Melbourne Genomics
Health Alliance

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Clinical utility of genomics in complex neurological and neurodegenerative diseases

Background

Melbourne Genomics' 16 Clinical Flagships have been at the forefront of determining when genomic testing makes a demonstrable difference to the safety and quality of patient care.

Diagnosis of complex neurological and neurodegenerative conditions typically takes at least three to five years, and can involve multiple, costly and invasive medical procedures. The Melbourne Genomics Complex Neurological and Neurodegenerative Diseases (CNND) Flagship investigated whether genomic sequencing can circumvent this 'diagnostic odyssey' in conditions including: ataxia, early-onset dementia, hereditary spastic paraplegia (HSP), early-onset Parkinson's disease, dystonia, early-onset motor neurone disease and undiagnosed multi-system disease.

Publication

"The clinical utility of exome sequencing and extended bioinformatic analyses in adolescents and adults with a broad range of neurological phenotypes: an Australian perspective", Dhamidhu Eratne, Amy Schneider, Ella Lynch, Melissa Martyn, Dennis Velakoulis, Michael Fahey, Patrick Kwan, Richard Leventer, Haloom Rafehi, Belinda Chong, Zornitza Stark, Sebastian Lunke, Dean G. Phelan, Melanie O'Keefe, Kirby Siemering, Kirsty West, Adrienne Sexton, Anna Jarmolowicz and Samuel F. Berkovic, Journal of the Neurological Sciences (2020) https://doi.org/10.1016/j.jns.2020.117260

Project description

The objective: to determine if genomic sequencing can provide a molecular diagnosis and improve care of patients with complex neurological disorders.

Patients were referred to the Flagship for genomic testing by neurologists, neuropsychiatrists and geneticists from Melbourne Genomics' member hospitals, other hospitals and private practice.

To be eligible, patients could not have had investigations (within the past five years) that could be replaced by whole exome sequencing (WES); all referrals were reviewed for eligibility by the multidisciplinary Flagship team.

The CNND Flagship was led by Professor Samuel Berkovic (Austin Health), with key coordination by Dr Dhamidhu Eratne (The Royal Melbourne Hospital). More than 16 health and medical professionals were directly involved in the project.

Activities

A total of 160 patients were recruited at Austin Health, The Royal Melbourne Hospital, The Royal Children's Hospital and Monash Health, between August 2017 and September 2018.

Patients received WES with analysis targeted to condition-specific gene lists. Multiple gene lists were applied for many patients, especially those with complex or unknown disorders. Where assessed as necessary for individual patients, a list of all genes known to cause human disease was applied.

Outcomes

For all patients diagnosed, testing ended their diagnostic odyssey – an average of 13 years for these patients.

For example, one patient had been incorrectly diagnosed with ‘cerebral palsy’ as a child, had numerous subsequent investigations and was enrolled in a pharmaceutical trial. Genomic sequencing revealed she in fact had one of the most common forms of HSP. With a secure diagnosis, she has now ceased the trial medication (avoiding its related harms) and can now be managed appropriately.

Diagnosis allowed access to more appropriate medical and/or social care for almost two-thirds (61%) of those who received a molecular diagnosis. This not only includes starting or stopping therapies (pharmaceuticals, diets) but better multidisciplinary care coordination (e.g. rehab planning) as health professionals can now better delineate between symptoms associated with the neurological condition and co-conditions. Access to social care and insurance is an important outcome in this group: two patients are now accessing financial support following diagnosis, one through the NDIS and the other through insurance.

Genomic diagnosis appears to offer immediate mental health benefits. For HSP patients receiving a diagnosis, the number with moderate to severe depression or anxiety halved after testing.

Lessons learnt

- Genomic sequencing is most useful for patients with hereditary spastic paraplegia (HSP), ataxia and complex or unknown clinical diagnoses: 40% of patients with HSP received a molecular diagnosis (this number represents additional diagnoses to what would have been achieved through usual care).
- Genomic testing is cost-beneficial for those with HSP compared to panel testing and usual care. Genomics also enables reanalysis of stored data, which is likely to lead to additional diagnoses over time.
- Demand for testing exceeds neurogenetic clinic capacity. Testing for some indications should be performed by neurologists, but continuing education is required first.

Clinical Flagship team

Name	Organisation	Role
Samuel Berkovic	Austin Health	Neurologist
Dhamidhu Eratne	RMH	Neuropsychiatrist
Amy Schneider	Austin Health	Research assistant
Anna Jarmolowicz	RMH	Genetic counsellor
Belinda Creighton	Monash University	Genetic counsellor
Danny Liew	Monash University	Health economist
Dennis Velakoulis	RMH	Neuropsychiatrist
Heather Chalinor	Austin Health	Genetic counsellor
Kirsty West	RMH	Genetic counsellor
Martin Delatycki	MCRI/VCGS	Clinical geneticist
Melanie Bahlo	WEHI	Bioinformatician
Michael Fahey	Monash Health/RMH	Neurologist
Patrick Kwan	RMH	Neurologist
Rick Leventer	RCH	Neurologist
Saul Mullen	Austin Health	Neurologist
Yana Smagarinsky	RCH	Genetic counsellor

The health economists involved in this Clinical Flagship include: Danny Liew and Zanfina Delaney from Monash University, and Ilias Goranitis and Jay Stiles from the University of Melbourne.