

Genetic Testing for Predisposition to Dilated Cardiomyopathy: A Preliminary Evidence Review

J Franek

March 2012

Suggested Citation

This report should be cited as follows:

Franek J. Genetic testing for predisposition to dilated cardiomyopathy: a preliminary evidence review [Internet]. Toronto: Queens's Printer for Ontario; 2012 March. 14p. Available from: www.hqontario.ca/en/mas/per/pdfs/rev_DCM_March.pdf

Permission Requests

All inquiries regarding permission to reproduce any content in this document should be directed to MASinfo@hqontario.ca.

About Preliminary Evidence Reviews

Preliminary evidence reviews summarize existing evidence and information about health services and technologies that the Medical Advisory Secretariat (MAS) and the Ontario Health Technology Advisory Committee (OHTAC) have been asked to review, but for which there is insufficient evidence available to conduct a full evidence-based analysis. In each instance, OHTAC will have determined that a full review is not possible. In some instances, OHTAC may wish to make recommendations based on the information available in the preliminary evidence review.

About the Medical Advisory Secretariat

Effective April 5, 2011, MAS became a part of Health Quality Ontario (HQP), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by OHTAC—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series*.

Disclaimer

This preliminary evidence review was prepared by MAS for OHTAC and developed from the analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data and information provided by experts and applicants to MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all preliminary evidence reviews: www.hqontario.ca/en/mas/blue_ohtas_mn.html.

Table of Contents

TABLE OF CONTENTS	3
LIST OF ABBREVIATIONS	4
BACKGROUND	5
Objective	5
Clinical Need.....	5
Technology	5
Genetic Testing for Dilated Cardiomyopathy: Process of Testing.....	5
Genetics of DCM.....	6
EVIDENCE-BASED ANALYSIS	8
Research Questions	8
Research Methods	8
Literature Search.....	8
<i>Search Strategy</i>	8
<i>Inclusion Criteria</i>	8
<i>Inclusion Criteria (Research Question 1)</i>	8
<i>Inclusion Criteria (Research Question 2 and 3)</i>	8
<i>Inclusion Criteria (Research Question 4)</i>	9
<i>Exclusion Criteria</i>	9
Results of Evidence-Based Analysis	9
CONCLUSIONS	10
EXISTING GUIDELINES FOR TECHNOLOGY	11
REFERENCES	12

List of Abbreviations

DCM	Dilated cardiomyopathy
FDC	Familial dilated cardiomyopathy
IDC	Idiopathic dilated cardiomyopathy

Background

Objective

The objective of this analysis was to conduct a systematic review of genetic testing for predisposition to dilated cardiomyopathy (DCM) to help guide decisions regarding access to this technology in Ontario.

Clinical Need

Dilated cardiomyopathy is a disease of the heart muscle characterized by ventricular dilatation and impaired systolic function. Dilated cardiomyopathy is characterized as either *idiopathic* (IDC), when the disease appears sporadically, with all detectable causes of DCM being ruled out (excluding genetics); or *familial* (FDC), when IDC is suspected in 2 or more family members (see below). Potential known causes of DCM are vast and include toxic, infectious, or metabolic causes. Other causes include infiltrative and inflammatory diseases. (1)

Dilated cardiomyopathy is a leading cause of heart failure and arrhythmia. Though sudden death is also possible, it rarely constitutes the first symptom of disease. Instead, DCM typically presents clinically with cardiac symptoms including congestive heart failure, fatigue or shortness of breath, arrhythmias or chest pain, palpitations due to arrhythmia, and/or thromboembolic disease including stroke. (2)

Idiopathic DCM has a prevalence of 1 in 2,500 individuals with an incidence of 7 per 100,000 per year. (3) However, DCM is considered largely underdiagnosed since subjects often remain asymptomatic until serious ventricular dysfunction has occurred. (2)

Dilated cardiomyopathy is diagnosed according to specific clinical criteria set by a number of national/international organizations. Full diagnosis typically involves the use of various tests or instruments including serum creatine kinase (CPK) testing, chest x-ray, electrocardiogram, echocardiogram, and other diagnostics. In the absence of any familial linkage, and when detectable causes such as coronary artery disease or thyroid disease are ruled out, a DCM diagnosis is considered to be IDC. (2)

However, when a new IDC diagnosis is made, first-generation family members are typically clinically screened. At the same time, a 3-to 4-generation family history is obtained. Familial DCM is then determined by the presence of: a) 2 or more affected relatives with clinical DCM, or b) a relative of a DCM patient with unexplained sudden death before the age of 35. If other family members with the disease are identified according to the above clinical criteria, the original individual first identified with DCM is often labelled as the proband (or index case), and all affected individuals are now identified as having FDC. It is estimated from large cohort studies that 20% to 48% of those with IDC could be shown to have FDC; however, in the absence of family screening, there are no clinical or morphologic parameters to distinguish familial disease from idiopathic disease. (2)

Technology

Genetic Testing for Dilated Cardiomyopathy: Process of Testing

Genetic testing may be considered at either stage of diagnosis (IDC or FDC). The rationale for testing is multi-fold. Firstly, comprehensive multi-gene or targeted gene testing of the proband is important to i) confirm their cause of DCM and ii) to identify whether they are at highest risk of arrhythmia and

syndrome features. Testing of those individuals specifically with FDC will also facilitate cascade screening within their family, and may help with family planning. (4)

Genetic testing of family members will typically only be undertaken if a causative mutation is identified in the proband. In such scenarios, testing in the family will then proceed through a less expensive single-gene test meant to identify the causative gene mutation. A positive test will therefore identify at-risk asymptomatic family members harbouring the same causative gene mutation as the proband. This can allow for heightened clinical surveillance, better informed medical management/prevention therapy, and reproductive decision-making. A negative analysis, on the other hand, serves as reassurance that this disorder will not occur (for genetic reasons) in this family member. Such a finding is particularly important in children, allowing them to live a normal life (e.g., without needing to avoid high-intensity sport). (4) A negative finding will also allow the individual to discontinue having continued clinical surveillance. In the absence of genetic testing, first generation family members of individuals diagnosed with FDC are typically requested by their treating clinician to return for yearly clinical surveillance. It is however unclear to what extent individuals comply with this recommendation.

Despite the many implications of a positive or negative test, the clinical utility of such testing (i.e., whether testing has a positive impact on clinical outcomes in family members or on clinical decision-making) is unclear, as there have been no formal studies assessing medical intervention in asymptomatic or very early genetic DCM. (5)

Genetics of DCM

The genetics of DCM is complex. The genetic component of disease is confounded by locus and allelic heterogeneity, rare variants, variants that are not causative of disease, incomplete and variable penetrance (i.e., the onset of disease will vary by the individual, even if 2 individuals harbour the same causative mutation), and genotype-phenotype variability (i.e., mutations may result in phenotypically distinct disease). (5)

A recent review by Hershberger and Siegfried (5) now lists 33 genes, 31 autosomal and 2 X-linked, that are associated with DCM. Not only are there a large number of genes associated with DCM, but a mutation in any one gene accounts only for a small fraction of individuals with the disease. For example, mutations in the gene most commonly associated with DCM (known as *LMNA*) have been reported as being causative in only 6% of IDC/FDC unrelated index (proband) patients (meaning that only 6% of unrelated probands are estimated to carry a mutation in *LMNA*). (5) This is in contrast to hypertrophic cardiomyopathy, in which mutations in *MYH7*, for example, have been reported as being causative in 30% to 40% of probands with hereditary/sporadic hypertrophic cardiomyopathy. (6)

Because of the large number of genes associated with DCM and the low causative frequency of the various mutations in these genes, the application of genetic testing for DCM in the clinical setting requires sequencing multiple genes for each patient. A 2010 review by Ontario's Quality Management Program-Laboratory Services (QMP-LS) identified 4 major out-of-country referral laboratories being used by Ontarians for genetic testing of DCM. (7) All referral laboratories included sequence analysis for 3 genes: *LMNA*, *TAZ*, and *ZASP/LDB3*; however, the total number of genes sequenced ranged from 5 to 23. These labs also varied in test methodology, with 2 laboratories using conventional sequence analysis and 2 using a microarray-based next generation sequence analysis. (7) Next generation sequence technologies tend to improve throughput and decrease cost but may not be as accurate as conventional sequence analysis. (5)

With differences in the number and type of genes being sequenced, as well as the sequencing methodology/technology, one can expect large differences in performance from one genetic test to the

next. Genetic tests for DCM should therefore be evaluated independently for clinical accuracy, clinical utility, as well as cost-effectiveness.

Evidence-Based Analysis

Research Questions

1. What is the analytical validity of DCM genetic testing (i.e., how accurately does genetic testing identify mutation)?
2. What is the penetrance of DCM mutations?
3. What is the clinical validity of DCM genetic testing (i.e., how accurately does genetic testing estimate the presence of symptomatic disease)?*
4. What is the clinical utility of DCM genetic testing (i.e., does genetic testing lead to improved patient outcomes compared to no genetic testing and how does genetic testing influence patient and/or-provider decision-making)?*
5. How cost-effective is genetic testing for DCM?

* *primary research questions.*

Research Methods

Literature Search

Search Strategy

A literature search was performed on June 3rd, 2011 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, and EMBASE, for studies published from January 1, 2000 to June 2, 2011. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

Inclusion criteria varied by research question. For all research questions, studies had to include patients diagnosed with DCM using accepted methods and criteria, such as the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) criteria; the Guidelines of the National Heart, Lung, and Blood Institute Workshop on the Prevalence and the Etiology of Idiopathic Dilated Cardiomyopathy; or the Guidelines for the Study of Familial Dilated Cardiomyopathies.

Inclusion Criteria (Research Question 1)

- any technical laboratory report, observational trial, controlled clinical trial, or randomized controlled trial that reported on laboratory performance measures of genetic testing for DCM

Inclusion Criteria (Research Question 2 and 3)

- included a continuous cohort of unrelated index (proband) patients with DCM
- included at least 100 patients with DCM
- genetic testing performed for multiple DCM-related mutations including at minimum 5 genes (i.e., multigene), with at least 2 of those 5 genes being the genes most commonly associated with DCM (*LMNA* and [*MYH6* or *MYH7*])

Inclusion Criteria (Research Question 4)

- any observational trial, controlled clinical trial, or randomized controlled trial in which genetic testing information was used to determine individual treatment decisions
- must have applied an accepted treatment for DCM

Exclusion Criteria

- non-English studies
- articles which did not report original research (e.g., review articles)

Results of Evidence-Based Analysis

There were 2,611 citations identified through literature searching; however, no trials were identified that met the inclusion criteria for the primary research questions (Research Questions 2 and 3), thus preventing a full evidence-based review from proceeding.

Several multigene cohort trials were identified in searching; however, all failed to satisfy the inclusion/exclusion criteria and are referenced for completeness only. (8-16)

Only 1 trial included a cohort of more than 100 unrelated index patients but was excluded because it failed to account for mutations in the *LMNA* gene, the gene most commonly associated with DCM. That trial, by Hershberger et al, (8) used bidirectional sequencing of 6 genes—*MYH7*, *TNNT2*, *SCN5A*, *CSRP3*, *LBD3*, and *TCAP*—in 313 unrelated probands with IDC or FDC. The trial identified 36 of 313 subjects (11.5%) with protein-altering variants that were not observed in 253 control individuals. Of these 36 subjects, 32 were considered to be carrying possibly or likely disease-causing mutations indicating a clinical test sensitivity of 10.2% (32/313).

Please note: since the time of draft publication of this report, at least 1 trial that would have met the inclusion criteria has been published. That trial, by Millat et al, (17) tested 4 genes in 105 unrelated participants with DCM and reported a mutation positivity rate (i.e., sensitivity) of 19%. An abstract by Daly et al (18) reported testing of 27 genes in 248 unrelated participants with DCM and reported a sensitivity of 29%. These trials are referenced for informational purposes only.

Conclusions

- There is insufficient evidence at this time to draw conclusions regarding the clinical application of genetic testing for DCM.
- Due to a lack of clinical evidence, no economic evaluation could be undertaken.
- There is considerable uncertainty surrounding the clinical utility and cost-effectiveness of genetic testing for DCM.
- It is unclear whether sufficient evidence of clinical utility will emerge in the near future given the extreme length of follow-up required to appropriately study the impact of genetic testing on clinical outcomes for individuals with DCM and their families.

Existing Guidelines for Technology

Several professional guidelines are available that provide recommendations for genetic testing for DCM:

The Canadian Cardiovascular Society and Canadian Heart Rhythm Society (1) issued a joint position paper in 2011 that recommends the following: i) for clinically diagnosed DCM, genetic testing is not recommended in the absence of established or probable familial disease as determined by family history and clinical testing of first-degree relatives; and ii) for clinically diagnosed DCM with evidence of probable familial disease, genetic testing is recommended for the primary purpose of screening family members.

The Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) (4) issued a 2011 consensus statement that issues the following guidance: i) comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (i.e., first, second, or third-degree heart block) and/or a family history of premature unexpected sudden death; ii) genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning; and iii) mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.

Lastly, the Heart Failure Society of America issued a 2009 practice guideline that recommends that genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management (for DCM, this received a level of evidence grade of B). (19)

References

- (1) Gollob MH, Blier L, Brugada R, Champagne J, Chauhan V, Connors S, et al. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. *Can J Cardiol*. 2011 Mar;27(2):232-45.
- (2) Taylor MR, Carniel E, Mestroni L. Cardiomyopathy, familial dilated. *Orphanet J Rare Dis*. 2006;1:27.
- (3) Codd MB, Sugrue DD, Gersh BJ, Melton LJ, III. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. *Circulation*. 1989 Sep;80(3):564-72.
- (4) Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011 Aug;13(8):1077-109.
- (5) Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol*. 2011 Apr 19;57(16):1641-9.
- (6) Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. *Nat Clin Pract Cardiovasc Med*. 2008 Mar;5(3):158-68.
- (7) Quality Management Program-Laboratory Services. Project to establish a quality management program for repatriated genetic testing [Internet]. 2010 Mar [cited 2011 Jul 19]. 80p. Available from: <https://iqmh.org/LinkClick.aspx?fileticket=QgPOy7R2%2B%2FA%3D&tabid=244>
- (8) Hershberger RE, Parks SB, Kushner JD, Li D, Ludwigsen S, Jakobs P, et al. Coding sequence mutations identified in MYH7, TNNT2, SCN5A, CSRP3, LBD3, and TCAP from 313 patients with familial or idiopathic dilated cardiomyopathy. *Clin Transl Sci*. 2008 May;1(1):21-6.
- (9) Daehmlow S, Erdmann J, Knueppel T, Gille C, Froemmel C, Hummel M, et al. Novel mutations in sarcomeric protein genes in dilated cardiomyopathy. *Biochem Biophys Res Commun*. 2002 Oct 18;298(1):116-20.
- (10) Kamisago M, Sharma SD, DePalma SR, Solomon S, Sharma P, McDonough B, et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. *N Engl J Med*. 2000 Dec 7;343(23):1688-96.
- (11) Mogensen J, Murphy RT, Shaw T, Bahl A, Redwood C, Watkins H, et al. Severe disease expression of cardiac troponin C and T mutations in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2004 Nov 16;44(10):2033-40.
- (12) Moller DV, Andersen PS, Hedley P, Ersboll MK, Bundgaard H, Moolman-Smook J, et al. The role of sarcomere gene mutations in patients with idiopathic dilated cardiomyopathy. *Eur J Hum Genet*. 2009 Oct;17(10):1241-9.

- (13) Shimizu M, Ino H, Yasuda T, Fujino N, Uchiyama K, Mabuchi T, et al. Gene mutations in adult Japanese patients with dilated cardiomyopathy. *Circ J*. 2005 Feb;69(2):150-3.
- (14) Villard E, Duboscq-Bidot L, Charron P, Benaiche A, Conraads V, Sylvius N, et al. Mutation screening in dilated cardiomyopathy: prominent role of the beta myosin heavy chain gene. *Eur Heart J*. 2005 Apr;26(8):794-803.
- (15) Zeller R, Ivandic BT, Ehlermann P, Mucke O, Zugck C, Remppis A, et al. Large-scale mutation screening in patients with dilated or hypertrophic cardiomyopathy: a pilot study using DGGE. *J Mol Med (Berl)*. 2006 Aug;84(8):682-91.
- (16) Zimmerman RS, Cox S, Lakdawala NK, Cirino A, Mancini-DiNardo D, Clark E, et al. A novel custom resequencing array for dilated cardiomyopathy. *Genet Med*. 2010 May;12(5):268-78.
- (17) Millat G, Bouvagnet P, Chevalier P, Sebbag L, Dulac A, Dauphin C, et al. Clinical and mutational spectrum in a cohort of 105 unrelated patients with dilated cardiomyopathy. *Eur J Med Genet*. 2011 Nov;54(6):e570-e575.
- (18) Daly A, Macaya D, Betman L, Van Goor K, Mitkus S, Chung W, et al. Genetic testing panels as an aid to diagnosis of heritable dilated cardiomyopathy [abstract]. *J Am Coll Cardiol*. 2012;57(14):E2042.
- (19) Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009 Apr 14;119(14):1977-2016.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: MASinfo@hqontario.ca
www.hqontario.ca

© Queen's Printer for Ontario, 2012