Melbourne Genomics
Health Alliance

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Clinical utility of genomics in bone marrow failure

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. Bone marrow failure syndromes comprise one of 16 areas of health investigated.

Bone marrow failure syndromes (BMF) are a diverse group of potentially life-threatening diseases that can affect people of all ages. These syndromes can be either inherited or acquired, but are difficult to distinguish based solely on clinical presentation and examination.

The underlying cause of bone marrow failure determines the most effective treatment, as the mechanisms of acquired and inherited bone marrow failure are completely different. Thus, identifying the specific genetic change in patients with bone marrow failure is crucial to achieving an accurate diagnosis and has profound implications for care.

Publication

"Utility of clinical comprehensive genomic characterisation for diagnostic categorisation in patients presenting with hypocellular bone marrow failure syndromes", Piers Blombery, Lucy Fox, Georgina L. Ryland, Ella R. Thompson, Jennifer Lickiss, Michelle MCBean, Satwica Yerneni, David Hughes, Anthea Greenway, Francoise Mechinaud, Erica M. Wood, Graham J. Lieschke, Jeff Szer, Pasquale Barbaro, John Roy, Joel Wight, Elly Lynch, Melissa Martyn, Clara Gaff and David Ritchie, *Haematologica* (2020) doi:10.3324/haematol.2019.237693

Project description

The objective: to determine whether comprehensive genomic analysis improves care for patients with bone marrow failure.

Patients were eligible to be tested in the Flagship if they had a clinicopathological diagnosis (observed symptoms and laboratory diagnosis) of an acquired or inherited BMF, or a BMF syndrome unable to be categorised. Due to the rarity of bone marrow failure, the Flagship was open to adults and children (aged at least three months) from across Australia, being treated at the participating hospitals.

The Bone Marrow Failure Clinical Flagship was led by Professor David Ritchie and Dr Piers Blombery (The Royal Melbourne Hospital and the Peter MacCallum Cancer Centre). Key coordination was provided by Dr Lucy Fox (Peter MacCallum Cancer Centre and The Royal Melbourne Hospital); more than 17 health professionals were directly involved.

Activities

Between April 2017 and June 2018, 115 patients were recruited from The Royal Melbourne Hospital, the Peter MacCallum Cancer Centre, The Royal Children's Hospital and Austin Health; 36 of the 115 patients were children (all children were from Victoria).

Patients underwent multi-gene panel testing, with results delivered in real-time for clinical decision-making. Patients also received whole exome sequencing (WES) to capture genes not included in the panel test.

All cases were discussed at multidisciplinary team meetings, which included treating clinicians, molecular haematology scientists, clinical geneticists and genetic counsellors.

Health economists have also undertaken a micro-costing analysis using real-world hospital data from child and adult BMF cases, to determine healthcare resource usage and the difference in expenditure six months before and six months after genomic test results.

Outcomes

Genomic testing provided a specific diagnosis for 37% of patients, changing diagnostic categorisation for 26% of patients.

Among those initially thought to have acquired disease, genomic results changed the diagnosis for six patients. Three were found to have inherited disease and were able to cease treatment for acquired BMF that has significant side-effects and which would have, ultimately, proven ineffective. A further three were found to have progressed to blood cancer and required immediate, aggressive therapy.

Twenty-four patients with an uncertain clinical diagnosis now have a secure diagnosis, allowing treatment to progress with more confidence. One patient had a pre-emptive bone marrow transplant after testing resolved his uncertain diagnosis, showing he was at imminent risk of developing acute myeloid leukaemia. Others have ceased ineffective therapy, commenced therapy, commenced surveillance for known complications or the result is informing transplant planning.

Half of those with suspected inherited BMF (52%) now have a specific diagnosis, informing clinical management and family testing.

Micro-costing analysis demonstrated that genomic testing is only a fraction of the overall cost of managing patients with BMF – contributing to 1.9% of the total cost during patient management before genetic results were returned at The Royal Children's Hospital and 3.9% at The Royal Melbourne Hospital.

Lessons learnt

- The high rate of detection of inherited variants resulted in many family members being referred for genetic counselling and testing. Funding for a comprehensive bone marrow failure service must include consideration of the additional demand this will create for appointments in genetic services.
- Testing identified patients with inherited variants in genes that have only recently been associated with inherited BMF syndromes. Future management of these patients will require both genetic and haematological expertise.

Impact

Results from this study have helped secure research funding to continue to operate the comprehensive bone marrow failure clinic, generating further evidence to support a case for reimbursement for genomic testing (e.g. through Medicare).

The Evaluating Multidisciplinary Bone Marrow Failure Care (EMBRACE) trial at the Peter MacCallum Cancer Centre, led by Dr Piers Blombery and Dr Lucy Fox, is built upon the work completed in the Melbourne Genomics Bone Marrow Failure Clinical Flagship.

Clinical Flagship team

Name	Organisation	Role
David Ritchie	PeterMac/RMH	Haematologist
Piers Blombery	PeterMac/RMH	Haematologist
Lucy Fox	PeterMac	Haematologist
Alison Trainer	PeterMac/RMH	Clinical geneticist
Anna Jarmolowicz	MCRI/VCGS	Genetic counsellor
Anthea Greenway	RCH	Haematologist
Constantine Tam	PeterMac/RMH	Haematologist
David Hughes	RCH	Haematologist
Erica Wood	Monash Health	Haematologist/Registry Director
Francoise Mechinaud	RCH	Haematologist
Gemma Brett	MCRI/VCGS	Genetic counsellor
Georgina Ryland	PeterMac	Molecular scientist
Graham Lieschke	WEHI	Clinical/Research Haematologist
Heather Chalinor	Austin Health	Genetic counsellor
Janine Campbell	RCH	Haematologist
Joel Wight	Austin Health	Haematologist
Kirsty West	PeterMac/RMH	Genetic counsellor

Health economic evaluation for this Flagship was led by Prof Maarten IJzerman at The University of Melbourne and Peter MacCallum Cancer Centre.