BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024681
Article Type:	Protocol
Date Submitted by the Author:	13-Jun-2018
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Keywords:	Genomics, complexity, implementation, behaviour change, sustainability, translation

A transformative translational change programme to introduce genomics into healthcare: a complexity and implementation science study protocol

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Word count: 5194

ABSTRACT

Introduction: Translating scientific advances in genomic medicine into evidence-based clinical practice is challenging. It is essential to study the natural translation of genomics into 'early-adopting' health system sectors, such as the Australian and Melbourne Genomics Health Alliances. We outline a novel methodological approach, taking a complexity science perspective, using implementation-effectiveness, translation, and behaviour change frameworks for a) examining 29 health systems (Australian and Melbourne Genomics Health Alliance Flagships) integrating genomics into practice, and b) combining this learning to co-design and test an evidence-based generalisable toolkit for translating genomics into Australian healthcare.

Methods and analysis: 29 Flagships integrating genomics into clinical settings are studied as individual complex adaptive systems (CASs) to understand emergent and self-organising behaviours amongst interrelated actors and processes. The Effectiveness-Implementation Hybrid approach is applied to gather information, alongside extended comparative-effectiveness tests of genomics, on the delivery and potential for real-world implementation of genomics. Study stages '1' and '2a' represent Hybrid Model 1 and are the focus of this protocol. Nested within Hybrid Model 1 and applied across both stages, the Translation Science to Population Impact (TScImpact) framework is used to study policy decisions and service provision. The Theoretical Domains Framework (TDF) is used to understand individual level behaviour change.

Stage 1 synthesises interview data from 32 participants involved in developing the genomics clinical practice systems and approaches across five 'demonstration-phase' (early adopter) Flagships. In Stage 2a, service provision, policy, and clinical stakeholders are providing quantitative and qualitative data on process mapping, clinical audits, uptake and sustainability (TScImpact), and psychosocial and environmental determinants of change (TDF). Findings will be synthesised before co-designing a foundation intervention toolkit to

facilitate implementation of genomic testing. Study methods to test the implementation toolkit effectiveness are summarised.

Ethics and dissemination: Ethical approval has been granted. The results will be disseminated in traditional academic forums and will be used to refine interventions to translate genomics evidence into healthcare practice.

Key words: Genomics, complex adaptive systems, evidence based implementation, natural experiment, behaviour change, policy, sustaintability, translation

Strengths and limitations of this study

Strengths and limitations of this study include:

- A naturalistic study of complex change for the application of genomics into the health system
- A novel methodological approach to the study of complexity that could be applied more widely
- An approach to understanding reality and how to generate the ideal for implementation
- A demonstration of how complexity principles can be incorporated into the application of behaviour change theory
- A challenging undertaking to consolidate multiple components of complexity into a generalisable implementation package

INTRODUCTION

Since the birth of the genomic era almost 15 years ago,[1] substantial efforts have focussed on developing laboratory based genomic sequencing capabilities and large scale sequencing studies to understand the significance of sequence variation on health. In recent years there has been an increasing focus on the application of this information in health care, for example

to improve the diagnosis and/or treatment of disease. The speed of scientific advances, however, has exceeded the ability of health systems to establish what the ideal conditions, systems, and behaviours ought to be for using genomics in complex healthcare settings. Rather, iterative attempts to apply genomics within existing (often pre-genomics) clinical practice, generate emergent routines with varying levels of suitability, efficiency and sustainability. This *'real'* state of affairs is influencing the implementation of genomics into routine care in the absence of evidence based, *'ideal'* approaches. A lack of implementation science evidence is one of a long list of well documented challenges limiting the effective implementation of genomic research into complex healthcare systems.[2] A 2017 review highlighted the lag in evidence to support implementation, demonstrating that very few studies to date have: a) incorporated implementation science theoretical frameworks, sustainability measures, or capacity building, b) focussed on macro-level factors (e.g., health systems, policies, financing), and c) attempted to develop and evaluate evidence based strategies for enhancing the implementation of genomic medicine.[3]

The continuous adhoc, emergent and self organised translation modes manifesting within complex health care systems, as they attempt to keep pace with the constant stream of new genomic evidence, undoubtedly contribute to the challenges faced in designing protocols to study and test approaches to implementation. Disentangling the way in which the actors in the system (e.g., clinicians, patients, researchers, policymakers, planners and decision makers) perceive, experience, and *naturally behave* under these real world complex conditions is crucial for understanding the true adoption, impact, and likely sustainability of genomic testing. It is also key to discovering the *'ideal'* and to designing real-world interventions to support the implementation of long-term, cost-effective genomics policy and practice. In this paper, we outline a novel methodological approach, using complexity science, translation, and behaviour change frameworks, to study the integration of genomics

into clinical practice as part of a national natural experiment, and develop a generalisable, evidence based package for implementation.

The Australian Genomics Health Alliance (Australian Genomics) is a national network of state-based genomics initiatives, working together to translate genomic approaches into clinical practice. In 2014, the Melbourne Genomics Health Alliance (Melbourne Genomics) commenced a demonstration project, which laid the foundations for Australian Genomics, was awarded $25M over five years (2016-2020). Together these Alliances have placed emphasis on understanding, from a service level and clinical practice perspective, how genomic sequencing can be implemented in health care. Their Flagship programs are central to achieving these insights. A Flagship is a multidisciplinary clinical group (e.g., medical professionals, diagnostic laboratory staff, genetics counsellors, etc.) working together, often across multiple hospital sites, to provide genomic sequencing for defined clinical indications according to a broad framework.[4] From the inception of the demonstration project in 2014 through to 2020, 29 Flagships will be evaluating the use of genomics in clinical practice, across diverse clinical conditions (Figure 1), involving specialists from at least 16 different health professional disciplines from up to 18 hospitals and 4 hospital laboratories across Australia. The first five Melbourne Genomics flagships have already undergone a formal evaluation to assess the effectiveness of genomic sequencing for the purposes of early detection, treatment and, where possible, prevention of major disease.[5-7]

There is an immediate need to understand the emergent service provision pathways and clinical processes for genomic sequencing to ensure that its impact in widespread practice lives up to the promise of the results of the Flagships[7 8] established under the auspices of a research program. The Flagships exemplify a large scale attempt to integrate genomics into everyday healthcare. Therefore, in addition to establishing the clinicial validity

and utility of genomics, Flagships are perfectly positioned for a naturalistic experiment of the factors affecting the successful implementation of genomics into the Australian healthcare system, and for testing the impact of evidence based approaches to ensure sustained, effective use. Each Flagship represents a complex adaptive system (CAS);[9-11] there are a number of complex features (e.g., emergent behaviours, self-organisation, non-linear processes, co-evolution, behaviours at the edge of chaos, nested systems, interconnectivity and networks, and simple rules which beget complex behaviours)[12-15] within each of the participating Flagships, and interactions between their component parts. As such, this research will use a complexity science lens, combined with implementation science and behavioural approaches, to investigate and support the integration of genomics into the health system. Whilst the Flagships are distinguishable in form, with unique structural and cultural characteristics, each has been established with a common underpinning framework (Australian and Melbourne Genomics). Therefore, studying all 29 Flagships using a common approach is invaluable, as this permits evidence based examination of their functioning and outcomes.[16] It also provides insights into improvements in processes and procedures over time, and enables comparison and, where appropriate, consolidation of findings across Flagships. Uniquely, then, we are able to study each individual Flagship as a CAS and also identify commonalities across them to produce generalisable knowledge to support the translation of genomics evidence into practice.

There are three broad and interacting elements of complexity within a Flagship, or CAS, model (Figure 2). First, *'clinical versus implementation effectiveness'*: whilst attempting to test the effectiveness of genomics in the clinical setting, the impact of the broader health system (e.g., behaviours, resources, logistics, politics, etc.) can often distort what we come to understand about the success of diagnostic testing and subsequent treatment decisions.[17-19] Determining, through rigorous research designs, how best to work with these

health system factors to implement testing and treatment effectively is crucial.[20] Second, '*policy decisions and service provision'*: for the sustained and evidence-based use of clinically effective genomics, it is important to identify which of the key resources needed for sound genomics practice are being funded through the Melbourne Genomics/Australian Genomics program, and plan for the commissioning of these resources once programmatic funding has ended. Furthermore, organisational, local area, and national level policy decisions (relating to, for example, Medicare funding, resourcing, management, de-implementation, etc.), are likely to be affected if genomic practice is endorsed. Therefore, understanding and planning for the management of such changes will be key for successful long-term implementation.[4] Third, *'individual level behaviour change'*: the implementation of genomics into clinical practice will inevitably require both clinical and administrative practice change.[2 21]

Sitting both within and across each of these three broad elements of complexity are key complexity principles, which include, behaviours at the edge of chaos (high variety and creativity; the boundary between chaos and order), self-organisation (constant reorganisation of hierarchies and behaviours to adapt to the environment), and emergence (random actions that eventually generate patterns which change behaviour and the system). Studying the emergent and self-organising behaviours within different Flagships throughout the continuous flux will be vital for both identifying which of these behaviours to embed,[22] and where support through evidence based implementation can be beneficial.[14] Furthermore, whilst we cannot study the elements and principles of complexity in isolation, using appropriate frameworks to understand them, and synthesising this information in a way that helps to understand both successful emergent behaviours and gaps in practice, is likely to facilitate more effective intervention development.[23]

To address the first element of complexity (*clinical versus implementation effectiveness*) the Effectiveness-Implementation Hybrid approach – a way of blending design components of clinical effectiveness and implementation research,[20] will be applied to the Flagships across the five year research program (see Figure 1). To summarise, first (the focus of this protocol) we will test a clinical intervention (in our case 'genomic sequencing') whilst gathering information on its delivery during the effectiveness trial and/or on its potential for implementation in a real world setting (Hybrid model 1); second we will test a clinical intervention and an implementation/intervention strategy simultaneously (Hybrid model 2); and finally an implementation /intervention strategy will be tested while observing/gathering information on the clinical intervention and related outcomes (Hybrid model 3).

Nested within the Hybrid Model 1 approach, the Translation Science to Population Impact (TSci Impact)[24] framework will be used to study the second element of complexity (*policy decisions and service provision*), and the Theoretical Domains Framework (TDF)[25-31] will be used to study the third (*'individual level behaviour change*). The TSci Impact framework provides a systematic approach to investigate the complex processes and mechanisms through which tested and proven interventions are integrated into practice and policy in a large scale and sustainable way. This framework was designed with complexity (or 'systems') science in mind,[32-35] to take into account the complex interrelationships between infrastructure and contextual influences within and across translation phases, and promotes the study of complex interactions within and across implementation systems. The TSci Impact framework favours and facilitates the synthesis of information to understand clinical trial outcomes within organisational settings, combined with community action research for rich accounts of how culture, context, local decision making and history influence implementation of evidence based practice.[24]

The TDF is a psychosocial and environmental framework of behaviour change that enables reliable and valid identification of psychosocial and environmental barriers and facilitators (e.g., motivation, emotions, resources, social influences) to practice change. A key feature of the TDF includes the need to establish key target behaviours, and so as part of this work and aligning with ideas drawn from complexity science, we will incorporate the development of clinical process maps to understand the emergent, self-organising, and networking behaviours within and between individuals in the system, and to establish the *ideal* from the *reality*[36 37] as these Flagships initiate the foundations of genomics in their local setting. In addition, investigating facilitators of behaviour change (or intuitively derived interventions[38]) allows for the naturalistic assessment of emergent and self-organised behaviours central to complexity theory. Finally, the TDF has previously been successfully used to synthesise determinants of behaviour and interventions collected using no prior framework, or alternative frameworks.(e.g.,[39 40 41)] By studying Flagships as CASs, this work aims to identify common features of these systems and networks. As such, this is an unrivalled opportunity to use the TDF to synthesise the complexity across and within Flagships into a holistic intervention package, combining knowledge of successful emergent behaviours with strategies to address genomics implementation problems in a targeted, standardised, and generalisable fashion.

Aim and objectives

This paper provides an outline of a five year transformative translational change program, and specific details for the initial two-year phase, to study and support the implementation of genomic testing into routine healthcare in clinical, organisational and policy contexts across Australia. The objectives of the first phase are to study Melbourne Genomics and Australian Genomics Flagships to:

1) Understand the emergent and self-organising behaviours during the implementation of genomics into practice
2) Identify successful emergent behaviours and gaps in practice
3) Synthesise this information using a theoretical framework
4) Co-design, with clinicians, a foundation intervention package to facilitate the implementation of genomic testing into clinical practice

METHODS AND ANALYSIS

Context: Flagships

Under the Melbourne Genomics and Australian Genomics program of research, each of the 29 Flagships represents a test of the integration of genomics into the clinical setting in parallel with usual (non-research funded) care, incorporating research consent processes into care processes delivered by genetic counsellors. Given this is a test of diagnostic capability, as opposed to a treatment intervention, it is possible to administer both usual investigations and the new investigation (genomic sequencing) to the same patient. Both the yield of the test and the clinical decisions resulting can be determined.[42] As such, as opposed to a randomised controlled trial, which is both unnecessary and inequitable under the given circumstances, each flagship is incorporating an extended version of a comparative effectiveness research (CER) design,[43 44] which adds the assessment of clinical and patient utility to the standard CER health outcome measure.

The interrelated actors and processes manifesting as part of each Flagship represent a CAS, as demonstrated by generic Flagship context examples of key CAS components in Table 1. Flagships will, therefore, be studied as an individual CAS to understand the emergent and self-organising behaviours. In addition, commonalities of integration across

CASs will be studied to support the development of an implementation framework for future real world healthcare organisations planning to translate genomics into practice.

Table 1. Flagships as CAS

CAS component	Flagship example
A large number of elements which interact dynamically	Key Flagship elements include patients (and their own influences outside the official health care system), staff (different professions, different hierarchies, different approaches to decision making), locations (multiple sites and also labs and clinicians not colocated), resources (time, money etc), organisations, leadership, clinical processes, research processes – all of which will interact
Any element in the system is affected by and affects several other systems	For example, the flagship is operating within the broader health system CAS incorporating new genomic investigations and procedures within existing patient care pathways and evaluating the process and outcomes. This involves an iterative process affected by and affecting pre-existing clinical and laboratory systems for patient assessment, decision making and patient consent for the genetic diagnostic process, sign off, counselling, sampling, transit, batching, sequencing, computational access, analysis, interpretation, reporting, etc. Different professions interact throughout this process to make a final decision
Non linear interactions, so small changes can have large effects	Whilst the necessary steps must be taken to start and complete the process to finalise and communicate any given genetic diagnosis, the interactions within and between each stage are non-linear and iterative. Furthermore, the exploratory nature of Flagships under a research program introduces further ambiguity.
Openness, so it may be difficult to define system boundaries	As a broad example, the funding of resources for genomic sequencing within the participating health services overlaps with existing government commissioned resources for a Flagship. As a research program operating in a real-world health system, this scenario may affect clinical decision making for patients due to boundaries within which clinicians must operate stipulated in research protocols A more specific example includes the uncertainty held regarding whether or not and when to communicate incidental findings to patients, and the ethical decision making behind undertaking secondary analysis of previously collected samples as new genes are

	discovered Whilst knew knowledge for patient diagnosis and treatment is a clear benefit from the continuously evolving basic and clinical research perspective, impact on practice can involve period of time where there is more ambiguity and uncertainty about what is best for patients. Policies help to define this but generate boundaries, which can be frustrating, particularly if they are not up to date with new evidence. This can be where deviations can arise and new, informal, unrecorded patterns emerge.
A constant flow of energy to maintain the organisation of the system	Flagships require all those involved in completing the diagnostic process to be on board, but as with any health system, perceptions of value of different parts of the process, including the outcome, can vary and evolve amongst both patients and professionals. This affects the willingness to participate and the flow of energy in the system
A history whereby the past helps to shape present behaviour	The involvement of genetics – and genetic specialists – in patient care differs across Flagships. The extent of this past involvement and the nature of the relationships between disciplines and different locations influences the introduction of genomics, specifically the protocols and procedures, as well as dynamics within a Flagship.
Elements in the system are not aware of the behaviour of the system as a whole and respond only to what is available or known locally.	For example, Flagships are operating as externally funded entities within the existing health care system – individuals are well aware of the need for funding but not so much the need to disinvest; they are also primarily concerned with the operations and need of their own Flagship(s), whilst there are other Flagships as well as the health system as a whole, which have different circumstances, and are having an impact/being impacted upon

Research design

As part of the five year complexity-implementation science research plan, our design provides methodological details for the two stages used to investigate Hybrid Model 1: gathering information during the effectiveness trial (in this case an extended CER) of a clinical intervention on its potential for implementation in a real world situation. Stage 1, a data recoding exercise, has been completed and stage 2a is underway, collecting data across

at least a further 6 project areas Flagships (see Figure 1). A summary of methods to be applied for the Hybrid Model 2 and 3 are also provided. A Logic Model (Figure 3) presents the activities, outputs, and outcomes of Stage 1 and 2a. The Standards for Reporting Implementation Studies (StaRI) Checklist[45] will be used to support the planning and reporting of intervention strategies and implementation effectiveness.

Participant identification and data analysis will involve an expert resource group for interpretation and clarification of findings, consisting of experienced clinicians and researchers, each bringing academic and/or contextual knowledge from participating sites. The following section contains details of participants and recruitment, data collection tools, research procedures and data analysis plan for stage 1 (post flagship implementation) and stage 2a (pre, during and post flagship implementation).

Stage 1: Hybrid Model 1; post-implementation

Stage 1 Participants and recruitment

Stage 1 builds on the work of the Melbourne Genomics evaluation team interviewing 32 clincians across five Flagships in the demonstration phase. Individuals who were involved in developing the systems and approaches [e.g., variant curation pipeline, variant classification frameworks, consent forms and reporting templates for Whole Exome Sequencing (WES) etc.], including genetic clinical specialists, and non genetic clinical specialists who attended more than two multidisciplinary meetings over the demonstration phase, were invited to participate via email.

Stage 1 Data collection tools

Structured interview schedule (Supplementary file 1): The schedule was used to gather data retrospectively for the Melbourne Genomics evaluation from stakeholders in the

demonstration phase. Questions focussed on aspects of the first implementation of WES into clinical practice: a) role in the project, b) experience (as a clinician or medical scientist), c) perceptions of multi-disciplinary variant meetings, d) views on policy decisions and procedures e) impact on their understanding, and f) factors affecting integration into practice. Probes for questions in each topic area are also provided for interviewers to maximise the quality of information gathered.

Evidence based interview coding tools: Whilst the data from these interviews was originally used to obtain insights into the *'what'* of the flagship, additional tools have been selected to code these interviews from an evidence based, behavioural perspective. More specifically, TDF coding and behaviour change techniques guidance,[25-27] and agreed definitions of the TDF in the genomic context (see Table 2)[46] was used to: 1) identify behavioural areas for change, 2) group key barriers and enablers to implementation of genomic sequencing according to theoretical domains of behaviour change, to 3) capture any behaviour change techniques (BCTs)[26] represented in any exisiting or new intuitive intervention strategies described by participants.

Table 2: Recoding Guide

TDF domain	TDF domain definition (Cane et al. 2012)	Definition in context
Knowledge	An awareness of the existence of something	Clinicians' actual awareness and understanding (through education/training) of the principles and process of offering genetic testing in clinical practice
Skills	An ability or proficiency acquired though practice	Clinicians' actual physical and psychological ability or proficiency acquired through actual practice (as opposed to education/training – cannot get skills through education) to make decisions whether or not to offer genetic testing in practice
Memory, Attention and Decision	The ability to retain information focus selectively on aspects of the	Clinicians' ability to remember to consider genetic testing alongside other interventions

Processes	environment and choose between two or more alternatives	for health risk identification, diagnosis, management, and therapy
Behavioural Regulation	Anything aimed at managing or changing objectively observed or measured actions	Clinicians' self-created or self-imposed regulation to help make decisions about offering genetic tests
Social Influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours	Interpersonal interactions between professionals that can influence clinicians' thoughts, feelings or behaviours (ie anything in Motivation) regarding offering genetic testing
Environmental Context and Resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities independence, social competence and adaptive behaviour	Any external circumstance of a clinicians' situation or environment that clinicians consider discourages or encourages them to offer genetic testing in practice, including impacting the development of capability, motivation or social opportunity to offer genetic testing.
Social/Professional Role and Identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting	Clinicians' perceived professional role and identity in relation to offering genetic tests
Beliefs about Capabilities	Acceptance of the truth, reality or validity about at ability, talent, or facility that a person can put to constructive use	Clinicians' perception about their own capability to consider genetic testing (terms used in literature: confidence, comfort, control)
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Clinicians' optimism or pessimism that genetic testing will be appropriately integrated into clinical practice and will improve healthcare generally
Beliefs about Consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation	Clinicians' perceptions about the value of offering genetic testing in clinical practice – whether it is worthwhile in that it will improve patient outcomes in their own practice (term used in literature: attitude)
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way	Clinicians' intentions to consider genetic testing
Goals	Mental representations of outcomes or end states that an individual wants to achieve	Whether clinicians offering genetic testing is a priority within their practice
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency,	Incentives, rewards, sanctions, reinforcement at any level (eg patient satisfaction; better client health; economic incentives) that

	between the response and a given stimulus	encourage or increase clinicians' decisions to offer genetic testing
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter	Clinicians feelings when they consider genetic testing

Stage 1 Procedures

Two behavioural researchers independently recoded ten of the Melbourne Genomic evaluation interview data according to the TDF, then compare findings for inter-rater reliability. The remaining 22 interviews will be recoded by one researcher. Where there are differences or queries a TDF expert will be used to advise on the appropriate coding. Once complete the recoded data will be discussed with the expert resource group for sense checking.

Stage 1 Data Analysis Plan

Interview data will be audio recorded, fully transcribed and entered into NVivo 11 (QSR International Pty Ltd., 2015). Analysis will vary dependent on the interview intent. The TDF reanalysis of the Melbourne Genomic data will establish target behaviour areas and key barriers to focus on in subsequent interviews. The recoding process using the TDF will also allow identification of psychosocial domains within each target area. Domains not identified will be included in the stage 2a clinical process interviews to identify if they have relevance within each target area.

Stage 2a: Hybrid Model 1 pre, during, and post implementation

Stage 2a Participants and recruitment

Two key participant groups, each of which will be recruited for one or more of the different interviews and focus groups will be drawn from the Australian and Melbourne Genomic Flagships. Given the focus on service provision and policy, and clinical process aspects of implementation, the target groups for participation represented these areas:

a) Service provision pathway participants: Decision-makers and stakeholders (both clinical and administrative) who play a key role in either flagship leadership, funding and financing strategies, genomic testing characteristics and costs, organisational and community factors or policy.

b) Clinical process delivery participants: Clinical non-genetics medical specialists (e.g., oncologists, neurologists,).

Table 3: Stage 2a Interview Inclusion Criteria

Service provision participant inclusion criteria	
Inclusion Criteria	**Justification**
Strategic decision makers or	Involved with direction and funding for services including genomics
Service level managers or above (e.g. CEO) or	Will have either signed off on a flagship application, have a flagship running in their organisation, or be managing a flagship
Senior clinical geneticists	Will have an overview of genomic testing in more than one flagship across clinical genetics and medical specialities
Flagship involvement from any phase of implementation	To gather views across the implementation journey
Draw participants from a cross section of locations	To ensure a broad representation of views
Clinical processes participant inclusion criteria	
Inclusion Criteria	**Justification**
Medical specialists (excluding clinical geneticists)	Focus of study is mainstream tertiary implementation in the long term
AND working within a flagship	Practitioner will have genomics knowledge

Flagship involvement from any phase of implementation	To gather views across the implementation journey
Working in Australian Genomics or Melbourne Genomics flagship	These are the sites for the genomic work
Draw participants from a cross section of locations	To ensure a broad representation of views

Selection criteria will be established (see Table 3) to facilitate recruitment of expert informers for interview based on their experiences of implementation of genomics in their organisation. Individuals fulfilling the inclusion criteria will be identified using the knowledge of the expert resource group. Recruitment for individual interviews and focus groups will consist of multiple strategies, including making use of the networks of the expert resource group to facilitate research-participant contact; individual emails will be sent. Interview times and locations will be arranged based on convenience for interviewees to enhance the likelihood of participation.

Stage 2a Data collection tools

A process mapping guide (Figure 4), a clinical audit, two semi structured interview schedules (Supplementary File 2 and 3), and an intervention co-design guide (Supplementary File 4) will be used to gather qualitative and quantitative data.

Clinical process mapping template: informed by stage 1 interviews and the expert resource group, the template (Figure 4) will present an outline of the WES process to participants, covering a) the patient presenting at clinic, b) the process for analysis, and c) communication of results to patient. Each section will act as a prompt to clarify processes and an opportunity for participants to amend the outline process map in relation to processes specific to their clinical area (e.g., childhood syndromes, cancer, etc.) with regards to where processes begin and end, tasks involved, who contributes, who is affected, and where glitches occur in the

system. This will enhance understanding as to how current clinical processes have emerged and are currently operating from a pre-, during-, and/or post-implementation of WES perspective. Furthermore, emergent barriers to implementation, and any current or suggested intervention strategies captured as part of these discussions will be noted.

Clinical practice audit tools: collects information about recorded practice prior to, during and post-implementation of genomic sequencing. Audit data will be collected to reflect key components of the process map to demonstrate where gaps, blocks, and problems exist in the system. For example, date stamped data of the detailed patient journey from referral into WES, test ordering and interpretation, and communication of results to patients will be collected and matched to specific process map steps.

Clinical processes interview schedule: collects views from non-genetic clinical specialists on the early, mid and late phases of implementing a flagship. The interview schedule, informed by the results of the Stage 1 TDF-coded interviews, and informed by the Melbourne Genomics Community Advisory Group, is framed according to relevant TDF domains. Questions enquire about the same three key behavioural areas examined in the process map: a) the patient presenting at clinic, b) the process for analysis, and c) communication of results to patient. For example, in the third behavioural area, 'communicating results,' the question relating to the 'emotion' TDF domain is *When results are uncertain how do you feel about feeding this back to the patient*? And for the 'optimism' TDF domain; *What gives you confidence that this process is being handled well?*.

Service provision interview schedule: collects views from key decision makers and stakeholders on factors influencing the uptake of genomic medicine at different phases of implementation, and on preparing for the transition from flagship to ordinary clinical service status for the sustainability of genomic testing once programmatic funding has ended. Areas

identified for exploration at interview were debated with the expert resource group, with Spoth et al's (2013) TSci Impact framework being favoured for investigating translation phases of pre-adoption, adoption, implementation, and sustainability from a service provision and policy perspective. Some interviewees will need to reflect back on the early phases of pre adoption, while others will be in the translation function so will be able to draw on current experiences. To facilitate interview participants' focus on the phase under discussion a graphic has been developed to use at interview (see Figure 5). Working through the translation phases, questions focus on the following topic areas: 1) gaining clinical genomic knowledge; 2) influences on the decision to adopt; 3) the impact of the organisational setting and health system; and 4) influences on sustainability including disinvestment.

Barrier verification and implementation intervention co-design guide: This two-phase guide will present a summary of information gathered in the process mapping interviews and audit data cross-matching exercise, and the clinical processes and service provision interviews (across the respective associated behavioural/topic areas covered), synthesised according to the TDF domains and BCTs. In phase 1, prompts and materials (Supplementary File 4) will be provided to encourage discussion about the barriers list presented, to elicit information about any additional barriers, and to narrow down a list of key barriers to focus upon. In phase 2b, a provisional list of intervention strategies that could be used to address those barriers will be presented. Guidance will be provided to facilitate the design of any new interventions using BCTs. A matrix will be provided to facilitate ranking of the interventions according to feasibility and impact on the associated barriers and subsequent behavioural areas (Supplementary File 4).

Stage 2a procedures for interviews and pre-focus group data synthesis

Generic interview procedure: Before commencing all interviews, the interviewer (SB) will go over consent procedures, provide a Participant Information Sheet, obtain permission to record the interview, and then record verbal consent. The interview, which is likely to last around 60 minutes, will be recorded using a digital recorder, then transcribed. All participants will be assigned a code (e.g.Participant CP/SL 1, 2 3 etc) and interviewees will only be identified via these codes. Digital audio files will be imported into the software Nvivo 11 (QSR International Pty Ltd., 2015) to facilitate analysis.

***Process mapping interview and integration with audit data*:** Hard copies of outline process maps (Figure 4) will be handed to clinical process interviewees to prompt discussion about the process for that particular clinical area (e.g., paediatric rare diseases, cancer, etc.), inform refinements to the map, and elicit information about barriers and facilitators to undertaking the process. These data will be transferred into Microsoft Visio software; participants will be contacted via email, and asked to review their revised map and suggest any refinements. The provisional list of audit data collection variables will be finalised on the basis of the process map, collected via organisation electronic and/or paper based patient records, with relevant information cross-matched to specific parts of the process. The outputs of this stage of the project will be: a) a detailed, visual, and data-verified outline of clinical area-specific processes for genomic testing pathways, and b) a data-driven method of identifying key gaps or imperfections in the process, and c) a set of emergent barriers and existing or potential interventions for improvement of processes.

Clinical process: The TDF based interview schedule (see Supplementary File 2) will be used with clinical process interviewees to discuss, using the lens of a psychosocial and environmental theoretical framework, barriers and facilitators to implementation of genomics in clinical practice, and to elicit information about existing or potential interventions for

improvement. The outputs from this data collection procedure will be information on TDF based barriers and emergent interventions.

***Service provision and policy interviews*:** The TSci Impact framework based interview schedule (see Supplementary File 3) will be used with service provision and policy interviewees to discuss factors influencing the uptake of genomic medicine at different phases of implementation using the lens of translating science into policy and services perspective. Outputs here will include, data on policy and service provider factors affecting implementation pathway, and information on emergent barriers and interventions.

Stage 2a Data-informed focus group schedule development and data collection

***Preparation of focus group materials through synthesis of interview data**:* Data from the stage 1 recoding, and stage 2a process mapping/audit data, clinical process, and service provision interviews will be synthesised by the expert resource group in preparation for the focus groups (Supplementary File 4). For both clinical processes and service provision and policy, summary tables will be developed with a set of key target areas for improvement, context specific barriers and corresponding TDF domains, emergent intervention strategies alongside corresponding BCTs, and instructions for ranking the likely impact and feasibility of intervention strategies. Key barriers from all the clinical speciliaties will be combined to develop generalisable interventions.

Focus Groups (two phases): The synthesised data will be used with a multidisciplinary group of clinicians and service provision/policy decision makers to verify barriers and co-design an implementation strategy using both emergent and evidence based behaviour change approaches. Using the materials from the data synthesis exercise, the discussion in phase 1 will be used to verify and identify any additional barriers, and to rank barriers according to level of impact on behavioural areas. Phase 2 discussions, informed by phase 1 and with a

provisional list of intervention strategies, will be used to co-design interventions to address the high impact barriers to implementation using the most feasible and likely impactful intervention strategies.

Stage 2a Development of foundation intervention package

A draft intervention package will be developed using the recorded and written focus group data to present intervention strategies to address key barriers to clinical processes and service provision implementation of genomics evidence into practice. Both interview/focus group participants, the expert resource group, and the Consumer Advisory groups of the Australian and Melbourne Genomics Health Alliances will be invited to review the contents of the first iteration of the genomics implementation toolkit.

Stage 2a Data Analysis Plan

***Data Synthesis prior to focus groups*:** Intial synthesis will be undertaken by SB. The process mapping and clinical audit data will be analysed for data on processes, individual interactions, data driven gaps (within the four target areas) and also emergent barriers and interventions. Clinical process interview data will be analysed deductively using the TDF to identify key domains representing barriers to change, and appropriate BCTs will be mapped to these domains as an evidence based approach to intervention strategy development.[25-27] Service provision interviews will be thematically analysed and used to identify key areas for development of service provision planning. These data will also be analysed according to the TDF and BCTs to facilitate the combined approach to developing clinical process and service provision interventions for the two phase focus groups. These processes, barriers and intervention data within the target areas will be collated and shared with the expert resource group. The expert resource group will analyse these data and develop the focus group

materials to demonstrate key reported barriers to and suggested intervention strategies for effective implementation of genomics in practice.

Focus group analysis: Individual focus group analysis will be undertaken using the TDF and BCTs to identify validated and new barriers to change, and BCTs, respectively. Results of this exercise from each focus group will be provisionally combined to generate the first iteration of the genomics implementation toolkit.

Patient and Public Involvement

The Stage 2a clinical processes interview schedule is informed by the results of the Stage 1 TDF-coded interviews. Patient and public involvement was sought from the Melbourne Genomics Community Advisory Group. Through a facilitated discussion the group identified their priorities areas for implementation and sustainable delivery of genomics (for example "how do you manage patient expectation?") which were incorporated into the interview schedule. Findings from data collection will be discussed with the Consumer Advisory groups of the Australian and Melbourne Genomics Health Alliances and they will be invited to review the contents of the first iteration of the genomics implementation toolkit.

ETHICS AND DISSEMINATION

Ethical approval for this study has been granted by Melbourne Health HREC on November 3, 2017, approval number: HREC/13/MH/326. Governance approval has been provided by participating organisations.

Dissemination of results will be undertaken through traditional academic forums, but also through the information generated through this research being used to refine and apply evidence based and pragmatic interventions into health systems for the translation of genomics into practice.

DISCUSSION

In Australia, the majority of clinical genomic sequencing is currently funded through research activities. Melbourne Genomics and Australian Genomics bridge the gap between research and established clinical practice. They represent systematic national and state-based efforts to integrate genomics into everyday healthcare at the coal-face. For the majority of Flagships and health professionals working within them – many of whom are not experts in the field of genomics – this is the first time genomic sequencing tests have been available to them 'in real time'. Whilst they are making efforts to incorporate this into their practice, it is impossible for clinicians – genetic and non-genetic alike – to know what the '*ideal*' is yet. Therefore, no precedent exisits for *effectively* implementing genomics into practice for numerous clinical conditions across different contexts. The diversity of health professional disciplines, health care organisations and clinical indications participating across the 29 Flagships, will realise the ultimate goal of this work: to establish the '*ideal*' and develop a generalisable model of implementation that future organisations can apply and tailor to their local contexts.

The detailed methods for the current body of work – stage 1 and 2a, forming the foundations of this transformative translational change program, have been presented here. Future work will then build on data and strategies developed as part of Hybrid Model 1. To summarise, Hybrid Model 2 (see Figure 1 - Stage 2b) will consist of a simultaneous test of the clinical effectiveness of genomic sequencing and the implementation toolkit concurrently[20] in new Flagships. Quantitative and qualitative measures for assessing implementation effectiveness will be developed. A formal, concurrent test of the clinical effectiveness of genomics and the implementation toolkit will be undertaken, allowing for a detailed analysis, distinction, and explanation of the complex factors associated with clinical versus implementation effectiveness. These findings will be used to further refine the toolkit.

The final stage (Hybrid model 3) (see Figure 1 - Stage 3) will focus on testing the refined implementation toolkit while simply observing the genomics intervention, and related outcomes.[20] Consolidating the earlier work, this stage will include real world testing of the implementation toolkit (e.g., RCT; stepped wedge trial) against a comparison, and/or with a standard roll out, with the aim of informing state and national policy and decision making.

This is the first nationally based real-world study of a large cohort of CASs, deliberately attempting to integrate genomics into a real world, complex health system. To study and support implementation of a technology with far-reaching consequences but currently limited evidence base, we have developed a novel methodological approach consisting of complexity science, policy and service provision, and individual level behaviour change frameworks, and progressively more rigorous research designs. Disentangling clinical research processes from those which support adoption of a new standard of care, our work will provide streamlined recommendations for future healthcare organisations planning to translate genomics into their health system. This methodology may be one that lends itself to study and support the adoption of other potentially 'paradigm shifting' technologies.

LIST OF ABBREVIATIONS

BCT	Behaviour change technique
CAS	Complex adaptive system
TDF	Theoretical Dmains Framework
TSci Impact	Translation Science to Population Impact
WES	Whole Exome Sequencing

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AUTHORS' CONTRIBUTIONS

NT conceived, designed and developed the detail of the study, provided advice for ethical approval, led and coordinated writing the paper. SB developed the detail of the study design, co-led the ethical approval and co-led writing the paper. MM conceived and co-designed the study details, led the ethical approval process, and reviewed the paper. JCL co-designed the study details, provided advice for ethical approval and reviewed the paper. KN is the Chief Investigator for the Australian Genomics Health Alliance NHMRC grant; she contributed to conception of the study, provided strategic input and reviewed the paper. JB contributed to conception of the study, provided advice, strategic input and expertise in implementation and complexity science, and reviewed the paper. CG conceived and co-designed the study, provided advice, strategic input and reviewed the paper. All authors read and approved the final manuscript. KN, CG and JB are chief investigators on the National Health and Medical Research Council grant funding the Australian Genomics Health Alliance.

FUNDING STATEMENT

The Melbourne Genomics Health Alliance is funded by the Victorian Government and the ten Alliance members (Royal Melbourne Hospital, Royal Children's Hospital, the University of Melbourne, Waltear and Eliza Hall Institute, Murdoch Children's Research Institute, Commonwealth Scientific and Industrial Research Organisation, Australian Genome

Research Facility, Peter MacCallum Cancer Centre, Austin Health, Monash Health). The Australian Genomics Health Alliance is funded by NHMRC grant 1113531.

COMPETING INTERESTS STATEMENT

NT, SB, MM, JCL, KN, JB, CG have declared that no competing interests exist.

Tables, Figures and Additional Files

Tables

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Supplementary Files

Supplementary File 1: Stage 1 Evaluation Structured Interview Schedule

Supplementary File 2: Stage 2a, Semi Structured Interview Schedule, Clinical Processes

Supplementary File 3: Stage 2a, Semi Structured Interview Schedule Service Provision

Supplementary File 4: Co design guide for Focus Groups

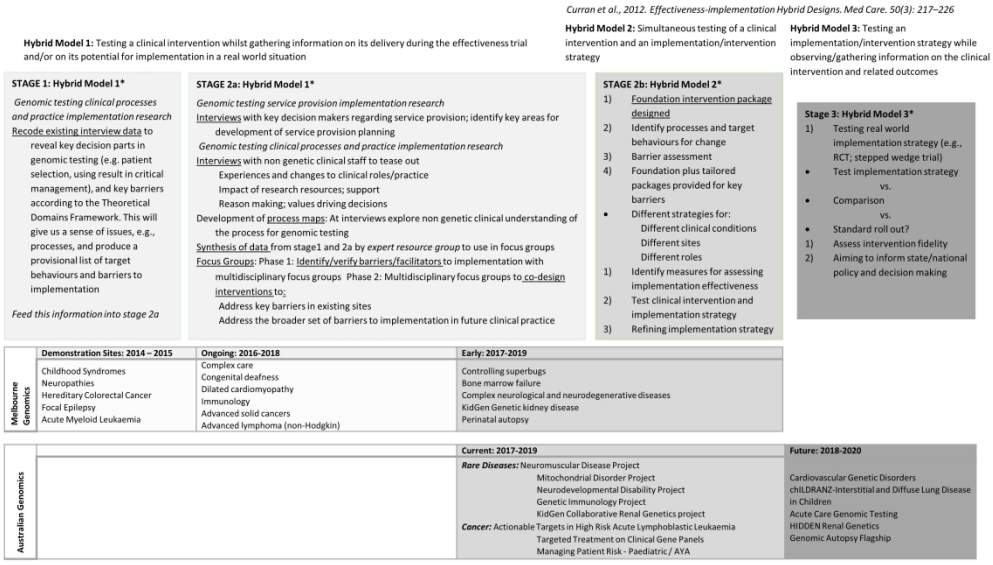

Figure 1: Implementation Research Plan

338x190mm (300 x 300 DPI)

Broad elements of complexity	Principles of complexity	Model or Framework used to understand and respond to complexity
Clinical effectiveness versus implementation effectiveness	- Edge of chaos - Self-organisation - Emergence - Simple rules - Iteration - Sub-optimal - Requisite variety - Interconnectivity and networks - Co-evolution - Nested systems	Effectiveness-Implementation Hybrid Model
Policy decisions and service provision		TSCimpact Model
Individual level behaviour change in a complex adaptive system		Theoretical Domains Framework

Figure 2: Frameworks to manage Complexity

338x190mm (300 x 300 DPI)

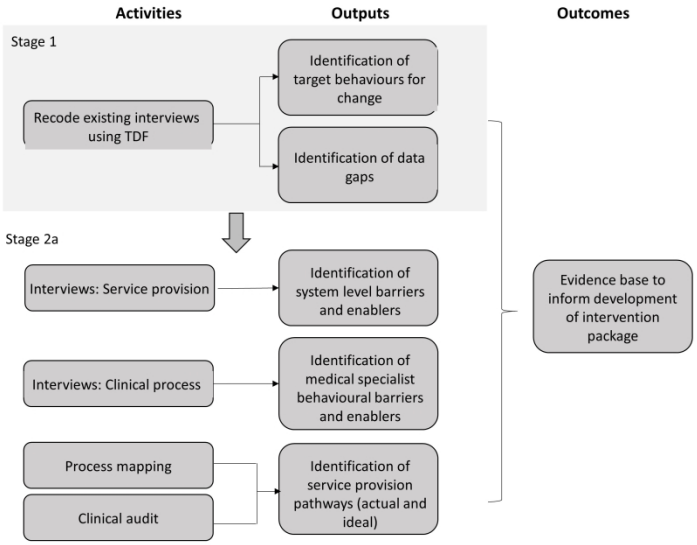

Figure 3: Logic Model

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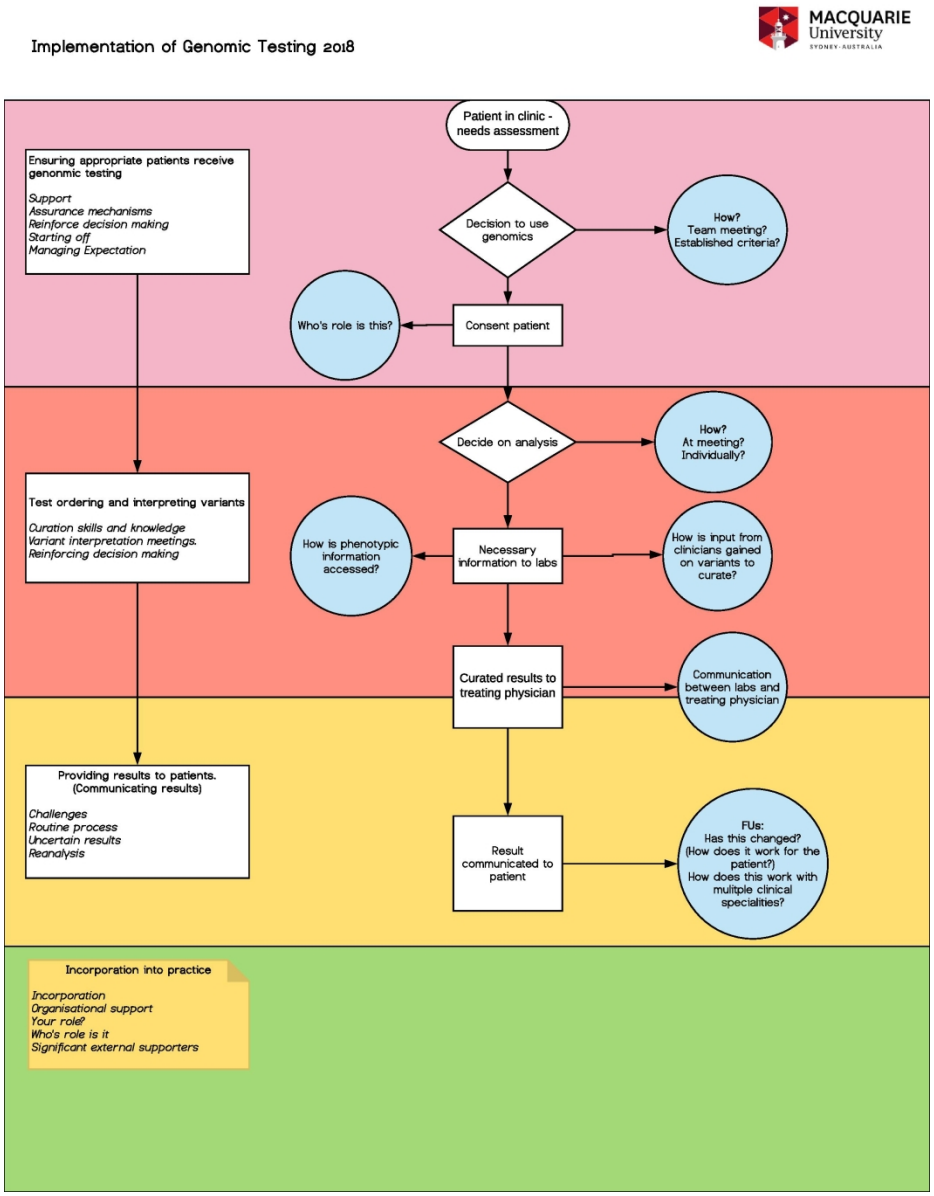

Figure 4: Process Mapping Guide

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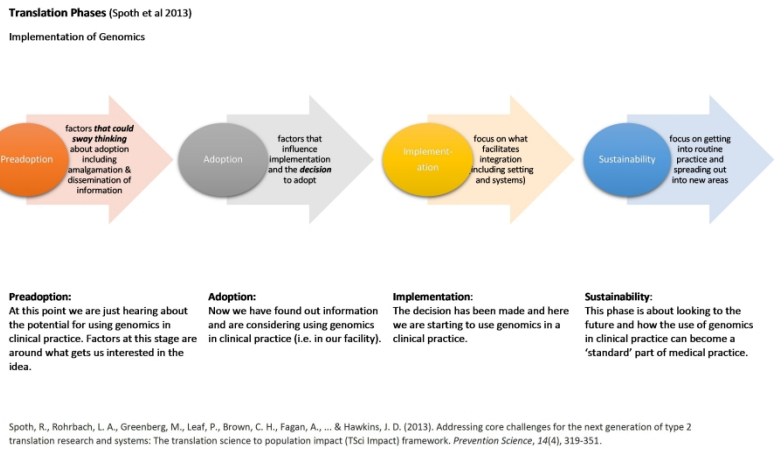

Figure 5: Service Provision Interview Translation Phases Graphic

338x190mm (300 x 300 DPI)

Supplementary Files

Supplementary File 1: Stage 1 Evaluation Structured Interview Schedule

Supplementary File 2: Stage 2a, Semi Structured Interview Schedule, Clinical Processes

Supplementary File 3: Stage 2a, Semi Structured Interview Schedule Service Provision

Supplementary File 4: Co design guide for Focus Groups

Supplementary File 1: Stage 1 Evaluation Structured Interview Schedule

Clinician Interviews – themes and questions

Theme	Questions
Experience of participating in the demonstration project	1. Please tell me about your involvement in the demonstration project 2. From your perspective, what was the purpose of the MDT? How clear was this to you at the beginning? 3. Do you feel the MDT altered over time? How? 4. What did you like about the MDTs? 5. What do you think should be done differently? 6. On a scale of 1-5 how satisfied were you with the MDTs? *(5 very satisfied, 4 satisfied, 3 neither satisfied nor dissatisfied, 2 dissatisfied, 1 very dissatisfied)* 7. What do you think is important to discuss during pre-test counselling? *8.* Did you receive a research report on any of your patients? How many? What type? *(1/2nothing reported, 3 VUS, 4b, 4a/ 5)* 9. Were you involved in returning results to patients? 9.1. If yes, How did you approach this? *Be aware may differ for diff types of result (nothing found, 3 VUS, 4a or 4b, 5).* 10. Thinking about the sorts of results you usually communicate to patients, was there anything different about returning this sort of result? 11. So if I were to ask you to rate the difficulty you'd say it was… *More difficult, the same as, less difficult* do you agree?'
Impact (What has the impact been? How have results impacted?)	12. What impact has participating in this project had on your (clinical) practice? 13. What impact has participating in this project had on your understanding of genomics?

Integration in future practice	14. Putting issues of funding aside, would you use/support the use of clinical genomic sequencing if it were available in (your) practice? If yes – when is there value in using it If unsure/ no – tell us more about this. 15. What do you anticipate the barriers to incorporating genomics into practice (*in your specialty*) might be and how could these be overcome? *(funding model, clinician time, support for clinicians to attend from clinical managers)* 16. If genomic sequencing were to be offered in routine clinical practice, how do you think decisions would be made about 16.1. when to use exome sequencing? 16.2. interpretation of results 16.3. which genes to analyse 17. What did you think about the approach Melbourne Genomics took of excluding genes for unrelated adult onset conditions to minimise incidental findings? Do you think patients should have the choice to receive information about variants that show a future risk of disease unrelated to their condition? 18. Given that new genes are being identified and VUS are being reclassified as more is known, who do you think should be responsible for initiating a re-analysis in the future?
Resources to support integration	19. For which of these stages do you think resources would be helpful? 20. What information would need to be included? 21. What other resources might be helpful? 22. What are the advantages/disadvantages of an online portal?
Final messages	23. From your involvement in the demonstration project, what are the 3 things you want your hospital to keep in mind as genomics is implemented in clinical practice? 24. Is there anything else you want to make sure the Alliance of organisations takes into account?

Supplementary File 2: Stage 2a, Semi Structured Interview Schedule, Clinical Processes

Could you tell me what your role is and how you have been involved with the use of genomics in the clinical setting?

Ensuring appropriate patients receive exome sequencing **(Emotion,** Reinforcement, Behavioural regulation)	**Domain**
What measures are in place to assure yourself that you are selecting the appropriate patients?	Behavioural regulation
Is there anything in place that makes this process work well routinely?	Reinforcement
What were your experiences of starting off offering testing - how did you become more proficient? What helped (or would have helped)? Have you always been comfortable offering genomic testing in your clinical practice? What changed your mind?	Skills, Beliefs about capabilities, Beliefs about consequences, Emotion
What are your experiences of managing expectation? How have you found this? What has made it easier?	Exploratory q from patient consultation Emotion
Test ordering and interpreting variants **(Emotion,** Reinforcement)	**Domain**
What do you see as your role in determining the pathogenicity of a variant and its clinical significance)? (Who's role is it, how do you feed in?) What would you (or did you) need to participate in the curation process (if you feel this is part of your role)?	Skills and knowledge
There is a large focus on multidisciplinary variant interpretation meetings as a way of interpreting results. What works/doesn't work? What interventions have been put in place to aid the way they work? How would you find variant interpretation if these didn't exist?	Reinforcement Emotion
Final decision making around variant classification – is there a standard process in place?	Reinforcement
Providing results to patients. (Communicating results) **(**Emotion, Goals, Optimism**, Reinforcement, Behavioural regulation)**	**Domain**
Have there been (are you aware of) any issues around communicating results back to patients? *No*: What has been put in place to ensure it worked well? *Yes*: What has been challenging? What needs to be put in place to overcome this?	Exploratory
Has a routine process been established? How do you manage this?	MAD, Behavioural regulation
When results are uncertain how do you feel about feeding this back to the patient? How would you support a less experienced doctor with this? What gives you confidence that this process is being handled well?	Emotion Optimism
Has a routine process been put in place for reanalysis of results? How do you feel about this?	Reinforcement Emotion
Incorporation into practice **(**Emotion, **Reinforcement)**	**Domain**
What do you feel should be put in place (if anything) to incorporate genomic testing into standard clinical practice? How could this be facilitated? (is there anything other than funding) that is needed? How do we support people to change (attitudes, behaviours, habits, skills)?	Reinforcement
Are you happy to play a role in mainstreaming genomics?	Emotion
What sort of role do you envisage?	Prof ID
How do you keep up with the evolving evidence base?	Skills, knowledge
Is your organisation supportive of adopting genomics in clinical practice? In what way?	Organisational Knowledge
Is there anybody (or any role) outside your organisation who is key to ensuring mainstreaming?	Prof role, environmental context
For others starting out now, what advice would you give – maybe what you did or wish you had known?	

Are there any other barriers, maybe one you have overcome, that we haven't discussed and you would like to share?

Supplementary File 3. Interview Schedule, Service Provision

Could you tell me what your role is and how you have been involved with the use of genomics in the clinical setting?

Pre-adoption: focus on factors *that could sway thinking* about adoption including amalgamation & dissemination of information
What got you interested in the idea of genomic testing being used in clinical practice?
Where do you look for information around the use of clinical genomics? And where would you look for more?
How do you go about deciding what information, about adopting genomics, into clinical practice has value? Are there any networks that you find more helpful than others?
Adoption: focus on factors that influence implementation and the *decision* to adopt
What was the key reason for deciding to adopt/invest genomics in this clinical setting?
What specific data did you need or would like to see, to support the decision to use genomics?
What have been the key factors to influence (fellow) physicians to participate in the use of genomic testing?
Implementation: focus on what facilitates implementation (including setting and systems)
What do you think makes it easier for some clinical areas to implement genomic testing?
What do you think makes it easier for some organisations to implement genomic testing?
How do you know if implementation has been successful?
In developing your (organisational) processes, what have you learnt about what can be changed and what is essential?
What have been the best strategies to enhance participation/engagement? (with clinicians and non clinical staff)
Sustainability: focus on getting into routine practice and spreading out into new areas
As a (clinical) leader how do you nurture those who are advocating for change in genomics?
What do you feel should be done (if anything) to facilitate the incorporation of genomic testing?
How do you keep up with the evolving evidence base?
How do you go about deciding what to disinvest in to bring in a new intervention
Do you feel you have a particular part to play in getting genomics incorporated into routine practice?
Who should facilitate mainstreaming?
What organisation and community influences would support greater sustainability?
How do you think genomic sequencing needs to be financed in the future to ensure sustainability?
What national and/or state networks can most effectively support sustainability?
What policies do you/would you find most helpful to support stable funding streams?
For others starting out now, what advice would you give – maybe what you did or wish you had known

Are there any other barriers, maybe one you have overcome, that we haven't discussed and you would like to share?

Supplementary File 4: Co design guide for Focus Groups

Clinical processes phase 1 focus group material 1

Clinical processes target behaviour/area from process map and audit data	Barriers in context*^+	TDF domain	Impact of barrier (high/moderate/low)	Ranking of barriers to target (1 being most important)
Target behaviour 1	Barrier from data synthesis	XXX		
	Barrier from data synthesis	XXX		
	Space for additional barrier			
	Space for additional barrier			

*emerged from process mapping interviews ^emerged from clinical process interviews +emerged from service provision interviews

Clinical processes phase 2 focus group material

Clinical processes target behaviour/area from process map and audit data	Top barrier in context*^+	TDF domain	Suggested intervention strategies*^+	Behaviour change strategy represented	Likely impact of strategy (high/moderate/ low)	Likely feasibility of strategy (difficult/ possible)	Ranking of intervention strategy (1 being most favourable)
Target behaviour 1	XXX		Ideas from data synthesis	XXX			
			Ideas from data synthesis	XXX			
			Space for more ideas				
			Space for more ideas				

Service provision phase 1 focus group material 1

Service provision/policy target behaviour/area	Barriers in context*^+	TSCi area	TDF domain	Impact of barrier (high/moderate/low)	Ranking of barriers to target (1 being most important)
Target behaviour X	Barrier from data synthesis		XXX		
	Barrier from data synthesis		XXX		
	Space for additional barrier				
	Space for additional barrier				

*emerged from process mapping interviews ^emerged from clinical process interviews +emerged from service provision interviews

Service provision phase 2 focus group material

Service provision/policy target behaviour/area	Top barrier in context*^+	TDF domain	Suggested intervention strategies*^+	Behaviour change strategy represented	Likely impact of strategy (high/moderate/ low)	Likely feasibility of strategy (difficult/ possible)	Ranking of intervention strategy (1 being most favourable)
Target behaviour X	XXX		Ideas from data synthesis	XXX			
			Ideas from data synthesis	XXX			
			Space for more ideas				
			Space for more ideas				

BMJ Open

A transformative translational change programme to introduce genomics into healthcare: a complexity and implementation science study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024681.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2018
Complete List of Authors:	Taylor, Natalie; Cancer Council, Cancer Research Division Best , Stephanie ; Australian Institute of Health Innovation, Centre for Healthcare Resilience and Implementation Science; Murdoch Childrens Research Institute, Australian Genomics Martyn , Melissa ; Walter and Eliza Hall Institute of Medical Research, Melbourne Genomics Health Alliance ; Royal Children's Hospital Melbourne, Murdoch Children's Research Institute Long , Janet; Australian Institute of Health Innovation, Centre for Healthcare Resilience and Implementation Science North, Kathryn; Murdoch Childrens Research Institute, Australian Genomics ; Royal Children's Hospital Melbourne, Murdoch Children's Research Institute Braithwaite, Jeffrey; Australian Institute of Health Innovation, Centre for Healthcare Resilience and Implementation Science ; Murdoch Childrens Research Institute, Australian Genomics Gaff , Clara; Walter and Eliza Hall Institute of Medical Research, Melbourne Genomics Health Alliance ; University of Melbourne, Department of Paediatrics and Medicine
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Genetics and genomics, Qualitative research, Research methods
Keywords:	Genomics, complexity, implementation, behaviour change, sustainability, translation

A transformative translational change programme to introduce genomics into healthcare: a complexity and implementation science study protocol

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Word count: 6215

ABSTRACT

Introduction: Translating scientific advances in genomic medicine into evidence-based clinical practice is challenging. Studying the natural translation of genomics into 'early-adopting' health system sectors is essential. We will a) examine 29 health systems (Australian and Melbourne Genomics Health Alliance Flagships) integrating genomics into practice, and b) combine this learning to co-design and test an evidence-based generalisable toolkit for translating genomics into healthcare.

Methods and analysis: 29 Flagships integrating genomics into clinical settings are studied as complex adaptive systems to understand emergent and self-organising behaviours amongst interrelated actors and processes. The Effectiveness-Implementation Hybrid approach is applied to gather information on the delivery and potential for real-world implementation. Stages '1' and '2a' (representing Hybrid Model 1) are the focus of this protocol. The Translation Science to Population Impact (TScImpact) framework is used to study policy decisions and service provision, and the Theoretical Domains Framework (TDF) is used to understand individual level behaviour change; both frameworks are applied across Stages 1 and 2a.

Stage 1 synthesises interview data from 32 participants involved in developing the genomics clinical practice systems and approaches across five 'demonstration-phase' (early adopter) Flagships. In Stage 2a, stakeholders are providing quantitative and qualitative data on process mapping, clinical audits, uptake and sustainability (TScImpact), and psychosocial and environmental determinants of change (TDF). Findings will be synthesised before co-designing

an intervention toolkit to facilitate implementation of genomic testing. Study methods to simultaneously test the comparative effectiveness of genomic testing and the implementation toolkit (Stage 2b), and the refined implementation toolkit while simply observing the genomics intervention (Stage 3), are summarised.

Ethics and dissemination: Ethical approval has been granted. The results will be disseminated in academic forums and used to refine interventions to translate genomics evidence into healthcare. Non-traditional academic dissemination methods (e.g., change in guidelines or government policy) will also be employed.

Key words: Genomics, complex adaptive systems, evidence based implementation, natural experiment, behaviour change, policy, sustaintability, translation

Strengths and limitations of this study

Strengths and limitations of this study include:

- A naturalistic study of complex change for the application of genomics into the health system
- A novel methodological approach to the study of complexity that could be applied more widely
- An approach to understanding reality and how to generate the ideal for implementation
- A demonstration of how complexity principles can be incorporated into the application of behaviour change theory
- A challenging undertaking to consolidate multiple components of complexity into a generalisable implementation toolkit

INTRODUCTION

Since the birth of the genomic era almost 15 years ago,[1] substantial efforts have focussed on developing laboratory based genomic sequencing capabilities and large scale sequencing studies to understand the significance of sequence variation on health. In recent years there has been an increasing focus on the application of this information in health care, for example to improve the diagnosis and/or treatment of disease. The complex and unpredictable nature of scientific advances, however, has exceeded the ability of health systems to establish what the ideal conditions, systems, and behaviours ought to be for using genomics in complex healthcare settings. Rather, iterative attempts to apply genomics within existing (often pre-genomics) clinical practice, generate emergent routines with varying levels of suitability, efficiency and sustainability. This *'real'* state of affairs is influencing the implementation of genomics into routine care in the absence of evidence based, *'ideal'* approaches. A lack of implementation science evidence is one of a long list of well documented challenges limiting the effective implementation of genomic research into complex healthcare systems.[2] A 2017 review highlighted the lag in evidence to support implementation, demonstrating that very few studies to date have: a) incorporated implementation science theoretical frameworks, sustainability measures, or capacity building, b) focussed on macro-level factors (e.g., health systems, policies, financing), and c) attempted to develop and evaluate evidence based strategies for enhancing the implementation of genomic medicine.[3]

The continuous adhoc, emergent and self organised translation modes manifesting within complex health care systems, as they attempt to keep pace with the constant stream of new genomic evidence, undoubtedly contribute to the challenges faced in designing protocols to study and test approaches to implementation. Disentangling the way in which the actors in the system (e.g., clinicians, patients, researchers, policymakers, planners and decision makers) perceive, experience, and *naturally behave* under these real world complex conditions is crucial for understanding the true adoption, impact, and likely sustainability of genomic testing. It is also key to discovering the *'ideal'* and to designing real-world interventions to support the implementation of long-term, cost-effective genomics policy and practice. Furthermore, it has been argued that interventions to improve implementation of evidence into practice will be most effective when developed by those with local 'expertise' and tacit knowledge,[4-6] but which take account of evidence and external expertise.[7 8] In this paper, we outline a novel methodological approach, using complexity science, translation, behaviour change frameworks, and co-design between healthcare professionals and stakeholders, and implementation and behavioural researchers, to study the integration of genomics into clinical practice as part of a national natural experiment, and develop a generalisable, evidence based toolkit for implementation.

The Australian Genomics Health Alliance (Australian Genomics) is a national network of state-based genomics initiatives, working together to translate genomic approaches into clinical practice. In 2014, the Melbourne Genomics Health Alliance (Melbourne Genomics) commenced a demonstration project, which laid the foundations for Australian Genomics, which was awarded $25M over five years (2016-2020). Together these Alliances have placed emphasis on understanding, from a service level and clinical practice perspective, how genomic testing can be implemented in health care. Their Flagship programs are central to achieving these insights. A

Flagship is a multidisciplinary clinical group (e.g., medical professionals, diagnostic laboratory staff, genetics counsellors, etc.) working together, often across multiple hospital sites, to provide genomic testing for defined clinical indications according to a broad framework.[9] From the inception of the demonstration project in 2014 through to 2020, 29 Flagships will be evaluating the use of genomics in clinical practice, across diverse clinical conditions (Figure 1), involving specialists from at least 16 different health professional disciplines from up to 18 hospitals and 4 hospital laboratories across Australia. The first five Melbourne Genomics flagships have already undergone a formal evaluation to assess the effectiveness of genomic sequencing for the purposes of early detection, treatment and, where possible, prevention of major disease.[10-13]

There is an immediate need to understand the emergent service provision pathways and clinical processes for genomic testing to ensure that its impact in widespread practice lives up to the promise of the results of the Flagships[12 14] established under the auspices of a research program. The Flagships exemplify a large scale attempt to integrate genomics into everyday healthcare. Therefore, in addition to establishing the clinicial validity and utility of genomics, Flagships are perfectly positioned for a naturalistic experiment of the factors affecting the successful implementation of genomics into the Australian healthcare system, and for testing the impact of evidence based approaches to ensure sustained, effective use. Each Flagship represents a complex adaptive system (CAS);[15-17] there are a number of complex features (e.g., emergent behaviours, self-organisation, non-linear processes, co-evolution, behaviours at the edge of chaos, nested systems, interconnectivity and networks, and simple rules which beget complex behaviours)[18-21] within each of the participating Flagships, and interactions between their component parts. As such, this research will use a complexity science lens, combined with implementation science and behavioural approaches, to investigate and support the integration of

genomics into the health system. Whilst the Flagships are distinguishable in form, with unique structural and cultural characteristics, each has been established with a common underpinning framework (Australian and Melbourne Genomics). Therefore, studying all 29 Flagships using a common approach is invaluable, as this permits evidence based examination of their functioning and outcomes.[22] It also provides insights into improvements in processes and procedures over time, and enables comparison and, where appropriate, consolidation of findings across Flagships. Uniquely, then, we are able to study each individual Flagship as a CAS and also identify commonalities across them to produce generalisable knowledge to support the translation of genomics evidence into practice.

There are three broad and interacting elements of complexity within a Flagship, or CAS, model (Figure 2). First, *'clinical versus implementation effectiveness'*: whilst attempting to test the effectiveness of genomics in the clinical setting, the impact of the broader health system (e.g., behaviours, resources, logistics, politics, etc.) can often distort what we come to understand about the success of diagnostic testing and subsequent treatment decisions.[23-25] Determining, through rigorous research designs, how best to work with these health system factors to implement testing and treatment effectively is crucial.[26] Second, '*policy decisions and service provision'*: for the sustained and evidence-based use of clinically effective genomics, it is important to identify which of the key resources needed for sound genomics practice are being funded through the Melbourne Genomics/Australian Genomics program, and plan for the commissioning of these resources once programmatic funding has ended. Furthermore, organisational, local area, and national level policy decisions (relating to, for example, Medicare funding, resourcing, management, de-implementation, etc.), are likely to be affected if genomic practice is endorsed. Therefore, understanding and planning for the management of such changes

will be key for successful long-term implementation.[9] Third, *'individual level behaviour change'*: the implementation of genomics into clinical practice will inevitably require both clinical and administrative practice change.[2 27]

Sitting both within and across each of these three broad elements of complexity are key complexity principles, which include, behaviours at the edge of chaos (high variety and creativity; the boundary between chaos and order), self-organisation (constant reorganisation of hierarchies and behaviours to adapt to the environment), and emergence (random actions that eventually generate patterns which change behaviour and the system). Studying the emergent and self-organising behaviours within different Flagships throughout the continuous flux will be vital for both identifying which of these behaviours to embed,[28] and where support through evidence based implementation can be beneficial.[20] Furthermore, whilst we cannot study the elements and principles of complexity in isolation, using appropriate frameworks to understand them, and synthesising this information in a way that helps to understand both successful emergent behaviours and gaps in practice, is likely to facilitate more effective intervention development.[29]

To address the first element of complexity (*clinical versus implementation effectiveness*) the Effectiveness-Implementation Hybrid approach – a way of blending design components of clinical effectiveness and implementation research,[26] will be applied to the Flagships across the five year research program (see Figure 1). To summarise, first (the focus of this protocol) we will test a clinical intervention (in our case 'genomic testing') whilst gathering information on its delivery during the effectiveness trial and/or on its potential for implementation in a real world setting (Hybrid model 1); second we will test a clinical intervention and an implementation/intervention strategy simultaneously (Hybrid model 2); and finally an

implementation /intervention strategy will be tested while observing/gathering information on the clinical intervention and related outcomes (Hybrid model 3).

Nested within the Hybrid Model 1 approach, the Translation Science to Population Impact (TSci Impact)[30] framework will be used to study the second element of complexity (*policy decisions and service provision*), and the Theoretical Domains Framework (TDF)[8 31-35] will be used to study the third (*'individual level behaviour change*). The TSci Impact framework provides a systematic approach to investigate the complex processes and mechanisms through which tested and proven interventions are integrated into practice and policy in a large scale and sustainable way. This framework was designed with complexity (or 'systems') science in mind,[36-39] to take into account the complex interrelationships between infrastructure and contextual influences within and across translation phases, and promotes the study of complex interactions within and across implementation systems. The TSci Impact framework favours and facilitates the synthesis of information to understand clinical trial outcomes within organisational settings, combined with community action research for rich accounts of how culture, context, local decision making and history influence implementation of evidence based practice.[30]

The TDF is a psychosocial and environmental framework of behaviour change that enables reliable and valid identification of psychosocial and environmental barriers and facilitators (e.g., motivation, emotions, resources, social influences) to practice change. A key feature of the TDF includes the need to establish key target behaviours, and so as part of this work and aligning with ideas drawn from complexity science, we will incorporate the development of clinical process maps to understand the emergent, self-organising, and networking behaviours within and between individuals in the system, and to establish the *ideal* from the *reality*[40 41] as these Flagships initiate the foundations of genomics in their local setting.

In addition, investigating facilitators of behaviour change (or intuitively derived interventions[42]) allows for the naturalistic assessment of emergent and self-organised behaviours central to complexity theory. Finally, the TDF has previously been successfully used to synthesise determinants of behaviour and interventions collected using no prior framework, or alternative frameworks.(e.g.,[43 44 45]) By studying Flagships as CASs, this work aims to identify common features of these systems and networks. As such, this is an unrivalled opportunity to use the TDF to synthesise the complexity across and within Flagships into a holistic implementation toolkit, combining knowledge of successful emergent behaviours with strategies to address genomics implementation problems in a targeted, standardised, and generalisable fashion.

Aim and objectives

This paper provides an outline of a five year transformative translational change program, and specific details for the initial two-year phase, to study and support the implementation of genomic testing into routine healthcare in clinical, organisational and policy contexts across Australia. The objectives of the first phase are to study Melbourne Genomics and Australian Genomics Flagships to:

1) Understand the emergent and self-organising behaviours during the implementation of genomics into practice
2) Identify successful emergent behaviours and gaps in practice
3) Synthesise this information using a theoretical framework
4) Co-design, with clinicians, a foundation implementation toolkit to facilitate the translation of genomic testing into clinical practice

METHODS AND ANALYSIS

Context

Australian Healthcare and Genomics

The Australian public health system is accessible to the public for free or at a lower cost through Medicare (funded by tax). The private system includes health service providers that are owned and managed privately, such as private hospitals, specialist medical and allied health, and pharmacies. The national health insurance scheme funded by the Australian Government currently funds few genetic and no genomic sequencing (whole exome/whole genome) tests. The largest expenditure in health - almost 40% - is on public hospital care, which includes some specialist genetic services and is the responsibility of the state governments. Genetic/genomic testing is funded through State government health budgets with availability of tests and funding varying across State. Governance structures exist to enable coordinated action and response to matters of national significance, such as genomics, across all Australian governments. Australian Genomics was established based on a national call from the National Health and Medical Research Council (NHMRC) for research on the application of genomics within the Australian public health system. Melbourne Genomics is funded by the Victorian Department of Health to support the integration of genomics in the Victorian health care system. The implementation science component of this work is embedded in the overall planned research program.

Flagships

Under the Melbourne Genomics and Australian Genomics program of research, each of the 29 Flagships represents a test of the integration of genomics into the clinical settings within public hospital health care in parallel with usual (non-research funded) care, incorporating research consent processes into care processes delivered by genetic counsellors. The initial focus was on

five conditions (childhood syndromes, neuropathies, hereditary colorectal cancer, focal epilepsy, acute myeloid leukaemia), with a total of 24 additional conditions planned for commencement over the following 2-3 years (Figure 1). Given this is a test of diagnostic capability (which may lead to more personalised treatment interventions, as opposed to being a treatment intervention in of itself) , it is possible to administer both usual investigations and the new investigation (genomic sequencing) to the same patient. Both the yield of the test and the clinical decisions resulting can be determined.[46] As such, as opposed to a randomised controlled trial, which is both unnecessary and inequitable under the given circumstances, each flagship is incorporating an extended version of a comparative effectiveness research (CER) design,[47 48] which adds the assessment of clinical and patient utility to the standard CER health outcome measure.

The interrelated actors and processes manifesting as part of each Flagship represent a CAS, as demonstrated by generic Flagship context examples of key CAS components in Table 1. Flagships will, therefore, be studied as an individual CAS to understand the emergent and self-organising behaviours. In addition, commonalities of integration across CASs will be studied to support the development of an implementation framework for future real world healthcare organisations planning to translate genomics into practice.

Table 1. Flagships as CAS

CAS component	Flagship example
A large number of elements which interact dynamically	Key Flagship elements include patients (and their own influences outside the official health care system), staff (e.g., different professions, hierarchies, and approaches to decision making), locations (multiple sites,labs and clinicians not colocated), resources (time, money, etc.), organisations, leadership, clinical processes, research processes – all of which will interact

Any element in the system is affected by and affects several other systems	For example, the flagship is operating within the broader CAS – incorporating new genomic investigations and procedures within existing patient care pathways, and evaluating the process and outcomes. This involves an iterative process affected by (and impacting) pre-existing clinical and laboratory systems for patient assessment, decision making and patient consent for the genetic diagnostic process, sign off, counselling, sampling, transit, batching, sequencing, computational access, analysis, interpretation, reporting, etc. Different professions interact throughout this process to make a final decision
Non linear interactions, so small changes can have large effects	Whilst the pathway that must be taken to complete the process for any given genetic test is generally linear, the interactions within and between each stage are non-linear (e.g., within the decision about which test is most appropriate for a patient, there is formal and informal discussion between clinicians and clinical geneticists about the appropriateness of genomic testing and the area of focus required), and iterative (e.g., first analysis of the results may prompt re-examination of the clinical picture and alter decisions about the focus of the genomic analysis). Furthermore, the exploratory nature of Flagships under a research program introduces further ambiguity (e.g., around future funding or clinical utility of genomic testing in that condition)
Openness, so it may be difficult to define system boundaries	As a broad example, the funding of resources for genomic sequencing within participating health services overlaps with existing government commissioned resources for a Flagship. As a research program operating in a real-world health system, this scenario may affect clinical decision making for patients due to boundaries stipulated in research protocols within which clinicians must operate A more specific example includes the uncertainty held regarding whether or not and when to communicate incidental findings to patients, and the ethical decision making behind undertaking secondary analysis of previously collected samples as new genes are discovered. Whilst knew knowledge for patient diagnosis and treatment is a clear benefit from the continuously evolving basic and clinical research perspective, impact on practice can involve period of time where there is more ambiguity and uncertainty about what is best for patients. Policies help to define this but generate boundaries, which can be

	frustrating, particularly if they are not up to date with new evidence. This can be where deviations arise and new, informal, unrecorded patterns emerge.
A constant flow of energy to maintain the organisation of the system	Flagships require all those involved in completing the diagnostic process to be on board, but as with any health system, perceptions of value of different parts of the process, including the outcome, can vary and evolve amongst both patients and professionals. This can affect the willingness to participate and the flow of energy in the system.
A history whereby the past helps to shape present behaviour	The involvement of genetics and genetic specialists in patient care differs across Flagships. The extent of this past involvement, and the nature of the relationships between disciplines and different locations, influences the introduction of genomics, specifically the protocols and procedures, as well as dynamics within a Flagship.
Elements in the system are not aware of the behaviour of the system as a whole and respond only to what is available or known locally.	For example, Flagships are operating as externally funded entities within the existing health care system – individuals are well aware of the need for funding but not so much the need to disinvest; they are also primarily concerned with the operations and needs of their own Flagship(s). There are also other Flagships as well as the health system as a whole, which have different circumstances, and are having an impact/being impacted upon.

Research design

As part of the five year complexity-implementation science research plan, our design provides methodological details for the two stages used to investigate Hybrid Model 1: gathering information during the effectiveness trial (in this case an extended CER) of a clinical intervention on its potential for implementation in a real world situation. Stage 1, a data recoding exercise, has been completed and stage 2a is underway, collecting data across at least a further 6 project areas Flagships (see Figure 1). A summary of methods to be applied for the Hybrid

Model 2 and 3 are also provided. A Logic Model (Figure 3) presents the activities, outputs, and outcomes of Stage 1 and 2a.

Participant identification and data analysis will involve an expert resource group of multi-disciplinary research, clinical, and contextual expertise (Table 2) for interpretation and clarification of findings, consisting of experienced clinicians and researchers, each bringing academic and/or contextual knowledge from participating sites. The following section contains details of participants and recruitment, data collection tools, research procedures and data analysis plan for stage 1 (post flagship implementation) and stage 2a (pre, during and post flagship implementation).

Table 2: Expert Resource Group expertise

Expert identifier number	Genetic clinical expertise	Non Genetic Clinical expertise	Laboratory Expertise	Genetic Operational Knowledge	Implementation Science Expertise
1	X			X	
2			X	X	
3			X	X	
4					X
5		X			X
6		X			X

Stage 1: Hybrid Model 1; post-implementation (2015-2017 timeframe)

Stage 1 Participants and recruitment

Stage 1 builds on the work of the Melbourne Genomics evaluation team interviewing 32 clincians across five Flagships in the demonstration phase. Individuals who were involved in developing the systems and approaches [e.g., variant curation pipeline, variant classification frameworks, consent forms and reporting templates for Whole Exome Sequencing (WES) etc.], including genetic clinical specialists, and non genetic clinical specialists who attended more than

two multidisciplinary meetings over the demonstration phase, were invited to participate via email.

Stage 1 Data collection tools

Structured interview schedule (Supplementary file 1): The schedule was used to gather data retrospectively for the Melbourne Genomics evaluation from stakeholders in the demonstration phase. Questions focussed on aspects of the first implementation of WES into clinical practice: a) role in the project, b) experience (as a clinician or medical scientist), c) perceptions of multi-disciplinary variant meetings, d) views on policy decisions and procedures e) impact on their understanding, and f) factors affecting integration into practice. Probes for questions in each topic area are also provided for interviewers to maximise the quality of information gathered.

Evidence based interview coding tools: Whilst the data from these interviews was originally used to obtain insights into the *'what'* of the flagship, additional tools have been selected to code these interviews from an evidence based, behavioural perspective. More specifically, TDF coding and behaviour change techniques guidance,[31-33] and agreed definitions of the TDF in the genomic context (see Table 3)[49] was used to: 1) identify behavioural areas for change, 2) group key barriers and enablers to implementation of genomic sequencing according to theoretical domains of behaviour change, to 3) capture any behaviour change techniques (BCTs)[32] represented in any exisiting or new intuitive intervention strategies described by participants.

Table 3: Recoding Guide

TDF domain	TDF domain definition (Cane et al. 2012)	Definition in context
Knowledge	An awareness of the existence of something	Clinicians' actual awareness and understanding (through education/training) of the principles

		and process of offering genetic testing in clinical practice
Skills	An ability or proficiency acquired though practice	Clinicians' actual physical and psychological ability or proficiency acquired through actual practice (as opposed to education/training – cannot get skills through education) to make decisions whether or not to offer genetic testing in practice
Memory, Attention and Decision Processes	The ability to retain information focus selectively on aspects of the environment and choose between two or more alternatives	Clinicians' ability to remember to consider genetic testing alongside other interventions for health risk identification, diagnosis, management, and therapy
Behavioural Regulation	Anything aimed at managing or changing objectively observed or measured actions	Clinicians' self-created or self-imposed regulation to help make decisions about offering genetic tests
Social Influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours	Interpersonal interactions between professionals that can influence clinicians' thoughts, feelings or behaviours (ie anything in Motivation) regarding offering genetic testing
Environmental Context and Resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities independence, social competence and adaptive behaviour	Any external circumstance of a clinicians' situation or environment that clinicians consider discourages or encourages them to offer genetic testing in practice, including impacting the development of capability, motivation or social opportunity to offer genetic testing.
Social/Professional Role and Identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting	Clinicians' perceived professional role and identity in relation to offering genetic tests
Beliefs about Capabilities	Acceptance of the truth, reality or validity about at ability, talent, or facility that a person can put to constructive use	Clinicians' perception about their own capability to consider genetic testing (terms used in literature: confidence, comfort, control)
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Clinicians' optimism or pessimism that genetic testing will be appropriately integrated into clinical practice and will improve healthcare generally
Beliefs about Consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation	Clinicians' perceptions about the value of offering genetic testing in clinical practice – whether it is worthwhile in that it will improve

		patient outcomes in their own practice (term used in literature: attitude)
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way	Clinicians' intentions to consider genetic testing
Goals	Mental representations of outcomes or end states that an individual wants to achieve	Whether clinicians offering genetic testing is a priority within their practice
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Incentives, rewards, sanctions, reinforcement at any level (eg patient satisfaction; better client health; economic incentives) that encourage or increase clinicians' decisions to offer genetic testing
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter	Clinicians feelings when they consider genetic testing

Stage 1 Procedures

Two behavioural researchers independently recoded ten of the Melbourne Genomic evaluation interview data according to the TDF, then compared findings for inter-rater reliability. The remaining 22 interviews are being recoded by one researcher. Where there are differences or queries a TDF expert is being used to advise on the appropriate coding. Once complete the recoded data will be discussed with the expert resource group for sense checking.

Stage 1 Data Analysis Plan

Interview data will be audio recorded, fully transcribed and entered into NVivo 11 (QSR International Pty Ltd., 2015). Analysis will vary dependent on the interview intent. The TDF

reanalysis of the Melbourne Genomic data will establish target behaviour areas and key barriers to focus on in subsequent interviews. The recoding process using the TDF will also allow identification of psychosocial domains within each target area. Domains not identified will be included in the stage 2a clinical process interviews to identify if they have relevance within each target area.

Stage 2a: Hybrid Model 1 pre, during, and post implementation (2018-2019 timeframe)

Stage 2a Participants and recruitment

Two key participant groups, each of which will be recruited for one or more of the different interviews and focus groups will be drawn from the Australian and Melbourne Genomic Flagships. Given the focus on service provision and policy, and clinical process aspects of implementation, the target groups for participation represented these areas:

a) Service provision pathway participants: A total of 37 decision-makers and stakeholders (both clinical and administrative, playing a key role in either flagship leadership, funding and financing strategies, genomic testing characteristics and costs, organisational and community factors or policy) who have been identified as fulfilling the inclusion criteria across the flagships and states will be invited to participate in an interview.

b) Clinical process delivery participants: A total of 27 clinical non-genetics medical specialists (e.g., oncologists, neurologists,) who have been identified as fulfilling the inclusion criteria across the flagships and states will be invited to participate in an interview.

Across both participant groups, up to 12 people will be invited to participate a focus group to be held in each state (i.e., Victoria, Tasmania, New South Wales, and South Australia, and

Westwern Australia). The participants invited will depend on the findings from the individual interviews.

Table 4: Stage 2a Interview Inclusion Criteria

Service provision participant inclusion criteria	
Inclusion Criteria	**Justification**
Strategic decision makers or	Involved with direction and funding for services including genomics
Service level managers or above (e.g. CEO) or	Will have either signed off on a flagship application, have a flagship running in their organisation, or be managing a flagship
Senior clinical geneticists	Will have an overview of genomic testing in more than one flagship across clinical genetics and medical specialities
Flagship involvement from any phase of implementation	To gather views across the implementation journey
Draw participants from a cross section of locations	To ensure a broad representation of views
Clinical processes participant inclusion criteria	
Inclusion Criteria	**Justification**
Medical specialists (excluding clinical geneticists)	Focus of study is mainstream tertiary implementation in the long term
AND working within a flagship	Practitioner will have genomics knowledge
Flagship involvement from any phase of implementation	To gather views across the implementation journey
Working in Australian Genomics or Melbourne Genomics flagship	These are the sites for the genomic work
Draw participants from a cross section of locations	To ensure a broad representation of views

Selection criteria will be established (see Table 4) to facilitate recruitment of expert informers for interview based on their experiences of implementation of genomics in their organisation. Individuals fulfilling the inclusion criteria will be identified using the knowledge of

the expert resource group. Recruitment for individual interviews and focus groups will consist of multiple strategies, including making use of the networks of the expert resource group to facilitate research-participant contact; individual emails will be sent. Interview times and locations will be arranged based on convenience for interviewees to enhance the likelihood of participation.

Stage 2a Data collection tools

A process mapping guide (Figure 4), a clinical audit, two semi structured interview schedules (Supplementary File 2 and 3), and an intervention co-design guide (Supplementary File 4) will be used to gather qualitative and quantitative data.

Clinical process mapping template: informed by stage 1 interviews and the expert resource group, the template (Figure 4) will present an outline of the WES process to participants, covering a) the patient presenting at clinic, b) the process for analysis, and c) communication of results to patient. Each section will act as a prompt to clarify processes and an opportunity for participants to amend the outline process map in relation to processes specific to their clinical area (e.g., childhood syndromes, cancer, etc.) with regards to where processes begin and end, tasks involved, who contributes, who is affected, and where glitches occur in the system. This will enhance understanding as to how current clinical processes have emerged and are currently operating from a pre-, during-, and/or post-implementation of WES perspective. Furthermore, emergent barriers to implementation, and any current or suggested intervention strategies captured as part of these discussions will be noted.

Clinical practice audit tools: collects information about recorded practice prior to, during and post-implementation of genomic sequencing. Audit data will be collected to reflect key

components of the process map to demonstrate where gaps, blocks, and problems exist in the system. For example, date stamped data of the detailed patient journey from referral into WES, test ordering and interpretation, and communication of results to patients will be collected and matched to specific process map steps.

Clinical processes interview schedule: collects views from non-genetic clinical specialists on the early, mid and late phases of implementing a flagship. The interview schedule, informed by the results of the Stage 1 TDF-coded interviews, and informed by the Melbourne Genomics Community Advisory Group, is framed according to relevant TDF domains. Questions enquire about the same three key behavioural areas examined in the process map: a) the patient presenting at clinic, b) the process for analysis, and c) communication of results to patient. For example, in the third behavioural area, 'communicating results,' the question relating to the 'emotion' TDF domain is *When results are uncertain how do you feel about feeding this back to the patient*? And for the 'optimism' TDF domain; *What gives you confidence that this process is being handled well?*.

Service provision interview schedule: collects views from key decision makers and stakeholders on factors influencing the uptake of genomic medicine at different phases of implementation, and on preparing for the transition from flagship to ordinary clinical service status for the sustainability of genomic testing once programmatic funding has ended. Areas identified for exploration at interview were debated with the expert resource group, with Spoth et al's (2013) TSci Impact framework being favoured for investigating translation phases of pre-adoption, adoption, implementation, and sustainability from a service provision and policy perspective. Some interviewees will need to reflect back on the early phases of pre adoption, while others will

be in the translation function so will be able to draw on current experiences. To facilitate interview participants' focus on the phase under discussion a graphic has been developed to use at interview (see Figure 5). Working through the translation phases, questions focus on the following topic areas: 1) gaining clinical genomic knowledge; 2) influences on the decision to adopt; 3) the impact of the organisational setting and health system; and 4) influences on sustainability including disinvestment.

Barrier verification and intervention strategies co-design guide: This two-phase guide will present a summary of information gathered in the process mapping interviews and audit data cross-matching exercise, and the clinical processes and service provision interviews (across the respective associated behavioural/topic areas covered), synthesised according to the TDF domains and BCTs. In phase 1, prompts and materials (Supplementary File 4) will be provided to encourage discussion about the barriers list presented, to elicit information about any additional barriers, and to narrow down a list of key barriers to focus upon. In phase 2b, a provisional list of intervention strategies that could be used to address those barriers will be presented. Guidance will be provided to facilitate the design of any new interventions using BCTs. A matrix will be provided to facilitate ranking of the interventions according to feasibility and impact on the associated barriers and subsequent behavioural areas (Supplementary File 4).

Stage 2a procedures for interviews and pre-focus group data synthesis

Generic interview procedure: Before commencing all interviews, the interviewer (SB) will go over consent procedures, provide a Participant Information Sheet, obtain permission to record the interview, and then record verbal consent. The interview, which is likely to last around 60

minutes, will be recorded using a digital recorder, then transcribed. All participants will be assigned a code (e.g.Participant CP/SL 1, 2 3 etc) and interviewees will only be identified via these codes. Digital audio files will be imported into the software Nvivo 11 (QSR International Pty Ltd., 2015) to facilitate analysis.

***Process mapping interview and integration with audit data*:** Hard copies of outline process maps (Figure 4) will be handed to clinical process interviewees to prompt discussion about the process for that particular clinical area (e.g., paediatric rare diseases, cancer, etc.), inform refinements to the map, and elicit information about barriers and facilitators to undertaking the process. These data will be transferred into Microsoft Visio software; participants will be contacted via email, and asked to review their revised map and suggest any refinements. The provisional list of audit data collection variables will be finalised on the basis of the process map, collected via organisation electronic and/or paper based patient records, with relevant information cross-matched to specific parts of the process. The outputs of this stage of the project will be: a) a detailed, visual, and data-verified outline of clinical area-specific processes for genomic testing pathways, and b) a data-driven method of identifying key gaps or imperfections in the process, and c) a set of emergent barriers and existing or potential interventions for improvement of processes.

Clinical process: The TDF based interview schedule (see Supplementary File 2) will be used with clinical process interviewees to discuss, using the lens of a psychosocial and environmental theoretical framework, barriers and facilitators to implementation of genomics in clinical practice, and to elicit information about existing or potential interventions for improvement. The outputs from this data collection procedure will be information on TDF based barriers and emergent interventions.

***Service provision and policy interviews*:** The TSci Impact framework based interview schedule (see Supplementary File 3) will be used with service provision and policy interviewees to discuss factors influencing the uptake of genomic medicine at different phases of implementation using the lens of translating science into policy and services perspective. Outputs here will include, data on policy and service provider factors affecting implementation pathway, and information on emergent barriers and interventions.

Stage 2a Data-informed focus group schedule development and data collection

***Preparation of focus group materials through synthesis of interview data**:* Data from the stage 1 recoding, and stage 2a process mapping/audit data, clinical process, and service provision interviews will be synthesised by the expert resource group in preparation for the focus groups (Supplementary File 4). For both clinical processes and service provision and policy, summary tables will be developed with a set of key target areas for improvement, context specific barriers and corresponding TDF domains, emergent intervention strategies alongside corresponding BCTs, and instructions for ranking the likely impact and feasibility of intervention strategies. Key barriers from all the clinical speciliaties will be combined to develop generalisable interventions.

Focus Groups (two phases): The synthesised data will be used with a multidisciplinary group of clinicians and service provision/policy decision makers to verify barriers and co-design intervention strategies using both emergent and evidence based behaviour change approaches. Using the materials from the data synthesis exercise, the discussion in phase 1 will be used to verify and identify any additional barriers, and to rank barriers according to level of impact on behavioural areas. Phase 2 discussions, informed by phase 1 and with a provisional list of

intervention strategies, will be used to co-design interventions to address the high impact barriers to implementation using the most feasible and likely impactful intervention strategies. A hypothetical example mapping how the flow of data from interviews in stage 2a will flow to intervention design is provided in supplementary file 4.

Stage 2a Development of foundation implementation toolkit

A draft implementation toolkit will be developed using the recorded and written focus group data to present intervention strategies to address key barriers to clinical processes and service provision implementation of genomics evidence into practice. Both interview/focus group participants, the expert resource group, and the Consumer Advisory groups of the Australian and Melbourne Genomics Health Alliances will be invited to review the contents of the first iteration of the genomics implementation toolkit.

Stage 2a Data Analysis Plan

***Data Synthesis prior to focus groups*:** Intial synthesis will be undertaken by SB. The process mapping and clinical audit data will be analysed for data on processes, individual interactions, data driven gaps (within the four target areas) and also emergent barriers and interventions. Clinical audit data analysis will consist of computation of descriptive statistics, proportions, and timeframes between steps in clinical processes. This information, where available, will be matched to the relevant steps in the process map to highlight gaps or bottlenecks. Clinical process interview data will be analysed deductively using the TDF to identify key domains representing barriers to change, and appropriate BCTs will be mapped to these domains as an evidence based approach to intervention strategy development.[31-33] Service provision interviews

will be thematically analysed and used to identify key areas for development of service provision planning. These data will also be analysed according to the TDF and BCTs to facilitate the combined approach to developing clinical process and service provision interventions for the two phase focus groups. These processes, barriers and intervention data within the target areas will be collated and shared with the expert resource group. The expert resource group will analyse these data and develop the focus group materials to demonstrate key reported barriers to and suggested intervention strategies for effective implementation of genomics in practice.

Focus group analysis: Individual focus group analysis will be undertaken using the TDF and BCTs to identify validated and new barriers to change, and BCTs, respectively. Results of this exercise from each focus group will be provisionally combined to generate the first iteration of the genomics implementation toolkit.

Patient and Public Involvement

The Stage 2a clinical processes interview schedule is informed by the results of the Stage 1 TDF-coded interviews. Patient and public involvement was sought from the Melbourne Genomics Community Advisory Group. Through a facilitated discussion the group identified their priorities areas for implementation and sustainable delivery of genomics (for example “how do you manage patient expectation?”) which were incorporated into the interview schedule. Findings from data collection will be discussed with the Consumer Advisory groups of the Australian and Melbourne Genomics Health Alliances and they will be invited to review the contents of the first iteration of the genomics implementation toolkit.

ETHICS AND DISSEMINATION

Ethical approval for this study has been granted by Melbourne Health HREC on November 3, 2017, as an amendment to the Melbourne Genomics approved protocol number: HREC/13/MH/326. Governance approval has been provided by Australian Genomics and Melbourne Genomics participating instituions.

Dissemination of results will be undertaken through traditional academic forums, but also through the information generated through this research being used to refine and apply evidence based and pragmatic interventions into health systems for the translation of genomics into practice. In addition, the Translational Science Benefits Model (TSBM)[50] will be used to further understand the actual and potential value of genomics to society, and open up further opportunities for dissemination.

DISCUSSION

In Australia, the majority of clinical genomic sequencing is currently funded through research activities. Melbourne Genomics and Australian Genomics bridge the gap between research and established clinical practice. They represent systematic national and state-based efforts to integrate genomics into everyday healthcare. For the majority of Flagships and health professionals working within them – many of whom are not experts in the field of genomics – this is the first time genomic sequencing tests have been available to them 'in real time'. Whilst they are making efforts to incorporate this into their practice, it is impossible for clinicians – genetic and non-genetic alike – to know what the '*ideal*' is yet. Therefore, no precedent exisits for *effectively* implementing genomics into practice for numerous clinical conditions across different contexts. The diversity of health professional disciplines, health care organisations, clinical indications participating across the 29 Flagships (all of which are at different stages of

implementation and involve a mixture of early, mid, and late adopters), will realise the ultimate goal of this work: to establish the '*ideal*' and develop a generalisable model of implementation that future organisations can apply and tailor to their local contexts. The planned work for the remainder of this project will determine the finer details of this model, but the vision is for an interactive, theoretically underpinned, continuously refined toolkit informed by real-world data. This approach will enable diverse healthcare organisations at any stage of implementation to tailor their context-driven approach based on tried and tested intervention strategies used to address key challenges experienced by others.

The detailed methods for the current body of work – stage 1 and 2a, forming the foundations of this transformative translational change program, have been presented here. Future work will then build on data and strategies developed as part of Hybrid Model 1. To summarise, Hybrid Model 2 (see Figure 1 - Stage 2b; 2019-2020 timeframe) will consist of a simultaneous test of the clinical effectiveness of genomic sequencing and the implementation toolkit concurrently[26] in new Flagships. Quantitative and qualitative measures for assessing implementation effectiveness will be explored and developed[51] (Figure 1). A formal, concurrent test of the clinical effectiveness of genomics and the implementation toolkit will be undertaken, allowing for a detailed analysis, distinction, and explanation of the complex factors associated with clinical versus implementation effectiveness. During this stage (and stage 3), the Standards for Reporting Implementation Studies (StaRI) Checklist[52] will be used to support the planning and reporting of intervention strategies and implementation effectiveness.These findings will be used to further refine the toolkit.

The final stage (Hybrid model 3) (see Figure 1 - Stage 3; 2020-2021 timeframe) will focus on testing the refined implementation toolkit while simply observing the genomics

intervention, and related outcomes.[26] Consolidating the earlier work, this stage will include real world testing of the implementation toolkit (e.g., RCT; stepped wedge trial) against a comparison, and/or with a standard roll out, with the aim of informing state and national policy and decision making. Following recommendations by Curran and colleagues,[26] summative outcomes – including adoption/uptake of the clinical intervention, process measures, and quality measures – will be assessed using data collection tools and approaches specifically designed for measuring implementation outcomes developed in Stage 2b[51] (see Figure 1). Furthermore, these outcomes will be mapped against the TSBM[50] to demonstrate implementation outcomes across clinical, community, economy and policy contexts – a hypothetical example of this is provided in Table 5.

Table 5: Translational Science Benefits Model applied to genomics context and implementation outcomes

TSBM Domain	Potential Benefit	TSBM indicator	Potential Proctor et al (2017) Implementation Outcome
Clinical and medical	Streamlining processes	Development of procedural guidelines	Acceptability Adoption
Community and public health	Saving patients from unnecessary procedures Reduces diagnostic odyssey	Decrease non essential tests ordered Time to diagnosis	Appropriateness Fidelity Feasibility
Economic benefits	Increase in genomic testing and reduction in non essential testing	Tests ordered	Implementation cost
Policy and legislation	Disinvest in unnecessary procedures	Change in government and organisation policies to support increased use of genomic testing	Penetration Sustainability

This study is not without limitations. First, recoding interviews undertaken in 2015 as part of Stage 1 may not remain entirely representative of stakeholder perceptions that exist at

present. However, these views may be representative of individuals based at new sites which have not yet been exposed to genomic sequencing. Further to this, interview data from Stage 1a are being coded retrospectively using the TDF. While this will allow for identification of the issues most salient to interviewees, using the TDF to inform the interview schedule may have elicited information about barriers that are less spontaneously reported.[53] Moving forward beyond the original interviews, however, interview schedules have been designed based on the TDF; this will not only enhance the evidence based by which information is collected, but may also allow for a comparison of answers provided by participants using both interview approaches. Finally, the study is based on the implementation of genomics into the Australian health system which, like any health system globally, has a unique composition and combination of idiosyncrasies in terms of infrastructure and funding. However, the varied nature of the Australian system (e.g., the combined private/public system) has its benefits in that it bares some resemblance with countries that have publicly funded (e.g., UK, Canada), but also with those operating insurance based funding (e.g., Germany, USA).the novel approach taken here aims to enable the ability to identify generalisable interventions for addressing common challenges across contexts.

This is the first nationally based real-world study of a large cohort of CASs, deliberately attempting to integrate genomics into a real world, complex health system. To study and support implementation of a technology with far-reaching consequences but currently limited evidence base, we have developed a novel methodological approach consisting of complexity science, policy and service provision, and individual level behaviour change frameworks, and progressively more rigorous research designs. Disentangling clinical research processes from those which support adoption of a new standard of care, our work will provide streamlined

recommendations for future healthcare organisations planning to translate genomics into their health system. This methodology may be one that lends itself to study and support the adoption of other potentially 'paradigm shifting' technologies.

LIST OF ABBREVIATIONS

BCT	Behaviour change technique
CAS	Complex adaptive system
TDF	Theoretical Dmains Framework
TSci Impact	Translation Science to Population Impact
TSBM	Translational Science Benefits Model
WES	Whole Exome Sequencing

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AUTHORS' CONTRIBUTIONS

NT conceived, designed and developed the detail of the study, provided advice for ethical approval, led and coordinated writing the paper. SB developed the detail of the study design, co-led the ethical approval and co-led writing the paper. MM conceived and co-designed the study

details, led the ethical approval process, and reviewed the paper. JCL co-designed the study details, provided advice for ethical approval and reviewed the paper. KN is the Chief Investigator for the Australian Genomics Health Alliance NHMRC grant; she contributed to conception of the study, provided strategic input and reviewed the paper. JB contributed to conception of the study, provided advice, strategic input and expertise in implementation and complexity science, and reviewed the paper. CG conceived and co-designed the study, provided advice, strategic input and reviewed the paper. All authors read and approved the final manuscript. KN, CG and JB are chief investigators on the National Health and Medical Research Council grant funding the Australian Genomics Health Alliance.

FUNDING STATEMENT

The Melbourne Genomics Health Alliance is funded by the Victorian Government and the ten Alliance members (Royal Melbourne Hospital, Royal Children's Hospital, the University of Melbourne, Waltear and Eliza Hall Institute, Murdoch Children's Research Institute, Commonwealth Scientific and Industrial Research Organisation, Australian Genome Research Facility, Peter MacCallum Cancer Centre, Austin Health, Monash Health). The Australian Genomics Health Alliance is funded by NHMRC grant 1113531.

COMPETING INTERESTS STATEMENT

NT, SB, MM, JCL, KN, JB, CG have declared that no competing interests exist.

Tables, Figures and Additional Files

Tables

Figures

Supplementary Files

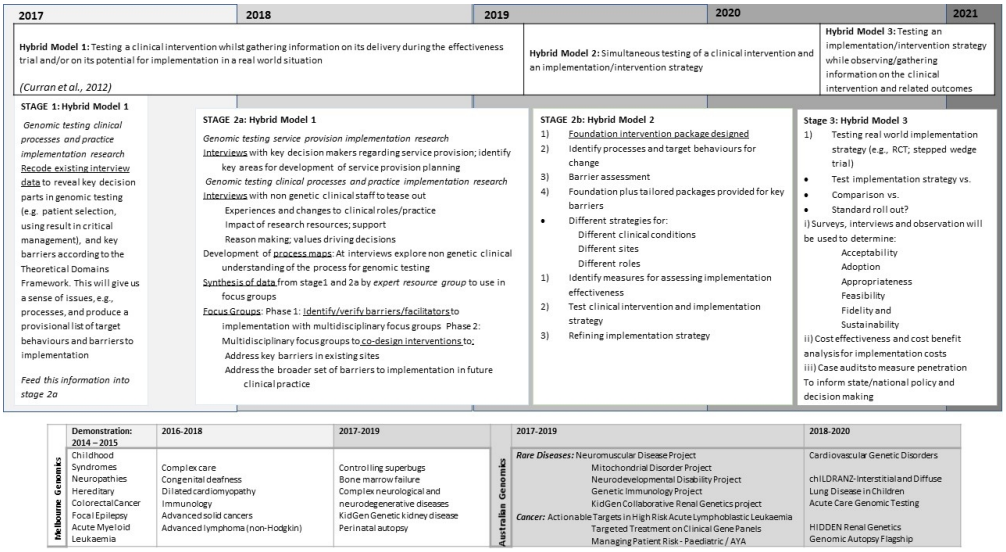

Figure 1: Implementation Research Plan

108x60mm (300 x 300 DPI)

Broad elements of complexity	Principles of complexity	Model or Framework used to understand and respond to complexity
Clinical effectiveness versus implementation effectiveness	- Edge of chaos - Self-organisation - Emergence - Simple rules - Iteration - Sub-optimal - Requisite variety - Interconnectivity and networks - Co-evolution - Nested systems	Effectiveness-Implementation Hybrid Model
Policy decisions and service provision		TSCimpact Model
Individual level behaviour change in a complex adaptive system		Theoretical Domains Framework

NB: The principles of complexity (column 2) overlap across all three broad elements of complexity (column 1). Using the proposed frameworks (column 3), we aim to understand the influence of, and interplay between, these principles across each broad element. More specifically, the effectiveness-implementation hybrid model is being applied to unpick the broad element of complexity related to clinical versus implementation effectiveness; the TSCimpact Model is being used to disentangle the broad element of complexity related to policy decisions and service provision; The TDF is being used to understand the broad element of complexity related to individual level behaviour change in a complex adaptive system.

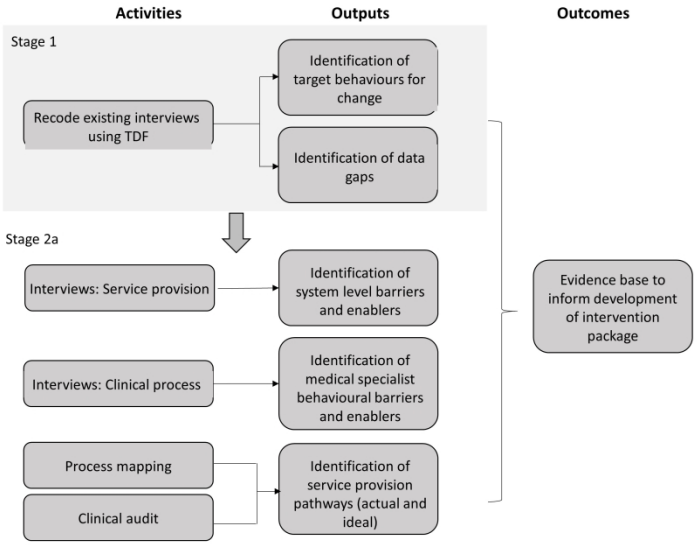

Figure 3: Logic Model

338x230mm (300 x 300 DPI)

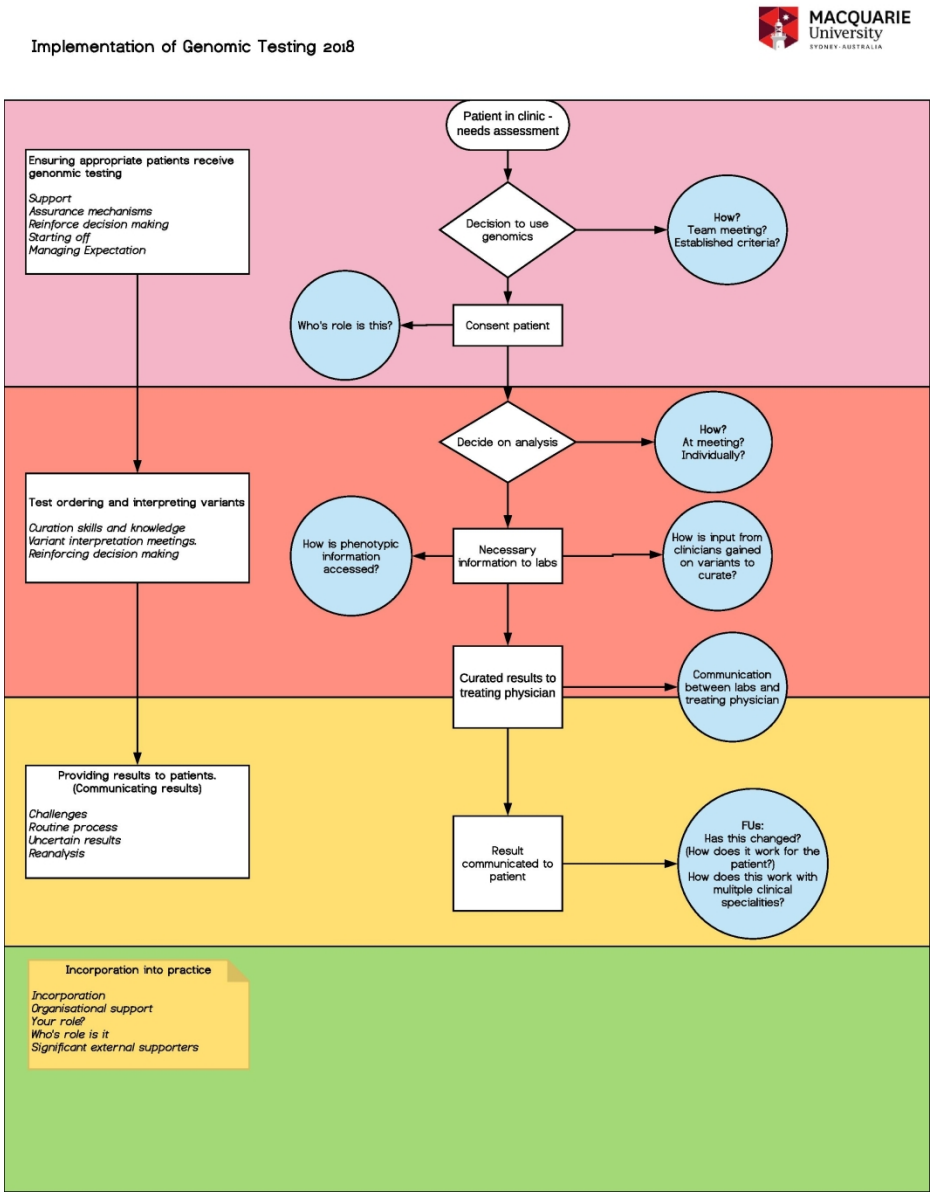

Figure 4: Process Mapping Guide

215x279mm (300 x 300 DPI)

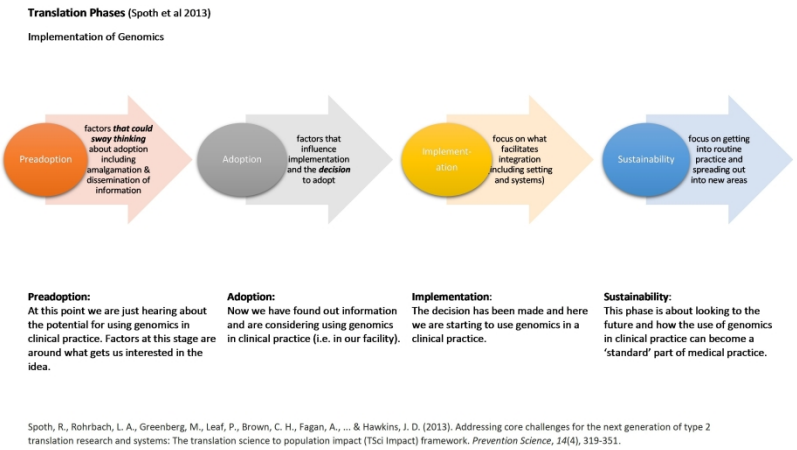

Figure 5: Service Provision Interview Translation Phases Graphic

338x190mm (300 x 300 DPI)

Supplementary Files

Supplementary File 1: Stage 1 Evaluation Structured Interview Schedule

Supplementary File 2: Stage 2a, Semi Structured Interview Schedule, Clinical Processes

Supplementary File 3: Stage 2a, Semi Structured Interview Schedule Service Provision

Supplementary File 4: Co design guide for Focus Groups with hypothetical intervention mapping scenario

Supplementary File 1: Stage 1 Evaluation Structured Interview Schedule

Clinician Interviews – themes and questions

Theme	Questions
Experience of participating in the demonstration project	1. Please tell me about your involvement in the demonstration project 2. From your perspective, what was the purpose of the MDT? How clear was this to you at the beginning? 3. Do you feel the MDT altered over time? How? 4. What did you like about the MDTs? 5. What do you think should be done differently? 6. On a scale of 1-5 how satisfied were you with the MDTs? *(5 very satisfied, 4 satisfied, 3 neither satisfied nor dissatisfied, 2 dissatisfied, 1 very dissatisfied)* 7. What do you think is important to discuss during pre-test counselling? *8.* Did you receive a research report on any of your patients? How many? What type? *(1/2nothing reported, 3 VUS, 4b, 4a/ 5)* 9. Were you involved in returning results to patients? 9.1. If yes, How did you approach this? *Be aware may differ for diff types of result (nothing found, 3 VUS, 4a or 4b, 5).* 10. Thinking about the sorts of results you usually communicate to patients, was there anything different about returning this sort of result? 11. So if I were to ask you to rate the difficulty you'd say it was… *More difficult, the same as, less difficult* do you agree?'
Impact (What has the impact been? How have results impacted?)	12. What impact has participating in this project had on your (clinical) practice? 13. What impact has participating in this project had on your understanding of genomics?

Integration in future practice	14. Putting issues of funding aside, would you use/support the use of clinical genomic sequencing if it were available in (your) practice? If yes – when is there value in using it If unsure/ no – tell us more about this. 15. What do you anticipate the barriers to incorporating genomics into practice (*in your specialty*) might be and how could these be overcome? *(funding model, clinician time, support for clinicians to attend from clinical managers)* 16. If genomic sequencing were to be offered in routine clinical practice, how do you think decisions would be made about 16.1. when to use exome sequencing? 16.2. interpretation of results 16.3. which genes to analyse 17. What did you think about the approach Melbourne Genomics took of excluding genes for unrelated adult onset conditions to minimise incidental findings? Do you think patients should have the choice to receive information about variants that show a future risk of disease unrelated to their condition? 18. Given that new genes are being identified and VUS are being reclassified as more is known, who do you think should be responsible for initiating a re-analysis in the future?
Resources to support integration	19. For which of these stages do you think resources would be helpful? 20. What information would need to be included? 21. What other resources might be helpful? 22. What are the advantages/disadvantages of an online portal?
Final messages	23. From your involvement in the demonstration project, what are the 3 things you want your hospital to keep in mind as genomics is implemented in clinical practice? 24. Is there anything else you want to make sure the Alliance of organisations takes into account?

Supplementary File 2: Stage 2a, Semi Structured Interview Schedule, Clinical Processes

Could you tell me what your role is and how you have been involved with the use of genomics in the clinical setting?

Ensuring appropriate patients receive exome sequencing **(Emotion,** Reinforcement, Behavioural regulation)	**Domain**
What measures are in place to assure yourself that you are selecting the appropriate patients?	Behavioural regulation
Is there anything in place that makes this process work well routinely?	Reinforcement
What were your experiences of starting off offering testing - how did you become more proficient? What helped (or would have helped)? Have you always been comfortable offering genomic testing in your clinical practice? What changed your mind?	Skills, Beliefs about capabilities, Beliefs about consequences, Emotion
What are your experiences of managing expectation? How have you found this? What has made it easier?	Exploratory q from patient consultation Emotion
Test ordering and interpreting variants **(Emotion,** Reinforcement)	**Domain**
What do you see as your role in determining the pathogenicity of a variant and its clinical significance)? (Who's role is it, how do you feed in?) What would you (or did you) need to participate in the curation process (if you feel this is part of your role)?	Skills and knowledge
There is a large focus on multidisciplinary variant interpretation meetings as a way of interpreting results. What works/doesn't work? What interventions have been put in place to aid the way they work? How would you find variant interpretation if these didn't exist?	Reinforcement Emotion
Final decision making around variant classification – is there a standard process in place?	Reinforcement
Providing results to patients. (Communicating results) **(**Emotion, Goals, Optimism**, Reinforcement, Behavioural regulation)**	**Domain**
Have there been (are you aware of) any issues around communicating results back to patients? *No*: What has been put in place to ensure it worked well? *Yes*: What has been challenging? What needs to be put in place to overcome this?	Exploratory
Has a routine process been established? How do you manage this?	MAD, Behavioural regulation
When results are uncertain how do you feel about feeding this back to the patient? How would you support a less experienced doctor with this? What gives you confidence that this process is being handled well?	Emotion Optimism
Has a routine process been put in place for reanalysis of results? How do you feel about this?	Reinforcement Emotion
Incorporation into practice **(**Emotion, **Reinforcement)**	**Domain**
What do you feel should be put in place (if anything) to incorporate genomic testing into standard clinical practice? How could this be facilitated? (is there anything other than funding) that is needed? How do we support people to change (attitudes, behaviours, habits, skills)?	Reinforcement
Are you happy to play a role in mainstreaming genomics?	Emotion
What sort of role do you envisage?	Prof ID
How do you keep up with the evolving evidence base?	Skills, knowledge
Is your organisation supportive of adopting genomics in clinical practice? In what way?	Organisational Knowledge
Is there anybody (or any role) outside your organisation who is key to ensuring mainstreaming?	Prof role, environmental context
For others starting out now, what advice would you give – maybe what you did or wish you had known?	

Are there any other barriers, maybe one you have overcome, that we haven't discussed and you would like to share?

Supplementary File 3. Interview Schedule, Service Provision

Could you tell me what your role is and how you have been involved with the use of genomics in the clinical setting?

Pre-adoption: focus on factors *that could sway thinking* about adoption including amalgamation & dissemination of information
What got you interested in the idea of genomic testing being used in clinical practice?
Where do you look for information around the use of clinical genomics? And where would you look for more?
How do you go about deciding what information, about adopting genomics, into clinical practice has value? Are there any networks that you find more helpful than others?
Adoption: focus on factors that influence implementation and the *decision* to adopt
What was the key reason for deciding to adopt/invest genomics in this clinical setting?
What specific data did you need or would like to see, to support the decision to use genomics?
What have been the key factors to influence (fellow) physicians to participate in the use of genomic testing?
Implementation: focus on what facilitates implementation (including setting and systems)
What do you think makes it easier for some clinical areas to implement genomic testing?
What do you think makes it easier for some organisations to implement genomic testing?
How do you know if implementation has been successful?
In developing your (organisational) processes, what have you learnt about what can be changed and what is essential?
What have been the best strategies to enhance participation/engagement? (with clinicians and non clinical staff)
Sustainability: focus on getting into routine practice and spreading out into new areas
As a (clinical) leader how do you nurture those who are advocating for change in genomics?
What do you feel should be done (if anything) to facilitate the incorporation of genomic testing?
How do you keep up with the evolving evidence base?
How do you go about deciding what to disinvest in to bring in a new intervention
Do you feel you have a particular part to play in getting genomics incorporated into routine practice?
Who should facilitate mainstreaming?
What organisation and community influences would support greater sustainability?
How do you think genomic sequencing needs to be financed in the future to ensure sustainability?
What national and/or state networks can most effectively support sustainability?
What policies do you/would you find most helpful to support stable funding streams?
For others starting out now, what advice would you give – maybe what you did or wish you had known

Are there any other barriers, maybe one you have overcome, that we haven't discussed and you would like to share?

Supplementary File 4: Co design guide for Focus Groups

Clinical processes phase 1 focus group material 1

Clinical processes target behaviour/area from process map and audit data	Barriers in context*^+	TDF domain	Impact of barrier (high/moderate/low)	Ranking of barriers to target (1 being most important)
Target behaviour 1	Barrier from data synthesis	XXX		
	Barrier from data synthesis	XXX		
	Space for additional barrier			
	Space for additional barrier			

*emerged from process mapping interviews ^emerged from clinical process interviews +emerged from service provision interviews
NB: XXX indicate where data would be populated. See 'hypothetical scenario below to follow the flow of data collection to intervention design'

Clinical processes phase 2 focus group material

Clinical processes target behaviour/area from process map and audit data	Top barrier in context*^+	TDF domain	Suggested intervention strategies*^+	Behaviour change strategy represented	Likely impact of strategy (high/moderate/ low)	Likely feasibility of strategy (difficult/ possible)	Ranking of intervention strategy (1 being most favourable)
Target behaviour 1	XXX		Ideas from data synthesis	XXX			
			Ideas from data synthesis	XXX			
			Space for more ideas				
			Space for more ideas				

NB: XXX indicate where data would be populated. See 'hypothetical scenario below to follow the flow of data collection to intervention design'

EXAMPLE HYPOTHETICAL INTERVENTION MAPPING SCENARIO: CLINICIANS

Hypothetical flow from data collection to focus group

Target behaviour 1: Ensuring appropriate patients receive genomic testing

Interviews/Process map		**Focus Group**			
Indicative hypothetical quote	*Theme & TDF domain*	*Barrier*	*Enabler*	*BCT*	*Intervention*
"*Care is needed that you don't create an environment where you don't feel you have confidence as this transfers to the patients*" "*Having worked in the flagship you develop the 'patter' and ability to run the clinic*"	Clinicians gaining confidence in their ability to do genomic testing *TDF Domain* Belief about capabilities	• Lack of hands on experience • Unable to attend MDT meetings	• CG and GC support • Access to flagship experience	Environmental changes Social processes of encouragement, pressure or support Framing/reframing	Ensuring clinicians have an opportunity (e.g., by quarantining time to attend) to learn skills through participation in multidisciplinary processes in the flagships (or processes that eventually replace flagships). Framing of the multidisciplinary meetings as 'hands on' learning to encourage support and shared expertise.

Service provision phase 1 focus group material 1

Service provision/policy target behaviour/area	Barriers in context*^+	TSCi area	TDF domain	Impact of barrier (high/moderate/low)	Ranking of barriers to target (1 being most important)
Target behaviour X	Barrier from data synthesis		XXX		
	Barrier from data synthesis		XXX		
	Space for additional barrier				
	Space for additional barrier				

*emerged from process mapping interviews ^emerged from clinical process interviews +emerged from service provision interviews
NB: XXX indicate where data would be populated. See 'hypothetical scenario below to follow the flow of data collection to intervention design'

Service provision phase 2 focus group material

Service provision/policy target behaviour/area	Top barrier in context*^+	TDF domain	Suggested intervention strategies*^+	Behaviour change strategy represented	Likely impact of strategy (high/moderate/ low)	Likely feasibility of strategy (difficult/ possible)	Ranking of intervention strategy (1 being most favourable)
Target behaviour X	XXX		Ideas from data synthesis	XXX			
			Ideas from data synthesis	XXX			
			Space for more ideas				
			Space for more ideas				

NB: XXX indicate where data would be populated. See 'hypothetical scenario below to follow the flow of data collection to intervention design'

EXAMPLE HYPOTHETICAL INTERVENTION MAPPING SCENARIO: SERVICE PROVISION

Translation Phase 1: Preadoption

Interviews		**Focus Group**			
Indicative hypothetical quote	*Theme & TDF domain*	*Barrier*	*Enabler*	*BCT*	*Intervention*
"*Less academic hospitals see genomics as the future rather than current practice*" "*Cost is secondary, hospital X has genomics, so we want it too*"	Need for organisational knowledge *TDF Domains* Professional identity Environmental context and resources	• Understanding that genomics is only for research (or has clinical application) • Lack of integration of genomics into clinical practice	• Organisational reputation • Costs of genomics aligning with 'traditional' procedures	• Social reward • Framing/ reframing • Goal setting (outcome) • Goal setting (behaviour) • Information about social and environmental consequences	• Frame genomics as current best practice to hospital executive and clinicians • Articulate a goal and strategy for implementing genomics at the hospital • Provide information about genomics and benefits that patients at other hospitals have from using genomics