Melbourne Genomics
Health Alliance

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Clinical utility of genomics in dilated cardiomyopathy

Background

Melbourne Genomics' Clinical Flagships have been at the forefront of determining when genomic testing makes a demonstrable difference to the safety and quality of patient care.

Dilated cardiomyopathy (DCM) is one of 16 areas of health investigated by Melbourne Genomics. This condition reduces the heart's pumping function – the heart muscle stretches and thins (dilates) which can cause heart failure and sudden cardiac death.

At least one-third of DCM cases are believed to be inherited; genomic sequencing can identify the gene change responsible.

Publications

"A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy", Max Catchpool, Jay Ramchand, Melissa Martyn, David L. Hare, Paul A. James, Alison H. Trainer, Josh Knight and Ilias Goranitis, *Genetics in Medicine* (2019) https://doi.org/10.1038/s41436-019-0582-2

"Mapping the Minnesota Living with Heart Failure Questionnaire (MLHFQ) onto the Assessment of Quality of Life 8D (AQoL-8D) utility scores", Max Catchpool, Jay Ramchand, David L. Hare, Melissa Martyn and Ilias Goranitis, Quality of Life Research (2020) https://doi.org/10.1007/s11136-020-02531-4

"Prospective evaluation of the utility of whole exome sequencing in dilated cardiomyopathy", Jay Ramchand, Mathew Wallis, Elly Lynch, Omar Farouque, Melissa Martyn, Dean Phelan, Belinda Chong, Siobhan Lockwood, Robert Weintraub, Tina Thompson, Alison Trainer, Dominica Zentner, Jitendra Vohra, Michael Chetrit, David L. Hare and Paul James, *Journal of the American Heart Association* (2020) https://doi.org/10.1161/JAHA.119.013346

Project description

The objective: to determine if genomic sequencing can provide a more exact diagnosis from a single test for DCM patients, and whether it can better identify other at-risk family members who may benefit from early intervention.

Patients from four major tertiary cardiovascular centres participated. The inclusion criteria were either a DCM diagnosis before the age of 40, or a family history of DCM and/or early sudden unexplained death.

Patients who agreed to participate in the project underwent genomic testing (whole exome sequencing, WES, with analysis targeted to 247 clinical genes). If testing identified a gene change responsible for DCM in the patient, then 'cascade' single-gene testing was subsequently offered to their relatives to look for the same gene change.

The Dilated Cardiomyopathy Flagship was led by Associate Professor Paul James from The Royal Melbourne Hospital, with key coordination from Dr Jay Ramchand of Austin Health.

Activities

Between April 2016 and August 2017, a total of 94 adult and child patients were recruited from Austin Health, Monash Health, The Royal Melbourne Hospital and The Royal Children's Hospital.

A multidisciplinary team of 21 health professionals from Melbourne Genomics' member organisations were directly involved in this project. Additionally, a team of health economists undertook a model-based cost-utility analysis on whether a genomic diagnosis for DCM patients and cascade testing in asymptomatic relatives was more cost-effective than usual clinical management for at-risk relatives.

Outcomes

Five patients received a diagnosis through WES that would have been missed in usual care. This included a patient and sibling whose risk of sudden death was reduced with defibrillator implants as a result of their testing.

Genomic testing enabled the relatives of patients who received a diagnosis to definitively identify whether or not they require ongoing medical monitoring for DCM. In usual care scenarios (i.e. no genomic testing), heart monitoring is generally offered to *all* relatives of someone diagnosed with DCM. This can mean regular cardiology specialist appointments and monitoring, or defibrillator implantation in some cases.

Lessons learnt

- Compared to offering surveillance to all at-risk relatives, genomic testing of patients with DCM is a more cost-effective means to identify relatives requiring ongoing medical monitoring and intervention.
- The recommended way forward is to prioritise molecular diagnostic testing (WES with targeted gene analysis or multi-gene panel testing) for children with DCM and for adults with DCM with a family history and without hypertension. The costs of WES and multi-gene panel testing are similar.
- Although WES has the advantage of reanalysis as new cardiac genes are identified, cardiologists prefer the more familiar multi-gene panel testing. Any change in testing methodology should be accompanied by continuing education for cardiologists.

Impact

The Flagship highlighted the differences in usual care across four hospital sites in Victoria. All hospitals involved in this Flagship have now implemented testing (either WES or multi-gene panel testing) for patients with DCM as part of standard care for the condition.

Clinical Flagship team

Name	Organisation	Role
Paul James	RMH	Clinical geneticist
Jay Ramchand	Austin Health	Cardiologist
Alison Trainer	PeterMac	Clinical geneticist
Belinda Chong	VCGS	Scientist
Belinda Creighton	Monash Health	Genetic counsellor
David Hare	Austin Health	Cardiologist
Dean Phelan	VCGS	Scientist
Domenica Zentner	RMH	Cardiologist
Emma Creed	RMH	Genetic counsellor
Giulia Valente	Austin Health	Genetic counsellor
Ivan Macciocca	RCH/MCRI	Genetic counsellor
Jitu Vohra	RMH	Cardiologist
Kirsty West	RMH	Genetic counsellor
Matthew Hunter	Monash Health	Clinical geneticist
Matthew Wallis	Austin Health	Clinical geneticist
Omar Farouque	Austin Health	Cardiologist
Robert Weintraub	RCH	Cardiologist
Samia Toukhsati	Austin Health	Cardiologist
Siobhan Lockwood	Monash Health	Cardiologist
Tina Thompson	RMH	Nurse
Yael Prawer	Monash Health	Genetic counsellor