Melbourne Genomics
Health Alliance

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# Clinical utility of genomics in complex genetic conditions of children

## 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.

The Melbourne Genomics Childhood Syndromes Demonstration Flagship (2014 to 2015) found that early genomic sequencing for children with suspected monogenic conditions results in five times more diagnoses for at least half the cost of usual testing and care.

But it was unknown was how this test performs for infants, children and adolescents with complex medical presentations.

Many complex paediatric conditions have an underlying genetic basis, often caused by one affected gene (monogenic). These conditions are lifelong and impact multiple body systems. Children are typically acutely unwell, their everyday functioning and daily life is limited, and they require support from many different medical services. Although complex conditions are largely incurable, a clear diagnosis enables optimal and individualised care.

In 2014 to 2015, the average time taken to receive a genomic test result was 136 days. 'Rapid' genomic testing – established in this Flagship for the first time in Australia – aims to return results quickly enough to guide urgent medical care.

In Melbourne Genomics Flagships, 'singleton' (child-only) sequencing is typically performed. Trio testing (child and parents) is used extensively overseas, as it is said to improve diagnostic yield. However, no study to date has directly compared trio and singleton testing in the same group of patients.

## Publications

"A cost-effectiveness analysis of genomic sequencing in a prospective versus historical cohort of complex paediatric patients", Alison Yeung, Natalie B. Tan, Tiong Y. Tan, Zornitza Stark, Natasha Brown, Matthew F. Hunter, Martin Delatycki, Chloe Stutterd, Ravi Savarirayan, George Mcgillivray, Rachel Stapleton, Smitha Kumble, Lilian Downie, Matthew Regan, Sebastian Lunke, Belinda Chong, Dean Phelan, Gemma R. Brett, Anna Jarmolowicz, Yael prawer, Giula Valente, Yana Smagarinsky, Melissa Martyn, Callum McEwan, Ilias Goranitis, Clara Gaff and Susan M. White, Genetics in Medicine (2020) https://doi.org/10.1038/s41436-020-0929-8

"A head-to-head evaluation of the diagnostic efficacy and costs of trio versus singleton exome sequencing analysis", Tan, T., Lunke, S., Chong, B., Phelan, D., Fanjul-Fernandez, M., Marum, J. E., Kumar, V.S., Stark, Z., Yeung, A., Brown, N.J., Stutterd, N.J., Delatyki, M.B., Sadedin, S., Martyn, M., Goranitis, I., Thorne, N., Gaff, C.L., White, S.M., *European Journal of Human Genetics* (2019) doi.org/10.1038/s41431-019-0471-9

"Genetic, radiologic and clinical variability in Brown-Vialetto-van Laere syndrome", Ian R. Woordrock, Manoj P. Menezes, Lee Coleman, Joy Yaplito-Lee, Heidi Peters, Susan M. White, Rachel Stapleton, Dean G. Phelan, Belinda Chone, Sebastian Lunke, Zornitza Stark, James Pitt, Monique M. Ryan, Colin Robertson and Eppie M. Yiu, Semin Pediatr Neurol (2018) doi: 10.1016/j.spen.2017.03.001

"Meeting the challenges of implementing rapid genomic testing in acute pediatric care", Stark, Z., Lunke, S., Brett, G.R., Tan, N.B., Stapleton, R., Kumble, S., Yeung, A., Phelan, D.G., Chong, B., Fanjul-Fernandez, M., Marum, J.E., Hunter, M., Jarmolowicz, A., Prawer, Y., Riseley, J.R., Regan, M., Elliott, J., Martyn, M., Best, S., Tan, T.Y., Gaff, C.L., White, S.M., *Genetics in Medicine* (2018) doi:10.1038/gim.2018.37

# Project description

The objective: to determine the impact of genomic sequencing for children with complex conditions – specifically investigating the usefulness and role of rapid sequencing, and of singleton and trio analysis.

Participating patients were from The Royal Children's Hospital (RCH), Monash Children's Hospital and Austin Health.

The Complex Care Clinical Flagship was led by Associate Professor Sue White (Flagship leader), Associate Professor Zornitza Stark (rapid sequencing) and Associate Professor Tiong Tan (trio sequencing). Dr Alison Yeung provided key coordination for the Flagship, and another 19 health professionals were directly involved.

# Activities

## Rapid genomics

A cohort of 40 critically unwell infants and children with suspected single gene conditions received rapid whole exome sequencing (WES) between March 2016 and October 2017.

A dedicated 'rapids team' – including specimen reception staff, diagnostic laboratory scientists, clinical bioinformaticians, variant curators, referring ICU clinicians, clinical geneticists and genetic counsellors – was established, making large changes to workflow to deliver WES results rapidly.

## Singleton genomics

Between March 2016 and September 2017, 92 children aged 0 to 18 years with complex conditions were offered genomic testing (WES). Information on each child's investigations, diagnosis and care was collected from the time of their tertiary presentation to the year following genomic testing.

A comparator group (who underwent usual investigations only) was established by reviewing all patients referred to the RCH clinical genetics service in 2012 and 2013 (before genomic testing was available). Children identified with complex conditions who would have been offered genomic sequencing (had they been seen in the study period) were selected. Information on investigations, diagnosis and impact on care was collected from the time of a child's tertiary presentation[1] to the year following assessment in genetics.

## Trio genomics

A cohort of 30 infants and children were offered trio testing (in the period March 2016 to October 2017).

Two different approaches to interpreting sequencing data were performed on each case: one analysis included parent data (trio) and the other analysis was only of the child's data (singleton). The two analyses were performed in parallel by randomly allocated teams blinded to one another's analysis.

[1] 'Tertiary' care is here defined as a level of health care obtained from specialists in a large hospital after referral from the providers of primary care and secondary care (such as general practitioners and community paediatricians).

# Outcomes

## Rapid genomics

The median time to a genomic result for these complex, urgent clinical cases was reduced from 136 days to 16 days – almost 10 times faster than standard testing.

Importantly, the majority of children (78%) received results during their first hospital admission.

Rapid testing enabled faster diagnoses, reduced use of other diagnostic tests and procedures, and reduced the length of hospital admissions. For one patient, the resulting reduction in length of stay in ICU is estimated to have saved in excess of $500,000 – more than the cost of testing all 40 children in the study.

Of the 40 children tested, 21 received a diagnosis (53%); care changed for more than half of these children (57%).

## Singleton genomics

Genomic testing as a first-line test almost doubles the diagnostic rate among children with complex conditions. The study cohort had a diagnostic rate of 43%, compared to the 23% in the historical cohort (who underwent usual investigations only).

Additionally, the use of genomic testing decreases the number of invasive tests ordered regardless of the test result. Four times fewer invasive tests were performed.

Diagnoses made through genomic testing had an impact on care, with management changing for one-third (33%) of the study cohort. Care changed for only 8% of children in the historical cohort.

Genomic testing is cost-saving: the total cost of testing and investigations in the historical cohort was $794,026 for 21 diagnoses made, compared to the total cost of $426,387 for the genomic testing cohort with 40 diagnoses made (where the cost of exome sequencing is $2000). Genomic sequencing represents a cost-saving of $19,349 for each additional diagnosis made.

## Trio genomics

Trio testing reduces uncertainty for parents, reduces the need for further testing and avoids false positives (as analysis of both parents and the child together strengthens interpretation of gene changes).

Trio analysis more than halved the time doctors spent prioritising gene changes and freed medical scientists from investigating (interpreting) gene variants shown by parental data to not be disease-causing.

Doctor time per case was reduced from 1,641 minutes for singleton to 697 minutes for trio. Medical scientist time was reduced from 111 minutes to 75.5 minutes.

This means that for every two cases analysed as a trio (rather than a singleton), clinical geneticists would be able to see one new patient and medical scientists can prioritise, interpret and discuss one additional case – increasing overall system throughput.

# Lessons learnt

## Rapid genomics

- Changes to work processes are key to the successful implementation of rapid testing: having a dedicated team reduced delays, with testing moving efficiently from one stage to the next.
- Regular feedback of results between the ‘rapids team’ and intensive care specialists demonstrated the clinical value of genomic testing, leading to earlier referral of patients (before other testing occurs). Over the course of this Flagship, median time to referral reduced from 149 days to 12 days.

- Rapid testing required dedicated laboratory infrastructure, as genomic samples are usually run in batches on large machines. To enable rapid results, a dedicated small-sample sequencer and priority access to computing infrastructure was needed.
- While rapid testing is more expensive than standard genomic testing, there were substantial overall cost-savings through reduced hospital stays and avoidance of other tests, as well as reduced emotional impact on families. Cost-savings were estimated at $543,178 across the rapid cohort (rapids in this study cost $3,949 per patient compared to $2,200 per patient for standard testing, due to amended work practices and dedicated infrastructure).

### Singleton genomics

- Genomic testing ends the usual pathway of invasive investigations, even for children who did not obtain a diagnosis.

### Trio genomics

- Trio analysis reduces workforce burden and would enable more patients to be tested.
- Trio analysis did not lead to more answers for patients, with only one additional diagnosis made. However, the singleton diagnosis rate in this study is much higher than seen at laboratories without integrated clinician input into variant interpretation.
- Trio testing doubles overall costs but saves workforce time. The choice to employ singleton or trio testing is nuanced and should consider system throughput – different approaches will be better suited at different locations across Victoria.

## Impact

This Flagship marks the first time in Australia that genomic testing was offered as a first-line diagnostic test for infant, child and adolescent patients with complex medical needs.

This project was the first study worldwide to compare trio and singleton analysis in the same cohort.

As a direct result of the ‘rapids’ study, clinicians and researchers secured $2.4 million in funding to extend this project in Victoria and roll it out nationally[2] (an Australian Genomics project).

[2] https://www.australiangenomics.org.au/our-research/disease-flagships/rare-disease-flagships/

## Clinical Flagship team

| Name | Organisation | Role |
|---|---|---|
| Sue White | MCRI/VCGS | Clinical geneticist |
| Zornitza Stark | MCRI/VCGS | Clinical geneticist |
| Tiong Tan | MCRI/VCGS | Clinical geneticist |
| Alison Yeung | MCRI/VCGS | Clinical geneticist |
| Anita D'Aprano | RCH | Paediatrician |
| Anna Jarmolowicz | MCRI/VCGS | Genetic counsellor |
| Belinda Chong | MCRI/VCGS | Medical scientist |
| Chloe Stutterd | MCRI/VCGS | Clinical geneticist |
| Dean Phelan | MCRI/VCGS | Medical scientist |
| Gemma Brett | MCRI/VCGS | Genetic counsellor |
| Justine Marum | MCRI/VCGS | Medical scientist |
| Katrina Harris | Monash Health | Paediatrician |
| Martin Delatycki | MCRI/VCGS | Clinical geneticist |
| Mathew Wallis | Austin Health | Clinical geneticist |
| Matthew Hunter | Monash Health | Clinical geneticist |
| Matthew Regan | Monash Health | Genetics fellow |
| Miriam Fanjul-Fernandez | MCRI/VCGS | Medical scientist |
| Natalie Tan | MCRI/VCGS | Genetics fellow |
| Natasha Brown | MCRI/VCGS | Clinical geneticist |
| Rachel Stapleton | MCRI/VCGS | Genetics fellow |
| Sam Ayres | MCRI/VCGS | Genetic counsellor |
| Smitha Kumble | MCRI/VCGS | Genetics fellow |
| Vanessa Siva Kumar | MCRI/VCGS | Medical scientist |
| Yael Prawer | Monash Health | Genetic counsellor |
| Yana Smagarinsky | MCRI/VCGS | Genetic counsellor |

This Clinical Flagship collaborated with Dr Stephen Kingsmore, President and CEO of the Rady Children's Institute for Genomic Medicine.