Melbourne Genomics
Health Alliance

Global knowledge. Individual care.

Evaluating clinical utility of genomics: Overview

Background

When Melbourne Genomics commenced there was a dearth of evidence to guide the cost-effective use of genomics in clinical care.

Previous studies had been retrospective: that is, they showed the value of 'catching up' on testing patients who had already been extensively investigated, often for many years. Melbourne Genomics has been first to look *prospectively and comparatively*, through Clinical Flagships that measure the impact of genomics head-to-head with usual investigations in real-world hospital care.

Project description

A Clinical Flagship is a multi-disciplinary team of specialist doctors, geneticists, researchers and medical scientists working together in a specific area of medicine over a two-year period to prospectively provide genomic sequencing to patients and generate evidence for decision-making.

The objective: to provide patients with genomic sequencing and evaluate its effectiveness – in parallel with usual care, in real-time hospital settings, across a wide range of conditions[1].

Flagships identify when genomics is a better approach than usual care and, crucially, when it isn't. They also give insight into health system changes needed to implement genomics into mainstream medical care. Evaluation of each Clinical Flagship built the robust, real-world evidence-base needed to guide clinical and policy decision-making on the implementation of genomic testing in healthcare.

Flagships provide the opportunity to simultaneously:

- Build the expertise of healthcare professionals
- Collect evidence for the optimal use of genomics
- Provide access to genomic testing for patients
- Test clinical workflows
- Test and implement information management systems
- Enable innovation and rapid adoption of new technologies and working practices

Project delivery

Each Flagship addressed one of 16 specific medical conditions (or a group of related conditions)[2]. Patients fitting specific medical criteria were invited by their treating specialists to have genomic

[1] "Preparing for genomic medicine: a real world demonstration of the future" Gaff et al. Genetics in Medicine (2017) doi:10.1038/s41525-017-0017-4

[2] 11 areas of medicine were addressed in the 2016-2019 program (see list in this summary); 5 areas of medicine were addressed in the Melbourne Genomics Demonstration Project (2014-2015). The Demonstration Project Flagships were: Childhood Syndromes, Acute Myeloid Leukaemia, Hereditary Colorectal Cancer, Focal Epilepsy, and Hereditary Neuropathies.

sequencing *at the same time* as the usual testing and care for their condition. The outcomes of each approach were compared to understand what advantage genomic sequencing might offer.

Patients were being treated at one of five major hospitals: The Royal Melbourne Hospital, The Royal Children's Hospital, Austin Health, Monash Health and the Peter MacCallum Cancer Centre. Each Flagship team agreed to commit time and in-kind resources to their project.

Melbourne Genomics gave support to each Flagship:

- A mutually agreed number of funded tests and patients
- Funds for a dedicated clinician-researcher to coordinate recruitment, test results and perform clinical aspects of evaluation (generally 0.3 or 0.4 full-time equivalent)
- At least one dedicated genetic counsellor at each recruiting site to provide pre- and post-test patient counselling
- Core research management expertise: Human Research Ethics Committee and site-specific governance applications and reporting, design of study database and data entry support
- Central evaluation expertise, including facilitation of multidisciplinary collaboration with health economic and other experts
- Laboratory testing pathways, including relevant bioinformatics 'pipelines' and data storage
- Opportunities to communicate and gain profile for the Flagship and its results

A clinical governance framework delineated the responsibilities of laboratories, clinical services, researchers and the Melbourne Genomics program team.

Health economic analyses were also planned, and appropriate expertise secured to undertake these activities.

Activities

Application and selection

Two 'tranches' of Clinical Flagships were selected through independent expert review. Six were selected from a first round of applications in late 2015 (for projects running 2016 to 2018) and a further five from a second round in late 2016 (for projects running 2017 to 2019).

The application process called for potential Flagship teams to be formed among the 10 Melbourne Genomics Health Alliance member organisations. Teams were required to be cross-hospital and cross-disciplinary. They were asked to demonstrate a case for: genomics' likely benefit in their area of medicine, their capability to run a two-year clinical research project, and their willingness to collaborate as a team and with the Melbourne Genomics program team across evaluation, professional education and data and technology.

A total of 34 applications[3] were received in the two rounds, demonstrating the wide potential for genomics in healthcare and the high level of enthusiasm among health professionals.

Individually, the selected Flagships represented those best demonstrating the case for genomics; as a group, they were chosen to provide perspective across healthcare – adult/paediatric care, conditions with a well-established/recently established genetic basis, and germline (rare and inherited diseases) / somatic (cancer) / bacterial (superbugs) testing – and to enable development of expertise across the Alliance.

The goal was to enable optimal evaluation of genomics' effectiveness broadly in practice.

[3] 15 in the first round (2015) and 19 in the second round (2016).

Establishment and patient recruitment

To ensure quality and consistency across projects, each Flagship worked closely with the Melbourne Genomics program team to establish and refine:

- Key evaluation questions and evaluation plans
- Patient recruitment criteria
- Genomic testing pathway/workflows, including return of results
- Data collection and data management processes

Between April 2016 and December 2018, a total of 3,539 patients at the five participating hospitals received genomic sequencing across 11 Clinical Flagship projects. More than 5,000 individual genomic tests were completed.

Patients' genomic testing was performed in NATA-accredited laboratories, with Flagship clinicians providing clinical input into variant prioritisation and participating in multidisciplinary review before written reports were issued.

Every Clinical Flagship had to establish and then continuously improve workflows and processes for genomics to be incorporated into patient care. This process is breaking the ground for future, larger-scale application of genomics within the healthcare system in Victoria.

Evaluation and evidence

The Melbourne Genomics evaluation team collaborated with Victoria's Department of Health and Human Services to devise a format for evidence to be reported directly from the Clinical Flagships to Government. These evidence reports have enabled a pipeline for Flagship key findings to rapidly and effectively flow to government, informing policy in real-time, pre-publication.

Twenty-six evidence reports have been delivered to the Victorian Government since mid-2018 communicating clinical utility findings, health economic analyses, and implementation lessons or challenges identified. Other evidence reported includes overall patient experience data, impact of genomics on genetic services, implications from a demonstration study offering additional genomic findings, professional education and workforce development, and genomic data storage.

List of Clinical Flagships

The six Clinical Flagships running during the period 2016 to 2018 were:

- Advanced Non-Hodgkin Lymphoma
- Advanced Solid Cancers
- Complex Care in Children
- Congenital Deafness
- Dilated Cardiomyopathy
- Immunology

The five Clinical Flagships running during the period 2017 to 2019 were:

- Bone Marrow Failure
- Complex Neurological and Neurodegenerative Diseases
- Controlling Superbugs
- Genetic Kidney Disease
- Perinatal Autopsy

More than 200 healthcare and research professionals were directly involved across the 11 Clinical Flagships in the 2016 to 2019 program[4]. Many more professionals were involved indirectly, for example in referring patients and/or in attending multidisciplinary meetings.

Outcomes

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.

Overall, across the 11 Clinical Flagships, 19 times more patients received informative results[5] through genomic testing in comparison with usual care. Informative results were given to 42% of patients tested for cancer or rare disease, leading to more precise care for half of those with such results.

Individual patient diagnoses and treatments resulting from Flagships have been life-changing for hundreds of patients, and life-saving in some cases.

Through the Flagships, genomic testing has helped some patients avoid further invasive, painful and unnecessary tests, some to receive more precise and personalised treatment, and some to stop receiving potentially harmful therapies.

Genomics also identified almost one-third more superbug transmissions than usual testing alone.

Actual healthcare dollars were saved – more than half a million dollars in one project alone – and health economic analyses point to more cost-effective healthcare in a number of areas that could be realised through evidence-based use of genomics.

Efficiencies in the test process were also gained. Two laboratories introduced new multidisciplinary meetings as a fixed element in the testing workflow: to prioritise variants for interpretation (for genetic conditions), and to obtain oncology input into variant interpretation prior to reporting (for cancer).

Impact

Evidence from the Flagships has to date resulted in national Medicare funding – for genomic testing for children with some suspected rare genetic disorders – with others likely to follow. Evidence has also informed the addition of superbugs *Acinetobacter*, *Pseudomonas* and *vanA* VRE to the list of notifiable infections in Victoria.

The cost-effectiveness evaluations have proved world-leading, attracting international interest and frequently cited (including in calls for reimbursement for genomic testing).

Results from the Flagships have garnered recognition and additional funding for Victoria's clinicians and researchers (e.g. in the field of the genomics of bone marrow failure), and national-scale projects (e.g. in rapid genomic testing for infants in intensive care, which was pioneered in Victoria through the Flagships).

Confidence and knowledge in using genomic testing to improve patient care has grown among a wide cohort of healthcare and laboratory professionals – providing a strong footing for future larger-scale implementation in Victoria.

Evaluation results demonstrating the clinical utility and cost-effectiveness of genomic testing have been presented nationally and internationally, and 24 peer-reviewed publications have been published up to March 2020.

[4] A further 50 health professionals were directly involved in the Demonstration Project Flagships.

[5] An 'informative result' is a genomic result that contributes to diagnosis and/or is potentially actionable. This encompasses results that exclude suspected genetic conditions (informative negative result) and/or the identification of a variant that allows use/cessation of a particular therapy.

Lessons learnt

Conduct of Flagships

- Funding for dedicated clinician time is crucial to successful Flagship delivery.
- A clear, documented delineation is required between activities that fit under clinical governance and those that fit within research governance.
- Central evaluation expertise with linkages to other experts, including health economics, enables experience and learnings from Flagships to be applied across different settings.
- Evidence generated from Flagships can lead to change in government and hospital policy.

Evaluation of Flagships

- Evaluation must be planned at the outset of each Clinical Flagship. Continual review and iteration are required to produce robust evidence to guide the use of genomics in clinical care.
- Experts in clinical care need to work with a range of research disciplines to design and conduct a meaningful evaluation.
- Genomics necessitates new methodologies for health service evaluation and health economic analysis, and the data needed for this kind of evaluation is *not* routinely captured during patient care.
- The two-year duration of Flagships precluded longer-term follow-up of impact and health economics.

Genomics is here, now

- There is demand for access to genomics across most medical specialities. The number of applications for Flagships was more than triple the number of Flagships available.
- An increase in the ability to diagnose earlier and potentially influence management has created demand and changes in referral patterns from other clinical services to genetics services.
- Clinical genetics services are now interacting with more medical specialities than ever before and seeing patient groups they would not have seen in the past.

One size does not fit all

- Flagships required varying levels of interaction with hospitals' clinical genetic services, but all (except Controlling Superbugs) required some interaction.
- Genomics can be complex for patients to understand. In addition to the genetic-counselling-related issues that have always been present, there are additional challenges, including concerns around privacy and protection of data.
- Treatment-directed genomic testing adds extra complexity for patients and clinicians.

Resourcing to enable change

- Investment in workforce is required to support mainstreaming of genomics. This includes clinical geneticists, genetic counsellors, medical scientists, bioinformaticians and administrative staff.
- Flagship clinicians play an important role in providing discipline-specific genomics education and expertise within their medical speciality.
- Genomics is not just about funding the test – there are system-level changes that need to occur when establishing a genomic medicine service. These include system-level changes in laboratories – including bioinformatic pipelines and data management – and within existing hospital systems.

- Effective and efficient communication between clinical and laboratory staff is critical to delivering an efficient service.
- The increasing numbers of patients accessing testing is resulting in unmet need for post-test support.
- Models tested may not adequately support genomic testing for rural and regional patients. The nature and magnitude of barriers are not known, but are likely to include local providers' knowledge and availability of locally funded tests.