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Evidence Check

Frameworks to support the implementation of genomics into clinical care

An **Evidence Check** rapid review brokered by the Sax Institute for the NSW Ministry of Health. November 2019.

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This report was prepared by:

Stephanie Best, Clara Gaff, Natalie Taylor and Helen Brown.
November 2019

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Frameworks to support the implementation of genomics into clinical care

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Contents

Executive summary

Establishing genomics (and other 'omics') within existing clinical practice is recognised as challenging. Traditional barriers for these emerging technologies such as funding, stakeholder acceptance and a conservative healthcare ecosystem are evident. However, the implementation of genomics into clinical practice is further complicated by the number of stages involved in getting genomics from the bench to the bedside (from gene discovery to financing and regulation), the myriad of people and professions involved (from policy makers to frontline clinicians) and the dynamic nature of genomics knowledge and application. Frameworks that work within this complex environment/ecosystem exist but are not always employed.

Background

The Translational Medicine Committee of the NSW Genomics Health Strategy commissioned a wide-reaching review of the literature to ascertain what frameworks have been used and what has been found to successfully translate genomics into clinical practice. The NSW Ministry of Health wanted to identify existing state, national, international and or global guidelines, frameworks and/ or policies in relation to the translation and/ or implementation of genomics into complex health systems as part of routine care. The focus was on finding existing—and preferably evaluated and preferably tested—structured approaches to the implementation of genomics, from data management through to frontline clinical care.

Review question

What frameworks have been implemented to support the translation of genomic research into clinical practice?

Summary of methods

A rapid, structured review of the peer reviewed and grey literature. The search was broad and covered publications and reports ranging across topics such as ethics, oncology and precision medicine.

Key findings

The review returned 12 peer reviewed papers and 15 items of interest from the grey literature. The overarching message from the existing literature is the limited evidence for the use, or evaluation of, frameworks to support the implementation of genomics into clinical practice. Key themes included:

- The crucial need for formal evaluation of the implementation of genomic medicine in real-world circumstances to understand what works and what does not
- The necessity of a collaborative approach across disciplines
- The importance of supporting medical professionals who are not genetic specialists integrate genomics into their practice
- The need for shared learning.

Gaps in the evidence

Drawing on the limited extant literature demonstrates:

- A lack of implemented and evaluated frameworks for implementation of genomics in clinical practice

- Limited reporting (or publishing) of community engagement with genomics.

Relevance to NSW

In relation to the key recommendations made in the NSW health genomics strategy implementation plan 2018-20 (pages 4-9):

1. **Governance**: *Establish a Governance Committee to guide the strategic direction for clinical genomics in NSW.*
   - The need for standardisation, equity of access, economies of scale and maintaining high quality
   - The need for agile regulatory structures for cell therapies, gene therapy, medical devices and manufacturing facilities
   - The importance of multidisciplinary models to implement, for example, pharmacogenomics
   - Significance of institutional leadership.

2. **Mechanisms for assessment – clinical need, validity and utility**: *Enhance, simplify and expedite the mechanisms for assessing the clinical need, validity and utility of new developments in health genomics and prioritise their potential for translation into the NSW public health system.*
   - For example, the MARS EXCITE model (https://www.marsdd.com/service/mars-excite/) to enable rapid delivery of products to market
   - A combination of processes in place for clinical approval of pharmacogenomics and importance of identifying and securing participation from clinical champions
   - The need to shift the conversation from worried well to cascade testing of relatives of the person with a positive result.

3. **Service delivery models**: *Develop new service delivery models linked to clinical pathways that incorporate genomic and digital advances to provide safe and equitable access across NSW.*
   - The importance of patient engagement alongside active collaboration with laboratory staff and clinicians
   - Engaging patients in designing service delivery models with emphasis on improving access for people from culturally and linguistically diverse(CALD) communities
   - Funding to follow the evidence and the importance of flexible funding structures
   - Addressing clinical, regulatory, manufacturing and reimbursement requirements to facilitate new products to market
   - Ensuring laboratories are networked and developing a single directory of tests (to ensure decommissioning where appropriate)
   - Importance of the multidisciplinary team
   - Devising strategies to overcome system-level barriers.

4. **Information standards and enabling infrastructure**: *Work with relevant parties to define the information standards, protocols and enabling infrastructure required to integrate clinical genomics into mainstream care.*
   - The findings relevant to this section largely related to laboratory practice and data sharing
   - The importance of focusing on 1) quality of data, and 2) development of bioinformatic tools
   - The challenges of big data and the concomitant need for information and communication technology
   - The need for definitions around 'Good Manufacturing Practice' as it relates to Cell Therapy Products
   - Use of interventions to support the use of genomics in clinical practice. For example, streamlining laboratory results, and the use of clinical decision support embedded in the electronic health record

- Defining standards, protocols and infrastructure (particularly noted in oncology)
- Engagement of the community when developing data registries.

5. **Workforce requirements**: *Work with relevant NSW stakeholders and national bodies to identify future workforce requirements, including awareness and genomic literacy within NSW Health, and develop a plan to address these needs.*

    - The necessity of roles changing
    - The essential role that education plays as part of an implementation strategy.

6. **Engaging the community**: *Work with key stakeholders, including general practitioners and Primary Health Networks, to engage the community regarding clinical genomics to build and sustain public confidence. This includes working with consumers as equal partners to develop services that reflect their needs and preferences in line with ethical, legal and professional standards.*

    - The need to educate and empower patients and the importance of early community engagement
    - Encourage the involvement of the underserved community with strategic level activities
    - At a strategic level, support the community to engage for example, with designing services, commissioning decisions and involving others.

Conclusion

This review has highlighted the limited published activity in the use and evaluation of frameworks that have actively translated genomics from the laboratory into clinical settings. To date there is limited information available to support the use of one framework above another for the implementation of genomics. This may be attributed to the early stage of genomic medicine and also to the scope of the current review.

Possible future directions:

- Development of communities of practice (national and international) to share learnings
- Follow up with national and international interviews with leads of clinical genomic implementation projects relevant to NSW Health and beyond
- Identification of more specific areas of interest within the field of genomics and implementation
- Encouragement for organisations to publish evaluations of implementation activities and evaluations.

Background

A major priority for researchers, clinicians, public health practitioners and policy makers is to determine pathways to transition research from the laboratory into clinical practice. However, rapid advances in genomics coupled with the increasing volumes and multidisciplinary nature of published studies and commentaries make it difficult for organisations to develop relevant and novel frameworks to move genomic research to clinical and public health practice. Similarly, moving any scientific discovery into clinical practice has historically been slow and difficult to achieve. These difficulties have been highlighted in publications such as the *Evaluation of Genomic Applications for Practice and Prevention* (Centers for Disease Control and Prevention (CDC, ND) and the CDC's *National Office of Public Health Genomics Human Genome Epidemiology Review* (https://www.cdc.gov/genomics/hugenet/default.htm).

In light of increasing and associated expectations of public health benefit, a comprehensive research agenda is required to move genomic findings into health systems in a way that maximises health benefits and minimises harm. Despite the attention paid to improving workforce knowledge and skills in genomics, in isolation education is not enough. Due to the complex, dynamic systems within which genomic medicine are implemented [1] frameworks are needed to generate the evidence to support the uptake of genomics through the complex facets of the health system such as data collection and analysis, ethical consent procedures, treatment and management provision. This review therefore aims to explore existing frameworks that have been implemented to support the translation of genomic research into clinical practice, to generate 'lessons learned' and further the development of strong, evidence-based frameworks.

Review questions

This review aimed to address the following question:

What frameworks have been implemented to support the translation of genomic research into clinical practice?

Methods

Two searches were undertaken to answer the research question "*What frameworks have been implemented to support the translation of genomic research into clinical practice*?"

- A systematic review of the peer reviewed literature and
- A review of the grey literature.

For the purposes of this review, genomic research included research on genomic testing, functional genomics, genomic therapies, and findings from laboratory research and applied research. "Genomics" incorporated other 'omics' such as proteomics, metabolomics etc. "Frameworks" included frameworks, guidelines and policies. All aspects of clinical practice were considered relevant, including prevention, diagnosis, early intervention, management and therapeutic interventions.

a. Peer reviewed literature search process

In consultation with a health specialist librarian, two databases were identified as relevant to the research question: Ovid Embase and Medline. Table 1 shows the search terms developed by the review team (and ratified by the Sax Institute).

Table 1: Search terms for peer reviewed search

1.	exp Genomics/
2.	proteomics/ or protoeogenomics
3.	(genome* or genomic*1 or exome* or proteomic* or gene-therap*).tw,kf.
4.	Precision medicine/
5.	Genetic Therapy/
6.	((personali#ed or individual* or precision) adj medicine).tw,kf.
7.	Health plan implementation/ or health planning guidelines/ or health priorities/ or health resources/
8.	Implementation science/ or technology transfer/
9.	Exp guideline/
10.	Health policy/
11.	Program Evaluation/
12.	(guideline* or framework* or policy or policies).tw,kf.
13.	Implementation.tw,kf
14.	(1 or 2 or 3 or 4 or 5 or 6) and (7 or 8 or 13) and (9 or 10 or 11 or 12)
15.	Exp animals/not human*.sh
16.	14 not 15
17.	Limit 16 to (comment or editorial or letter)
18.	16 not 17
19.	Limit to English language

The search ran from 2009 until June 2019, yielding 203 papers. Initial screening was undertaken using the inclusion and exclusion criteria listed resulting in 39 papers for full text review. Following removal of duplicates and second review, 12 papers were accepted for inclusion (see figure 1).

Inclusion criteria:

- Published in English since 2009 and up to May 2019
- Referred to genomics (incl. proteomics, gene therapy, precision/individualised medicine) in combination with health planning, implementation (science), technological transfer; and described in a public health or healthcare setting
- Explicitly or implicitly mentioned a theory, framework, model, program evaluation, guidelines or policy; any form of structured approach that related to the clinical service delivery of genomics.

Exclusion criteria:

- Conceptual frameworks that have not been implemented
- Studies unrelated to clinical service delivery of genomics (and/or proteomics, gene therapy, precision/individualised medicine), such as studies focused on research or gene discovery
- Highly technical process information
- Specific clinical information.

b. Grey literature search

Informed by the project brief, input from the NSW expert review panel and the collective experiences of the review team, 13 countries (including overarching international projects) were searched using Google (see appendix). More than 40 genomic initiatives were identified and were searched for reports or papers relating to areas of interest including:

- Collaboration across professions/groups
- Systems to support clinicians engage with genomics
- Funding
- Engagement with industry
- Governance structures
- Data and information sharing
- Tools, resources and measures – following evaluation

More than 70 reports and publications were identified and screened for evidence of a structured approach to implementation and signs of implementation (i.e. not conceptual). Publications (found on websites) were assessed against the peer reviewed findings to avoid duplication. Full text reviews resulted in the inclusion of 15 publications/reports (see figure 1 Prisma diagram).

The grey literature includes reports and/or articles from peer reviewed journals. Commentaries, editorials etc. were included within the grey literature where a genomic initiative had signposted the article even though it may have not fulfilled the peer reviewed search criteria.

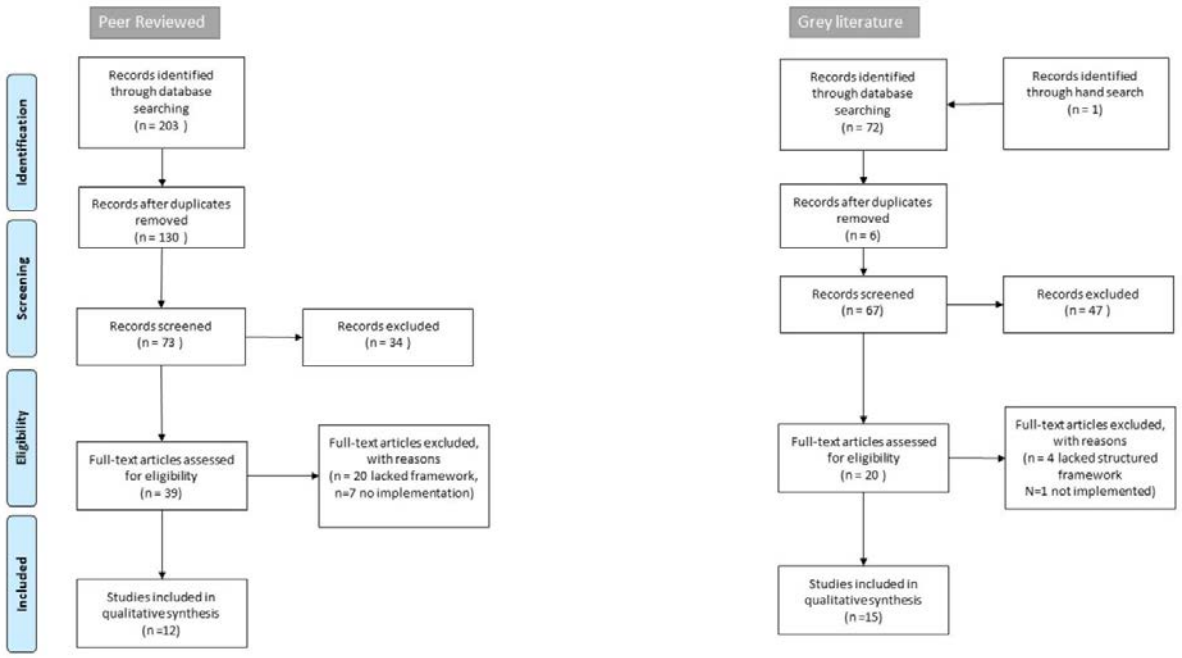

Figure 1 Prisma diagram

Process for scoping study and numbers of papers identified (adapted from Moher et al. 2009)

Key findings

The findings from the systematic peer reviewed and grey literature search are outlined separately, including an overview of the papers/reports and a summary of the key findings from each document.

Peer reviewed literature

The focus of this part of the review was to identify published, peer reviewed papers that reported on studies in relation to the translation and /or implementation of genomics into complex health systems as part of routine care.

An initial systematic search identified 203 studies, however after further review, the majority of these (n=191) were commentaries or conceptual studies that had yet to be implemented or evaluated.

International representation

Twelve studies published between 2009 and May 2019 were therefore eligible for inclusion in this review. Ten studies were undertaken in the US, one in the UK, and one involved a European collaboration.

Resources used to support implementation

A diverse range of studies were identified, including the development and implementation of educational resources for nurses, clinical decision support tools, knowledge bases, case studies, a risk-benefit framework and a knowledge translation framework. Due to the diversity of the studies, common themes relating to the effectiveness of these tools were difficult to discern.

Use of specific implementation frameworks

Consolidated Framework for Implementation Research: The Consolidated Framework for Implementation Research (CFIR) is a conceptual framework developed from exisiting implementation frameworks to facilitate systematic evaluation of the determinants of implementation (Damschroder et al. 2009). Two papers reported on the Implementing Genomics in Practice (IGNITE) Network's efforts to promote a broader understanding of genomic medicine implementation research and sharing of knowledge generated by the network. Orlando et al. (2017) described the development of a common framework for evaluating implementation of genomic medicine interventions in clinical care, producing a draft genomic medicine implementation model. The paper outlined the work of the Common Measures Working Group of IGNITE, which adopted the CFIR to guide the approach to identifying constructs, surveys and measures relevant to evaluating genomic medicine. A feature of this study was the ability to standardise data from across all IGNITE projects leading to a number of practical outputs, including the development of a centralised resource (toolkit) for cross-network analyses. The work of IGNITE was also reported in a paper by Zebrowski et al. [2] who used the CFIR model to identify system-level factors that played a role in the implementation of genomic medicine within IGNITE projects.

Working healthcare system: Two papers provided case studies to describe the implementation of genomics into a working healthcare system, however no implementation frameworks were described. [3, 4] Dunnenberger et al. [4] described the development and implementation of a multidisciplinary pharmacogenomics clinic within the framework of an existing community health system, highlighting the multidisciplinary approach required (geneticists, pharmacists, nurse practitioners, genetic counsellors).

Implementation was based on five key program elements developed from an initial literature review: 1) a billable- service provider, 2) a process for documentation of relevant medication and family histories, 3) personnel with the knowledge required to interpret pharmacogenomic results, 4) personnel to discuss risks, benefits and limitations of testing, and 5) mechanisms for reporting results. The paper provided a workflow process, however no overall framework for driving implementation was described.

Integrated healthcare delivery system: Williams et al. [3] also provided a working example of an integrated healthcare delivery system (Geisenger), which had an emphasis on developing and testing innovative approaches. Oversight was provided by the Geisenger Institutional Review Board and the MyCode Governing Board with input from a variety of stakeholders, a genomic council, and external ethics and scientific advisory boards. A novel component of this approach was that all employees and units (e.g., researchers, clinicians, stakeholders etc.) were part of the overall success of the enterprise. The paper reported that the implementation required "multidisciplinary expertise coupled with a communication strategy that crosses institutional boundaries to capture and integrate data".[3] Also included was a set of outcomes to help inform ongoing implementation evaluation, including the use of health, cost, behavioural, process and patient-reported outcome types. The evaluation of this system is ongoing, with next steps including identification and lowering of implementation barriers.

Knowledge bases: The development and implementation of knowledge 'bases' in two papers 2018; [5, 6] provided insight into global initiatives created to support the dissemination and implementation of genomic studies and resources relevant to clinical and public health practice. The Mensah et al. [5] study outlines a knowledge base ('HLBS-PopOmics') developed by the National Heart, Lung and Blood Institute in the US, based on the Public Health Genomics Knowledge Base (PHGKB), which was developed by the Office of Public Health Genomics at the Centers for Disease Control and Prevention. The Savatt et al. [6] study describes the implementation of GenomeConnect, a clinical genome resource patient registry, funded by the US National Institute of Health (NIH) which engages patients in data sharing to support the goal of creating a genomic knowledge based to inform clinical care and research.

Risk-benefit framework: A risk-benefit framework for assessing the health-related utility of genomic tests was outlined in a paper by Veenstra et al. .[7] This framework was developed to accelerate the use and practice-based evidence development of genomic tests that pose low risk and offer plausible clinical benefit, while discouraging premature use of tests that provide little benefit or pose significant health risks compared with usual care. A highlight of this paper was the incorporation of approaches from a variety of established fields, including decision science, outcomes research and health technology assessment as well as the consideration of physician – rather than consumer – stakeholder perspectives in the development of the framework.

Genome-based Knowledge Management in Cycles Model: Another framework reported in this review by Arar et al. [8] outlined a knowledge translation framework known as Genome-based Knowledge Management in Cycles Model (G-KNOMIC). This framework was developed by the GAPPN (Genomic Applications in Practice and Prevention Network) that aims to 'advance collaborative efforts involving partners across the public health sector to realise the promise of genomics in healthcare and disease prevention'. G-KNOMIC highlights the need for a collaborative approach across multidisciplinary groups to maximise translation, using ongoing knowledge 'cycles' that are adapted to specific circumstances.
It also highlights the importance of feedback and the self-organisation required by teams in a dynamic system.

A workflow clinical decision support framework: A workflow clinical decision support framework was outlined in a paper by Bucur et al. [9] This framework helps the complex decisions required for stratification and personalised patient treatment and supports the high rate of change in therapeutic options and

knowledge. This was a large collaborative study across Europe (funded by the European Commission – 7th Framework Program), involving collaboration between modellers, biomedical researchers and clinicians, data miners and CDS implementers.

Genomic competency models: Two papers outlined the development and evaluation of genomic competency models for nurses with the aim of supporting genomics into clinical practice [10, 11], highlighting the need to consider nurses as a major contributor to the genomic workforce.

CDC Science Impact Framework: Lastly, Green et al. [12] explored the impact of public health activities and partnerships in the implementation of two screening recommendation tools (hereditary cancers - EGAPP and USPSTF), using an existing framework (CDC Science Impact Framework). The paper highlighted the need to consider disparities in implementation based on race, ethnicity and rural residence in future public health approaches.

Summary of peer review findings

Overall, there was a lack of published studies that informed comprehensive implementation models. The IGNITE network outlined an evidence-based toolkit which included a draft genomic medicine implementation model, however no evaluation has been conducted to date. Other frameworks tended to be for specific purposes, such as for risk-benefit evaluation or for clinical decision support.

The lack of published studies highlighted the need for papers evaluating the implementation of genomic medicine in real-world circumstances. Lessons learnt through case studies inform potential barriers and facilitators to implementation, *enabling* the development of more effective processes for workflow and *use of* resources. The case studies also highlight the challenges of working in the health system: a complex, adaptive system that is dynamic and requires ongoing adaptations to occur.

Another key feature of the studies reported in this Evidence Check was the collaborative approach across multidisciplinary areas used when developing and evaluating frameworks for translation / implementation. Health systems are complex and for new technology to be introduced into clinical care, detailed input and feedback from a variety of stakeholders including patients, clinicians, researchers, bioinformaticians and policy makers is required.

The importance of sharing knowledge as genomics becomes more intergrated into the roles of non-genetic specialists was also highlighted in this Evidence Check. The development of online knowledge bases such as the 'HLBS-PopOmics' provide an opportunity to do this globally. The IGNITE network also provides an opportunity for sharing of research findings across the funded projects, using cross-network analyses for gaining learnings.

There is a lack of published frameworks that have been implemented and formally evaluated at this time. It is suggested that researchers consider more broadly how other similar scientific areas have approached the issue of translating and/or implementing research into complex healthcare systems as part of routine care, i.e. look outside the field of genomics and consider lessons learnt from established areas such as genetics. It is also suggested that global knowledge sharing of future frameworks/approaches implemented in practice is encouraged to allow shared learnings and more effective uptake in new settings.

Grey literature

The grey literature (n=15) ranged across commentaries and workshop reports (n=6), studies (n=2) with an array of descriptions of policy development, case studies, and health technology assessment (n=5). The remaining literature presented as board papers and presentations (n=2). Four papers were included from

the UK, followed by the US (n=3) and Canada (n=3), with the rest of the literature being multinational (n=5). The majority of the grey literature was generated between 2013-2018; one item had no date but contained content from 2011. Topic areas were wide reaching from inclusion of diverse populations to pharmacogenomics. Over a third of papers focused on cell therapies, regenerative medicine and/or regulation system, while others centred on topics such as personalised medicine. Several groups, such as IGNITE, Nordic Alliance and 100,000 Genomes Project focused on reporting best practice and offered recommendations for future service delivery.

Papers and reports offering particularly useful insights from across the world are highlighted in green in Table 3. They include:

- PerMed *Shaping Europe's Vison for Personalised Medicine.*[13]*:* This report provides examples where implementation work has been or is being undertaken.
- Carabello et al. *Multidisciplinary Model For Implementation of Pharmacogenomics*. [14] This paper uses a case study approach to outline work undertaken in the Mayo clinic.
- Nordic Alliance for Clinical Genomics *Workshop report*.[15] Presenting the proceedings of this workshop offers some experiences and perceptions of best practice.
- Barwell et al. *Challenges In Implementing Genomic Medicine: The 100,000 Genomes Project*. [16] Although the UK and Australia have different models of care this paper provides 10 recommendations for implementing genomics into the clinical setting that may be of significance to the Australian healthcare system.

The focus of the papers in terms of specific aspects of genomics to implement varied largely by country.

Cell therapy: Canada (i.e. Bedford et al.[17]; and Viswanathan and Bubela[18], and Cell Catapult in the UK) returned several papers on cell therapy. These made reference to the significance of 'Good Manufacturing Practice' while also noting that cell therapy is different to other areas of manufacturing. Bubela et al. [19] discuss methods to consider the notion of what different countries value (Canada and the UK), and how products can make it to market. They highlight the process in Japan where following the passing of the Pharmaceutical and Medical Devices Act, they can now get 'conditional approval' which allows early access to the market while the product is still under refinement. In an undated report, the Ontario Personalised Medicine Network investigated mechanisms to develop a pre-market framework to facilitate moving technologies to the clinical setting and provide a set of recommendations (see Table 3).

Pharmacogenomics: Two papers (from the US) focus on pharmacogenomics (Caraballo et al.[14] and Vitek et al.[20]). Vitek et al.[20] are interested in the impact of provider education on the use of pharmacogenomics (across 10 institutions) and note, "*lesson 4: building the plane while flying is not easy or free*". They provide a series of strategies and recommendations. Caraballo et al.[14], as noted previously, developed a model of implementation for pharmacogenomics which the team are particularly interested in scaling up.

Data sharing: Data sharing is raised in several papers across a variety of countries. In particular, the Nordic Alliance for Clinical Genomics (NACD) [15], PerMed (ND) [13] and Genome BC.[21] The latter of these shares their very proactive approach to data sharing and with three key policies 1) supporting rapid prepublication of data; 2) publishing must be through open access (or within 6/12); 3) discourages the use of patents. PerMed provides examples from across Europe of data-sharing approaches and the NACD has a theme devoted to data sharing.

Broad genomics implementation experiences: Several genomic initiatives share their experiences of implementing genomics. For example, Levy et al.[22] offer insight from the IGNITE program highlighting three

key areas: the need for training for providers, embedding a clinical decision support tool in their electronic health record, and the importance of third-party reimbursement. Some of these lessons may not be directly translatable to the Australian context but may be adapted to become more relevant. Another genomic initiative sharing early findings is the UK 100,000 genomes project, Keogh et al.[23] Not only is NHS England's strategic approach outlined, the planning for future implementation is considered, including areas such as procurement.

Community involvement: One area lacking in the international debate is the involvement of the community. Mathew et al.[24] provide an international perspective with a particular focus on underserved communities. No framework is offered in this paper though suggestions for future action are provided.

Conclusion of grey literature findings

Overall there is a lack of formal frameworks identified in the grey literature. Here we have noted papers and reports that provide some sort of structured path including recommendations and reflections on experiences of implementation of genomics in the clinical setting (rather than hypothetical views). This highlights one of the gaps in the literature.

Frameworks

Five specific purpose frameworks that had been implemented were reported in the peer reviewed literature. These were:

1. *Risk Benefit Framework*[7] used to assess the health-related utility of genomic tests
2. *Consolidated Framework for Implementation Research (CFIR)*[2] used by IGNITE network to identify system level factors that played a role across the six IGNITE projects undertaken
3. *G-KNOMIC (Genomic-Based Knowledge Management in Cycles Model)*[8] used to guide knowledge translation of research evidence into practice
4. *Workflow clinical decision support framework (online)*[9] used to support clinical processes and knowledge models for healthcare organisations, and
5. *CDC Science Impact Framework*[9] used to assess the impact of public health activities and partnerships in implementation of cancer screening tools.

Barriers and enablers

Barriers and enablers were identified by many of the paper and report authors. The barriers and enablers could be further synthesised according to a theoretical framework to allow for evidence-based targeting of intervention strategies to facilitate future implementation. They could also be presented to organisations implementing genomics to help identify potential barriers and possible solutions prior to implementation. Tables 4 and 5 highlight the principal factors affecting implementation.

Analysis in relation to NSW

To enhance the relevance of these findings for the NSW health system, specific analysis of the peer reviewed and grey literature was also undertaken in relation to the key recommendations made in the NSW Health genomics strategy implementation plan 2018-20 (pages 4-9). Table 6 summarises direct links between specific publications/reports and each of the recommendations. While the evidence available did not allow for this section to incorporate recommendations for the use of specific frameworks relevant to the NSW health system, it has drawn on a range of implementation approaches and/or strategies identified through this review.

1. **Governance:** *Establish a Governance Committee to guide the strategic direction for clinical genomics in NSW.*

   Governance is discussed in the grey literature across a range of settings. Keogh et al.[23] highlight the need for a joint commissioning model with the Clinical Commissioning Groups in the UK. Using the examples of panel tests for cancer and WGS, this board report stresses the need for **standardisation, equity of access, economies of scale and maintaining high quality**. The need for **regulatory structures** is identified for cell therapies, gene therapy, medical devices and manufacturing facilities. For example, Viswanathan and Bubela[18] describe the flexibility available within the Canadian regulatory system, which facilitates the development of cell, gene and tissue-based therapies in Canada. **Policies** to support data sharing are outlined by others. For example, Genome BC[21] outline three policies 1) Data release and resource sharing; 2) Access to research publications; 3) Intellectual property. Uncovered through the grey literature search and using the experiences of the EMERGE work, Caraballo et al.[14] report the need for a **multidisciplinary model** to implement pharmacogenomics. More specifically Caraballo et al.[14] note that to achieve this model of joint working required **institutional leadership** and pharmacogenomics governance. The governance model took the form of a **multidisciplinary 'task force of experts'** who could oversee the implementation coordinating efforts and resources. There was less reference to governance in the peer reviewed literature with Williams et al.[25] referring to their institutional review board.

   Orlando et al.[26] reported the **development of a framework for evaluating genomics**, highlighting the role of the IGNITE Common Measures Group (CMG) group. However, to date, this work is yet to be implemented.

2. **Mechanisms for assessment – clinical need, validity and utility:** *Enhance, simplify and expedite the mechanisms for assessing the clinical need, validity and utility of new developments in health genomics and prioritise their potential for translation into the NSW public health system.*

   The Ontario Personalised Medicine Network (OPMN) (post 2013) discuss the MaRS EXCITE work which aims to 'demystify the health adoption process'. MaRS EXCITE aimed to become involved early on in the pre-market development process to help health technologies get to market as quick as possible. Their role was to facilitate the generation of evidence-based practice and economic analysis. A **process for clinical approval of pharmacogenomics** is stressed by Caraballo et al.[14], including the need to **identify and secure participation from clinical champions**. The input of the champions served to highlight the potential impact of pharmacogenomics among clinicians including approving, developing and monitoring specific drug-gene interactions. From the peer reviewed literature, Barwell et al. (2018) discuss the need to **shift the conversation** from worried well over to cascade testing out from the person with a positive result. Bucur et al.[9] presents a **clinical decision support** (CDS) framework for

informatic and implementation in oncology recommendations. The use of a CDS Science Impact Framework to trace the impact of two recommendations (one from EGAPP Lynch syndrome and one from United States Preventative Services Task Force breast cancer recommendations) is provided by Green et al. (2019).

3. **Service delivery models:** *Develop new service delivery models linked to clinical pathways that incorporate genomic and digital advances to provide safe and equitable access across NSW.*

   There was discussion in the grey literature realting to getting products to market (noting the need to be mindful of the difference between commercialisation and getting a product in use) and mechanisms of delivery of care in clinical genomics. The importance of **patient engagement** was noted by Savatt et al. [6] who stress the need for **active collaboration** with labs, clinicians and patients to enable submission of genomic data to ClinVar, while Mathew et al.[24] highlighted the need to **design systems to improve access** for people from CALD communities. Funding is highlighted by several authors for example; Bubela et al.[19] stressing the need to **match evidence with the funders decision making** (rather than a specific service delivery model), and Levy et al.[22] raises the importance of **funding structures**. Several reports were found outlining processes used to get new products to market. For example, the PerMed report (post 2015)[13] outlines the development of **new clinical trial designs to facilitate new and innovative products getting to market**, and Mount et al.[27] discuss cell therapies and how to **address clinical, regulatory, manufacturing and reimbursement requirements**. Keogh[23] raises the development of **networked labs and a genomic medical service** and significantly developing a **single directory of tests** (to ensure decommissioning where appropriate). As noted in other sections, the **role of the MDT** within the service delivery model is raised again by Dunnenberger et al.[28] The 2019 study by Zebrowski et al.[2] identified **system level barriers** related to both research and practice existing within the IGNITE projects, suggesting that devising strategies to reduce these barriers will further enhance the implementation of genomics in practice.

4. **Information standards and enabling infrastructure:** *Work with relevant parties to define the information standards, protocols and enabling infrastructure required to integrate clinical genomics into mainstream care.*

   The findings relevant to this section largely relate to laboratory practice and data sharing. The grey literature focuses on process with several papers concentrating on the early phase of getting genomic products to market. Bedford et al.[17] discuss the **need for definitions around 'Good Manufacturing Practice' as it relates to Cell Therapy Products**. The Catapult presentation shares their experiences of 'navigating the early stage interactions with global regulatory authorities'. They highlight **nonclinical considerations** (such as published data/clinical experience and risk benefit assessment) **and when to engage**. In addition, they offer advice on how to **gain regulatory advice,** stressing that the global regulatory authorities note that legislation and guidance can not keep pace with the speed at which science is moving.

   Two of the sessions from the Nordic Alliance for Clinical Genomics workshop[15] refer to enhancing; 1) quality of data, with four areas in the clinical reporting session established as difficult to manage; **variants of uncertain significance** (VUS), **secondary findings**, **reanalysis** and **providing the patient with information** and 2) **development of bioinformatic tools** with the session noting an **enthusiasm to collaborate**.

   The **challenges of big data** and the concomitant need for information and communication technology is raised in the PerMed report (ND) with data sharing explicitly discussed by NACG in the 'vehicle for sharing' session. The NACG discussed vehicles such as the Matchmaker Exchange, Trusted Variant

eXchange and EllA. The data sharing emphasis in the Barwell et al. (2018) is more on **engaging patients** to ensure they know what is happening and so are **reassured about the processes around data sharing**.

Other papers and reports focus on the clinical arena with experiences in pharmacogenomics of Carballo et al.[14] at the Mayo clinic highlighting not only the process they used to **streamline laboratory results**, but also the need for a **clinical decision support embedded in the electronic health record** – the latter of which is supported by Levy et al.[22]

The peer reviewed literature provides several examples of initiatives relating to data sharing and information standards. Bucur et al.[9] helps define standards, protocols and infrastructure in oncology. They stress the **complexity of the workflow considerations** when implementing a bioinformatics platform. Veenstra et al.[7] developed a three-tiered framework to determine **risk benefit** assessment of genomic testing, which was valuable for **prioritising** which genomic tests to take forward.

Engagement of the community is discussed in two peer-reviewed papers: The development of a Geisenger MyCode biorepository system in 2007—used in the MyCode Community Health Initiative (2007) —is discussed by Williams et al.[3], while Savatt et al.[6] share the NIH GenomeConnect – Clinical Genomic Resource (ClinGen) patient registry to engage patients in data sharing. With a focus on providing resources and expertise to programme investigators Mensah et al.[5] outline the HLBS-PopOmics, an online database for the ever-changing dynamic field.

5. **Workforce requirements:** *Work with relevant NSW stakeholders and national bodies to identify future workforce requirements, including awareness and genomic literacy within NSW Health, and develop a plan to address these needs.*

   Successful implementation will be dependent on roles changing[16] and there is a consensus in the grey and peer reviewed literature about the need for education, for example, **nursing education programs**[11] and **training for providers**.[22] Education in pharmacogenomics is also raised by Caraballo et al.[14] who discuss the delivery of education and actionable pharmacogenomic knowledge (rather than identifying requirements) and Vitek et al.[20] who identify lessons learnt for education from the EMERGE work (with a useful table including education strategies used in different centres).

6. **Engaging the community:** *Work with key stakeholders, including general practitioners and Primary Health Networks, to engage the community regarding clinical genomics to build and sustain public confidence. This includes working with consumers as equal partners to develop services that reflect their needs and preferences in line with ethical, legal and professional standards.*

   The literature did not return a plethora of information about community engagement in isolation; many papers and reports discuss community engagement within other topics (see for example section 4. Information standards and enabling infrastructure). **Educating and empowering patients** is highlighted[24,13] with Mathew et al.[24] noting the need to **engage the underserved community** at strategic levels including **funding, commissioning and designing services**. Interestingly Barwell et al.[16] note the need to for **early community engagement** and the role of **patient stories** is essential combined with academic rigour.

Gap analysis

There is a lack of literature to clearly identify specific gaps that could be used to inform each of the NSW key recommendations. Each of these fields, from governance to identifying workforce considerations, require further investigation including the use of a relevant theoretical frameworks in action.

Drawing on the extant literature in relation to the NSW context (Table 6), the most limited area of investigation is community engagement. Where acknowledged, it is clearly considered highly relevant for the sustainable implementation of genomics but as yet is an understudied (or underpublished area).

Limitations

This work is limited by an active exclusion of any conceptual studies, which restricted the number of frameworks that could be synthesised in this review. In addition, the wide-reaching requirements of this rapid systematic review negated an opportunity to explore any specific area, for example getting products to market or community engagement, in any depth.

Conclusion and possible future directions

In conclusion, the literature review undertaken to explore the range of frameworks being used to actively implement genomics from the laboratory to the clinical setting has highlighted the limited progress in this area. To date there is limited information available revealing the impact of frameworks for the implementation of genomics. This may be attributed to the early stage of genomic medicine and also to the scope of the current review.

Possible future directions:

- Development of communities of practice (national and international) to share learnings
- Follow up with national and international interviews with leads of clinical genomic implementation projects relevant to NSW Health and beyond
- Identification of more specific areas of interest within the field of genomics and implementation
- Encouragement for organisations to publish evaluations of implementation activities and evaluations.

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Additional tables

	Table 2. Peer reviewed high level extraction table						
Paper no.	**Source (author/year)**	**Country**	**Aim of paper**	**Study type/approach i.e. RCT etc**	**Level under consideration ie systems, hospital, team**	**Findings**	**Level of maturity/ phase of implementation**
1	Arar et al. 2011[8]	US	To evaluate the new G-KNOMIC (Genome-based Knowledge Management in Cycles model) to support the GAPPN (Genomic Applications in Practice and Prevention Network) mission - a new framework to enhance the translation of evidence-based genomic findings by creating knowledge management cycles)	Case study demonstration of a knowledge translation framework application	Systems (multidisciplinary)	Recognition of need for ongoing knowledge cycles rather than traditional linear aggregation processes (helps to address issues that emerge during implementation) Recognises importance of relationships, feedback loops and ability of multidisciplinary teams to self- organise within a dynamic system	Part of the overall GAPPNet, well established
2	Bucur et al. 2016[9]	Netherlands	To present a clinical decision support framework and its implementation in p-medicine. (oncology specific)	Experimental trial of model adoption	Systems (multidisciplinary)	The need for clinical 'models' for use in decision making was supported – customising both the clinical processes and the knowledge models for each healthcare organisation is important	A newly designed model
3	Dunnenberger et al. 2016[28]	US	To describe the development and implementation of a multidisciplinary pharmacogenomics clinic within the framework of an established community-based genetics program	Descriptive case study.	Clinical system	The referral process was identified as a barrier to using the clinic, therefore a referral order was built in. Education sessions were introduced to providers. The demand for services grew quickly and demand outgrew clinic's capacity. Need to therefore consider workflow patterns for staff	A newly designed clinic

Table 2. Peer reviewed high level extraction table

Paper no.	Source (author/year)	Country	Aim of paper	Study type/approach i.e. RCT etc	Level under consideration ie systems, hospital, team	Findings	Level of maturity/ phase of implementation
4	Green et al. 2019[12]	US (Atlanta)	To evaluate the role of public health in implementation of genomics-related recommendations: case study in hereditary cancers using the CD science impact framework. • The Centers for Disease Control and Prevention in Atlanta used the CDC Science Impact Framework to trace the impact of 2 recommendations (one from EGAPP Lynch syndrome and one from USPSTF breast cancer recommendations)	Review of public health activities	Public health	Public health efforts to implement hereditary cancer prevention activities can be useful for future integration of genomics into public health prevention programs	n/a
5	Veenstra et al. 2010[7]	US (Washington)	To present a risk-benefit framework for assessing the health-related utility of genomic tests	Development and trial of a 3-tiered framework and policy matrix		A formal risk-benefit framework may accelerate the use and practice-based evidence development of genomic tests that pose low risk and plausible clinical benefit, while discouraging premature use of tests that provide little benefit or pose significant risks compared to usual care	No update of progress located
6	Zebrowski et al. 2019[2]	US	To identify system-level factors that played a role in implementation of genomic medicine with the IGNITE network. (Implementing Genomics in practice) projects (all funded by the NIH National Human Genome Research Institute) Conducted in a large collaboration – researchers, pharmacogenomics, bioinformaticians, medical practitioners	Qualitative interviews using CFIR	Clinician	Key barriers were outlined (limitations in integrating data and CDS into EHRs, physician reluctance towards participating in genomics due to limited evidence base, lack of funding, communication – investigators and clinicians – and lack of clinician and leadership engagement	IGNITE developed in 2013

	Table 2. Peer reviewed high level extraction table						
Paper no.	**Source (author/year)**	**Country**	**Aim of paper**	**Study type/approach i.e. RCT etc**	**Level under consideration ie systems, hospital, team**	**Findings**	**Level of maturity/ phase of implementation**
7	Williams et al. 2018[25]	US (Geisenger)	To describe the implementation of population - based genomic medicine in an integrated learning healthcare system within the setting of a learning healthcare system. • Implementation of population-based genomic medicine in an integrated learning healthcare system (Geisenger) • Geisenger is an integrated learning health care system involving researchers, providers and payers • Geisenger developed a MyCode biorepository system in 2007 (now called MyCode Community Health Initiative) • Has established several institutes using their model including the Genomic Medicine Institute	Case study – in an existing healthcare system	High level systems	2 necessary conditions were identified for the convergence of implementation science, precision medicine and learning healthcare system: 1. Clinical research need not be complete prior to implementation 2. Research and practice must coexist	Established
8	Savatt et al. 2018[6]	US	To explore patient engagement in data sharing to support the goal of creating a genomic knowledge base to inform clinical care and research.	Data sharing - using ClinGen's GenomeConnnect registry to curate and share with public databases		Through GenomeConnect and collaborations with external patient groups, the utility of patient-share data is highlighted. Increased patient engagement in genomic data sharing benefits both patients and genomics community	
9	Flynn et al. 2019[10]	US	To discuss the clinical research hospital's experience in integrating genomics into nursing practice, using the new competency model (MINC)	Case study demonstration of framework application		A suite of educational resources developed and introduced for nurses (competency levels). Evaluation is being undertaken currently	n/a

Table 2. Peer reviewed high level extraction table

Paper no.	Source (author/year)	Country	Aim of paper	Study type/approach i.e. RCT etc	Level under consideration ie systems, hospital, team	Findings	Level of maturity/ phase of implementation
10	Mensah et al. 2019[5]	US	To describe the creation of an HLBS (heart, lung, blood and sleep) population genomics knowledge base (HLBS-PopOmics) to support the dissemination and implementation of studies and resources relevant to clinical and public health practice	Descriptive		Majority of information in the database comes from epidemiological studies. there has been a steady increase in review /commentaries since 2012. There has not been a significant change in number of publications centred on evidence synthesis, tools or guidelines since 2014. ELSI issues are key areas of growth and should be focused on to determine best ways to communicate information	Developed in 2014
11	Kirk et al. 2014[11]	UK	To review a nurse genetics/genomics education framework using a consensus approach	Qualitative approach - consensus meeting (nominal group technique)	Nurse education	Deficiencies in relation to advocacy, information management and ongoing care were identified. All competencies of the original framework were revised and an extra competency included	n/a
12	Orlando et al. 2018[26]	US	To describe the IGNITE network's efforts to promote a broader understanding of implementation research and sharing of knowledge generated in this network by the development of a genomic medicine framework for evaluating the implementation of genomic medicine interventions in clinical care	Case study	Health systems	A framework was developed to identify constructs deemed valuable for implementation	IGNITE has been working since 2013

Table 3 Grey literature - high level extraction table

	Key Reports/papers of particular interest						
Paper no.	**Author /year**	**Country (& signposted by)**	**Aim/area of interest**	**Study type or data collection approach**	**Level under consideration ie systems, hospital, team**	**Findings (with signposting to sections of papers where appropriate)**	**Level of maturity/ phase of implementation**
1	Mathew et al. 2017[24]	Multiple (via Melbourne Genomics)	Inclusion of diverse populations in genomics	Qual: Genomix workshop at ESHG identified solutions	Popln level impact Multi level actions	Evident from the workshop and corresponding literature is that a multi-faceted approach to engaging communities is essential. This needs to be complemented by redesigning healthcare systems that improves access and raises awareness of the needs of these communities. At a more strategic level, institutions involved in funding research, commissioning and redesigning genetic health services also need to be adequately represented by underserved populations with intrinsic mechanisms to disseminate good practice and monitor participation. Further, as genomic medicine is mainstreamed, educational programs developed for clinicians should incorporate approaches to alleviate disparities in accessing genetic services and improving study participation	Started
2	Bedford et al. 2018[17]	Multiple (via CCRM)	Regulatory frameworks for cell therapy development	Qual: Text analysis - Canada, US and EU	Regulatory system	Useful summary table on page 2. Good Manufacturing Practice evolved for pharmacy industry rather than cell therapy. As a result, GMP means different things to different people. Further confusion as most cell therapy evolves in an academic/industry place. Different countries offer different approaches. Article discusses US, EU and Canadian approaches.	Ongoing
3	Viswanathan and Bubela 2015[18]	Canada (via CCRM)	An overview of the Canadian regulatory framework for evaluating advanced medicinal products including cell and gene therapy	Qual: Text analysis of policies, guidance docs and regulations. Plus discussions with Health Canada officials	Regulatory system	Executive summary of framework on page 660. Headings include: • **R**egulations for cell therapies • Regulations for gene therapy products • Medical devices for diagnostics/delivery of cell or gene therapies • Regulation of manufacturing facilities • Prochymal	Ongoing

						• Process for regulatory reform and new regulations in the pipeline	
4	Bubela et al. 2015[19]	UK, Canada and US (via CCRM)	The need to align evidence and decision making considerations for regulators, health system funders and developers - including a pathway into clinical practice	Qual: Report from two workshops (NICE, University of Alberta, Cell Therapy Catapult and Centre for Commercialization of Regenerative Medicine)	Regulatory system	Methods to support assessment of value are discussed including the different countries approaches to reimbursement, Pathway to clinical practice discussion includes: regulation and reimbursement; licensing frameworks. Discussion about the process in Japan is outlined	Ongoing
5	Genome BC 2017[21]	Canada (Genome BC)	Describes three Genome Canada policies: 1. Data Release and Resource Sharing 2. Access to Research Publications 3. Intellectual Property to be used by all Genome Canada projects	Qual: Summary of policy development by the Data Sharing Policies Advisory Committee	Data sharing	**Policy 1**: to support rapid prepublication of data including open access and controlled repositories. Supports open access **Policy 2**: Publishing must be through open access (or within 6/12) **Policy 3**: Discourages use of patents. Encourages multiple translation channels (e.g., open innovation, public domain open science, click-wrap licensing) that may encourage development of further tools/activities	Ongoing
6	Ontario Personalised Medicine Network Post 2012[29]	Canada (OPMN)	To develop a pre-market framework to facilitate getting market approved technologies into the clinical setting	Sub committee report	Health Technology Assessment	Uses the model of MaRS Excellence in Clinical Innovation and Technology Evaluation ("EXCITE") which works with companies early in product development to initiate "health technology assessment" (HTA) to guide product development and facilitate uptake (an example of a pre HTA is given in the text). **Recommendations:** 1. Look into the major challenges in evaluating evidence for PM technologies and determine an appropriate methodology that would be acceptable to most of the stakeholders in the healthcare system (i.e. associate with the Evaluation of Genomic Applications in Practice and Prevention [EGAPP] initiative) 2. Gather stakeholders to establish a working group to identify key societal/ethical issues in PM technologies and	Ongoing

						develop a regulatory framework that is transparent, consistent, fair, and equitable (i.e. involvement of members in the Ontario Personalized Medicine Network throughout this process is vital)	
7	PerMed post 2015[13]	EU (from PerMed	Identifies research topics, poses relevant questions and provides recommendations that will support the successful implementation of PM	Evaluation of PM reports, interviews with stakeholders and partners, workshops	Multiple	Identifies 5 challenges: • Developing awareness and empowerment • Integrating big data and ICT challenges • Translating basic and clinical research and beyond • Bringing innovation to market Shaping sustainable healthcare includes recommendations	Report completed
8	Caraballo et al. 2017 Genetics in Medicine[14]	US (via Emerge)	Designing a comprehensive and systematic implementation model for Pharmacogenomics	Case study approach using the Pharmacogenomcis set up at the Mayo Clinic to investigate 8 areas. Reasoning for each intervention not given	Frontline clinical care	Developed a model of implementation though identify challenges of scalability, how to continuously identify and prioritise the implementation of newly discovered drug-gene interactions. Eight headings: • Institutional leadership • Pharmacogenomics governance • Clinical approval • Laboratory results • Pharmacogenomics education • Pharmacogenomics knowledge • CDS-HER Implementation • Long term maintenance	only seen used in the Mayo clinic setting
9	Levy et al. 2019 Genetics in Medicine[22]	US (via GA4GH)	Description of the findings from the National Human Genome Research Institute's (NHGRI) Implementing GeNomics In pracTicE (IGNITE) Network in identifying key constructs, opportunities, and challenges associated with driving sustainability of genomic	Quant: Surveys of IGNITE members experiences	Four stakeholders: providers, payers, patients, and government agencies	Three key areas: 1. Genomic training for providers 2. Genomic clinical decision support (CDS) tools embedded in the electronic health record (EHR) 3. Third party reimbursement for genomic testing	IGNITE (https://ignite-genomics.org/) is ongoing

			medicine inclinical practice				
10	Nordic Alliance for Clinical Genomics 2018[15]	Denmark, Iceland, Norway, Sweden, UK (via NACG)	The objective of the workshop was to progress and include new participants in NACG's work to share experiences, data and best practices relevant for the clinical implementation of genomics, and to collaboratively explore pain points in producing and using genomic data to the best of the patient	Workshop report		Main topics discussed during the workshop group to three of the NACG working group themes: • Benchmarking, harmonisation and standardisation - Enhancing quality of data and processes • Bioinformatic tools development • Data sharing - Vehicles for sharing	Ongoing
11	Catapult 2018[30]	UK (from Catapult)	How to get Advanced Medicinal Therapy Products (AMTP) to the regulator: 1. Cell and gene therapy product classification 2. Nonclinical considerations and when to engage? 3. How to gain early regulatory advice and address early engagement meetings: MHRA, EMA, and FDA 4. Engineering T cells to target the tumour vasculature: Case study Q&A --with the MHRAwith the MHRA	Presentation	Labs/industry to regulators	**Take home messages** • The approach of each agency is similar, but take note of subtle differences in scope and required content • Consider the choice of agency in the context of scope e.g. national agencies in Europe may be better suited to non--clinical advice related to a FTIH trial, the EMA may be better for wide reaching development issues for ATMPs linked to centralised procedures **Early interactions do not replace scientific advice and are not likely to be accepted for products close to or already, in clinical development** • Meetings are informal but the manner in which they are conducted should be professional • Meeting materials should be of high quality e.g. questions submitted should always be supported with a company position and suitable background information Keep the briefing materials concise; 25–30 pages is advisable	Ongoing

12	Mount et al. 2015 Philosophical transactions[27]	UK (Catapult)	A description of a classification of cell therapies on the basis of their underlying technologies rather than the more commonly used classification by cell type because the regulatory path and manufacturing solutions are often similar within a technology area due to the nature of the methods used. We analyse the progress of new cell therapies towards clinical translation, examine how they are addressing the clinical, regulatory, manufacturing and reimbursement requirements, and describe some of the remaining challenges and provide perspectives on how the field may progress for the future	Commentary	Labs/industry to regulators	Useful table on page 6 outlining the different technologies and the outstanding challenges "The acceleration through clinical development without investment in underlying manufacturing processes (often termed 'fail-quickly fail-cheaply')". Cost-based manufacturing development model from page 9 and manufacturing model on page 10	Ongoing
13	Barwell et al. 2018[16]	UK (Genome England)	Using the American College of medical Genetic framework for evaluating and reporting sequence variants. Sharing learning from the previous years of 100,000 genomes	Commentary	Multiple	Scoring system of process to date Ten recommendations: 1. Speak to stakeholders prior to starting a program for operational design and buy-in; 2. Build on existing expertise and strength using universal business templates and a combination of implementation incentives but also clear economic reasons for compliance with transformation - the "no diagnostic, no surgery" approach	Ongoing

						3. Test and learn through rapid cycles based on simple criteria to inform implementation 4. Consider patient pathway economic modelling 5. Liaise with therapeutic companies around companion diagnostics 6. Consider impact on primary care of genomic results and how they are implemented 7. Be mindful of variable degrees of cynicism in primary and acute care around the importance of Mendelian disease in every day practice. Place an emphasis on approach to microbiology, cancer diagnostics and non-invasive disease 8. Ask patients about communication preferences around consent, re-contact and results 9. Don't underestimate the power of patient stories but these anecdotal reports are not a substitute for academic rigour Be aware that genomic testing does not mean sequencing alone. It involves identification registration and phenotyping, consent, sampling, processing, sequencing, interpretation, result giving, treatment and cascading.	
14	Vitek et al. 2017[20]	US (via eMERGE)	Incorporating provider education to support implementation: historic, descriptive experience of 10 institutions' approaches to provide PGx education, common and distincteducation strategies, and exemplars. Furthermore, we offer insights and recommendations to inform otherinstitutions	Commentary	Providers of pharmacogenomics	Lessons learnt and future perspective. Lesson 1: develop a comprehensive tool-box, but be strategic Lesson 2: enlist champions as part of a change management strategy Lesson 3: education is no magic pill. Lesson 4: building the plane while flying is not easy or free. Lesson 5: develop a long-term strategy	Ongoing

			considering the integration of PGx				
15	Keogh et al. 2017[23]	UK (via Genome England)	Sets out NHS England's strategic approach for building a genomic medicine service, building on the legacy of the 100,000 Genomes Project. Further planning to develop detailed implementation plans is now required, the immediate next steps of which include formalising the partnership approach with Genomics England, and launching the procurement process for the genetic laboratories by the end of Quarter 1 of 2017/18	Board paper	Mainly strategic	Early findings from the project are included. Successful implementation will require the NHS to establish the following underpinning elements: • A new networked genetic laboratory and genomic medicine service infrastructure – consolidated genomic laboratory infrastructure for rare, and inherited diseases and cancer operating to a defined service model; and a transitional role for the existing Genomic Medicine Centres to establish comprehensive coverage and access to genomic medicineacross the NHS. • A comprehensive genomic testing strategy for the NHS - initially for rare and inherited disease and cancer, that encompasses the entire testing repertoire from whole genome sequencing to tests for single genes; molecular markers and other functional genomic tests that are important to fully determine the patients predicted response to treatment. The NHS will require a single directory of tests, informed by evidence and based on the latest technological advances, to ensure that the tests that are no longer clinically or cost effective are decommissioned or replaced. • A joint-commissioning model with CCGs to achieve standardisation, equity of access, economies of scale and the high quality required for the future. For example, panel tests for cancer and WGS will need to be delivered at a centralised and aggregated level, which will not be possible without a joined-up approach to commissioning. • Further evolution of the NHS informatics environment through continued HMT capital investment to ensure that the interoperability and data sharing across the NHS is fully functional and can interface effectively with the Genomics England platforms.	Ongoing

Table 4 Barriers and enablers to implementation of genomics: Peer reviewed literature

Author	Barriers and Facilitators mentioned
Arar et al. 2011[8]	• Recognition of need for ongoing knowledge cycles rather than traditional linear aggregation processes (helps to address issues that emerge during implementation) • Recognises importance of relationships, feedback loops and ability of multidisciplinary teams to self- organise within a dynamic system
Bucur et al. 2106[9]	• None explained
Dunnenberger et al. 2016[28]	• Requires third party laboratory services (lack of flexibility in gene and variant selection) • Referral process: the EHR did not allow clinicians to order a pharmacogenomic clinic referral, which was usual practice. A 'referral order' was developed with a series of questions to guide clinicians to making appropriate referrals • GC's conducting medication and family history taking. 1. Time taken (form developed to speed process) and; 2. Issues understanding the medications (Pharmacists were called in to help GCs) • Change in workflow patterns and personnel disruptive • Catering for large increase in cases difficult
Green et al. 2019[12]	• None explained
Veenstra et al. 2010[7]	• Valuable tool for prioritising genomic tests for development in the translational pathway • Use of QALYs as a summary measure of HRU (health related utility) is problematic
Zebrowski et al. 2019	• Barriers identified in study: - Limitations integrating genomic data and clinical decisions support tools into EHRs - Physician reluctance to use GT due to limited evidence base - Inadequate reimbursement for genomic medicine - Communication between investigators and clinicians - Lack of clinical and leadership engagement
Williams et al. 2018[25]	• Effective collaboration between Primary Care Providers and Clinical Genomics required
Savatt et al. 2018[6]	• Allows data sharing – allows more effective interpretation of variants. Will improve the quality, consistency and accuracy of variant interpretation and better inform patient care
Flynn et al. 2019[10]	• Use of 'unit champion' nurses successful • Peer support strategies effective

Table 4 Barriers and enablers to implementation of genomics: Peer reviewed literature	
Author	**Barriers and Facilitators mentioned**
Mensah et al. 2019[5]	• Database keeping up with such an everchanging, dynamic field • Data in aggregation levels dependent on health topic listed which may not be complete (synonyms etc)
Kirk et al. 2013[11]	• Nurses lack competence and confidence towards genomic medicine • Scale and pace of developments in genomics have implications on education
Orlando et al. 2018[26]	• Six existing IGNITE projects were used to develop the IGNITE genomic medicine implementation research conceptual model

Table 5 Barriers and enablers to implementation of genomics: Grey literature	
Report	**Benefits, barriers and facilitators mentioned**
1. Mathew et al. 2017 [24]	Historical poor access for the CALD community Inadequate development of services in underserved communities
2. Bedford et al. 2018 [17]	• 'Good manufacturing practice' (GMP) guidelines not developed with Cell Therapy Products (CTP) in mind • Inspections may be undertaken by different groups of professionals with a range of different views, skills etc • Enabler is to minimise the number of regulatory bodies ie across states – eases the burden of gaining a manufacturing site licence • Suggest having a premarket cell therapy review against GMP for phase 1 or 2 trials rather than having facility GMO experts assess cell therapy manufacturing facilities
3. Viswanathan & Bubela 2015 [18]	Enabler "*Under the conditional approval plan in Canada, sponsors can technically apply for this evaluation and can receive a recommendation to be reimbursed by the provincial plans prior to full market approval.*" Stress the need for a flexible though stringent regulation process to ensure regulatory approval and commercialisation Barriers – multiple regulatory bodies – esp across states
4. Bubela et al. 2015 [19]	Barrier – complex payer ecosystems (e.g. US) and heavily insurance dependent systems (as high cost drugs get costed out) Enabler – collaborative discussions between regulators, healthcare payers Potential model from Japan

Table 5 Barriers and enablers to implementation of genomics: Grey literature

Report	Benefits, barriers and facilitators mentioned
5. Genome Canada (post 2017)[21]	No Bs and Es discussed
6. OPMN (post 2013)[29]	Barriers – unclear utility and cost effectiveness, clinical labs struggle with regulations, payment and speed of change in tech Enablers – early intro of HTA, early feedback to innovators
7. PerMed(2015)[13]	Identifies five challenges: • Developing awareness and empowerment • Integrating big data and ICT challenges • Translating basic and clinical research and beyond • Bringing innovation to market • Shaping sustainable healthcare
8. Caraballo et al. 2017[14]	Identify a need for multidisciplinary and multi-institutional efforts to ensure pharmacogenomics is implemented. "*Challenges surround the implementation of PGx-based medicine on a wider scale, including reimbursement for genetic testing, development of infrastructure and standardized processes for storing, accessing, and interpreting genomic data, evidence of clinical utility, ethical and legal concerns, and prescriber uncertainty about the clinical and financial benefits of genome-guided therapy. Furthermore, the dynamic nature of discovering new clinically actionable variants increases the complexity of the implementation*" Enablers: leveraging EHR (also use education interventions)
9. Levy et al. 2018[22]	Barriers: • For providers lack of education, need for genomic focused CDS tools • For payers- reimbursement Discussion notes provide technology fatigue and the need to include only clinically validated 'pop ups' to prevent disruptions in workflow
10. Nordic Alliance for Clinical Genomics 2018[15]	No specific barriers identified – the workshop itself acted as an enabler
11. Catapult UK 2018[30]	Enabler – classifying the Advanced Medical Therapy Product early
12. Mount et al. 2015[27]	Enabler – using technology as the classification emphasises the similarities between in translation challenges
13. Barwell et al. 2018[16]	Barriers – failure to understand impact of molecular developments on patient outcomes and 2. Staff resistance to changing roles, plus discarding current practices
14.Vitek et al. 2017[20]	Emerge network – healthcare provider education for pharmacogenomics. Lessons learnt

Table 5 Barriers and enablers to implementation of genomics: Grey literature	
Report	**Benefits, barriers and facilitators mentioned**
	1. Develop a comprehensive tool box but be strategic 2. Enlist champions 3. Education is not a magic pill 4. Building the plane while flying is not easy or free 5. Develop a long-term strategy
15. NHS England 2017	Ten recommendations, see Table 3

Table 6 Relevance to NSW Health Genomic Strategy						
Author /year	**Governance structures**	**Mechanisms for assessing clinical need**	**Service delivery models**	**Define information standards, protocols, infrastructure**	**Identify workforce requirements**	**Engage the community to build public confidence**
	Grey Literature					
Mathew et al. 2017[24]			Need to redesign healthcare systems to improve access and awareness of CALD communities			Stress importance of education for the public. Also need to involve underserved community at a more strategic level ie funding, research, commissioning, designing services
Bedford et al. 2018[17]				Clarity needed around Good Manufacturing Practice for Cell Therapy Products		

Table 6 Relevance to NSW Health Genomic Strategy

Author /year	Governance structures	Mechanisms for assessing clinical need	Service delivery models	Define information standards, protocols, infrastructure	Identify workforce requirements	Engage the community to build public confidence
Grey Literature						
Viswanathan and Bubela 2015[18]	Need for regulatory structures around cell therapies, gene therapy etc					
Bubela et al. 2015[19]			Not so much a specific service delivery model but the need to match evidence with funders decision making			
Genome BC 2017[21]	Policy frameworks to encourage data sharing					
Ontario Personalised Medicine Network Post 2013[29]		MaRS EXCITE aims to 'demystify the health adoption process'				
PerMed post 2015[13]			Development of new clinical trial designs to facilitate new and innovative products come to market	Discusses the challenges of big data and need for ICT	Sustainable PM only possible if all stakeholders participate in the process	Need to empower patients (and health professionals. Encourage active engagement with health (crosses over with service models)

Table 6 Relevance to NSW Health Genomic Strategy

Author /year	Governance structures	Mechanisms for assessing clinical need	Service delivery models	Define information standards, protocols, infrastructure	Identify workforce requirements	Engage the community to build public confidence
Caraballo et al. 2017[14]	Institutional leadership and Pharmacogenomics governance in model	Process for clinical approval (Ax of practice impact)		Lab results, CDS-HER implementation in model	Delivery of ed and actionable pharmacogenomic knowledge (rather than identify requirements)	
Levy et al. 2019[22]			Funding structures	Need for tools	Training for providers	
Nordic Alliance for Clinical Genomics 2018[15]				Three sessions fit here: Enhancing quality of data Bioinformatic tools Vehicle for sharing		
Catapult 2018[30]				Cell and gene therapy product classification; Nonclinical considerations and when to engage; How to gain early regulatory advice and address early engagement meetings: MHRA, EMA, and FDA		

Table 6 Relevance to NSW Health Genomic Strategy

Author /year	Governance structures	Mechanisms for assessing clinical need	Service delivery models	Define information standards, protocols, infrastructure	Identify workforce requirements	Engage the community to build public confidence
Mount et al. 2015[27]			Cell therapies and addressing clinical, regulatory, manufacturing and reimbursement requirements			
Barwell et al. 2018[16]		Discusses shift from worried well to cascade testing out from person with a positive result		Data sharing	Discusses changing clinical roles	Emphasis on early patient and community engagement. Importance of patient stories, but not as a substitute for academic rigour
Vitek et al. 2017[20]					Identifies lessons learnt for education	
Keogh, B 2017[23]	Joint commissioning model with CCGs		Networked labs and genomic medical service. Developing a single directory of tests (to ensure decommissioning where appropriate). Evolution of the NHS informatics services			
Peer reviewed						
Arar et al. 2011[8]			G-KNOMIC framework for developing knowledge in cycles			
Peer reviewed						

Table 6 Relevance to NSW Health Genomic Strategy

Author /year	Governance structures	Mechanisms for assessing clinical need	Service delivery models	Define information standards, protocols, infrastructure	Identify workforce requirements	Engage the community to build public confidence
Bucur et al. 2015[9]		Clinical decision making tool for oncology		Helps define standards, protocols and infrastructure		
Dunnenberger et al. 2016[28]			Need for MDT within the service delivery model			Need to engage the community to build confidence
Green et al. 2019[12]		Use of CDC Science Impact Framework to trace impact of two recommendations				
Veenstra et al. 2010[7]				Development of three tiered framework to determine risk benefit of genomic testing		
Zebrowski et al. 2019[31]			Identification of system level factors involved with IGNITE			
Williams et al. 2018[25]	Mention of their Institutional review board		Integrated learning healthcare system. Established several institutes using their model including the Genomic Medicine Institute	Development of MyCode Community Health Initiative (2007)		

Table 6 Relevance to NSW Health Genomic Strategy

Author /year	Governance structures	Mechanisms for assessing clinical need	Service delivery models	Define information standards, protocols, infrastructure	Identify workforce requirements	Engage the community to build public confidence
Savatt et al. 2018[6]			Active collaboration with labs, clinicians, patients to enable submission of genomic data to ClinVar	GenomeConnect - Clinical Genonmic Resource (ClinGen) patient registry for data sharing		
Flynn et al. 2019[10]					Role of champions	
Mensah et al. 2019[5]				HLBS-PopOmics - online database for ever changing dynamic field		
Kirk et al. 2014[11]					Nurse education program	
Orlando et al. 2018 [26]	Ignite Common Measures Group (CMG) developing a framework for evaluating genomics - NOT YET IMPLEMENTED					

Appendices

Appendix 1 Genomic Inititives (as of July 2019)

Country	National Clinical Genomic Body/ Genomic Initiatives	Link	Aim or Mission of body/initiative	Link to strategic plan if available	Link to peer reviewed papers
UK	Genomics England / The 100,000 Genomes Project	https://www.genomicsengland.co.uk/	Genomics England, with the consent of participants and the support of the public, is creating a lasting legacy for patients, the NHS and the UK economy, through the sequencing of 100,000 genomes.	The 100,000 Genomes Project: bringing whole genome sequencing to the NHS The rise of the genome and personalised medicine Global implementation of genomic medicine: we are not alone	
	UK Cell & Gene Therapy Catapult	https://ct.catapult.org.uk/	The Cell and Gene Therapy Catapult is a centre of excellence in innovation, with the core purpose of building a world-leading cell and gene therapy sector in the UK as a key part of a global industry. Supported by Innovate UK, our mission is to drive the growth of the industry by helping cell and gene therapy organisations across the world translate early stage research into commercially viable and investable therapies.	https://ct.catapult.org.uk/sites/default/files/publication/Establishing the cost of implementing a performance based managed entry agreement for a hypothetical CAR T cell therapy_0.pdf	

Canada and Canadian state-based genomic initiatives	Genome Canada	https://www.genomecanada.ca/	Genome Canada harnesses the transformative power of genomics for the benefit of all Canadians. They make strategic investments in large-scale science, leading-edge technology and translation programs and initiatives to ensure genomics knowledge is applied to maximum benefit for Canada. The programs are designed based on engagement with a broad range of stakeholders, including sector-specific users of genomics, especially in the private sector. They are implemented through a rigorous international peer-review system, which ensures only the highest-quality research proposals with the greatest potential for impact are funded.	https://www.genomecanada.ca/sites/default/files/publications/gc_strategic-plan-full-version.pdf Data Release and Sharing Policies (Data Release and Resource Sharing, Access to Research Publications & Intellectual Property) https://www.genomecanada.ca/sites/default/files/GE3LSsurvey/integrated_ge3ls_research_report_-_final.pdf https://www.genomecanada.ca/sites/default/files/ige3ls_implementation_plan_en.pdf	
	Genome British Columbia	http://www.genomebc.ca/	Genome BC, a non-profit research organisation, leads genomics innovation on Canada's West Coast and facilitates the integration of genomics into society. Major investors are the Province of British Columbia and the Government of Canada through Genome Canada and Western Economic Diversification Canada. This funding is complemented by partnerships with many national and international public and private funding organisations to drive BCs bioeconomy.	https://www.genomebc.ca/wp-content/uploads/2019/06/Genome-BCs-Health-Sector_May-28-2019_FINAL.pdf	
	Genome Alberta	http://genomealberta.ca/	Genome Alberta is a publicly funded not-for-profit corporation that initiates, funds, and manages genomics research and partnerships. It strives to be the leading source of information and administration	http://genomealberta.ca/files/Annual_Reports/Genome_Alberta_2018_AR_ONLINE_hyperlinked.pdf	

			related to genomics, metabolomics, bioinformatics, and biotech research in Alberta.		
	Genome Prairie	http://www.genomeprairie.ca/	Genome Prairie is a non-profit organisation that supports stakeholders across Manitoba and Saskatchewan in capturing and maximising the benefits of advanced research in genomics and related biosciences. This role is achieved by aligning the partners and resources needed to develop and manage targeted projects addressing regional priorities. Genome Prairie also enables participation among regional researchers in Genome Canada's competitive granting process for large-scale projects.	https://www.genomecanada.ca/sites/default/files/pdf/en/gc-gappinvestmentstrategyandguidelines.pdf	Arar et al. 2011
	Ontario Genomics – linked to OPMN	https://www.ontariogenomics.ca/	Its mission is to spark, support and sustain Ontario's genomics technology pipeline as a key driver of the province's knowledge-based economy. To accomplish this, it works with four key stakeholders:	Personalized Medicine Coalition 2015 Annual Report	
	Ontario Personalized Medicine Network (OPMN)	https://www.ontariogenomics.ca/provincial-strategies/opmn/	The Ontario Personalized Medicine Network (OPMN) is led by an expert panel to assess the challenges and opportunities presented by personalized medicine. The objective of the OPMN is to ensure Ontario is well positioned to capitalise on the exciting and transformative technology revolutionising the medical care landscape. Membership in the OPMN is voluntary.	Summary of International Strategies for Personalized Medicine "Call for an Ontario Health Data Ecosystem"	
	Génome Québec	http://www.genomequebec.com/	Génome Québec's mission is to catalyse the development and excellence of genomics research and promote its integration and	http://www.genomequebec.com/DATA/PUBLICATION/33_en~v~2018-2023_Strategic_Plan.pdf	

			democratisation. It is a pillar of the Québec bioeconomy and contributes to Québec's influence and its social and sustainable development.		
	Genome Atlantic	http://genomeatlantic.ca/	We aim to develop genomics R&D projects in seven key sectors - agriculture, fisheries and aquaculture, energy, the environment, forestry, mining and human health. We work with a range of public and private partners to help companies and organisations use genomics to solve problems in these sectors. Our services are diverse and highly flexible, but are generally focused on helping teams identify, develop or manage results-focused genomics R&D projects. (Find out more in our **Services** section.)	http://genomeatlantic.ca/wp-content/uploads/2015/08/Toolkit-Full-Report.pdf http://genomeatlantic.ca/wp-content/uploads/2018/10/Genome-Atlantic-Annual-Report-2017-18-DIGITAL-1.pdf	
	Canada Centre for Regenerative Medicine	https://www.ccrm.ca/regenerative-medicine-executive-summary	Regenerative Medicine (RM), which aims to harness the power of stem cells, biomaterials and molecules to repair, regenerate or replace diseased cells, tissues and organs, has the promise to treat, manage and perhaps cure some of the most devastating and costly diseases in the world today. Many new and potentially life-changing RM-based treatments never reach patients because they are not successfully moved from the laboratory to a stage where they can be used in medicine. In order to fulfill RM's promise to treat the many diseases affecting our population, a world-renowned group of stem cell scientists and bioengineers have come together to form CCRM.	https://www.ccrm.ca/sites/default/files/pdfs/Multi-Year%20Accessibility%20Plan%20Final.pdf	

			CCRM's mission is to generate sustainable health and economic benefits through global collaboration in cell and gene therapy, and regenerative medicine.		
	Ontario Institute for Regenerative Medicine (OIRM) - partner organisation with CCRM	https://oirm.ca/	The Ontario Institute for Regenerative Medicine (OIRM) is a non-profit stem cell institute dedicated to transforming discoveries into clinical trials and cures. Through our commitment to collaboration and partnerships, we leverage our resources to fund and support promising advances. OIRM is a passionate champion for investigators and their patients as we build a healthier future for Ontario, Canada and the world. OIRM was established on November 25, 2014 and is currently funded by the Government of Ontario with $25M in support over five years (2015-2020). By leveraging the many advantages in Ontario, such as world-class science and clinical infrastructure, a supportive regulatory environment, and facilities across the province that support manufacturing, commercialization and the launch of spin-offs, OIRM augments its government funding to deliver on its promise of better health and prosperity for Ontarians		
	CanDIG - Canadian Distributed Infrastructure for Genomics	https://candig.github.io/	Fundamental to CanDIG is national scale analysis, but over locally controlled data. Our platform is completely distributed, with no central infrastruture to maintain or secure. But atop that, researchers need to be able to readily discover, access and analyse this	Cross-Canada Project CanDIG Selected to Help Drive International Genomics Standards	

			information, possibly jointly across sites, while allowing the data stewards to ensure the security and privacy of their data.	CANARIE selects CanDIG project as basis for a prototype National Data Service for Health Genomics	
US	California Stem Cell Agency Links to OIRM	https://www.cirm.ca.gov/	When taking action, they consider what impact their efforts will have in these areas: Will it speed up the development of a stem cell treatment? Will it increase the likelihood of success? Will it fill an unmet medical need? Is it efficient? In addition, their Standards Working Group has developed research standards that make sure our grantees are following the highest standards in their research. They've worked closely with other state and federal agencies to align our standards and to protect patients. Some therapies that come out of stem cell research involve transplanting the cells themselves. Others will be drugs that were discovered through modeling diseases in a petri dish. Still others will be diagnostics that allow doctors to diagnose and treat diseases more effectively — or through technologies that open up whole new fields of research. Our funding promotes all areas of stem cell research that show promise to accelerating treatments to patients in need.	Strategic Plan Annual Report https://www.cirm.ca.gov/sites/default/files/files/about_cirm/CIRM%202018%20Annual%20Report.pdf	
	National Human Genome Research Institute (National Institute of Health)	https://www.genome.gov/	NHGRI believe that advances in genomics research are transforming understanding of human health and disease. Building on a leadership role in the initial sequencing of the human genome, they collaborate with the scientific and medical communities to enhance genomic technologies that	https://www.genome.gov/about-nhgri/strategic-plan/overview	

			accelerate breakthroughs and improve lives. At NHGRI, they are empowering and expanding the field of genomics. They are charting one of humankind's newest frontiers.		
	Materials Genomics initiative	https://www.mgi.gov/	The **Materials Genome Initiative** is a multi-agency initiative designed to create a new era of policy, resources, and infrastructure that support US institutions in the effort to discover, manufacture and deploy advanced materials twice as quickly, and at a fraction of the cost. Advanced materials are essential to economic security and human wellbeing, with applications in industries aimed at addressing challenges in clean energy, national security and human welfare, yet it can take 20 or more years to move a material after initial discovery to the market. Accelerating the pace of discovery and deployment of advanced material systems will therefore be crucial to achieving global competitiveness in the 21st century. Since the launch of MGI, the federal government has been investing in the R&D infrastructure needed to accelerate the discovery, design, development and deployment of new, advanced materials into existing and emerging industrial sectors in the US	Equip the Next-Generation Materials Workforce	
	IGNITE	https://gmkb.org/?utm_source=ignite-genomics.org&utm_medium=referral	The Implementing GeNomics In pracTiCe (IGNITE) Pragmatic Clinical Trials Network is an NIH-funded network dedicated to	**Download a PDF of the CYP2C19 Guide** Challenges Associated with Implementing	_ Zebrowski et al. 2019N _ Orlando et al. 2018

			supporting the implementation of genomics in healthcare. The Network is comprised of five research sites, a coordinating center, a steering committee, and working groups. The National Human Genome Research Institute and a data safety and monitoring board provide oversight for all network activity and is intricately involved in all aspects of IGNITE design and operation	Pharmacogenomics into Clinical Practice Presentation	
	Centers for Disease Control and Prevention	https://www.cdc.gov/ https://www.cdc.gov/genomics/	CDC works to protect America from health, safety and security threats, both foreign and in the U.S. Whether diseases start at home or abroad, are chronic or acute, curable or preventable, human error or deliberate attack, CDC fights disease and supports communities and citizens to do the same. CDC increases the health security of our nation. As the nation's health protection agency, CDC saves lives and protects people from health threats. To accomplish our mission, CDC conducts critical science and provides health information that protects our nation against expensive and dangerous health threats, and also responds when these arise	"Beyond public health genomics: Can big data and predictive analytics deliver precision public health?"external icon	
	Emerge	https://emerge.mc.vanderbilt.edu/	eMERGE is a national network organised and funded by the National Human Genome Research Institute (NHGRI) that combines DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine	Implementation of Pharmacogenetics at Cincinnati Children's Hospital Medical Center: Lessons Learned Over 14 Years of Personalizing Medicine. Clinical Pharmacogenetics Implementation Consortium	

				(CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group. An information extraction framework for cohort identification using electronic health records. Should pretest genetic counselling be required for patients pursuing genomic sequencing? Results from a survey of participants in a large genomic implementation study. The Return of Actionable Variants Empirical (RAVE) Study, a Mayo Clinic Genomic Medicine Implementation Study: Design and Initial Results. Design and Implementation of the International Genetics and Translational Research in Transplantation Network Implementation and utilization of genetic testing in personalized medicine.Using systems approaches to address challenges	

				for clinical implementation of pharmacogen Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project.	
Australia and State-based clinical genomic bodies and state reports	Australian Genomics	https://www.australiangenomics.org.au/about-us/australian-genomics/	Genomic technology is a relatively new and disruptive technology in healthcare. Its successful implementation relies on whole-of-system change. Genomic medicine has the potential to transform delivery of healthcare. It promises better patient outcomes and a more efficient health system through rapid diagnosis, early intervention, prevention and targeted therapy.	**National Health Genomics Policy Framework and Implementation Plan 2018-2021**	
	Sydney Genomics Collaborative	https://sgc.garvan.org.au/initiatives	The Sydney Genomics Collaborative is a $24 million, four-year investment by the NSW State Government in using genetic technologies to improve patient outcomes. Genomics is one of the fastest-growing areas of medical research and has emerged as a highly promising source of new insights into the genetic cause of disease. The Sydney Genomics Collaborative program was established with NSW State Government funding in June 2014 to boost genomic research across NSW into inherited diseases and disorders with a genetic component, including cancer. The Collaborative utilises the Illumina HiSeq X Ten, a high-speed genome sequencing system operated by the Garvan Institute of Medical Research. The Illumina HiSeq X Ten technology enables the	The Collaborative Program comprises: • Medical Genome Reference Bank – • NSW Genomics Collaborative Grants – • Genomic Cancer Medicine Program –	

			study of whole-genome sequences at the scale of large populations.		
	Melbourne Genomics Health Alliance	https://www.melbournegenomics.org.au/	Genomic medicine – healthcare informed by greater knowledge of our DNA – is advancing rapidly. Technology now enables us to 'read' our DNA, but this is only half the story. We need to put genomic medicine to use in our hospitals and clinics to help those living with disease achieve quicker, more accurate diagnosis and more personalised medical care.	"A transformative translational change programme to introduce genomics into healthcare: a complexity and implementation science study protocol", "A novel approach to offering additional genomic findings - A protocol to test a two-step approach in the healthcare system",	
	Queensland Genomics	https://www.qgha.org/	The integration of genomics into healthcare has the potential to transform health services globally with faster diagnosis, new treatments, and more cost-effective service delivery. Queensland Genomics is a $25 million Advance Queensland initiative which was established by the Queensland Government in 2016 to enable the implementation of genomics into Queensland's healthcare system. Queensland Genomics invests in genomics health implementation projects that bring together Queensland's health and hospital services' innovation, with advancing medical and social research, to accelerate the adoption of medical genomics into mainstream healthcare.	National Health and Medical Industry Growth Plan – Australian Genomics Health Futures Mission Global Implementation of Genomic Medicine National Health Genomics Policy Framework 2018-2021	

			Our work aims to benefit Queensland's patients, clinicians, the health system and leading research groups.		
	SA Genomics Health Alliance	https://www.sagenomics.org/	The SA Genomics Health Alliance is in its very first phase of development, linking together individuals and organisations with expertise in genetics and genomics so that we can better address the challenges and capitalise on the recent developments in this field.		
	WA	https://ww2.health.wa.gov.au/Articles/A_E/About-genetics-and-genomics https://ww2.health.wa.gov.au/Articles/N_R/Office-of-population-health-genomics	The Office of Population Health Genomics (OPHG) was established in 2001 to help optimise the health benefits of genomic knowledge for the population of Western Australia. To achieve this, we develop system-wide and service-specific public policy that draws on stakeholder engagement and collaboration, and research outcomes. This helps governments decide what actions should be taken to address genomics issues and deliver population-based screening programs, at the state and national levels. OPHG uses population health approaches to implement strategies that prevent disease and disability where possible, and promote health and wellbeing. These outcomes stem from: earlier diagnoses and interventions; more effective treatments; and provision of accessible and high-quality services; resulting in better outcomes for the population and the public health system more generally.	the WA Rare Diseases Strategic Framework 2015-2018 Guidelines for human biobanks , genetic research databases and associated data (PDF 4MB) Code of ethical practice for the provision of genetic services in Western Australia (PDF 542KB)	
NZ	Genomics Aotearoa	https://www.genomics-aotearoa.org.nz/	Genomics Aotearoa is an agile, leading-edge and collaborative platform, established to ensure that New Zealand is internationally	Aotearoa New Zealand Genomic Variome Clinical Genomics	

			participating and leading in the rapidly developing fields of genomics (the study of the genome, the complete set of genetic material present in a cell or organism) and bioinformatics (the development of methods and software tools for understanding the biological data derived from genomics).		
Netherlands	Genome of the Netherlands (GoNL)	http://www.nlgenome.nl/	The Genome of the Netherlands is a consortium of the UMCG,LUMC, Erasmus MC, VU university and UMCU, led by Professor Cisca Wijmenga. Samples where contributed by LifeLines, The Leiden Longevity Study, The Netherlands Twin Registry (NTR), The Rotterdam studies, and The Genetic Research in Isolated Populations program. All the sequencing work is done by BGI Hong Kong. Funding for the project was provided by the Netherlands Organization for Scientific Research under award number 184021007, dated July 9, 2009 and made available as a Rainbow Project of the Biobanking and Biomolecular Research Infrastructure Netherlands (BBMRI-NL)	The Genome of the Netherlands: design, and project goals pubmed http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3021.html *Whole-genome sequence variation, population structure and demographic history of the Dutch population*	
***Scandinavia*: Sweden**	Genomic Medicine Sweden Karolinka Institutet	https://ki.se/en/mmk/genomic-medicine-sweden-national-initiative-for-precision-medicine https://genomicmedicine.se/en/	Genomic Medicine Sweden is an initiative that aims to prepare a plan for a new type of infrastructure within Swedish Healthcare that implements Precision Medicine at a national level. The initiative was granted support from Swelife in June 2017 for a preparatory study. During September 2017 an initial start-up meeting was held at Karolinska Institutet, where Swedish clinicians, diagnosticians and technicians nationwide gathered together to		

			participate in and influence the design of Genomic Medicine Sweden, GMS.		
Finland	FINNGEN and Genome Center Finland	https://www.finngen.fi/en http://www.genomikeskus.fi/en/	**FinnGen** is one of the very first personalised medicine projects at this scale and the public-private collaborative nature of the project is exceptional compared to many ongoing studies. FinnGen brings together Finnish universities, hospitals and hospital districts, THL, Blood Service, biobanks and international pharmaceutical companies and hundreds of thousands of Finns. Because collaboration is the key to achieving breakthroughs in disease prevention, diagnosis, and treatment, we welcome everyone on this journey into our shared heritage. Genomic data will open up new opportunities for diagnostics and treatment of diseases. The Genome Center Finland will serve as an expert on the use of genomic data. Its task will to be to enhance the responsible use of genomic data in the promotion of human health and to administer the national genome database. The genomic data of the Finnish population will be stored in the Genome Center.		
Norway	Helsedirektoratet	https://www.helsedirektoratet.no/english			
	The Nordic Medical Research Councils (NOS-M) and	https://nos-m.org/ https://nordicclinicalgenomics.org/	The Joint Committee of the Nordic Medical Research Councils **(NOS-M)** is a collaborating body for the Nordic research councils that finance medical research.NOS-M aims to coordinate and promote medical	Nordic Potential in Medical Research - Cooperation for Success (2014) [PDF]	

	the Nordic Alliance for Clinical Genomics (NACG)		research in the Nordic countries, to monitor its progress, and to facilitate information exchange among the countries. The Committee also aims to promote concrete, collaborative Nordic projects in medical research. **NACG** aims to • Facilitate the responsible sharing of genomic data, bioinformatics tools, sequencing methods and best practices for interpretation of genomic data • Enhance quality of genomic data and processes and explore methodologies to provide assurance • Understand legal barriers to the implementation of personalised medicine and to engage with key stakeholders that influence these barriers • Develop demonstration projects that challenge perceived legal barriers that limit responsible and ethical sharing of genomic and health data • Build bridges between research and clinical communities, technologies and practices to foster innovation		
France	Aviesan	https://www.aviesan.fr/en	Set up in April 2009, the French National Alliance for Life Sciences and Health (Aviesan) groups together the main stakeholders of life and health sciences in France. The purposes of Aviesan are to:	https://aviesan.fr/content/download/8827/73797/version/1/file/Genomic+Medicine+France+2025+web.pdf	

			• Coordinate the strategic analysis, scientific programming and operational implementation of life and health science research • Give a fresh boost to translational research by speeding up the transfer of fundamental knowledge to clinical application • Increase cross-disciplinarity by opening biology and medicine up to contributions from mathematics, physics, chemistry, information technology, engineering sciences, human and social sciences • Ensure that projects are consistent in thematic and infrastructure terms • Carry out clinical, economic and social promotion of knowledge, particularly by facilitating industrial partnerships • Define shared standpoints in terms of European research and international cooperation • Harmonise and cut down on red tape for laboratories so as to free up the creativity and excellence of teams		
Germany	None available				
Overarching					
International e.g.	Global Genomic Medicine Collaborative (G2MC)	https://g2mc.org/	The Global Genomic Medicine Collaborative (G2MC) is an organisation that is creating a community of global leaders dedicated to advancing genomic medicine implementation in clinical care	https://www.sciencedirect.com/science/article/pii/S0749208118301323 https://www.nature.com/articles/s41436-018-0315-y	

				https://www.nature.com/articles/s41436-018-0080-y	
	Global Alliance for Genomic Health (GA4GH)		The **Global Alliance for Genomics and Health** (GA4GH) is an international, nonprofit alliance formed in 2013 to accelerate the potential of research and medicine to advance human health. Bringing together 500+ leading organisations working in healthcare, research, patient advocacy, life science, and information technology, the GA4GH community is working together to create frameworks and standards to enable the responsible, voluntary, and secure sharing of genomic and health-related data.	*Framework for Responsible Sharing of Genomic and Health-Related Data*. GA4GH-CONNECT-A-5-YEAR-STRATEGIC-PLAN VIEW THE STRATEGIC ROADMAP	
	International Cancer Genome Consortium for Medicine (ICGCmed)	https://icgcmed.org/ https://icgc.org/	The ICGC has evolved significantly since its inception in 2007. At its heart, ICGC is a consortium of experts in genomics and informatics. Its initial project was to define the genomes of 25,000 primary untreated cancers (the 25K Project); the second ICGC project, the Pan Cancer Analysis of Whole Genomes (The PCAWG Project), commenced in 2013 and continues to analyse ~3,000 of the highest quality whole cancer genomes of multiple cancer types. In 2015, the ICGC, in response to the realisation of the potential of genomics in healthcare, released a position "white paper" on the evolution of ICGC into more directly impacting on human health. Emanating from the ICGC for Medicine (ICGCmed) white paper is ICGC's next project which aims to Accelerate Research in Genomic Oncology (The ARGO Project),	https://icgcmed.org/files/ICGCmed_White_Paper_April_2016.pdf https://icgc-argo.org/	

			where key clinical questions and patient clinical data drive the interrogation of cancer genomes.		
	International 100K Cohort Consortium (IHCC)	https://ihcc.g2mc.org/	The International HundredK+ Cohorts Consortium (IHCC) aims to create a global platform for translational research – cohort to bedside and cohort to bench – informing the biological and genetic basis for disease and improving clinical care and population health. They are bringing large cohorts together to encourage data sharing, improve efficiencies and maximise benefits in addressing scientific questions none could answer alone. They have formed three teams focused around data standards and interoperability, scientific strategy and cohort enhancements, and policy and bio-data sharing to address the value and challenges of combining large cohort data across borders.	https://ihcc.g2mc.org/teamc/	
EU	European Alliance for Personalised Medicine	https://www.euapm.eu/research-objectives.html	The European Alliance for Personalised Medicine was launched in March 2012, with the aim of improving patient care by accelerating the development, delivery and uptake of personalised medicine and earlier diagnostics, through consensus Alliance began life as a response to the need for a wider understanding of priorities in personalised medicine and a more integrated approach among distinct lay and professional stakeholders.	Proposal for Horizon Europe regulation Impact assessment Annex Horizon Europe Programme-activities	
	European commission and million European genomes alliance (MEGA)	https://ec.europa.eu/digital-single-	The Signatories of the declaration of cooperation "Towards access to at least 1 million sequenced genomes in the EU by	1+ Million Genomes" initiative 2018 Declaration Genome (.pdf)	Bucur et al. 2015

		market/en/european-1-million-genomes-initiative	2022" are setting up a collaboration mechanism with the potential to improve disease prevention, allow for more personalised treatments and provide a sufficient scale for new clinically impactful research.	General Data Protection Regulation (GDPR) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2016:119:FULL&from=EN	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4965727/