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Genomic sequencing technologies for rare disease in mainstream healthcare: the current state of implementation

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ABSTRACT

Genomic sequencing technologies, which includes both exome and genome sequencing, as well as panels or targeted analyses using genome-wide approaches, are being implemented across healthcare. Implementation, however, varies greatly by application and jurisdiction, with a diversity of approaches being employed around the world. This review summarises the current state of implementation of genomic testing in mainstream healthcare for the detection of rare disease throughout the lifespan. Through a discussion of evidence gathered to date, highlighting exemplar studies, the following applications of genomic testing will be covered: (1) routine diagnostic genomic testing in the clinic; (2) rapid diagnostic genomic testing in the intensive care unit; (3) genomic newborn screening; and, (4) reproductive genetic carrier screening. Mainstream implementation necessarily extends beyond the clinical genetics service, where genomic testing has historically been offered. Given that the involvement of non-genetics clinicians in the delivery of these technologies has important implications for models of care and education, related areas of growing evidence are also discussed: (5) genetic counsellors working outside clinical genetics services; and, (6) workforce development considerations of mainstream genomics. The diversity of approaches and examples illustrates that integration of genomic technologies into mainstream healthcare is complex and requires significant health system transformation. Efforts to evaluate services, guided by implementation science, will be essential to ensure lessons are shared across jurisdictions and benefit is delivered to patients and the system at-large.

KEYWORDS

Genetic testing; genomic testing; mainstreaming; service delivery models; clinical genetics; implementation

INTRODUCTION

As understanding of the human genome and its role in health and human disease continues to expand, so do the indications for genomic testing (1). Concurrently, significant improvements in genome-wide sequencing technologies have been realised, increasing the diagnostic yield and cost-effectiveness of genomic testing strategies (2, 3). Once the exclusive purview of clinical genetics professionals, growing demand coupled with a stable genetics workforce (4) has necessitated increased involvement of non-genetics clinicians in genomic testing. This is facilitated by the increasing ability of genomic testing strategies to effectively replace multiple targeted tests (2, 5), reducing the need for specialised test selection expertise and improving their utility as hypothesis-naïve screening tools. This is especially the case with genome sequencing, which is increasingly preferred when clinically available (1). Together with supports such as digital tools and growing educational resources, these advances are facilitating the integration of genomic sequencing technologies into the clinical practices of diverse clinicians, medical specialties and mainstream healthcare, in both academic centres and in community settings.

Although clinical application of genomic testing was initially limited to the not-so-rapid diagnosis of patients with suspected genetic conditions, these advances are leading to a growing list of applications across healthcare. Areas of growth include acute settings (with a rapid turnaround) and in a screening capacity (pre-conception, during pregnancy, and at the time of birth). Implementation, however, varies greatly across applications and jurisdictions. In this review, the authors discuss the current state of implementation of genomic testing in mainstream

healthcare. Applications of genomic testing across the lifespan will be reviewed (Figure 1), exploring barriers and facilitators to adoption and implementation. Areas of related importance around the evolving role of genetic counsellors in mainstream healthcare and genomics education will also be discussed.

Scope and definitions

In this review, the authors intend “genomic testing” to refer to all genome-wide sequencing strategies, including exome (ES) and genome sequencing (GS), with both broad and targeted analytical strategies (e.g., *in silico* gene panels completed on an exome backbone). Ultimately, the available technology or analytical approach differs by program and are subject to change over time. Therefore, testing strategies will be described explicitly where relevant, but otherwise considered as a single entity, genomic testing. Throughout this review the term “mainstreaming” is used to describe a model of care, where all or part of the clinical genetic testing process is shifted to non-genetics clinicians to facilitate patient access (6). Relatedly, “mainstream healthcare” is intended to capture the use of genomic testing as standard or routine clinical care, particularly in areas outside of clinical genetics services. This review focuses on the application of genomic testing in the diagnosis of and screening for monogenic rare diseases, illustrating key considerations using examples in diagnostic settings such as routine diagnostic genomics and acute care settings, and in screening settings such as newborn and reproductive genetic carrier screening.

ROUTINE DIAGNOSTIC GENOMIC TESTING

Large-scale efforts to build evidence and health system capacity were important first steps in the translation of genomic sequencing technologies from the realm of research to mainstream clinical use (7). Following from its use in research, these capacity-building efforts largely focused on genomic testing for the diagnosis of patients with suspected genetic disorders. As the application for which mainstream implementation began, genomic testing as a diagnostic test is also the application for which implementation is most advanced and widespread.

At a national level, the United Kingdom (UK) was an early proponent of clinical genomic testing at scale, investigating its integration into the single-payer National Health Service (NHS) first through the Deciphering Developmental Disorders study, which involved ES of mainly paediatric patients (8), and followed by the flagship 100,000 Genomes Project (100KGP) (9). The 100KGP utilised short-read GS, and testing was offered to a broader range of adult and paediatric patients, through both clinical genetics services and non-genetics clinicians. Both programs helped establish the clinical utility of gene-agnostic technologies in a range of clinical settings. Importantly, the 100KGP led directly to the development of the NHS Genomic Medicine Service (GMS), launched in 2018.

Efforts to build capacity for genomic testing quickly followed in other jurisdictions (7). Early efforts in Australia addressed state-level fragmentation through a national collaborative partnership and many flagship genomics projects led by Australian Genomics (10). In the United States, public funding, through the National Human Genome Research Institute and the Precision Medicine Initiative All of Us Research Program, has helped demonstrate the value of genomic testing across diverse clinical domains, while the private sector has also embraced genomics and is offering testing to patients at-large (7). Efforts to build capacity for genomic testing, however, are not limited to well-resourced health systems. The breadth of such efforts

was well illustrated in a recent special issue from this journal, highlighting genomic testing initiatives in Chile, Iran, Iran, Sudan, Sri Lanka, and other countries (11).

Service models for implementation of mainstream genomic testing

As capacity is built to offer genomic testing at scale, service models to ensure its delivery must be developed and implemented. From the start, the NHS GMS has relied on a strategy of 'mainstreaming' to deliver diagnostic genomic testing across the health system. In the NHS GMS, this occurs for a range of clinical indications with indirect support from clinical genetics services. A living document called the Genomics Test Directory specifies which clinical indications genomic testing can be requested for, broad clinical eligibility criteria, and which specialists can request testing (12). England is served by supraregional Genomics Laboratory Hubs, which provide bioinformatics support and multidisciplinary team meetings to support non-genetics clinicians who are ordering genomic testing. Medical geneticists and genetic counsellors work within regional clinical genetics clinics and offer support to non-genetics clinicians.

Genomic testing in Australia and Canada is also available as a publicly funded test, which affords a centralised approach to adjudicating eligibility related to a shared responsibility between government and laboratories around resource allocation. However, funding is either partially or entirely provided at the state- or province-level; eligibility criteria and access are often also dictated at this as a result. Laboratory services are also largely regional and not necessarily consistent or universal in their analytical or reporting approach. In contrast to the UK, these jurisdictions have been slower to operationalise mainstreaming models and have relied longer on medical geneticists to deliver genomic testing. Access in Australia and Canada

has only recently expanded to non-genetics clinicians (13-15). Australia achieved national implementation in 2020 by leveraging the federally-funded Medical Benefits Scheme, funding genomic testing for some indications in children, ordered by paediatricians. This requires patient-specific approval, however, by a clinical geneticist (14). In Canada, genomic testing continues to be accessed through private out-of-country laboratories in many provinces, but some are increasingly implementing local genomic testing programs, such as Ontario, which has also expanded eligible ordering clinicians to include non-genetics specialists as of 2025 (15).

In contrast to publicly-funded systems, coverage for genomic testing in the United States has been through commercial insurance policies (16). While this has adversely impacted patient access to genomic testing, ordering has been open to any physician who is willing to arrange it for eligible patients. As a result, models of care are highly variable and site- and service-dependent.

Although the use of routine genomic testing is growing in specialties across medicine, some examples warrant highlighting. Thus, the authors present the current state of implementation in general paediatrics, adult neurology, and both paediatric and adult nephrology to shed light on the models employed and lessons learned, which can extend to other areas in healthcare.

Implementation of genomic testing in general paediatrics

Most rare genetic diseases present in childhood, making general paediatrics an important area in which to deploy genomic testing and monitor its implementation. For children with rare genetic diseases, a prompt diagnosis is important to: inform appropriate and personalised clinical management; improve prognostic information; determine accurate risk for relatives and

future pregnancies; unlock research opportunities and facilitate access to support from social and educational services, as well as disease-specific support networks. It can also provide emotional benefits for parents, including relief from guilt and validation that the child has a condition (see Supplementary Material 1 for additional references). Utilising genomic testing early in the diagnostic pathway can minimise the 'diagnostic odyssey' for families, an important part of improving their experience, mental wellbeing, and quality of life. As a result, genomic testing is now recommended as a first-line test for certain paediatric indications by the UK GMS, the American College of Medical Genetics and Genomics, and the Medical Services Advisory Committee in Australia (see Supplementary Material 1 for additional references).

The implementation of genomic testing for paediatric rare disease diagnosis into the NHS in England has been the focus of a mixed methods evaluation (17). This programme of work has highlighted a range of barriers and facilitators to implementation (18-23). In interviews with key stakeholders involved in designing and delivering the NHS GMS, the main barriers to implementation were considered to be: limited availability of a suitably trained workforce to consent, interpret findings, and communicate results from genomic testing; challenges related to the digital infrastructure needed to support delivery, exacerbating the onerous administrative aspects of taking consent and ordering genomic testing; reluctance from mainstream clinicians to incorporate GS into their role; and, overambitious timelines and targets for the new service (19). Insight into the administrative burden of taking consent and ordering genomic testing in the NHS GMS was provided in an observation study of consent appointments (18), highlighting the benefit of electronic methods. In a study that mapped the process of delivering GS for paediatric rare disease diagnosis and interviewed the clinicians involved (21), another barrier to taking consent was the shorter visits in mainstream clinics. In Australia, a survey among geneticists and genetic counsellors demonstrated the additional time required to deliver genomic testing

compared to conventional genetic testing, associated with several steps including analysis, consent, and attending multi-disciplinary meetings (MDTs) (24).

A number of workarounds to address some of the challenges of offering genomic testing as a routine clinical test have been identified including: hiring additional HCPs to support the consent process; capacity-building; enhancing collaboration between genetics and mainstream specialities; and co-creating services with patients and the public (18, 19, 21, 25, 26). In the UK, genomic associates, assistants, and practitioners represent novel roles introduced specifically to support genomic testing in the NHS, with guidance on role remit and training/qualification requirements now available (27). Emerging research has demonstrated the competence of these health professionals and associated positive parental experiences and understanding (18, 23).

In England, reluctance from mainstream clinicians to integrate genomic testing into their practice remains a challenge, attributable to lengthy administrative tasks and perceptions of political, rather than clinical, motives driving implementation (19-22). The most frequently cited barriers to mainstreaming genomics amongst paediatricians were lack of training and knowledge, determining patient eligibility, lack of time, and confidence, however, it was felt that support from clinical genetics services, simplified referral forms and online training sessions could improve engagement (20). Similarly, in Australia, reimbursement mechanisms for clinical geneticists to support paediatricians have been suggested to improve GS utilisation (14). This demonstrates that barriers to implementation exist at the individual level (e.g., beliefs, perceptions of knowledge, skills) and at the service level (e.g., related to lack of resources, networks, support from clinical geneticists, and time) (13, 14).

In fostering cultural transformation, embedding non-genetics ‘genomic champions’ in mainstream services to provide support and impart knowledge has been recognised as

important to successful implementation (19, 20, 22, 28). Other solutions for bridging the gap between paediatric and clinical genetics disciplines include the formation of MDTs to enhance collaboration and knowledge-sharing (19, 20, 22). This has proved an effective way to facilitate mainstreaming and increase testing uptake in Australia (29), although it requires significant post-MDT input from genetics for sustainability.

Implementation of genomic testing in adult neurology

In well-resourced healthcare settings genomic testing has been increasingly recommended and utilised for a comprehensive range of neurological conditions, including amongst adults. GS is of particular value in this population where underlying genetic mechanisms are diverse and frequently include repeat expansions which are not well-captured by other methods or require targeted tests (30, 31). However, it is unclear whether GS is being offered to all eligible neurology patients across all clinical settings. Genomic testing for motor neuron disease provides a useful example. Currently in the UK, patients with MND, including amyotrophic lateral sclerosis (ALS), are eligible for GS, with reporting of a panel of neurodegeneration-linked genes completed on a GS backbone (12). However, a recent survey of UK neurologists indicated that only a proportion of them would offer GS to patients with ALS (32).

Much like in general paediatrics, barriers to implementation of genomic testing in adult neurology appear to be both at the individual- and service-level. A survey of neurology teams in the UK indicated that perceived lack of training, burdensome paperwork, and turnaround time for results were barriers to offering GS in mainstream clinics (33). The same survey identified low levels of self-rated genomics knowledge, and confidence in genomic counselling skills relevant to neurology GS. Supporting resources for both clinicians and patients are lacking and

are without standardisation, further limiting the abilities of non-genetics clinicians to provide this testing (34).

At an organisational- and service-level, defining which neurology patients should be eligible for GS has also proven challenging (31). In the UK, initially age and family history were used to define eligibility for GS in ALS. These criteria were modified after UK researchers demonstrated that neither age nor family history identified those at higher risk of genetic forms of ALS. The precise testing modality to use has also proven controversial. Many neurologists and patients would prefer single gene or small panel testing, rather than comprehensive GS (32). This is related to factors such as timescale to obtain results and concern over secondary findings.

Notably, a recent qualitative study undertaken with patients with ALS identified variable experiences of, and satisfaction with, genetic counselling and testing delivered in adult neurology clinics (35). Some patients reported delayed access to information or unmet support needs, and some did not feel they made an informed decision around genomic testing. Although mainstreaming of GS in adult neurology is recommended, given the utility of earlier and broader testing, greater standardisation and ongoing evaluation is needed.

Implementation of genomic testing in nephrology

There is clear evidence for the use of genomic testing in the diagnosis and management of patients with suspected monogenic kidney disease. Genomic testing has demonstrated a diagnostic yield of 40% in adults with suspected monogenic disease in a recent systematic review, including a revised diagnosis in 17% (Supplementary Material 1). In children with kidney disease, the diagnostic yield is above 50% (36). Importantly, there is emerging data which demonstrates meaningful impacts to clinical management in nephrology, including prompting

cascade testing, changes to treatment, and facilitating transplantation, as well as cost-effectiveness. As a result, recommendations have been made for incorporating genetic testing in clinical guidelines.

Despite this, barriers remain to effective uptake of genomic tests by nephrologists (37, 38). Widespread use of genomic testing for patients with kidney disease poses many of the same implementation challenges described above, particularly with regards to developing evidence-based guidelines for testing, as well as the development of service delivery models that enable timely access to genetic counselling, genetics specialists, and testing services (39).

Several models of care have been described aiming to provide timely access to genetics care in nephrology, using both mainstreaming and multidisciplinary models of care (40-43). For example, in Australia, 20 multidisciplinary kidney genetics clinics have been established across the country, each with a geneticist, genetic counsellor, and nephrologist available to review patients potentially suitable for genetic testing (43). 1506 patients reviewed across these clinics, had a diagnostic yield of 46% (40). In the United States and Canada, a similar model exists, where patients are referred to tertiary kidney genetics clinics, where they are reviewed by nephrologists working collaboratively with genetic counsellors (41). Importantly, the multidisciplinary clinic model is both effective and preferred by nephrologists (37).

Given the current pressures on genetic services, there is a need for nephrologist-led models of care to evolve to meet increasing demand. To combat the issue of underutilisation in Singapore, a protocol has been developed for a nephrologist-led genetics service, whereby the nephrologist is trained to provide counselling, order targeted ES, and interpret results (44). Nephrologists in outside major referral centres, however, will need to refer patients to a genetics-trained nephrologist. In Victoria, Australia, an implementation project to facilitate widespread mainstreaming across nephrology services utilised a hub-and-spoke model, where four tertiary

hospitals acted as hubs, providing multidisciplinary review, coordinated central MDT meetings, and housed genomic champions (nephrologists and genetic counsellors) who served as contact points for support (45). Peripheral nephrologists were supported by decision support tools and genomics champions from the hubs, enabling local initiation of genomic testing.

Finally, in Alberta, Canada, a mainstreaming pathway for patients with suspected autosomal dominant polycystic kidney disease has been implemented (42). In this model, the nephrology team provided pre-test counselling and selection of patients for genetic testing prior to direct patient interaction by a medical geneticist. The study authors found a significant reduction in time to result disclosure, coupled with high patient satisfaction rates (42). The subspecialised and single-system nature of kidney disease, coupled with the efforts of champions in the nephrology community, has positioned kidney disease as an exemplar in the mainstreaming of genomic testing in the clinic room—one other specialties may look to as mainstreaming models are developed in their disease areas.

RAPID DIAGNOSTIC GENOMIC TESTING IN INTENSIVE CARE

Historically, the utility of genetic testing in critical care settings was limited by lengthy turnaround times. However, technological advances that enable faster results have made rapid genome sequencing (rGS) an integral tool in neonatal (NICUs) and paediatric intensive care units (PICUs) (46). By providing timely genetic diagnoses that impact real-time decision-making, rGS has revolutionised critical care, allowing for empiric treatment approaches to be replaced by precision medicine (46). Furthermore, given the high costs of ICU care, early identification of

genetic conditions is essential for optimising patient management and resource allocation (47, 48).

Clinical impact of rapid genome sequencing

Between 2012 and 2021, over 44 clinical studies evaluated the diagnostic and clinical utility of first-tier RGS in NICUs and PICUs, yielding an average diagnostic rate of 37%, with a range from 19% to 83% (Supplementary Material 1). Most of these studies were prospective cohort trials, which highlighted both the cost-effectiveness and actionable clinical benefits of rapid genomic testing in this setting. More recent work aiming to demonstrate the clinical role of this technology has placed a greater emphasis on clinical implementation and models of care. For example, the SeqFirst study in Washington, USA, demonstrated the value of simple and broad exclusion criteria in expanding access to rGS in the NICU, as well as the importance of a standardised workflow (49). In this study, the diagnostic yield remained high and rGS identified conditions that conventional genetic testing approaches may have missed (49). Importantly, parental perspectives towards rGS in critical care settings were largely favourable. However, emerging research has noted greater ambivalence or deprioritisation of genetic testing in these settings compared to others (Supplementary Material 1). Furthermore, the psychosocial impact of rGS results may differ from other settings, with differing parental priorities and a greater risk of adverse emotional effects, underscoring the need for tailored counselling.

The Human Genetics Society of Australasia published a position statement on rGS in 2024, affirming that rGS is becoming the standard of care for critically ill children “where there is a high suspicion of an underlying genetic condition,” and emphasised that it should be provided

equitably in acute care settings (50). This guidance highlights the importance of a multidisciplinary approach to rGS, with tailored pre- and post-test counselling.

The next frontier: long read and ultra-rapid genomic sequencing

Ultra-rapid genome sequencing is an emerging technology that delivers diagnostic results in two days or less, compared to the typical 7- to 10-day timeframe for rGS. Significant advancements in sequencing technology have led to a substantial reduction in the fastest turnaround times—from approximately 48 hours in 2012 to just 7 hours by 2022. Furthermore, in a recent study of 12 patients, one case achieved a diagnostic result in just five hours, emphasising the accelerating pace of sequencing technologies (51).

Currently, most sequencing rapid or otherwise, relies on short-read sequencing technology, however, long-read PacBio or Nanopore sequencing is gaining traction as a promising alternative (Supplementary Material 1). The long-read sequencing approach enables real-time sequence analysis, generates longer contiguous haplotypes, and can detect epigenetic modifications such as DNA methylation. These advantages are particularly relevant for diagnosing imprinting disorders and genetic diseases with distinct methylation episignatures. The growing adoption of long-read sequencing could further enhance the diagnostic capabilities of sequencing, especially in cases where standard sequencing methods fall short (52).

Artificial intelligence in rapid genome interpretation

Artificial intelligence (AI) is playing an increasingly vital role in the interpretation of sequencing data, enhancing variant analysis, clinical decision making, and patient selection (46, 53). One of AI's most promising applications in genomics is natural language processing, which can serve

to extract deep phenotypic data from electronic medical records to improve diagnostic accuracy (54). Additionally, AI-driven automation is streaming variant annotation, reducing the workload for clinical geneticists and laboratory scientists, and improving the efficiency of genomic data interpretation (54).

Beyond variant analysis, AI-powered clinical decision support tools are being developed to guide treatment selection following a genetic diagnosis. These tools aim to translate genomic findings into actionable medical interventions, particularly in rare disease where specialised knowledge is required. Moreover, machine learning models are being leveraged to predict which NICU patients are most likely to benefit from rapid sequencing, enabling clinicians to prioritise testing for critically ill infants with suspected genetic conditions. As adoption of sequencing expands, AI-driven solutions will be instrumental in ensuring high diagnostic accuracy and optimising patient outcomes.

Challenges for rapid genomic testing

Despite rapid advancements, several barriers continue to hinder the widespread adoption of genome sequencing in critical care. One key challenge is the under-recognition of genetic disorders by ICU physicians, which can lead to delays in test ordering and limit the potential benefits of genomic diagnostics. Additionally, reimbursement policies for rapid genomic testing remain inconsistent, creating financial obstacles for hospitals and healthcare providers. There is also a need for better infrastructure, ensuring that rGS results are seamlessly incorporated into ICU workflows to facilitate timely clinical decision-making.

Genomic newborn screening

Biochemical newborn screening (NBS) has been integrated into routine healthcare in many countries, typically focusing on a limited set of rare and treatable conditions. Genomic newborn screening (gNBS) now offers the ability to expand early detection capabilities substantially by screening for a broader range of treatable rare diseases (55). This has the potential to benefit both individuals and the health system through earlier detection of a broader range of treatable conditions, including some without biochemical markers that would not be detectable by traditional NBS. The data has the potential to be reanalysed over time and can be used to clarify ambiguous results from other methodologies (55, 56). Earlier detection has the benefit of shortening the diagnostic odyssey for families (and the health system), and prompt earlier treatment, which has been shown to lead to better long-term health outcomes for these children (57, 58).

Global landscape of genomic newborn screening

Globally, considerable interest in gNBS has driven numerous initiatives exploring its feasibility, clinical utility, and related ethical considerations (Supplementary Table 2). These diverse efforts, aiming to gather data to inform the eventual implementation of widespread gNBS, reflect international ambitions to enhance and expand traditional biochemical screening.

Prospective gNBS studies span the United States, Europe, Australia, and Asia, and represent a mix of subnational pilots to nationwide programs (Supplementary Material 1). More than half employ ES or GS as their technology of choice, while the others employ targeted gene panels. Importantly, the number of genes screened varies greatly across these programs. Some

programs are more targeted, focusing on a small number of genes, while others include many hundreds of genes. One of the largest prospective studies, the UK's Generation Study under the Genomics England Newborn Genomes Programme, launched in 2022 plans to sequence 100,000 newborns using GS to screen for 200 disorders (59). Notably, the largest population screened was done retrospectively: BeginNGS, led by Rady Children's Institute for Genomic Medicine in San Diego, USA, screened over 300 genetic disorders via GS in nearly half a million UK Biobank participants and nearly 5000 critically ill children, demonstrating feasibility and scalability, and catching 15 diagnoses that would not have been detected by conventional NBS (56).

Several notable trends emerge across gNBS programs. First, there is a clear preference for targeted gene panels in jurisdictions aiming for immediate clinical implementation, while larger-scale programs often utilise genomic sequencing approaches (GS or ES). Additionally, many projects faced practical barriers influencing implementation. For example, although the Belgium-based BabyDetect study aimed to recruit 40,000 infants, practical challenges resulted in a final recruitment of only several thousand newborns, highlighting significant recruitment barriers faced by large-scale gNBS initiatives (60).

Implementation of genomic newborn screening

For now, gNBS remains in the pre-implementation stage, without any programs broadly implemented. Importantly, clinical implementation of gNBS poses several significant challenges. One major consideration is deciding which conditions/genes to include–this is fundamentally a policy choice that balances conventional screening criteria (severity, treatability, prevalence, test accuracy, etc.) with the broad range of possibilities afforded by genomic testing (61). National advisory bodies (such as the U.S. Advisory Committee on Heritable Disorders in Newborns and

Children) will need to update their frameworks for evaluating conditions, potentially developing guidelines specific to genomic screening. Professional organisations, such as the European Society of Human Genetics, have cautioned that any use of genomic sequencing technologies in NBS should be justified by strong evidence of benefit and adhere to screening principles, favouring targeted approaches until more data is available (61).

Another challenge is around informed consent and the diverse ethical issues raised by a shift towards gNBS. For example, the possibility of incidental findings in gNBS presents distinct challenges compared to traditional screening. While traditional screening focuses on conditions with well-established treatments that manifest early in life, the broad nature of genomic technologies employed in gNBS can unexpectedly discover a wide array of genetic variations, including those linked to adult-onset diseases or conditions lacking effective interventions. This is no different from diagnostic genomic testing but is novel in this context where the goals and risk-benefit calculus differ. Importantly, the consent process must not be made so complex as to impair the ability of gNBS programs to recruit and identify children who may be at-risk (62, 63). As argued by Knoppers et al., “the right of the asymptomatic at-risk child to be found” must be balanced with the complexities of consent: consent should aim for families to be appropriately informed, and tailored to the range of conditions that are potentially reported (63).

Given the costs associated with genomic sequencing, cost-effectiveness analyses of gNBS are essential to inform decision-making. Modelling the cost-effectiveness of gNBS, however, is complex. Previous research has typically focused on single-condition assessments, which likely underestimate the broader value of gNBS, as a potential one-time test that can replace many separate tests and may avert expensive diagnostic odysseys later in childhood (56). As sequencing costs continue to drop—potentially reaching as low as USD 100 per newborn—the cost-effectiveness of gNBS may become increasingly favourable (56). Nevertheless,

comprehensive economic evaluations of gNBS incorporating multiple conditions and complex patient pathways remain critical. Future modelling should employ dynamic simulation models that capture these issues, as well as individual heterogeneity, long-term outcomes, and system-wide impacts (64, 65).

REPRODUCTIVE GENETIC CARRIER SCREENING IN THE GENOMICS ERA

Reproductive genetic carrier screening (RGCS) is designed to identify people with an increased chance of having children with serious autosomal recessive or X-linked genetic conditions. By providing this information before or early in pregnancy, RGCS promotes reproductive autonomy, enabling prospective parents to make informed decisions regarding reproductive options such as in vitro fertilisation (IVF) with pre-implantation genetic testing (PGT-M), prenatal diagnosis, or preparing for the possibility of raising a child with a genetic condition.

From targeted testing to population-wide screening

Historically, carrier testing was reserved for individuals with a known family history or those of specific ancestries associated with higher prevalence of certain conditions. Early methods relied on biochemical assays, but this was superseded by targeted genetic testing using allele-specific technologies for common pathogenic variants.

Genomic sequencing technologies have revolutionised carrier screening, allowing for the simultaneous analysis of hundreds of genes at a cost that continues to decline. In 2025, sequencing cost is no longer the primary determinant of panel size. For large panels, exome sequencing with analysis restricted to the panel is a viable approach, and is used by some laboratories. The low cost of sequencing enables comprehensive, equitable population-wide approaches (66, 67). This paradigm shift can improve access and clinical utility.

Despite these advances, government-funded RGCS programs remain limited globally (67). A notable exception is the Israeli national RGCS program, launched in 2013 and which now includes screening for 650 pathogenic variants in 290 genes (68). In Australia, government funded RGCS for cystic fibrosis, fragile X syndrome and spinal muscular atrophy became available in 2023 resulting in a substantial increase in access to RGCS (>110,000 tests annually for a country with an annual birth rate of about 300,000). However, in many countries, RGCS is primarily available through private services, accessible mainly to those who are well-informed and can afford it. This raises concerns about equity and access, prompting consideration about how to of integrate RGCS into publicly funded healthcare systems (69)

Australia's Mackenzie's Mission

In 2018, Australia launched a landmark project, the Australian Reproductive Genetic Carrier Screening Project known as 'Mackenzie's Mission' (MM), to investigate the acceptability and feasibility of population-wide RGCS. Through MM, screening was offered to 10,000 reproductive couples for approximately 1,300 genes associated with around 750 conditions (70).

MM demonstrated that large-scale RGCS is both feasible and acceptable to a diverse population. The study found that 1.9% of reproductive couples had an increased chance of having children with serious genetic conditions (70). Most of these couples used or intended to use reproductive interventions to reduce the chance of passing on the condition to their children (70).

Importantly, the study highlighted that thoughtful and innovative program design is critical for mainstreaming RGCS within the healthcare system. Key factors that contributed to the successful delivery of RGCS at scale included: reproductive utility-focused gene panel selection, considering condition severity in variant interpretation and result reporting, simultaneous reproductive couple-based screening, embedding genetic counselling in the program design and effective referrer education and engagement.

Selecting genes and interpreting variants

The question of which genes to include in RGCS panels remains a topic of debate. Recommendations vary, from the ACMG's 113-gene panel (71) to more expansive offerings, like the 1,280+ gene panel used in MM (72). The key goal is to identify reproductive couples who have an increased chance for offspring with clinically impactful conditions (72). "Severity", however, is a subjective and context-dependent concept (73). While some panels include only childhood-onset, life-limiting conditions, others allow the inclusion of moderate or mild conditions, such as non-syndromic hearing loss.

Variant interpretation further complicates matters. The presence of a pathogenic variant does not always result in disease if it is combined with a second variant of uncertain or milder impact. Ideally, only combinations predicted to cause a serious health condition in offspring should be reported. This safeguards against over-reporting leading to unnecessary reproductive intervention and helps ensure results are meaningful and actionable (73).

It is important to note that while current methodologies cover most genes reliably, technical limitations mean certain genes require specialised analysis due to complex genomic architecture or repeat sequences (e.g., *SMN1* in spinal muscular atrophy and *FMR1* in fragile X syndrome). Inclusion of such genes requires integration of specialised workflows to ensure test sensitivity and clinical validity. RGCS using GS would allow for the capture of such genes with a single technology.

Delivery models: sequential vs. simultaneous

RGCS can be delivered using either a sequential or simultaneous screening approach. *Sequential screening* involves testing one reproductive partner first. If that person is found to be a carrier, the partner is then tested. This method conserves resources when screening for a limited number of genes but is time-consuming and can heighten anxiety, especially if there is already an established pregnancy (74). *Simultaneous screening* involves testing both partners at the same time. This model is more suitable for large gene panels due to the higher likelihood that at least one partner will be a carrier for a recessive condition (70). It also streamlines workflows and reduces delays, making it a better fit for scalable, population-wide programs.

Reporting and interpretation: simplifying the complex

One of the challenges in mainstream RGCS is how to communicate results effectively. Many commercial services provide individual reports listing each person's carrier status across potentially hundreds of genes. While comprehensive, this approach places the burden of interpretation on clinicians, who may lack genetics expertise, and can overwhelm patients.

In contrast, combined couple-based reporting involves delivering a result that indicates either: *low chance*, where no concerning gene combinations are found; or, *increased chance*, where a variant combination in a gene associated with a serious condition is found in the couple. Choosing not to report individual carrier status for low chance couples (unless specifically requested or clinically indicated) serves to streamline analysis and reporting, reduce cognitive load, simplify genetic counselling, and enhance service efficiency while maintaining clinical relevance. However, this approach also has limitations—particularly if couples separate and form new partnerships, as re-screening is required.

Challenges and barriers in reproductive genetic screening programs

As RGCS becomes more integrated into routine care, attention must turn to service delivery models, especially in primary care settings. Most clinicians offering RGCS have limited training in genetics and patients often have little awareness of the conditions screened. To address this, online decision support tools for pre-test education and consent can increase knowledge and maintain autonomy in decision-making (70, 75). These tools are well-received by both patients and clinicians (75, 76) and demonstrate that scalable, digital education solutions can effectively support the mainstreaming of RGCS without overwhelming clinical workflows. Embedding

genetic counselling within the design of screening programs ensures access to specialist support when needed and enhances the confidence of non-genetics healthcare providers, who can offer screening knowing that expert guidance is readily available.

While RGCS enhances reproductive autonomy, equity in access to reproductive options remains a challenge. Studies indicate that 60% or more of those receiving an increased chance result pursue a reproductive intervention, such as IVF with PGT-M, to avoid passing on the condition (70, 77, 78). Others may choose adoption, gamete donation, or decide not to have children. IVF with PGT-M, for example, is expensive and access to this technology varies. Termination of pregnancy may not be accessible in some jurisdictions due to personal, cultural, political, or legal reasons. This can restrict a person's ability to use their RGCS results in a way that aligns with their values.

Ultimately, successful mainstreaming of RGCS will require thoughtful program design, streamlined reporting, integrated genetic counselling and provider education. However, to mainstream RGCS responsibly, health systems must ensure public funding or subsidies for reproductive interventions and follow-up care, as well as access to genetic counselling and psychological support.

GENETIC COUNSELLORS BEYOND THE CLINICAL GENETICS SERVICE

As illustrated in the many examples described in this review, mainstreaming models of care—where non-genetics clinicians integrate genetic and genomic testing into their own clinical practices, rather than having all testing be done by clinical genetics services—are increasingly employed in the era of genomic sequencing (6). However, while some clinicians have adapted their practice to incorporate genomic medicine, many lack knowledge and confidence and indicate a preference for genetics clinicians to manage genetic testing to inform management (Supplementary Material 1).

In this respect, genetic counsellors, post-graduate trained allied healthcare professionals, are key players in facilitating the integration of genomic sequencing into mainstream healthcare. Crucially, they support mainstreaming efforts from within clinical genetics services, through attendance at multi-disciplinary team meetings, participation in multi-disciplinary clinics, and more recently, by taking roles embedded within specialty services and contributing to program design (79, 80). Models of mainstreaming that include embedded genetic counsellors in specialty teams offer an additional way to facilitate integration of genetic and genomic testing into clinical care without over-burdening stretched health services (79, 81-83).

Optimising expertise and working at top of scope

As genomic medicine moves into mainstream settings, role delineation amongst clinicians providing genomic care must be carefully considered; it is crucial that roles and expertise are optimised in systems with limited resources. Until recently, genetic counsellors have been largely employed by clinical genetics services and see patients following referral from non-genetics physicians, with or without medical geneticists (24). However, there is a shift occurring with deliberate, structured design of mainstreaming models in which genetic counsellors are directly employed in medical departments outside of the clinical genetics service. In such

models, genetic counsellors help provide multidisciplinary care for patients through the entire diagnostic care pathway in collaboration with non-genetics physicians. In fact, a census of the global state of genetic counsellors found widespread opportunities for involvement in delivery of mainstream genomic care globally (84). Integrating genetic counsellors in mainstreaming models of care has clear benefits: genetic counsellors are highly skilled in facilitating patient decision-making, working with families to communicate and disseminate genetic information, optimising systems to improve patient experience and care, and providing education and support for clinicians as they interpret genetic information for patient management (24, 85, 86). When embedded in medical departments outside of genetics, genetic counsellors bring these complementary skills to the clinical practice of their non-genetics colleagues.

Genetic counselling in mainstream practice

In the context of diagnostic genomic testing, a recent Change Program in Victoria, Australia saw hospitals seeking to implement innovative models of care in specialities including neurology, nephrology, transplant, cardiology, and general paediatrics, where genetic counsellors were employed to work directly in the specialist services (81). The role of the genetic counsellor was a deliberate aspect of the model of care, requiring genetic counsellors to share their expertise with the medical specialty and to support specialists to begin integrating aspects of genomic medicine into their clinical practice. Genetic counsellors working in these roles reported they were working at the top of their scope of practice, modelling the unique genetic counsellor skillset in these settings, including providing relational care, expediting patient access to specialised genetic care, and considering the family unit as well as the individual (79).

In the context of RGCS, psychosocial support for families is crucial. Although receiving a low chance result generally leads to reassurance, low anxiety, and minimal regret, receiving an

increased chance result can be emotionally destabilising (Supplementary Material). Anxiety levels can remain elevated for months and many couples report experiencing grief for their anticipated reproductive journey, which may no longer be possible without medical intervention. Embedding genetic counselling directly within screening program design provides patients with access to necessary specialist support. Clinicians highly value accessible genetic counselling as part of equitable genomic service provision. In Mackenzie's Mission, primary healthcare providers ranked online information and funded genetic counselling among the top enablers for integrating RGCS into practice (76).

Genetic counsellors as leaders in mainstreaming

Mainstreaming models of care offer opportunities for genetic counsellors to work at the top of their scope of practice, and given their skillset genetic counsellors are well equipped to lead such efforts (83). However, to support successful mainstreaming, genetic counsellors require a sound understanding of core aspects of genomic medicine, including confidence working with medical specialists, skills in interpretation and communication of genomic test results, and involvement in mainstreaming program design and review (81). Importantly, genetic counsellors are embracing opportunities to move beyond the clinical genetics service and work in diverse positions across healthcare systems. An ability to confidently articulate the value they bring, including the difference between genetic counselling provided by genetic counsellors, and genetic counselling activities provided by other healthcare professionals is crucial. Access to regular reflective practice supervision and participation in a community of practice for genetic counsellors working in mainstream roles will support these aims and help build resilience (81, 87). This will help to ensure genetic counsellors maintain their professional identity, thrive in these emerging roles, and steward the integration of diverse applications of genomic

sequencing—both those discussed in this review and those yet to come—into mainstream healthcare.

WORKFORCE DEVELOPMENT CONSIDERATIONS FOR MAINSTREAM GENOMIC MEDICINE

Developing a broad, mainstream, genomics-capable workforce presents multiple challenges due to the multidisciplinary and emerging nature of genomic medicine (88, 89). A recent international survey of genomics health workforce education priorities reported that 70% of respondents from 34 countries felt a need for moderate to extensive modification of genomics training for physicians (90). As illustrated throughout this review, service models in genomic medicine are variable, and the roles of professions vary between models, necessitating different competencies and educational approaches. Although education alone is not sufficient to prepare professionals to incorporate genomics into their practice, it is both wanted and critical (91, 92).

Education to enable different models of genomic healthcare

Two large studies surveying US and Australian physicians (93, 94) found that, although they could order genomic tests, most responding physicians preferred genomics service delivery models that directly involved genetics health professionals, either through referral or ordering with support. Genomics research experience and continuing genomics education were associated with higher confidence to practise genomics and a preference for service models with less support from genetics (95, 96). These associations suggest the need to provide a

range of education formats and topics pitched to different levels of competence to enable mastery and increasing independence in mainstreaming, such as ordering autonomously, with the support of a genetics service, or within a multidisciplinary team.

Genomics education needs for different professions and roles

Needs assessments can inform targeted education programs and have been undertaken for many professions involved in genomic medicine (for a review, see (97); additional references in Supplementary Material 1). Educational needs have also been investigated for multidisciplinary settings, such as acute care, for professions that span different settings, such as hospital versus community pharmacists, and in contexts beyond screening or testing, for example, for research or clinical trials, or to guide treatment selection (e.g., oncology and precision medicine).

Establishing required competency levels across the workforce

The knowledge, skills and attributes (attitudes and/or behaviours) required for safe and responsible delivery of genomics applications have been outlined for some health professions (e.g., medical students, physicians, physician assistants, nurses) and can guide education and training (references in Supplementary Material 1). Competencies for physicians mostly relate to ordering or facilitating genomic testing, as minimum standards or entrustable professional activities. Competencies for nurses have been available and routinely updated for decades, and focus mostly on collecting health history, communicating and supporting care. There are no agreed competencies for broader allied health professions, although competencies for pharmacists exist in the emerging area of pharmacogenomics. Other emergent applications of genomic technologies, such as genetic carrier screening and polygenic risk scores, are increasingly included in updated competencies. As more genomics applications span

healthcare, organisations such as the European Society of Human Genetics and the National Health Service Health in England have developed competencies or competency frameworks that can be adapted and applied across multiple professions (98, 99).

While the need for professionals skilled in variant interpretation is growing exponentially with the spread of genomic testing, and continuing professional development, workplace training and university award subjects are emerging, there are no published competencies in variant interpretation. There are agreed capabilities for bioinformaticians, some of which are relevant to variant interpretation, but this critical step in genomic testing is being performed by a range of professionals, including medical/clinical scientists, physicians, and laboratory genetic counsellors.

Evaluation and coordinated efforts can reduce reinvention

There are increasing reports of genomics education programs in the literature, covering a breadth of topics, workforce sectors and contexts (97). Curricula may be general or specialty-specific, with more recent efforts focusing on offering education at scale, through wholly online or blended learning approaches (see Supplementary Material 1). However, as a field, evidence of global, effective genomics education is fragmented. Interventions are often developed and delivered by poorly-resourced and isolated clinicians or researchers, rather than qualified educators.

Evaluation can gather the evidence for engagement and impact, however evidence for specific educational approaches has been difficult to compare and synthesise due to limited, or varied approaches to evaluation and inconsistent descriptions in the literature. To support best practice in genomics education, Australian Genomics convened an international expert group to help

develop a flexible ‘toolkit’ for global genomics educators, including those with minimal experience in education or evaluation. Tools include: a program logic model to support effective planning, development, delivery and evaluation; adaptable needs assessment surveys; an evaluation framework; and reporting standards for genomics education and its evaluation (100). The framework and reporting standards, in particular, can assist educators to evaluate and share impact of their education, through evaluating immediate, intermediate, and long-term outcomes (100).

To reduce reinvention, networks have been proposed to share educational resources relating to content, delivery, assessments and evaluation. These have been supported on varying scales through professional societies and inter-society committees (101, 102).

Ultimately, education of health professionals in genomics has been described as desirable, critical and pivotal in the implementation of genomic medicine, However, many educational programs are still being created in isolation, by busy clinicians and scientists, with no sustainable delivery models in place after research funding ends. The approaches described above, and the growing suite of tools and examples in the literature, will hopefully begin to build an evidence base and repository of sharable resources and insights.

MOVING TO MAINSTREAM

The implementation of genomic testing in mainstream healthcare is a translational endeavour. Technologies must first be translated from the research space to clinical practice, commonly to the early adopters within the clinical genetics service. From there, these technologies move beyond the walls of the clinical genetics service and with a goal to be implemented at scale.

This is not new, other genetic tests, such as chromosomal microarrays and single-gene sequencing have followed this same path. Genomic technologies, however, are highly complex a growing list of applications, as highlighted in this review. Best et al., explains that, as a result, implementation of genomic technologies into mainstream healthcare requires whole-of-system change (103).

As illustrated in this review, approaches to this change, and the resulting state of implementation, varies both by application of genomic testing and by jurisdiction. This relates to a diversity of factors including local interests and expertise, resources, health system structures, and priorities of policy makers. For example, mainstreaming of genomic testing in the NHS benefitted from a top-down approach with support at the highest levels of government allowing for change to be driven (9, 104). Comparatively, progress in Australia has been driven by local interest and expertise, with organising structures and strong collaborative networks built largely from the bottom-up (10, 103).

Ultimately, to ensure these technologies provide benefit to patients at large, it is essential that the implementation of genomic testing, and these many influencing factors, are understood. Although structured approaches exist, implementation science theory has not been widely used to inform the design and evaluation of genomic testing programs in the past (105). Moving forward, program evaluation guided by implementation science that captures diverse outcomes and compares different approaches to implementation will be essential (103). As lessons are learned across jurisdictions, ongoing efforts to demonstrate value of mainstreamed implementation will also be key, to ensure benefit is delivered to patients and the system at large.

Limitations and areas of future growth

This review was limited to applications of genomic sequencing technologies currently being implemented clinically at scale. Important emerging applications related to monogenic rare disease include prenatal screening and diagnosis, screening of healthy adults, and post-mortem genomic testing. Evidence for the utility of pharmacogenomics and polygenic risk scores for common diseases is also growing and represent future potential applications of this technology in mainstream clinical practice. Consideration must also be given to the amalgamation of all of these technologies into one: where a single genomic sequence is generated once, such as at birth, and interrogated at the various points in the lifespan as needed for screening or clinical care. These applications, of course, will all present their own unique benefits and challenges. Additionally, most programs highlighted in this review are from the UK, Australia, and the US, indicating a need for both improved clinical access to genomic sequencing technologies globally as well as more research around implementation in diverse jurisdictions.

Equity considerations

Equity considerations in genomic medicine have been well described, particularly with respect to the implications of underrepresentation of ancestry groups in reference datasets, with efforts being made to identify and advance related solutions (106). These concerns apply to the mainstreaming of genomic technologies, but with important additional considerations. In particular, the mainstream implementation of to these technologies is inevitably influenced by geography. At present, access to applications earlier in the implementation pipeline remains largely concentrated at tertiary or academic centres with advanced resources and expertise. Although this may be necessary as a new technology penetrates a health system, to reduce the exacerbation of existing inequities efforts to counteract this must be considered.

Conclusions

Genomic sequencing technologies are being implemented across healthcare to support the screening for and diagnosis of rare genetic diseases. Most advanced in terms of implementation is that of diagnostic genomic testing, both rapid testing in the intensive care unit and standard testing in the clinic room. Genomic newborn screening and reproductive genetic carrier screening also represent important areas of current implementation with many jurisdictions taking steps to implement these technologies clinically. The involvement of non-genetics clinicians in the delivery of these technologies, however, has important implications on models of care and education—genetic counsellor support and evidence-informed education strategies are key to building a genomics-capable workforce. The integration of these technologies into health systems is complex and efforts to evaluate these programs guided by implementation science will be key to ensure jurisdictions learn from one another and benefit is delivered to patients and the system at-large.

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AUTHOR CONTRIBUTION STATEMENT

MPM assembled the manuscript, wrote the introduction and concluding sections. MPM and AMcN wrote the introductory section of “Routine diagnostic genomic testing in the clinic room”.

HE and CL authored the section “Implementation of genomic testing in general paediatrics”. AM authored the section on “Implementation of genomic testing in adult neurology”. KJ and CQ authored the section on “Implementation of genomic testing in nephrology”. PBA and SA authored the section on “Rapid diagnostic genomic testing in the intensive care unit”. SJ and YG authored the section on “Genomic newborn screening”. AA, LF, EK, and ET authored the section on “Reproductive carrier screening in the genomics era”. BDM and AMcE authored the section on “Genetic counselling beyond the clinical genetics service”. AN and BT authored the section on “Workforce development considerations of mainstream genomic medicine”. All authors critically reviewed and revised the manuscript.

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ETHICAL APPROVAL

Ethical approval was not required as no data was collected.

COMPETING INTERESTS

The authors have no competing interests to declare.

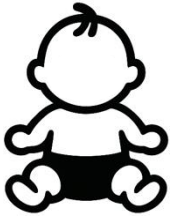
FIGURE LEGENDS

Figure 1. Applications of genomic testing for rare disease across the lifespan. Purple indicates screening application; blue indicates diagnostic testing.

GENOMIC NEWBORN SCREENING

- Emerging application with variable access.
- Not widely publicly-funded.
- Variability in gene lists and approaches.

Conducted shortly after birth



RAPID DIAGNOSTIC GENOMIC TESTING *in the intensive care unit*

- Clinically available across jurisdictions.
- Often publicly-funded where applicable.
- Variability in access and models of care.

Conducted commonly in infancy, but can be at any point in life

ROUTINE DIAGNOSTIC GENOMIC TESTING *in the clinic room*

- Clinically available across jurisdictions.
- Often publicly-funded where applicable.
- Variability in access and models of care.

Conducted completed in childhood, but can be at any point in life

REPRODUCTIVE GENETIC CARRIER SCREENING

- Clinically available across jurisdictions.
- Not widely publicly-funded.
- Variability in gene lists and approaches.

Conducted when planning a family or early in pregnancy

Birth