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Next generation genomic testing in chronic heart failure: A promising approach for targeted molecular diagnosis and management

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Chronic heart failure (CHF) is a major challenge to any secondary and tertiary care cardiology service facility. It remains a huge global health burden with significant lifelong morbidity and mortality. The multi-disciplinary care is now accepted norm. Beta blockers in combination with angiotensin receptor blockers and along with biventricular resynchronization have revolutionized therapeutic outcomes. Orthotic cardiac transplantation remains the final choice. Apart from ischemic factors, non-ischemic causes feature in around one third patients. Infections and toxic myocardial exposure are predominant non-ischemic causes with relatively poor outcomes. In around 15% of cases genetic factors play a major role in CHF causation and progression. Apart from clinical variation, associated genetic heterogeneity adds to the molecular complexity and phenotypic picture, collectively labeled as inherited cardiomyopathies, particularly hypertrophic, dilated, ventricular non-compaction, arrhythmogenic and restrictive types. The molecular biology of these specific types is now much clearer with a number of gene-molecular systems involved sarcomeres, desmosomes, phospholamban, dystrophoglycan, mitochondrial and many more. Specific molecular diagnosis is restricted due to high level of allelic and mutational heterogeneity along with a number of genomic variants without any functional annotations. Molecular diagnosis using the next generation sequencing (NGS) genomic methods has remarkably modified the quality and outcomes of specific cardiac disease manifesting with CHF. A number of genome testing platforms are now available that include up to 100 different mutations in selected genes. However, this approach requires a carefully evaluated inherited cardiac phenotype. The multi-gene NGS testing approach has many limitations and is now replaced with targeted clinical exome sequencing to allow genomic variation and mutations in practically all exomes of genes associated with inherited cardiomyopathies. This is supported with validation by Sanger sequencing and MLPA for dosage variation. Such an approach is widely accepted by patients and clinicians and offers much needed confidence of having absolute confirmation of the diagnosis and opportunity to evaluate the phenotype in molecular context. Moreover, the precise molecular abnormality is essential for selecting the close family member for lifelong cascade specialist cardiac surveillance.

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