ESC European Society of Cardiology
European Heart Journal - Case Reports (2021) **5**(11), 1–3
doi:10.1093/ehjcr/ytab391

EDITORIAL

The promise and challenges of precision medicine in dilated cardiomyopathy

Samantha Mason [1], **Ellie Quinn** [1], **and Brian P. Halliday** [1,2]*

[1]Inherited Cardiovascular Conditions Care Group, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; and [2]National Heart and Lung Institute, Imperial College London, Dovehouse St, London, SW3 6NP, UK

Received 30 July 2021; first decision 24 August 2021; accepted 20 September 2021; online publish-ahead-of-print 1 October 2021

This editorial refers to 'Laminopathies: should Wencke bach be a cause for concern? A case report', by G. Sen and T. Jackson. https://doi.org/10.1093/ehjcr/ytab331.

The case report 'Laminopathies: should Wenckebach be a cause for concern? A case report' by Sen and Jackson[1] illustrates many of the complexities and challenges in diagnosing and managing genetic cardiomyopathies. It emphasizes the importance of access to highly specialized services that bring together invasive and non-invasive cardiologists, specialist nurses, geneticists, and genetic counsellors. These skillsets are an invaluable resource when managing patients with rare and complex genetic heart conditions.[2] Timely involvement of these services was sought in this case and appropriate testing was performed. However, despite gold-standard management, a tragic outcome could not be prevented, highlighting many of the ongoing challenges when managing unpredictable conditions and awaiting important diagnostic information. In such difficult cases, involvement of a wider team not only ensures expert and informed decision-making but also provides the necessary psychological and emotional support to the attending team as well as the family and ensures appropriate follow-up of at-risk family members.

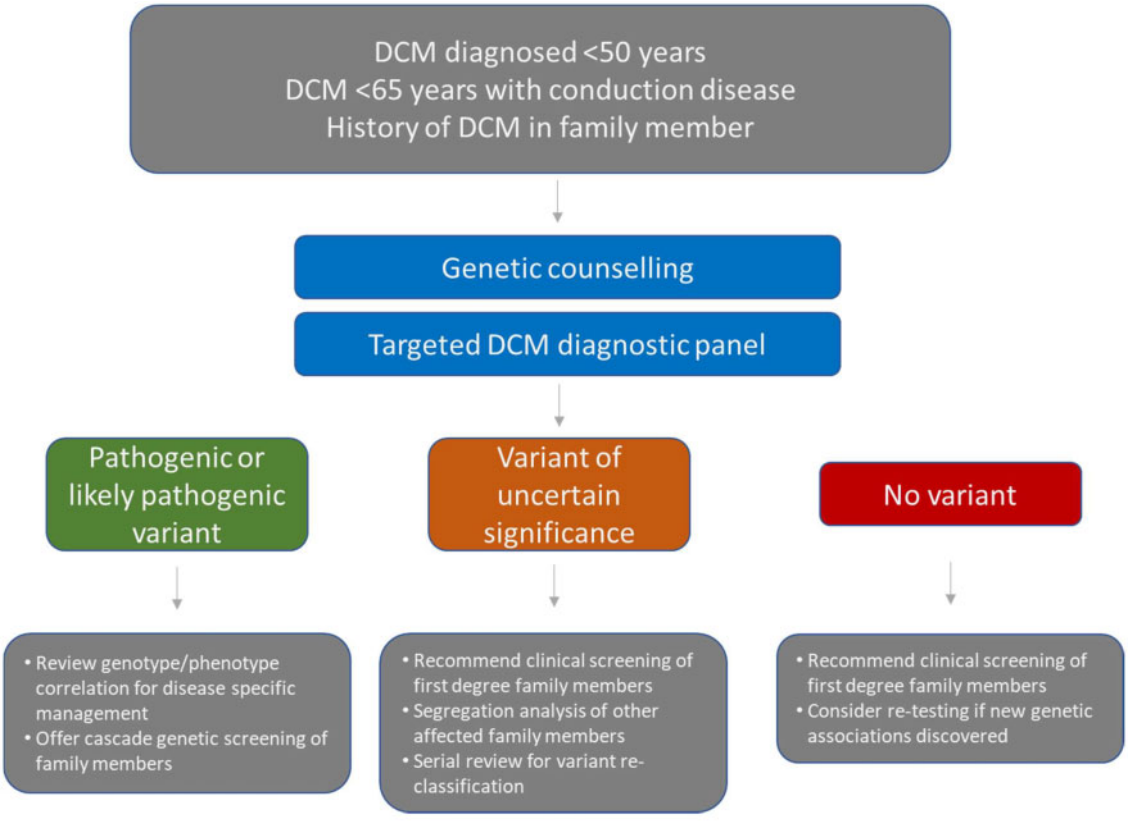
Genetic testing and family evaluation

A key factor in determining treatment in this challenging case was the lead time between initiating genetic testing and receiving a result. Had the genetic results been available during the index admission, a defibrillator would probably have been recommended. Conventional testing in dilated cardiomyopathy (DCM) using a next-generation sequencing panel of 20–30 genes, however, typically takes ∼4–5 months to process. Whilst specialist services, such as those available to us at the Royal Brompton Hospital, can often expedite these processes in cases where a specific genetic result may change patient management, this still typically takes several weeks. Dealing even with these shortened lead times can make decision-making challenging and emphasizes the importance of a shared and multidisciplinary approach and communicating elements of uncertainty to patients and their families.

When seeing a patient with a suspected cardiomyopathy taking a three-generation family history can be crucial for several reasons; it can alert you to cardiac disease in the family indicating an underlying genetic cause and the possible modes of inheritance; it also helps identify the family members who may be at risk and those who will require further screening. However, family histories may also be misleading if they do not fit into the expected pattern of disease, as demonstrated in this case report. The absence of a family history does not rule out a genetic contribution to disease. A patient may be the first person in the family to develop this condition if the variant has arisen *de novo*, as seen in this case. In DCM, we also frequently encounter genetic changes associated with incomplete penetrance and variable expressivity. Truncating variants in *TTN* are the most common genetic cause of DCM, accounting for ∼10–20% of cases.[3] Mounting evidence supports an oligogenic susceptibility to developing a phenotype with classic Mendelian inheritance often absent in family members who carry such variants.[4,5]

* Corresponding author. Tel: +44 2073518800, Fax: +44 20 73518816, Email: b.halliday@imperial.ac.uk

Handling Editor: Amardeep Ghosh Dastidar



LMNA-associated DCM		
Inheritance		Autosomal dominant
Penetrance		Complete by 50-60 years
Phenotype	Structural	Progressive LV impairment with myocardial fibrosis
	Electrical	Atrial fibrillation, ventricular tachycardia, atrioventricular block (may precede LV impairment)
	Extra-cardiac	Emery-Dreyfuss muscular dystrophy, limb-girdle muscular dystrophy
Risk factors for adverse events		NSVT, LVEF<45%, men, non-missense variants [1]

Figure 1 Genetic testing in dilated cardiomyopathy and clinical features typical of laminopathy. DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia.

Can genetic testing help guide treatment in dilated cardiomyopathy?

This leads us on to the importance of identifying individuals who could be at risk of carrying a malignant genetic change. The list of genes associated with adverse outcomes amongst patients with DCM is growing. Whilst the evidence base supporting a more malignant outcome is most convincing for DCM associated with variants in *LMNA*, it is also likely to be the case for disease caused by variants in *FLNC*, *DSP*, *BAG3*, *RBM20*, and *DES*.[5,6] Lower thresholds for device therapy may be warranted in such cases. Whilst these genetic forms of DCM are likely to make up <10% of all patients, it is imperative that such cases are identified rapidly, as exemplified in this report. Knowledge of the phenotypic features that are typical of these cardiomyopathies is important to guide the use of testing (*Figure 1*).[7] Genotype-specific medical therapies targeting the molecular consequences of the underlying genetic cause are also under investigation in phase III clinical trials.[8] Selective inhibition of mitogen-activated

protein kinase has shown potential to modify the disease course of laminopathies in both animal and human studies.[9] Gene editing therapies also offer huge promise in improving the outcome of patients with malignant genetic disease over the next 5–10 years.[10] Genotype is therefore likely to play an increasing role in the management of our patients.

We also use the results from genetic testing to identify those family members who need screening and discharge those who do not. Without actionable genetic findings it is typically recommended that first-degree relatives have clinical screening every 2–3 years. As cardiac genetic conditions are often inherited in an autosomal dominant manner it is expected the 50% of family members who are genotype negative can be discharged following testing, leading to an overall saving of money and resources.[10] When making such decisions, expert variant interpretation is essential, given the inherent risks of discharging individuals incorrectly if the significance of variants is misinterpreted. Frequently there is insufficient evidence to confirm the pathogenicity of a specific variant and it is classified as of uncertain significance. In these cases, having access to a team that can put together the clinical, family, and genetic data in order to help interpret these results is crucial.

It is clear that genetic testing will play an increasing role in the diagnosis and management of patients with cardiomyopathies, identifying at-risk family members, contributing to risk stratification and decision-making regarding implantable devices and also identifying patients who may gain benefit from genotype-targeted medical therapies. Integration of specialist and general services between hospitals in a hub-and-spoke model, as illustrated in this case, enables greater equity in access to genetic services and ensures sharing of relevant expertise and experience. The current COVID-19 pandemic has created many opportunities that enable such streamlined integration of services. Moving rapidly into a more digitally focused way of working has created many opportunities to connect people with diverse skillsets across many locations, many of whom did not have access to such resources previously. Fostering such multidisciplinary working relationships between hospitals will be essential as we move towards a precision medicine approach for patients with genetic heart disease.

Lead author biography

Ms Samantha Mason is a genetic counsellor working at Royal Brompton and Harefield Hospitals. She manages patients with a range of inherited cardiovascular conditions, including cardiomyopathies and inhertied arrhythmia syndromes.

Conflict of interest: none declared.

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