Melbourne Genomics
Health Alliance

*Global knowledge. Individual care.*

# Clinical utility of genomics in childhood syndromes (12-month follow-up)

## 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.

This study was a 12-month follow-up of the Melbourne Genomics Childhood Syndromes Demonstration Flagship (2014-2015). The follow-up study was designed to address questions remaining about the longer-term clinical and health economic impacts of early genomic sequencing.

One of the stated advantages of genomic sequencing (compared to other tests) is that genomic information can be stored and reanalysed in future, as more is learnt about the causes of disease. This study aimed to address whether reanalysis of stored genomic data led to new diagnoses, and the most cost-effective and clinically useful timeframe for reanalysis.

## Publications

"Exome Sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders", Dillon, O., Lunke, S., Stark, Z., Yeung, A., Thorne, N., Gaff, C., White, S., Tan, T., European Journal of Human Genetics (2018) doi:10.1038/s41431-018-0099-1

"Long-term economic impacts of exome sequencing for suspected monogenic disorders: diagnosis, management, and reproductive outcomes", Deborah Schofield, Luke Rynehart, Rupendra Shresthra, Susan M. White and Zornitza Stark, *Genetics in Medicine* (2019) doi.org/10.1038/s41436-019-0534-x

"Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness", Stark, Z., Schofield, D., Martyn, M., Rynehart,L., Shrestha, R., Alam, K., Lunke, S., Tan, T.Y., Gaff, C.L., White, S.M., *Genetics in Medicine* (2018) doi:10.1038/s41436-018-0006-8

## Project description and activities

In the Melbourne Genomics Health Alliance Childhood Syndromes Clinical Flagship, 80 children under two years with a likely clinical diagnosis received a genomic sequencing test at the same time as their usual investigations and the impact of each pathway was rigorously evaluated.

The follow-up study looked at both aspects of the child's care and family-related outcomes at least 12 months after test results were returned. Further investigations, health utilisation and health outcomes were determined for the children. Cost-effectiveness studies considered the downstream effects of early diagnosis, and were also performed for reanalysis of stored data.

The Childhood Syndromes 12-month follow-up study was led by Associate Professor Susan White and Associate Professor Zornitza Stark (both from Murdoch Children's Research Institute). Health economic analysis was performed with Professor Deborah Schofield.

## Outcomes

This study showed that changes in clinical management and health outcomes for children with an early diagnosis led to cost-savings of $1,578 per quality-adjusted life year (QALY) gained, without increasing the use of hospital services.

Cascade testing of family members resulted in diagnosis of an additional 12 relatives. Two of these had their clinical management altered.

The effect of a diagnosis on parents' reproductive confidence was striking, with nine pregnancies in the diagnosed group compared to one in the undiagnosed group. Genomic sequencing had an additional cost of $8,118 per QALY gained, when the costs and benefits of cascade testing and reproductive service use were considered.

Ongoing usual testing in undiagnosed children did not lead to any new diagnoses. In contrast, four diagnoses were made following reanalysis of stored genomic data. Cost-effectiveness investigations found reanalysis of undiagnosed patients at 18 months offered an incremental cost-saving, with $1,059 saved for each additional diagnosis, compared to the standard care pathway.

## Lessons learnt

- Early diagnosis and changes to management improved health outcomes for children in this cohort, without increasing downstream healthcare costs.
- Reanalysis of stored genomic data is more effective and cost-effective than ongoing testing.

## Impact

This was the first study internationally to systematically follow up patients who had undergone genomic sequencing early in their care.

The evidence generated in this study formed the basis of a Medicare Services Advisory Committee application, undertaken by Australian Genomics using Melbourne Genomics data. Genetic testing for childhood syndromes item numbers 73358, 73359, 73360, 73361, 73362 and 73363 came into effect on 1 May 2020 and is estimated bring at least $21.4 million funding for testing to Victorian patients over the next decade.

## Clinical Flagship team

| Name | Organisation | Role |
|---|---|---|
| Sue White | MCRI/VCGS | Clinical geneticist |
| Zornitza Stark | MCRI/VCGS | Clinical geneticist |
| Alicia Oshlack | MCRI | Bioinformatician |
| Alison Yeung | MCRI/VCGS | Clinical geneticist |
| Belinda Chong | MCRI/VCGS | Medical scientist |
| Charlotte Anderson | Victorian Life Sciences Computation Initiative | Bioinformatician |
| Christiane Theda | Royal Women's Hospital | Neonatologist |
| David Amor | MCRI/VCGS | Clinical geneticist |
| Deborah Schofield | MCRI | Health economist |
| Dylan Mordaunt | Women's and Children's Hospital | Pathologist |
| Emma Creed | Mercy Hospital | Genetic counsellor |
| Gemma Brett | MCRI/VCGS | Genetic counsellor |
| George McGillivray | RCH / MCRI/VCGS | Clinical geneticist |
| Heidi Peters | RCH | Metabolic physician |
| Ivan Macciocca | MCRI/VCGS | Genetic counsellor |
| Joy Yaplito-Lee | RCH | Metabolic physician |
| Katrina Bell | MCRI | Bioinformatician |
| Khurshid Alam | MCRI | Health economist |
| Lilian Downie | MCRI/VCGS | Genetics fellow |
| Luke Rynehart | MCRI | Health economist |
| Maie Walsh | MCRI/VCGS | Genetics fellow |
| Monique Ryan | RCH / MCRI | Neurologist |
| Patrick Yap | MCRI/VCGS | Genetics fellow |
| Paul Ekert | RCH / MCRI | Paediatrician |
| Paul James | RMH / PeterMac | Clinical geneticist |
| Peter Georgeson | UoM | Bioinformatician |
| Ravi Savarirayan | MCRI/VCGS | Clinical geneticist |
| Richard Leventer | RCH / MCRI | Paediatric neurologist |
| Rupendra Shrestha | University of Sydney | Health economist |

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|---|---|---|
| Sebastian Lunke | MCRI/VCGS | Medical scientist |
| Shannon Cowie | MCRI/VCGS | Medical scientist |
| Simon Sadedin | MCRI/VCGS | Bioinformatician |
| Tiong Tan | MCRI/VCGS | Clinical geneticist |