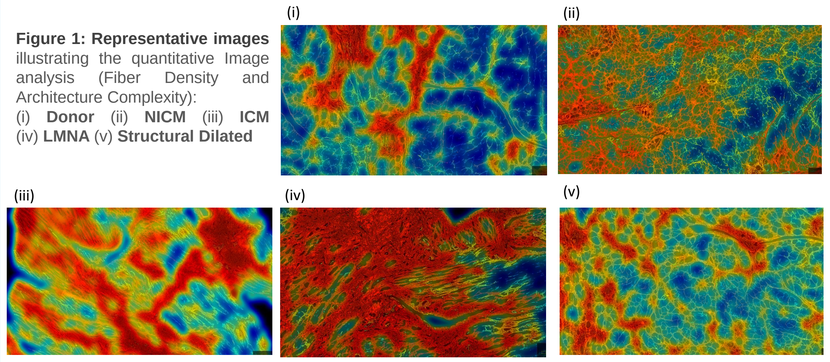


Figure 1: Representative images illustrating the quantitative Image analysis (Fiber Density and Architecture Complexity):
(i) **Donor** (ii) **NICM** (iii) **ICM** (iv) **LMNA** (v) **Structural Dilated**

Figure 2: Phenotypic Heat chart. Quantitative feature values for fibrosis, Collagen deposition, fiber Morphometry and fibrosis Architecture for each patient in the study cohort. Severity increases from green to red indicating the level of progression of diseases, or the deviation in pattern from baseline average of the Donor.

Figure 3: Phenotypic Fibrosis Composite Scores for the cardiomyopathies. Donor had a Ph-FCS Score of 4.2, while NICM, ICM, LMNA, and Structural had that of 5.5, 5.0, 5.9, and 5.7 along with p-values of 0.04, 0.17, 0.10, and 0.01, respectively compared to Donor.

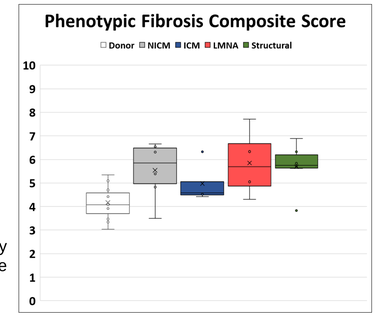


Fig 2

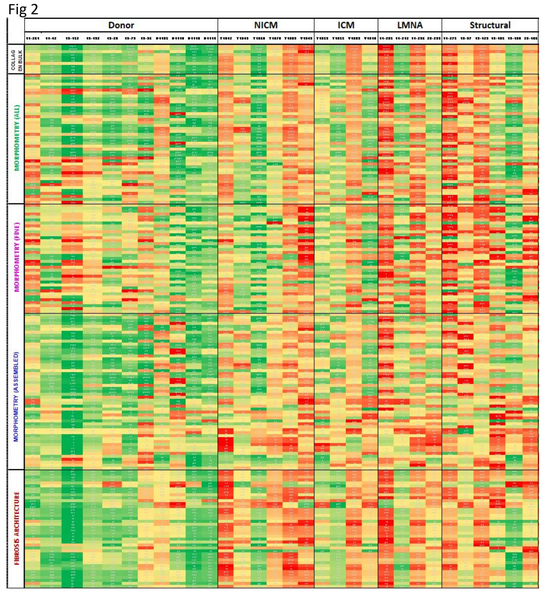
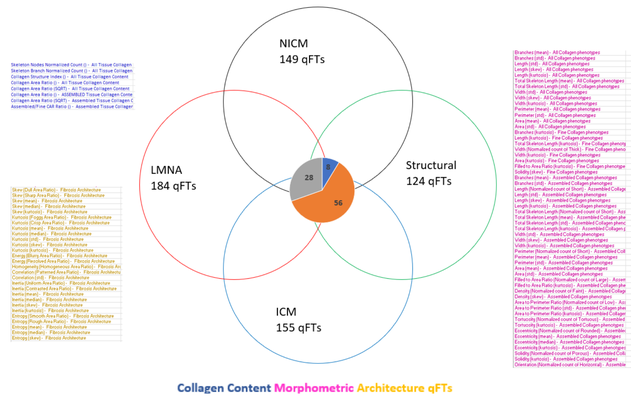


Figure 4. Veen Diagram of the Cardiomyopathies.
When analyzed individually comparing each disease group to the Donor Group to find which of 315 qFTs were significantly ($p < 0.05$) changed in disease state, we found 149, 155, 184, and 124 qFTs for NICM, ICM, LMNA and Structural, respectively. Of those significantly different phenotypic fibrosis traits, 92 qFTs were found to be in common in all 4 cardiomyopathies. This included average collagen area, fiber length, along with several others.



5 Conclusions

- Structural Dilated and LMNA cardiomyopathies have features overlapped as they have the same general impact on heart tissue.

-The same is true of Structural Dilated and NICM cardiomyopathies.

-FibroNest™ found a strong feature overlap in the heart between Ischemic (which operates on the vessels) and the others.

-ICM causes similar structural changes on heart muscle as other Cardiomyopathies, despite being based on blood vessels.

-Characterization of the fibrosis phenotypes in cardiomyopathies can lead to new understandings of how heart injury and fibrosis occurs and pave the way for new treatments.

6 Contact information:

adi.lightstone@pharmanest.com and li.chen@pharmanest.com