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INVITED EDITORIAL

Dissecting the heart failure phenotype through phenomics

Giorgia Panichella[1], Daniela Tomasoni[2,3], and Alberto Aimo[4,5]*

[1]Cardiology Division, Careggi University Hospital, Florence, Italy; [2]Cardiology Division, ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [3]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Interdisciplinary Center for Health Sciences, Scuola Superiore Sant'Anna, Pisa, Italy; and [5]Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy

This article refers to 'Distinguishing heart failure with reduced ejection fraction from heart failure with preserved ejection fraction: A phenomics approach' by B.J. van Essen *et al.*, published in this issue on pages 841–850.

Since 2016, patients with heart failure (HF) have been categorized into three groups based on their left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF, LVEF ≤40%), HF with mildly reduced EF (HFmrEF, LVEF 41–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%).[1] HFrEF has been extensively studied, but HFpEF represents over 50% of all HF cases.[2] Individuals with HFpEF are typically older, female, and have more often comorbidities such as hypertension, diabetes, obesity, pulmonary or liver disease, and sleep apnoea, compared to those with HFrEF.[3–5] These comorbidities likely contribute to HFpEF development through mechanisms like increased ventricular stiffness, inflammation, and oxidative stress.[6] A recent study showed that different, although somewhat overlapping, sets of proteins could predict both incident HFrEF and HFpEF.[7] Despite progress, the molecular pathways of HFrEF and HFpEF remain only partially understood.

Advances in omics technologies offer a comprehensive approach to elucidating the complex molecular pathways and clinical manifestations of HF. Each omics discipline focuses on a specific type of molecule: genomics on DNA sequences, epigenomics on epigenetic modifications, transcriptomics on RNA transcripts, proteomics on proteins, metabolomics on metabolites, and lipidomics on lipids. Historically, HF studies have examined single omics datasets in isolation, often without integrating these findings with clinical data.[8–12] Phenomics, integrating 'phenotypical' and 'omics' data, is a novel discipline seeking to understand the molecular underpinnings of disease manifestations, progression, prognostic markers and treatment responses.[13] Through a multi-step process, omics and phenotypic data are collected and analysed using bioinformatics and statistical tools to identify patterns, correlations, and networks that link specific protein signatures with particular phenotypes.[13]

In this issue of the Journal, van Essen and colleagues apply a phenomics approach to patients with HFrEF or HFpEF, using data from the Singapore Heart Failure Outcomes and Phenotypes (SHOP) study, a prospective, observational cohort study based in Singapore.[14] The study analysed data from 217 HFrEF patients, 213 HFpEF patients, and 216 age and sex-matched healthy controls, characterizing each participant through a comprehensive clinical, echocardiographic, and laboratory assessment.[14]

The phenomics analysis proceeded in stages. Initially, a multi-block projection analysis integrated clinical, echocardiographic, and biomarker variables to perform latent structure analysis. This method aimed to dissect and understand complex datasets by identifying relationships across variable blocks', thereby revealing underlying patterns. Subsequent comparisons between HFpEF and controls, HFrEF and controls, and HFpEF versus HFrEF sought to pinpoint attributes unique to each HF category. In the final step, the study established networks that illustrated the interplay between clinical, echocardiographic, and protein level data for both HF types. This phase included consulting external databases to identify proteins with potential as drug targets. The analysis successfully identified distinguishing features (93 for HFpEF vs. controls, 117 for HFrEF vs. controls, and 48 for HFpEF vs. HFrEF, respectively). Biomarkers demonstrated high accuracy in differentiating HF types from controls, with area under the curve values of 0.95 for HFpEF and 0.89 for HFrEF. Protein levels showed a greater correlation with patient characteristics than with echocardiographic measures, especially in HFpEF cases. The analysis further delineated specific attributes of HFpEF and HFrEF: HFpEF was associated with older age, hypertension, increased relative wall thickness, and higher levels of inflammatory proteins. Conversely, HFrEF characteristics included male sex, a history of coronary artery disease, and markers indicative of cardiac

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*Corresponding author. Interdisciplinary Center for Health Sciences, Scuola Superiore Sant'Anna, and Cardiology Division, Fondazione Toscana Gabriele Monasterio, Piazza Martiri della Libertà 33, 56124 Pisa, Italy. Tel: +39 347 7084391, Email: a.aimo@santannapisa.it, aimoalb@ftgm.it

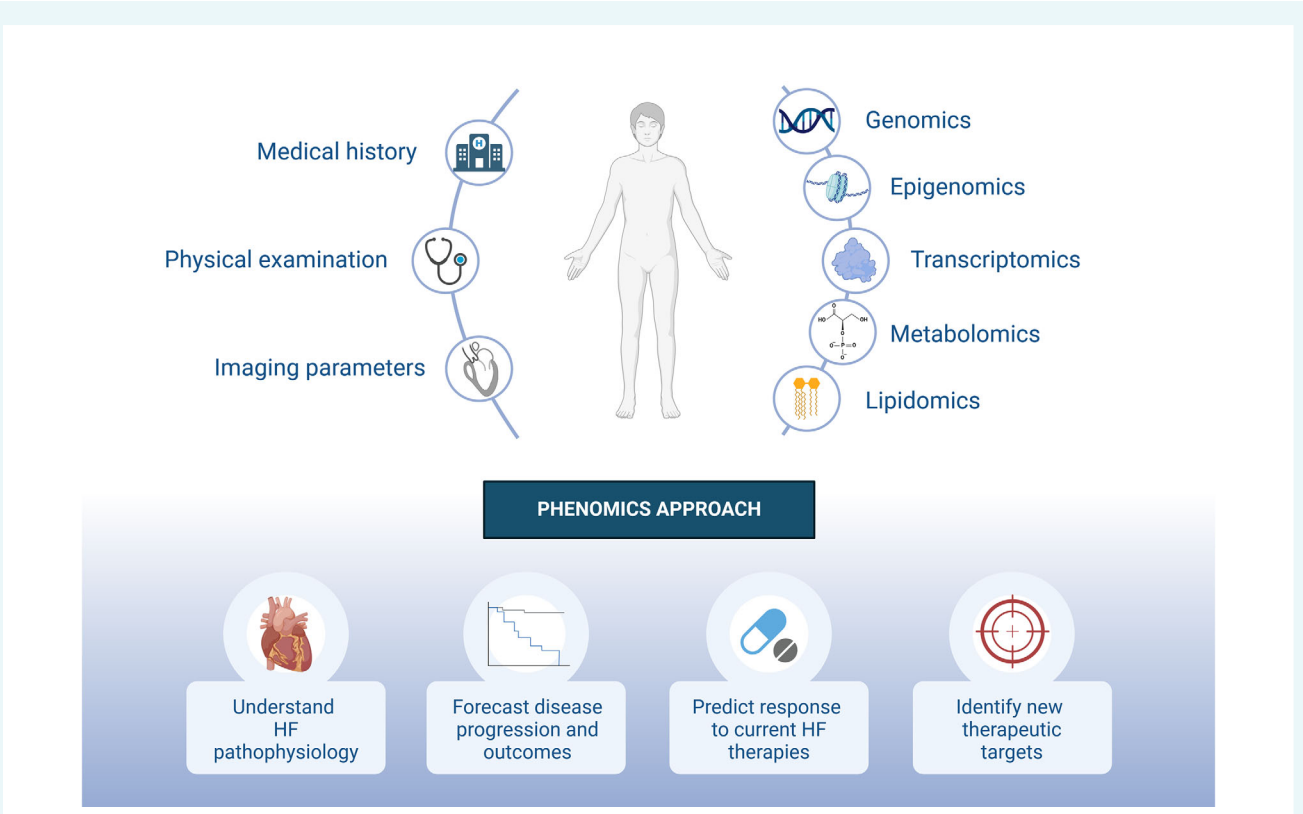

Figure 1 The potential applications of phenomic analysis in heart failure (HF) treatment. Phenomics is an emerging field that aims to combine omics data and phenotypic information to uncover patterns, correlations, and networks connecting specific molecular signatures to distinct phenotypes. So far, phenomics analysis has mainly focused on single omics areas, specifically genomics and proteomics. Yet, the future suggests phenomics could greatly benefit from merging various omics disciplines with clinical and imaging data. This approach could transform the management of HF by providing a more profound comprehension of its complex pathophysiology. Additionally, characterizing patients based on phenomics might improve predictions of disease progression and responses to treatment. Finally, this method holds the promise of disclosing new druggable targets.

metabolism. Differential biomarker levels, such as cathepsin L and galectin-3 among HFpEF, HFrEF, and control groups, were observed. Network analysis for HFpEF underscored the significance of wall thickness and its correlation with comorbid conditions like diabetes and hypertension. For HFrEF, the network emphasized the impact of age, wall thickness, and certain echocardiographic measures, linking older age to reduced heart function via elevated inflammatory markers.[14]

In summary, this comprehensive analysis not only differentiated between HFpEF and HFrEF, but also identified potential therapeutic targets, most notably within the tumour necrosis factor receptor superfamily for HFpEF, related to wall thickness and associated with hypertension and diabetes. Conversely, HFrEF-specific markers, interleukin-8 and -6, correlated with lower LVEF and worse renal function. Consistent with our current understanding of HFpEF pathophysiology, this study reinforces the critical role of comorbidities in HFpEF, contributing to a pro-inflammatory state, heart stiffening, and increased left ventricular filling pressures.[14]

The study's strengths lie in its innovative approach, correlating protein profiles with echocardiographic parameters and identifying new potential therapeutic targets. It confirms previous findings that HFrEF is associated with biomarkers of cellular proliferation, metabolism, and cardiac stretch, while HFpEF is linked to inflammation, extracellular matrix remodelling, and angiogenesis.[3,6] Moreover, the phenomics approach revealed that biomarker profiles in HFpEF display closer relationships with comorbidities than with the echocardiographic features, which is a novel finding.[14]

The study has also some limitations, including a lack of data on HFmrEF and HF secondary to specific aetiologies (e.g. infiltrative or congenital heart disease or severe valve disease).[14] We may add that HF therapy seemed to be suboptimal, with only 45% of HFrEF patients receiving a mineralocorticoid receptor antagonist, and no information regarding renin–angiotensin–aldosterone system or sodium–glucose cotransporter 2 inhibitors.[14] Furthermore, most participants were of Asian ethnicity,[14] raising the question of the applicability of findings to a broader, more heterogeneous population.

Despite the potential drawbacks, this research highlights the promise of phenomics in unravelling the intricate pathophysiology of HF. The phenomic approach stands out as a groundbreaking method for the discovery of new cardiovascular risk factors, diagnostic techniques, and therapeutic interventions (*Figure 1*). Future

clinical trials could be structured around phenomics-based patient subgroups, particularly in HFpEF, where phenotypic variability is notoriously high. To date, phenomics analysis has primarily utilized single omics, namely genomics and proteomics.[13] However, the future holds the potential for phenomics to benefit from the integration of various omics fields along with clinical and imaging data.

Phenomics analysis also presents significant challenges and tasks.[13] From a methodological perspective, it is crucial to develop standardized protocols for data collection, storage, distribution, and use. There is also a need to establish ethical and regulatory frameworks for phenomics research on diseases. While numerous analytical instruments have been designed for laboratory use, there is a pressing need for the development of equipment that can measure phenomic parameters in clinical settings. Additionally, the establishment of large-scale phenomics research centres could support research, education, and training in this burgeoning field.[13]

In conclusion, the study by van Essen *et al.*[14] illustrates that utilizing an integrated phenomics approach could unveil new insights into the intricate pathophysiology of HFpEF and HFrEF. This is achieved by contextualizing phenotypical and mechanistic aspects of potential therapeutic targets. While the study provides invaluable insights, it also highlights the complexity of these conditions and emphasizes the necessity for ongoing, diverse research methodologies. Although these findings necessitate further validation, they warrant a cautiously optimistic outlook towards the development of future personalized treatment modalities.

Conflict of interest: none declared.

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