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Beyond the phenotype: translating cardiomyopathy genetics into clinical decisions

Mario Udovičić[1,2]*, Ana Livun[1], Tomo Svaguša[1], Diana Rudan[1], Marija Radić[1], Danijela Grizelj[1], Vanja Ivanović Mihajlović[1], Petra Vitlov[1], Hrvoje Falak[1], Šime Manola[1]

[1]Dubrava University Hospital, Zagreb, Croatia
[2]University of Zagreb, School of Medicine, Zagreb, Croatia

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***ADDRESS FOR CORRESPONDENCE:** Mario Udovičić, Klinička bolnica Dubrava, Av. G. Šuška 6, HR-10000 Zagreb, Croatia. / Phone: +385-98-477-248 / E-mail: mario.udovicic@gmail.com

ORCID: Mario Udovičić, https://orcid.org/0000-0001-9912-2179 • Ana Livun, https://orcid.org/0000-0002-6758-1677
Tomo Svaguša, https://orcid.org/0000-0002-2036-1239 • Diana Rudan, https://orcid.org/0000-0001-9473-2517
Marija Radić, https://orcid.org/0000-0003-2317-6300 • Danijela Grizelj, https://orcid.org/0000-0002-8298-7974
Vanja Ivanović Mihajlović, https://orcid.org/0000-0001-6931-5404 • Petra Vitlov, https://orcid.org/0000-0001-6983-1409
Hrvoje Falak, https://orcid.org/0000-0002-6502-683X • Šime Manola, https://orcid.org/0000-0001-6444-2674

Cardiomyopathy is a phenotypic description rather than a definitive etiological diagnosis. The 2023 European Society of Cardiology guidelines incorporate genetic evaluation into a multiparametric diagnostic pathway that encompasses clinical presentation, family history, electrocardiography, and cardiac imaging[1]. Genetic testing is recommended when the findings may inform diagnosis, prognosis, treatment, or reproductive management, and facilitate cascade testing. This narrative review examines how these recommendations translate into clinical decision-making, drawing on examples from clinical practice at Dubrava University Hospital.

Molecular diagnosis can identify clinically actionable differences among patients with similar cardiac phenotypes. In LMNA cardiomyopathy, genotype informs arrhythmic risk assessment and may support primary-prevention defibrillator implantation before conventional ejection-fraction thresholds are reached. Recognition of LAMP2-related Danon disease supports close surveillance and timely assessment for transplantation. In desmoplakin (DSP) cardiomyopathy, myocarditis-like episodes have prompted investigation into immunosuppression; observational findings are encouraging, but treatment should not be based on genotype alone[2]. Diagnosing Fabry disease enables disease-specific therapy, with GLA variant amenability informing eligibility for migalastat. TTR testing identifies hereditary transthyretin amyloidosis and guides multisystem assessment and family screening. In MELAS, molecular diagnosis supports differentiation of mitochondrial stroke-like episodes from thromboembolic events, while cardiac surveillance remains necessary.

Across these conditions, pathogenic or likely pathogenic variants support targeted cascade testing. Genetic counseling, appropriate test selection, and expert interpretation remain essential, particularly as broader sequencing increases the complexity of findings. Genetic testing is becoming increasingly accessible, creating opportunities to implement guideline recommendations more widely. At Dubrava University Hospital, experience with targeted next-generation sequencing provides a foundation for planned whole-exome sequencing using virtual cardiomyopathy panels. Our clinical examples demonstrate the practical value of integrating genetic findings with phenotype and disease trajectory, connecting molecular diagnostics with the everyday challenges of cardiomyopathy and advanced heart failure care.

Genotype-informed care extends beyond diagnostic classification to include sudden death prevention, the selection of specific therapies, advanced heart failure assessment, and family management. Improving accessibility should promote timely referral and collaboration among cardiologists, specialist cardiomyopathy teams, and molecular laboratories, ensuring that expanded diagnostic capabilities translate into clinical benefits for patients and their families.

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