nature medicine

Review article

https://doi.org/10.1038/s41591-025-04061-3

Determining the value of genomics in healthcare

Received: 27 March 2025

Accepted: 17 October 2025

Published online: 27 November 2025

Check for updates

Ilias Goranitis[1,2] ✉, Robin Z. Hayeems[3,4], Hadley Stevens Smith[5,6], James Buchanan[7,8], Deirdre Weymann[9,10], Dean A. Regier[9,11], Michael P. Mackley[12], Richard H. Scott[13,14,15], Sue L. Hill[16], Brian H. Y. Chung[17,18], Claudia C. Y. Chung[18], Stephanie Best[2,19], Emma L. Baple[20,21] & Zornitza Stark[2,22,23] ✉

As genomic sequencing transitions into mainstream healthcare, critically appraising its value is key to informing evidence-based policy, practice and implementation strategies. Assessing the value of genomics is challenging, as traditional evaluation methods and frameworks do not capture many of the outcomes of genomics. This includes the personal value that genomic information provides individuals and family members, and the potential to reuse sequencing data to improve clinical care and drive research. Evaluation is hampered by lack of standardized outcome measures, small sample sizes, and uncertainties arising from the evolving nature of the technology, its applications and associated costs. Complex health system factors further influence real-world utilization and the value of genomic technologies and services within resource-constrained settings. In this Review, we discuss the need for robust yet agile approaches to evaluating genomic technologies that are dynamically informed by real-world data, and we provide examples of emerging methods and best practices. We emphasize the need for a whole-of-system approach and the need to further advance evaluation and implementation methods, to support health systems to sustainably and equitably integrate genomics into clinical care.

The transformative potential of genomic sequencing has led to sizable government investments in large-scale research studies for over a decade[1]. With the genomes of millions of individuals now sequenced, the value of genomics needs to be examined critically as part of its transition into mainstream healthcare—to ensure sustainable health system funding and evidence-based adoption at scale and pace.

The complexity of genomic testing, especially exome and whole-genome sequencing, challenges traditional methods for assessing value and value for money. The breadth of clinical applications is considerable and does not readily fit into the usual paradigm of value-based healthcare. Genomic testing can be applied to symptomatic and asymptomatic individuals across the lifespan, including prenatal, pediatric and adult settings. The purpose of testing can be to establish a diagnosis; inform prognostication; determine eligibility for treatment (including access to precision medicines and clinical trials); assess the risk of developing health conditions and adverse drug reactions; or to inform reproductive options. Genomic sequencing technologies are still evolving, and the future value of different testing methods needs to be considered within the context of other diagnostic approaches that may be replaced by genomics[2,3]. A key aspect of genomic data is that once generated, it can be reanalyzed over time, thus providing additional value that is difficult to quantify. This can include providing new diagnoses in patients with rare diseases as evidence and analytic tools improve[4]; enabling proactive health-related screening[5]; providing pharmacogenomic information to guide prescribing[6]; or driving discovery and innovation[7]. Value not only extends over long periods of time but also extends directly and indirectly beyond the individuals tested, informing personal, familial

A full list of affiliations appears at the end of the paper. ✉e-mail: ilias.goranitis@unimelb.edu.au; zornitza.stark@vcgs.org.au

https://doi.org/10.1038/s41591-025-04061-3

and reproductive risk and impacting psychosocial well-being and productivity, as well as driving health system efficiency.

Reflecting these complexities, the discourse about the utility of genomics has evolved from diagnostic outcomes and clinically actionable findings, to broader definitions of utility that encompass a range of clinical and personal outcomes relevant to individuals, families, health systems and society[8–13]. The importance of this broader range of outcomes is recognized by professional organizations, including the American College of Medical Genetics and Genomics[14]; health technology assessment (HTA) authorities, such as the Medical Services Advisory Committee (MSAC) in Australia[15] and the National Institute of Clinical Excellence (NICE) in the UK; and health systems such as NHS England (NHSE)[16]. However, there is still no internationally agreed way of defining and measuring the utility and value of genomics[12]. This lack of consensus hampers evaluation processes and the timely and equitable translation of effective applications of genomic sequencing.

In this Review, we provide international perspectives on how the value of genomics can be conceptualized and measured, and how current approaches to HTA, clinical implementation and data management can be adapted to address the challenges posed by a rapidly evolving technology and evidence base. This discussion is of relevance not only to countries at the forefront of translational genomics but also to countries that are in the process of setting up large-scale genomic initiatives or initiating integration of genomics into their healthcare systems[17].

Conceptualizing, measuring and valuing genomic utility

Critically and objectively assessing evidence of value underpins decisions about how healthcare interventions, such as genomic testing, should be prioritized and funded. The first step in this process is to conceptualize and operationalize the value proposition of a health intervention, commonly referred to as 'utility', before quantifying (that is, valuing) this in monetary terms. Traditionally, the value of health technologies has been determined by changes in patients' physical health outcomes, such as quality of life and life expectancy. Further, healthcare payers typically have limited budgets, so health must be maximized while also considering efficiency. This has three important implications for clinical genomics. First, impacts of medical conditions on carers (that is, spillover effects) are not commonly considered—and genetic conditions generate perhaps the largest health spillovers in the medical literature[18]. Second, genomic testing may have important non-health outcomes that contribute to patients' and families' well-being, such as the value of knowing the cause of a condition and the practical and psychological impacts of this. Third, equity is a key consideration as some groups may be disproportionately affected by rare diseases and cancers, or may be less likely to access and benefit from genomics owing to cultural or linguistic factors[19]. Extended evaluation frameworks (Table 1) seek to capture this more comprehensive set of outcomes in a standardized manner.

Conceptualizing genomic utility

In the context of genomic testing, defining these broader elements of utility (and hence value) is complex and multidimensional, requiring a multidisciplinary approach. Key domains of genomic utility that determine value relate to diagnostic, clinical and personal outcomes for patients and families, as well as wider health system, economic and societal outcomes[12,20–22] (Table 2). Within each of these domains, multiple types of outcomes may contribute to the overall value of the test in a nuanced way. For example, in terms of diagnostic utility, genomic testing in rare disease allows the elucidation of thousands of potential molecular diagnoses, including many that are not ascertainable by other means[23]. In addition, genomic testing can be used to confirm a clinical diagnosis that has already been established by other tests (for example, biochemical); establish a molecular diagnosis necessary to access a precision treatment or clinical trial; refine a diagnosis within a group of related disorders (for example, ciliopathies); or refute an erroneous clinical diagnosis[23]. Genomic testing that does not yield a molecular diagnosis can also have utility, for example, by redirecting diagnostic efforts toward nongenetic causes[24].

Table 1 | Health technology evaluation frameworks

Conventional valuation framework	Extended valuation framework
Health - A technology or intervention has value if it leads to changes in health outcomes or survival - Health narrowly defined in terms of key functioning (for example, mobility, anxiety, pain)	**Health and well-being** - The value of a technology or intervention is determined by health and non-health (personal) outcomes that it generates
Patient - Effects on those around them are rarely considered	**Patient and family** - Effects on family members are considered
Efficiency - Healthcare resource allocation decisions are made with the objective of health maximization	**Efficiency and equity** - Resource allocation decisions are made by considering both well-being and distributional effects at societal level

The clinical utility of genomic testing, whether a diagnosis is made or not, can include a range of impacts, from obviating the need for other tests, through to enabling access to precision treatments or informing surgical, transplantation and palliation decisions[24–26]. On a personal level, in addition to treatments improving quality of life, a specific diagnosis can have psychological effects, such as empowering patients and validating their experience, or providing certainty that enables decisions regarding employment, housing or having children[27,28]. Conversely, a genetic diagnosis can provoke anxiety, guilt, regret and sometimes denial and rejection. As genetic information is shared between relatives, these health and non-health impacts can extend to multiple family members and can unfold over many years[13]. At a system level, the use of genomics can streamline processes, improve efficiency and ensure earlier and more equitable access to support services and precision treatments. However, there are also concerns that it can entrench existing inequalities[29] and that it can generate findings of uncertain clinical relevance and value, adversely impacting the use of already limited healthcare resources.

Measuring genomic test utility

In the absence of genomic-specific outcome measures and validated instruments, early studies reported outcomes on an ad hoc basis, designed their own instruments or used a variety of single-dimensional and multidimensional tools, such as the Genetic Counselling Outcome Scale[27,30], which was not specifically designed for measuring genomic test outcomes[31]. While some studies have used measures of quality of life, there are concerns about face validity and sensitivity of these measures to changes in important outcomes following genomic testing in the context of rare diseases[32]. This early body of literature has prompted systematic efforts to develop and validate measures specific to genomics, which can now be used to measure utility from a variety of stakeholder perspectives (Table 2).

For example, an iterative process of literature review, stakeholder interviews, surveys and panel discussions was used to develop the 30-item C-GUIDE (Clinician-reported Genetic Testing Utility Index), which captures clinician perspectives[33]. Construct validity and inter-rater reliability have been demonstrated[34–36]. The tool has been translated into multiple languages and is in use by many groups internationally. Originally developed for the rare disease diagnostic setting, new versions cater to prenatal care[37] and critical care[38], with a version for genomic newborn screening undergoing validation.

Other tools such as the GENE-U (genetic utility) scale have been developed to assess utility from patient and family perspectives.

https://doi.org/10.1038/s41591-025-04061-3

Table 2 | Components of genomic utility and commonly used approaches to measurement and valuation

	Genomic utility outcomes				
	Diagnostic	**Clinical (patient and family)**	**Personal (patient and family)**	**Economic**	**Societal**
Measurement	Diagnostic yield	C-GUIDE	GENE-U, PrU	Cost of genomics	Equity metrics related to access and outcomes
	Diagnostic process efficiency	Quality-of-life measures	Quality-of-life and patient-reported experience measures	Healthcare resource utilization impacts	
	GUV scale	GUV scale	GUV scale	GUV scale	GUV scale
Valuation	Preference elicitation to value additional diagnoses	Preference elicitation to value clinical outcomes	Preference elicitation to value personal outcomes	Economic evaluation	Preference elicitation to value equity outcomes
	GUV scale	GUV scale	GUV scale	GUV scale	GUV scale

Informed by a conceptual model of perceived utility based on literature review and primary qualitative data[39], the GENE-U development process included cognitive interviews, psychometric analysis and validation. The pediatric diagnostic version of GENE-U measures perceived utility (both inside and outside clinical care) from the perspective of parents of children who have undergone diagnostic genomic testing[40], and the adult screening version measures perceived utility from the perspective of adults who have themselves undergone genomic screening[41]. Each version consists of two subscales: informational utility and emotional utility[40,41]. Additional versions for genomic newborn screening and diagnostic genomic testing for adults are being developed. Similarly, the PrU (personal utility) scale, another validated tool from the Clinical Sequencing Exploratory Research (CSER) consortium, has been developed to assess personal utility of genomics to adult patients and parents of pediatric patients[42,43]. The PrU scale focuses on aspects of utility that occur outside clinical care, emphasizing aspects such as self-knowledge, reproductive planning and practical benefits.

These validated instruments enable measurement of the clinical and personal utility of genomics, which is needed for a comprehensive evaluation of genomic testing. A challenge that remains with the use of C-GUIDE, GENE-U and PrU as outcome measures is that they do not allow for cardinal comparisons of different combinations of utility. To address this challenge, a Delphi study undertaken with healthcare system decision-makers explored priority indicators of genomic utility[44] and led to the development of the genomic utility valuation (GUV) scale[45]. The GUV scale measures genomic utility across diagnostic, clinical, family, economic and societal indicators of value, and enables a preference weighting of genomic utility on a 0–100% scale from a policymaker and clinician perspective[45]. To quantify genomic utility, the GUV scale requires information on the proportion of patients and family members achieving different levels of clinical and family utility, respectively, and the extent of diagnostic, economic and societal utility. Sufficient information may not always be available, but uncertainty can be incorporated into the weighting. Currently, the preference weighting of the GUV scale reflects preferences of experts involved in policy, clinical, research and consumer advocacy leadership in Australia. The transferability of these preferences to other countries needs to be validated; this process, and the generation of other country-specific decision-making weights, is ongoing.

Valuing genomic utility

Enabling a direct link between pragmatically capturing the utility of testing and objective value for money is an important step in decisions about funding. For genomics, however, the complex and multidimensional outcomes of genomic utility have proven difficult to capture within economic evaluations[46]. When the discourse on the clinical utility of genetic testing started to develop nearly 20 years ago[47], it was suggested that stated preference methods—such as discrete choice experiments and contingent valuations—could be used to quantify the broader clinical and personal value of testing, including health and non-health outcomes[48,49]. These methods recognize the importance of eliciting societal preferences to inform policy decisions[50,51], and guidance for their development and use within economic evaluations is emerging[52,53].

Stated preference methods have been used to quantify genomic utility in monetary terms across many clinical contexts[49,54–60]. Findings from these studies show that patients and the public place a high value on both the health and non-health outcomes of genomics[61]. This is especially true for childhood-onset genetic conditions (Fig. 1)[49,55,57,59,62]. This work has enabled the monetary valuation of genomic utility to be used in economic evaluations, either as part of cost–benefit analyses or within cost-effectiveness analyses, where these methods have allowed the determination of a cost-effectiveness threshold per additional genomic diagnosis[49,55–60,63–67].

Value as part of genomic test reimbursement and prioritization

In practice, decision-making about test reimbursement and prioritization frequently occurs as part of formalized processes, such as HTAs. These are designed to evaluate evidence using explicit and transparent methods[68] and can be undertaken by government bodies or commercial organizations (for example, insurance companies). Processes can vary between and within countries, depending on the perspective of the payer and the features of the healthcare system (for example, including private and/or public funding models). In addition to the conceptual and methodological issues discussed in the preceding section, it can be challenging to adjudicate genomic tests within existing HTA approaches owing to limitations relating to both evidence and process.

Evidentiary and process challenges

Large, randomized controlled trials (RCTs) are widely regarded as the 'gold standard' for establishing the efficacy of new health interventions and have traditionally formed the cornerstone of HTAs. However, many new health technologies, such as genomic sequencing, are used in highly selected, relatively small populations. In key applications, such as rare diseases and rare cancers, understanding the impact of testing is hampered by a dearth of data on epidemiology, natural history and existing care pathways, as well as marked within-cohort genetic and phenotypic heterogeneity. RCTs have only occasionally been conducted in rare disease or cancer cohorts undergoing genomic testing[69–74], with at least one RCT having been abandoned owing to loss of equipoise[72]. The predominant study design has been single-arm[75]. A few studies have used within-study comparators such as existing standard-of-care tests (for example, microarray)[23,76–81], or matched historical or contemporaneous cohorts to generate comparative evidence[82–85], but substantial uncertainty remains.

The complexity of conceptualizing the value of genomics and, until recently, the lack of validated outcome measures, have further hindered systematic evidence development and evidence

https://doi.org/10.1038/s41591-025-04061-3

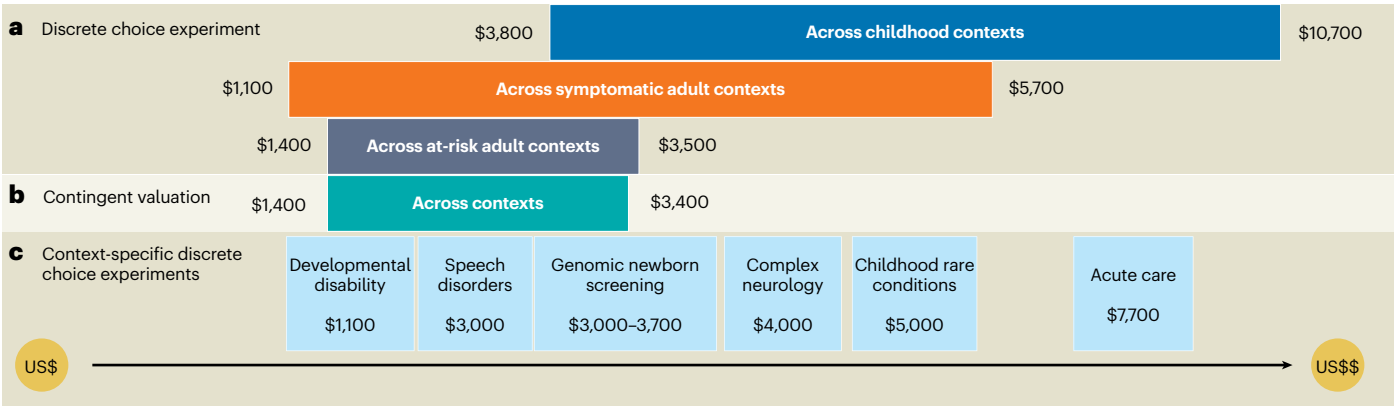

Fig. 1 | Valuing the outcomes of genomics using stated preference methods. a–c, Examples of results obtained through discrete choice experiments (**a**) and contingent valuations (**b**), in a range of diagnostic and screening contexts in both adults and children (**c**)[49,55–60,62]. Amounts are presented in US$.

appraisal. Diagnostic yield is frequently reported as the sole outcome measure. A recent meta-analysis of 161 genomic studies comprising 50,417 probands with rare disease in 159 cohorts found that while all reported diagnostic yield, clinical utility was only reported in 62 cohorts (40%)[86]. The reported changes in management ranged from 2% to 100%: this heterogeneity primarily reflects the broad range of inconsistent definitions used, reducing the quality of evidence available[87]. Further, the overwhelming majority of studies focus only on immediate results of genomic testing or intermediate outcomes, such as changes in clinical management. Long-term outcomes, for example, changes in quality and length of life, are rarely reported, with only two rare disease cohorts reporting longer-term outcomes to date[28,88]. These limitations are likely to be practical in nature, given the short funding cycles of most research studies—but collectively, these study design features increase the evidentiary uncertainty for policymakers and may hinder the sustainable and equitable implementation of genomics.

Another important source of uncertainty in HTAs has been the cost of genomic testing, which affects estimates of cost-effectiveness and budget impact[89,90]. Large differences have been observed in the cost estimates of genomic sequencing and the costing of patient diagnostic trajectories[90–93]. Microcosting studies provide a structured approach to identifying and measuring the costs of service delivery and have the potential to provide more robust, generalizable data. However, a recent systematic review of microcosting studies in diagnostic genomics identified analytical and reporting discrepancies, with reported costs ranging widely from US$716 to US$4,817 for exome and US$2,094 to US$9,706 for genome testing[92]. While the clinical context, the specific technology used and variations in the purpose of testing may explain some of the differences in costing estimates, we must embrace comprehensive reporting standards and analytical methods that reflect the uncertainty in workflow variations, costs and cost-effectiveness to support informed decision-making[94,95].

These evidentiary limitations mean that policy decisions on the prioritization and reimbursement of genomics are made with heightened uncertainty[96]. In addition, some aspects of genomics challenge HTA processes per se. Typically, HTA assessments occur at a point in time, and are not subject to iterative reappraisal. This has substantial implications. Delaying policy decisions while more evidence is generated risks delaying potential benefits to patients, families and healthcare systems. Conversely, premature decision-making can burden healthcare systems with unsustainable, low value implementation. Another important factor is the payer perspective, with single-payer, centralized national systems better positioned to take into consideration broader healthcare system and societal value propositions over longer time horizons, as part of overarching national strategies.

Practical solutions for policy decision-making

Pragmatic solutions to some of the challenges associated with evaluating genomic technologies are emerging in different jurisdictions. HTA bodies, such as the MSAC in Australia, have developed modifications to existing HTA processes and frameworks to accommodate genomics. The clinical utility card proforma for assessing genetic and genomic testing[15] combines elements of the EuroGentest clinical utility card[97] with the ACCE framework (analytical validity, clinical validity, clinical utility, and ethical, social and legal implications)[98] and the domains of cost and economic evaluation. The proforma introduces several concepts into decision-making. These include: the importance of patient selection for testing, based on >10% pre-test probability of a pathogenic finding; definition and inclusion of 'star performer' genes with the clearest evidence of clinical utility, with additional genes included at lower evidence thresholds; and taking into account health-related utility for family members in recognition of the benefits of cascade testing. In addition to cost per quality-adjusted life year, MSAC has considered other units to express cost-effectiveness, such as cost per diagnosis[15]. MSAC has sought to address the high rate of change in the technical and interpretational aspects of genomic testing by remaining largely agnostic to the molecular techniques used (for example, exome or genome) and by developing funding pathways for future re-interrogation of sequencing data[15]. Considering uncertainties relating to costs, rebates have often been set at 21–63% of the estimated cost of testing[94]. This currently favors the use of exome rather than genome testing, and can limit or delay access to funded testing, depending on whether laboratories choose to provide the test. The evaluation process typically lasts several years and, to date, nine genomic tests have been approved for funding in Australia, with annual rebates paid at AU$3.3 million in 2023 (<0.01% of overall health expenditure)[99]. This low budget impact is in part due to low uptake at around 20% of predicted, with marked geographical variation[99,100].

In the NHSE Genomic Medicine Service (GMS), a separate framework and process for the evaluation of genetic and genomic tests was established in 2018, which links to a nationally agreed genomic testing strategy that informs genomic laboratory funding. The National Genomic Test Directory was developed following consultation with an expert panel of clinicians, scientists, health economists, policy experts, public representatives and patient organizations led by the NHSE. It outlines the full range of genomic and other 'omic' tests that are funded by the NHSE, the technological approach for delivery and test eligibility criteria. The directory is updated annually based on stakeholder feedback, and updates are linked to NICE Technology Appraisal or approved NHSE National Clinical Policy changes, aligning testing to new therapies. Applications to add or remove tests and revise eligibility criteria are reviewed by one of the three (rare disease, cancer and pharmacogenomics) multidisciplinary test evaluation working

groups. A laboratory implementation and financial impact assessment informs final approval by the NHSE, with more than 350 changes made to the directory since its inception in 2018. More than 850,000 tests are currently delivered each year through the NHSE. Laboratory services are required to submit test volumes, turnaround times and diagnostic outcomes via Patient Level Contract Monitoring Data, with these data being used to revise the test directory. For example, stand-alone *FRAXA* testing for intellectual disability (700 tests per month) has been removed owing to low diagnostic yield (~0.4%), although patients will still receive *FRAXA* testing as part of genome sequencing for intellectual disability. This illustrates the value of ongoing monitoring in informing funding of genomic testing as part of an overarching national testing strategy, which responds to changing technologies and a growing clinical evidence base.

By contrast, the USA does not have a centralized HTA process for genomic technologies, and coverage of genetic and genomic testing and gene-based therapies varies by payer type (commercial versus public insurance), clinical indication and patient population[101–106]. Medical necessity and experimental status remain common reasons for denying reimbursement in pediatric outpatient settings[103]. Research on payer perspectives of genomic technologies and coverage decision-making processes suggests that payers are open to broader coverage of genome sequencing[107] and outcomes-based agreements to improve access to genomic technologies[108]. While some payers are open to considering outcomes beyond direct impacts on patient health, non-health outcomes alone are typically not sufficient to justify coverage[109].

Implementing genomics to deliver value

How a clinical intervention such as genomic testing is implemented determines the actual value delivered in real-world settings. Healthcare systems are complex, adaptive systems[110] and a clinical intervention (especially a complex one) will not work in real-world settings unless informed by implementation data—no matter how effective it is in a research study. Although cost and funding are frequently cited as important barriers to implementation of genomic testing[111,112], implementation requires whole-of-system approaches[113,114], driven by an overall strategy. Many issues need to be addressed simultaneously, including building workforce capacity and capability; establishing and implementing guidelines and standards; creating infrastructure for data generation, analysis and management; tackling ethical, legal and policy issues; and ensuring broad professional and community engagement[115]. Failure to adopt a whole-of-system approach may result in poor or inappropriate clinical uptake of testing, lengthy laboratory turnaround times, inequitable patient access and outcomes, delivery of low value care and healthcare system waste[16,99,100,116]. The importance of a whole-of-system approach has been demonstrated in the context of evaluating implementation of genomic sequencing[117], as a way of incorporating unique complexities within considerations of the system's capacity and constraints. Three key issues merit further discussion in this context: organization of genomic services, data management infrastructure and implementation strategies.

Organization of genomic services

Genomic service delivery models can have a profound impact on timely and equitable access, diagnostic outcomes, clinical utility and cost-effectiveness. In recognition of the scale of transformational change required, many countries have invested in the establishment of new genomic organizational structures outside existing clinical and laboratory services[1]. These have been variably tasked with the delivery of numerous components, ranging from sequencing and bioinformatics infrastructure through to evidence generation, guidance on policy and clinical implementation, and securing ongoing funding. Many have galvanized national efforts around projects designed to demonstrate value[25,115,118,119]. Setting up new organizations solely focused on genomics provides the opportunity to create agile, multidisciplinary environments that drive change, build expertise, foster innovation and advance system-wide consistency through the development of processes, resources and infrastructure. Barriers exist, however, to the formation of such organizations that may limit the scope of their impact, particularly in pluralistic healthcare systems where different components of genomics services fall under different jurisdictions. Furthermore, the dual demands of agility and scale can be difficult to balance. Long-term funding uncertainties, rapidly evolving mandates and poor integration with existing services can further affect not just the impact but also the sustainability of these organizations[120].

From a clinical service perspective, early access to genomic testing in rare disease has repeatedly been demonstrated to increase clinical utility and cost-effectiveness[121–123]. With the existing clinical genetics workforce in most high-income countries unable to meet growing demands[124,125], diverse non-geneticist clinicians are now engaged in mainstream delivery of genomics testing within their specialties[126–128], necessitating the development of education and training programs[129–132] and competency frameworks[133,134]. The role of clinical geneticists and genetic counselors is evolving, with a shift toward later involvement in the diagnostic pathway (for example, post-test result) and providing support for multidisciplinary models of care[128]. These changes are expected to promote wider, more equitable and timely access to genomic testing[135,136] with benefits for patients, families and health systems. However, evidence about the performance of mainstreamed models of care in genomics is lacking, and it remains to be seen whether their added value will be confounded by inappropriate test use, result misinterpretation or diminished provision of counseling. Evaluation of these new clinical models of care, including definition of appropriate outcome measures, will therefore be essential[137].

Clinical laboratory services are similarly evolving to meet growing demands and adapt to changing technologies. Many traditional test types have been superseded by genomic technologies; in addition, the recognition that greater economies of scale and efficiency are required to optimize value have led to organizational restructures[16,138]. For example, in England in 2018, the NHS Regional Genetic Laboratories were reconfigured and consolidated to form a network of seven geographically distributed Genomic Laboratory Hubs as part of the establishment of the NHSE Genomic Medicine Service. Genomic testing services are now centrally commissioned with common national diagnostic and research consent pathways, standards, protocols, contracts and pricing, and national coordination and oversight from the NHSE Genomics Unit, which reduces variation and promotes equitable genomic technology-driven care nationally[16]. Nevertheless, highly centralized approaches to service delivery such as these can slow down the pace of change. In England, these concerns have been counterbalanced by funding separate initiatives that promote innovation in areas of unmet need and that can rapidly generate evidence needed for decision-making. Such initiatives include the NHS genomic networks of excellence and the NHS partnership with Genomics England, which delivers national clinical knowledge bases and analytics and links routine care to research.

These extended periods of reorganization in many countries have demanded high levels of adaptability and challenged hierarchies and identities at individual, professional and organizational levels[139–141]. Managing this scale of transformational change requires leadership at multiple levels[140]. The growing shift toward population-based screening approaches across a range of adult[142,143] and pediatric[144] applications, wider implementation of pharmacogenomics[145] and polygenic risk scores[146], and the integration of machine learning and artificial intelligence into genomic analysis are likely to provide further major drivers for change over the next decade and will further challenge how we define and assess value, particularly over longer time horizons.

Data management infrastructure

Substantial investment in data management infrastructure is necessary to implement clinical genomics in a way that optimizes value and

efficiency. This includes data-sharing platforms that support accurate and evidence-based interpretation of genomic data by collating information about the association of particular genes and gene variants with disease[147–151]. More specialized and costly infrastructure as well as complex agreements are required to enable the flexible use and reuse of genomic data. This includes performing periodic reanalysis for the same or different clinical indications, which provides additional value and avoids waste through duplicative and redundant testing. At the population level, the ongoing analysis of genomic data and associated healthcare data can drive discovery and translational research, for example, to understand the long-term impacts of genomic testing. These activities provide an ongoing feedback loop to healthcare systems, improving outcomes[152]. However, the ability to reuse genomic data for clinical care and research requires the generation of data in standardized formats[153] and integration with local systems. Careful planning and considerable investment in data storage and computation are needed, together with a workforce that has high levels of technological expertise. These technical elements need to be combined with the development of appropriate consent and education processes to support informed choices and realize benefits for individuals, populations and healthcare systems.

Sustained investment from healthcare and research funders has enabled the establishment of such infrastructure by NHSE and Genomics England. The model has high public acceptance with >90% of those approached during the genomic test consenting process agreeing to join the National Genomic Research Library hosted by Genomics England. Data reuse in the National Genomic Research Library has now resulted in the return of more than 4,500 candidate diagnoses to the NHS, with over 85% subsequently reported as causative. However, the complexity and cost of establishing this data infrastructure, and the need for coordinated action across multiple organizations and jurisdictions, mean that in general, very few health systems have built such infrastructure. Instead, most genomic data, once generated, currently remain inaccessible in siloed storage at institutional level.

Implementation strategies

Lastly, theory-informed, data-driven approaches to implementation are critical to maximizing the value of genomics, particularly as delivery is scaled up[154,155]. Conceptualizing and measuring implementation outcomes enables better understanding of implementation processes, facilitates comparative studies evaluating the effectiveness of different implementation strategies, and ultimately enhances the efficiency of implementation[156]. A recent scoping review[157] identified a paucity of theoretically informed approaches in the implementation of genomics. Most theories, models or frameworks were applied at the 'pre-adoption' phase of implementation, and focus on feasibility and acceptability. Effectiveness–implementation hybrid study designs[158] have provided one pathway for incorporating implementation science research into translational genomics projects. In the initial implementation stages, this has included systematically investigating barriers and enablers to adoption[141,159], and progressing to designing and evaluating strategies to support implementation and behavior change as interventions scale up—for example, as part of rapid testing programs in the critical care setting[160], multidisciplinary models for genomics in nephrology clinics[161] and population-level reproductive genetic carrier screening programs[162,163]. While there is still a dearth of theory applied during full implementation or post-implementation phases[157], research is starting to explore health service variation[164,165] and adoption[100], particularly in relation to achieving equitable outcomes for underserved groups, such as those at geographical, social, cultural and linguistic disadvantage[166,167].

Life-cycle HTA and learning healthcare systems

With the immediate and downstream patient and population impacts of genomic technologies highly uncertain at the time of funding decisions[96] and with real-world utilization influenced by complex factors, healthcare systems must adapt their approach to evaluation and implementation. While modifications to existing processes may provide partial solutions, the 'life-cycle HTA' framework has been proposed as a more dynamic way of addressing evidentiary uncertainty[96,168]. Rather than relying upon a static estimate of value, life-cycle HTA continuously evaluates and reevaluates the health, economic and societal impacts of a technology throughout its life cycle, iteratively guiding investment and disinvestment decisions when allocating scarce healthcare resources.

Life-cycle HTA is premised on the ongoing generation of real-world evidence (RWE), using real-world data collected as part of a learning healthcare system. Real-world data include those collected from varying sources outside research studies or trials[169]. Real-world data may be used alone or concatenated with single-arm trial and experimental data to understand comparative health technology effects. Examples of successful use of RWE to model the outcome of different genomic testing strategies are starting to emerge in the fields of rare disease and cancer[85,123]. However, reliability of this evidence requires grounding in an underlying causal theoretical framework, adherence to study design principles and validation of analytic assumptions to avoid common observational study biases[170–172]. While some national regulatory and HTA bodies have released reporting standards for RWE studies (for example, US Food and Drug Administration, NICE and Canada's Drug Agency (CDA-AMC)) and a global task force has established a checklist for operationalizing life-cycle HTA[168], many countries, including Australia, have no consideration of RWE in their HTA guidelines, and there is no current consensus on methodological standards for achieving regulatory and reimbursement-grade RWE. Further efforts are needed to establish these best practices for RWE and to harmonize real-world data collection and sharing, to enable continual evidence generation for genomic technologies and integration into healthcare system decision-making processes[173,174] as part of learning healthcare systems[96,175]. In addition to genomic test evaluation, this must encompass evidence about the value of particular service delivery models, the value of infrastructure investments and the success (or not) of various implementation strategies. Overall, high quality, fit-for-purpose RWE holds great promise in enabling more efficient, robust and dynamic assessments and reassessments of genomic technologies throughout their life cycle, to support the scalable and sustainable translation of genomics.

Value of genomics beyond the healthcare system

So far, we have primarily discussed the value of genomics to individuals and families, and the health system processes required to ensure optimal healthcare system benefits. Another important value proposition of genomics is the impact on the broader economy. National investments in genomics research and translation[1] have resulted in rapid increases in genomic sequencing capacity and capability, biomedical research and innovation in a very short period of time. A recent report commissioned by the American Society of Human Genetics on the macroeconomic impact of human genomics investment in the USA concluded that it generated a US$4.75 return on every dollar invested, through 850,000 additional jobs and US$5.2 billion in direct tax revenues[176]. While there may be increasing returns on current investments in genomics research and translation, understanding and quantifying the macroeconomic impacts of genomics remains a highly under-researched area. This information is highly relevant to policymakers and can further support international efforts to advance access to genomics. In particular, fueling biomedical research and innovation further optimizes the value of genomics over time. The continued discovery of novel gene–disease associations[7] and functional characterization of genetic variation[177] increase diagnostic utility, while the growth in personalized and precision treatments[178] improves the clinical utility of testing.

Conclusions

The collective experience gained over the past 10 years—in measuring the value of genomic testing and navigating implementation and evaluation processes—now puts us in a position where international consensus is emerging on key outcome measures and approaches[179]. International consortia, such as the International Precision Child Health Partnership (IPCHiP) and International Consortium on Newborn Sequencing (ICoNS), are well placed to support collective efforts to align evidence generation using standardized measures.

To ensure the value of genomics in healthcare is realized in a sustainable and equitable manner, we must actively work on capturing appropriate outcomes of real-world implementation in diverse settings, including in mid- and low-income countries. Health systems must develop mechanisms to continuously integrate these outcome measures into decision-making as part of learning healthcare systems in which health and economic outcomes are optimized, particularly as they seek to scale genomics testing to the population level.

References

1. Stark, Z. et al. Integrating genomics into healthcare: a global responsibility. *Am. J. Hum. Genet* **104**, 13–20 (2019).
2. Sheikh Hassani, M. et al. Virtual gene panels have a superior diagnostic yield for inherited rare diseases relative to static panels. *Clin. Chem.* **71**, 169–184 (2025).
3. Wojcik, M. H. et al. Genome sequencing for diagnosing rare diseases. *N. Engl. J. Med.* **390**, 1985–1997 (2024).
4. Dai, P. et al. Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: a systematic review and meta-analysis. *Genet. Med.* **24**, 1618–1629 (2022).
5. Martyn, M. et al. Offering complex genomic screening in acute pediatric settings: Family decision-making and outcomes. *Genet. Med.* **27**, 101327 (2024).
6. Leong, I. U. S. et al. Large-scale pharmacogenomics analysis of patients with cancer within the 100,000 Genomes Project combining whole-genome sequencing and medical records to inform clinical practice. *J. Clin. Oncol.* **43**, 682–693 (2025).
7. Chen, Y. et al. De novo variants in the RNU4-2 snRNA cause a frequent neurodevelopmental syndrome. *Nature* **632**, 832–840 (2024).
8. Clark, M. M. et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom. Med.* **3**, 16 (2018).
9. Kohler, J. N., Turbitt, E. & Biesecker, B. B. Personal utility in genomic testing: a systematic literature review. *Eur. J. Hum. Genet* **25**, 662–668 (2017).
10. Best, S. et al. Clinical genomic testing: what matters to key stakeholders?. *Eur. J. Hum. Genet.* **28**, 866–873 (2020).
11. Pollard, S. et al. Toward the diagnosis of rare childhood genetic diseases: what do parents value most?. *Eur. J. Hum. Genet.* **29**, 1491–1501 (2021).
12. Smith, H. S. et al. Conceptualization of utility in translational clinical genomics research. *Am. J. Hum. Genet.* **108**, 2027–2036 (2021).
13. Smith, H. S. et al. Key drivers of family-level utility of pediatric genomic sequencing: a qualitative analysis to support preference research. *Eur. J. Hum. Genet.* **31**, 445–452 (2023).
14. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **17**, 505–507 (2015).
15. Norris, S., Belcher, A., Howard, K. & Ward, R. L. Evaluating genetic and genomic tests for heritable conditions in Australia: lessons learnt from health technology assessments. *J. Community Genet.* **13**, 503–522 (2022).
16. Ellard, S. et al. Rare disease genomic testing in the UK and Ireland: promoting timely and equitable access. *J. Med. Genet.* **61**, 1103–1112 (2024).
17. Expert Meeting on Accelerating Access to Human Genomics for Public Health Participants. Accelerating access to human genomics for public health: perspectives from the Western Pacific region. *Lancet Reg. Health West Pac.* **53**, 101265 (2024).
18. Wu, Y. et al. Parental health spillover effects of paediatric rare genetic conditions. *Qual. Life Res.* **29**, 2445–2454 (2020).
19. National Institute for Health and Care Excellence. Modular update to NICE manuals: health inequalities. https://www.nice.org.uk/process/pmg36/documents/supporting-documentation-3 (2025).
20. Hayeems, R. Z. et al. Clinical utility of genomic sequencing: a measurement toolkit. *NPJ Genom. Med.* **5**, 56 (2020).
21. Mallett, A., Stark, Z., Fehlberg, Z., Best, S. & Goranitis, I. Determining the utility of diagnostic genomics: a conceptual framework. *Hum. Genomics* **17**, 75 (2023).
22. Chung, C. C. Y., Chu, A. T .W. & Chung, B. H. Y. A roadmap for genome projects to foster psychosocial and economic evidence to further policy and practice. *Commun. Med.* **5**, 198 (2025).
23. Hartley, T. et al. Evaluation of the diagnostic accuracy of exome sequencing and its impact on diagnostic thinking for patients with rare disease in a publicly funded health care system: a prospective cohort study. *Genet. Med.* **26**, 101012 (2024).
24. Australian Genomics Health Alliance Acute Care Flagship; Lunke, S. et al. Feasibility of ultra-rapid exome sequencing in critically ill infants and children with suspected monogenic conditions in the Australian Public Health Care System. *JAMA* **323**, 2503–2511 (2020).
25. Lunke, S. et al. Integrated multi-omics for rapid rare disease diagnosis on a national scale. *Nat. Med.* **29**, 1681–1691 (2023).
26. Dimmock, D. et al. Project Baby Bear: rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. *Am. J. Hum. Genet.* **108**, 1231–1238 (2021).
27. Grant, P. E., Pampaka, M., Payne, K., Clarke, A. & McAllister, M. Developing a short-form of the Genetic Counselling Outcome Scale: The Genomics Outcome Scale. *Eur. J. Med Genet.* **62**, 324–334 (2019).
28. Stark, Z. et al. Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. *Genet. Med.* **21**, 173–180 (2019).
29. Khoury, M. J. et al. Health equity in the implementation of genomics and precision medicine: a public health imperative. *Genet. Med.* **24**, 1630–1639 (2022).
30. McAllister, M., Wood, A. M., Dunn, G., Shiloh, S. & Todd, C. The Genetic Counseling Outcome Scale: a new patient-reported outcome measure for clinical genetics services. *Clin. Genet.* **79**, 413–424 (2011).
31. Smith, H. S. et al. Clinical application of genome and exome sequencing as a diagnostic tool for pediatric patients: a scoping review of the literature. *Genet. Med.* **21**, 3–16 (2019).
32. Pan, T., Wu, Y., Buchanan, J. & Goranitis, I. QALYs and rare diseases: exploring the responsiveness of SF-6D, EQ-5D-5L and AQoL-8D following genomic testing for childhood and adult-onset rare genetic conditions in Australia. *Health Qual. Life Outcomes* **21**, 132 (2023).
33. Hayeems, R. Z. et al. The development of the Clinician-reported Genetic testing Utility InDEx (C-GUIDE): a novel strategy for measuring the clinical utility of genetic testing. *Genet. Med.* **22**, 95–101 (2020).
34. Hayeems, R. Z. et al. The Clinician-reported Genetic testing Utility InDEx (C-GUIDE): preliminary evidence of validity and reliability. *Genet. Med.* **24**, 430–438 (2022).

35. Hayeems, R. Z. et al. Assessing the performance of the Clinician-reported Genetic Testing Utility InDEx (C-GUIDE): further evidence of inter-rater reliability. *Clin. Ther.* **45**, 729–735 (2023).
36. Hayeems, R. Z. et al. Applying the Clinician-reported Genetic testing Utility InDEx (C-GUIDE) to genome sequencing: further evidence of validity. *Eur. J. Hum. Genet.* **30**, 1423–1431 (2022).
37. Hayeems, R. Z. et al. The Clinician-reported Genetic Testing Utility InDEx (C-GUIDE) for Prenatal Care: initial evidence of content and construct validity. *Genet. Med.* **27**, 101306 (2025).
38. Dolman, L. I. et al. The Clinician-reported Genetic Testing Utility InDEx for Neonatal Intensive Care (C-GUIDE NICU): quantifying genome-wide sequencing utility in the NICU. *Genet. Med.* **27**, 101503 (2025).
39. Smith, H. S. et al. Perceived utility of genomic sequencing: qualitative analysis and synthesis of a conceptual model to inform patient-centered instrument development. *Patient* **15**, 317–328 (2022).
40. Smith, H. S. et al. Measuring perceived utility of genomic sequencing: Development and validation of the GENEtic Utility (GENE-U) scale for pediatric diagnostic testing. *Genet. Med.* **26**, 101146 (2024).
41. Smith, H. S. et al. Measuring perceived utility of genomic sequencing: Development and validation of the GENEtic Utility (GENE-U) scale for adult screening. *Genet. Med.* **26**, 101240 (2024).
42. Turbitt, E. et al. The PrU: development and validation of a measure to assess personal utility of genomic results. *Genet. Med.* **25**, 100356 (2022).
43. Turbitt, E. et al. The Parent PrU: a measure to assess personal utility of pediatric genomic results. *Genet. Med.* **26**, 100994 (2024).
44. Fehlberg, Z., Goranitis, I., Mallett, A. J., Stark, Z. & Best, S. Determining priority indicators of utility for genomic testing in rare disease: a Delphi study. *Genet. Med.* **26**, 101116 (2024).
45. Goranitis, I. et al. A standardized measurement and valuation scale of genomic utility for policy decisions: The GUV Scale. *Value Health* **28**, 184–190 (2025).
46. Phillips, K. A. et al. Methodological issues in assessing the economic value of next-generation sequencing tests: many challenges and not enough solutions. *Value Health* **21**, 1033–1042 (2018).
47. Grosse, S. D. & Khoury, M. J. What is the clinical utility of genetic testing?. *Genet. Med.* **8**, 448–450 (2006).
48. Grosse, S. D., Wordsworth, S. & Payne, K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. *Genet. Med.* **10**, 648–654 (2008).
49. Regier, D. A., Friedman, J. M., Makela, N., Ryan, M. & Marra, C. A. Valuing the benefit of diagnostic testing for genetic causes of idiopathic developmental disability: willingness to pay from families of affected children. *Clin. Genet.* **75**, 514–521 (2009).
50. Regier, D. A., Ryan, M., Phimister, E. & Marra, C. A. Bayesian and classical estimation of mixed logit: an application to genetic testing. *J. Health Econ.* **28**, 598–610 (2009).
51. Ho, M. et al. A framework for incorporating patient preferences regarding benefits and risks into regulatory assessment of medical technologies. *Value Health* **19**, 746–750 (2016).
52. Bridges, J. F. P. et al. A roadmap for increasing the usefulness and impact of patient-preference studies in decision making in health: a good practices report of an ISPOR task force. *Value Health* **26**, 153–162 (2023).
53. Smith, H. S. et al. Approaches to incorporation of preferences into health economic models of genomic medicine: a critical interpretive synthesis and conceptual framework. *Appl. Health Econ. Health Policy* **23**, 337–358 (2025).
54. Strauss, K. A. et al. Genomic diagnostics within a medically underserved population: efficacy and implications. *Genet. Med.* **20**, 31–41 (2018).
55. Marshall, D. A. et al. The value of diagnostic testing for parents of children with rare genetic diseases. *Genet. Med.* **21**, 2798–2806 (2019).
56. Meng, Y., Clarke, P. M. & Goranitis, I. The value of genomic testing: a contingent valuation across six child- and adult-onset genetic conditions. *Pharmacoeconomics* **40**, 215–223 (2022).
57. Goranitis, I., Best, S., Christodoulou, J., Stark, Z. & Boughtwood, T. The personal utility and uptake of genomic sequencing in pediatric and adult conditions: eliciting societal preferences with three discrete choice experiments. *Genet. Med.* **22**, 1311–1319 (2020).
58. Goranitis, I., Best, S., Stark, Z., Boughtwood, T. & Christodoulou, J. The value of genomic sequencing in complex pediatric neurological disorders: a discrete choice experiment. *Genet. Med.* **23**, 155–162 (2021).
59. Goranitis, I., Best, S., Christodoulou, J., Boughtwood, T. & Stark, Z. Preferences and values for rapid genomic testing in critically ill infants and children: a discrete choice experiment. *Eur. J. Hum. Genet.* **29**, 1645–1653 (2021).
60. Meng, Y. et al. The value of genomic testing in severe childhood speech disorders. *Eur. J. Hum. Genet.* **32**, 440–447 (2024).
61. Regier, D. A., Weymann, D., Buchanan, J., Marshall, D. A. & Wordsworth, S. Valuation of health and nonhealth outcomes from next-generation sequencing: approaches, challenges, and solutions. *Value Health* **21**, 1043–1047 (2018).
62. Peters, R. et al. Public preferences for the value and implementation of genomic newborn screening: Insights from two discrete choice experiments in Australia. *Am. J. Hum. Genet.* **112**, 1515–1527 (2025).
63. Regier, D. A., Friedman, J. M. & Marra, C. A. Value for money? Array genomic hybridization for diagnostic testing for genetic causes of intellectual disability. *Am. J. Hum. Genet.* **86**, 765–772 (2010).
64. Goranitis, I. et al. Is faster better? An economic evaluation of rapid and ultra-rapid genomic testing in critically ill infants and children. *Genet. Med.* **24**, 1037–1044 (2022).
65. Wu, Y. et al. Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation. *Eur. J. Hum. Genet.* **30**, 577–586 (2022).
66. Downie, L. et al. Exome sequencing for isolated congenital hearing loss: a cost-effectiveness analysis. *Laryngoscope* **131**, E2371–E2377 (2021).
67. Jayasinghe, K. et al. Cost-effectiveness of targeted exome analysis as a diagnostic test in glomerular diseases. *Kidney Int. Rep.* **6**, 2850–2861 (2021).
68. O'Rourke, B., Oortwijn, W. Schuller, T. & International Joint Task Group The new definition of health technology assessment:a milestone in international collaboration. *Int. J. Technol. Assess. Health Care* **36**, 187–190 (2020).
69. Group, N. I. S. et al. Effect of whole-genome sequencing on the clinical management of acutely ill infants with suspected genetic disease: a randomized clinical trial. *JAMA Pediatr.* **175**, 1218–1226 (2021).
70. Kingsmore, S. F. et al. A randomized, controlled trial of the analytic and diagnostic performance of singleton and trio, rapid genome and exome sequencing in ill infants. *Am. J. Hum. Genet.* **105**, 719–733 (2019).
71. Dimmock, D. P. et al. An RCT of rapid genomic sequencing among seriously ill infants results in high clinical utility, changes in management, and low perceived harm. *Am. J. Hum. Genet.* **107**, 942–952 (2020).

72. Petrikin, J. E. et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. *NPJ Genom. Med.* **3**, 6 (2018).
73. Le Tourneau, C. et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol.* **16**, 1324–1334 (2015).
74. Ceyhan-Birsoy, O. et al. Interpretation of genomic sequencing results in healthy and ill newborns: results from the BabySeq Project. *Am. J. Hum. Genet.* **104**, 76–93 (2019).
75. Gibbs, S. N. et al. Comprehensive review on the clinical impact of next-generation sequencing tests for the management of advanced cancer. *JCO Precis. Oncol.* **7**, e2200715 (2023).
76. Stark, Z. et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. *Genet. Med.* **19**, 867–874 (2017).
77. Tan, T. Y. et al. A head-to-head evaluation of the diagnostic efficacy and costs of trio versus singleton exome sequencing analysis. *Eur. J. Hum. Genet.* **27**, 1791–1799 (2019).
78. Tuxen, I. V. et al. Copenhagen Prospective Personalized Oncology (CoPPO)-clinical utility of using molecular profiling to select patients to phase I trials. *Clin. Cancer Res.* **25**, 1239–1247 (2019).
79. Von Hoff, D. D. et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J. Clin. Oncol.* **28**, 4877–4883 (2010).
80. Weymann, D. et al. Clinical and cost outcomes following genomics-informed treatment for advanced cancers. *Cancer Med.* **10**, 5131–5140 (2021).
81. Vissers, L. et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet. Med.* **19**, 1055–1063 (2017).
82. Yeung, A. et al. A cost-effectiveness analysis of genomic sequencing in a prospective versus historical cohort of complex pediatric patients. *Genet. Med.* **22**, 1986–1993 (2020).
83. Weymann, D. et al. Early-stage economic analysis of research-based comprehensive genomic sequencing for advanced cancer care. *J. Community Genet.* **13**, 523–538 (2022).
84. Hernando-Calvo, A. et al. Impact on costs and outcomes of multi-gene panel testing for advanced solid malignancies: a cost-consequence analysis using linked administrative data. *EClinicalMedicine* **69**, 102443 (2024).
85. Krebs, E. et al. Real-world cost-effectiveness of multi-gene panel sequencing to inform therapeutic decisions for advanced non-small cell lung cancer: a population-based study. *Lancet Reg. Health Am.* **40**, 100936 (2024).
86. Chung, C. C. Y. et al. Meta-analysis of the diagnostic and clinical utility of exome and genome sequencing in pediatric and adult patients with rare diseases across diverse populations. *Genet. Med.* **25**, 100896 (2023).
87. Shickh, S., Mighton, C., Uleryk, E., Pechlivanoglou, P. & Bombard, Y. The clinical utility of exome and genome sequencing across clinical indications: a systematic review. *Hum. Genet.* **140**, 1403–1416 (2021).
88. Kobayashi, E. S. et al. Long term follow up of children who received rapid genomic sequencing. *Genet. Med.* **27**, 101403 (2025).
89. Payne, K., Gavan, S. P., Wright, S. J. & Thompson, A. J. Cost-effectiveness analyses of genetic and genomic diagnostic tests. *Nat. Rev. Genet.* **19**, 235–246 (2018).
90. Schwarze, K., Buchanan, J., Taylor, J. C. & Wordsworth, S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet. Med.* **20**, 1122–1130 (2018).
91. Grosse, S. D. & Gudgeon, J. M. Cost or price of sequencing? Implications for economic evaluations in genomic medicine. *Genet. Med.* **23**, 1833–1835 (2021).
92. Santos Gonzalez, F. et al. Microcosting diagnostic genomic sequencing: a systematic review. *Genet. Med.* **25**, 100829 (2023).
93. Fahr, P., Buchanan, J. & Wordsworth, S. A review of health economic studies comparing traditional and massively parallel sequencing diagnostic pathways for suspected genetic disorders. *Pharmacoeconomics* **38**, 143–158 (2020).
94. Santos Gonzalez, F. et al. Microcosting genomics: challenges and opportunities. *Genet. Med.* **27**, 101310 (2025).
95. Bourke, M. et al. The cost-effectiveness of genomic medicine in cancer control: a systematic literature review. *Appl. Health Econ. Health Policy* **23**, 359–393 (2025).
96. Regier, D. A. et al. A perspective on life-cycle health technology assessment and real-world evidence for precision oncology in Canada. *NPJ Precis. Oncol.* **6**, 76 (2022).
97. Schmidtke, J. & Cassiman, J. J. The EuroGentest clinical utility gene cards. *Eur. J. Hum. Genet.* **18**, 1068 (2010).
98. Burke, W. et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. *Am. J. Epidemiol.* **156**, 311–318 (2002).
99. Schilling, C. et al. Utilisation of subsidised genetic and genomic testing in a publicly funded healthcare system 2014-2023. *Eur. J. Hum. Genet.* **33**, 1044–1050 (2025).
100. Mordaunt, D. A., Dalziel, K., Goranitis, I. & Stark, Z. Uptake of funded genomic testing for syndromic and non-syndromic intellectual disability in Australia. *Eur. J. Hum. Genet* **31**, 977–979 (2023).
101. Douglas, M. P., Parker, S. L., Trosman, J. R., Slavotinek, A. M. & Phillips, K. A. Private payer coverage policies for exome sequencing (ES) in pediatric patients: trends over time and analysis of evidence cited. *Genet. Med.* **21**, 152–160 (2019).
102. Trosman, J. R. et al. Perspectives of US private payers on insurance coverage for pediatric and prenatal exome sequencing: results of a study from the Program in Prenatal and Pediatric Genomic Sequencing (P3EGS). *Genet. Med.* **22**, 283–291 (2020).
103. Smith, H. S. et al. Outcomes of prior authorization requests for genetic testing in outpatient pediatric genetics clinics. *Genet. Med.* **23**, 950–955 (2021).
104. Zion, T. N. et al. Insurance denials and diagnostic rates in a pediatric genomic research cohort. *Genet. Med.* **25**, 100020 (2023).
105. Lu, C. Y. et al. Insurance coverage policies for pharmacogenomic and multi-gene testing for cancer. *J. Pers. Med.* **8**, 19 (2018).
106. Beinfeld, M. T., Rucker, J. A., Jenkins, N. B., de Breed, L. A. & Chambers, J. D. Variation in Medicaid and commercial coverage of cell and gene therapies. *Health Policy Open* **5**, 100103 (2023).
107. Phillips, K. A. et al. US private payers' perspectives on insurance coverage for genome sequencing versus exome sequencing: a study by the Clinical Sequencing Evidence-Generating Research Consortium (CSER). *Genet. Med.* **24**, 238–244 (2022).
108. Smith, H. S., Sherman, M. & Cardeiro, D. Conversations with the editors: stewardship in genomic medicine-insights from health care payers at the forefront of clinical innovation and partnerships. *Clin. Ther.* **45**, 690–694 (2023).
109. Wiedower, J. et al. Payer perspectives on genomic testing in the United States: a systematic literature review. *Genet. Med.* **27**, 101329 (2025).
110. Braithwaite, J., Churruca, K., Long, J. C., Ellis, L. A. & Herkes, J. When complexity science meets implementation science: a theoretical and empirical analysis of systems change. *BMC Med.* **16**, 63 (2018).

111. Zebrowski, A. M. et al. Qualitative study of system-level factors related to genomic implementation. *Genet. Med.* **21**, 1534–1540 (2019).
112. Best, S., Long, J. C., Gaff, C., Braithwaite, J. & Taylor, N. Investigating the adoption of clinical genomics in Australia. An Implementation Science case study. *Genes* **12**, 317 (2021).
113. Gaff, C. L. et al. Preparing for genomic medicine: a real world demonstration of health system change. *NPJ Genom. Med.* **2**, 16 (2017).
114. Best, S., Long, J. C., Gaff, C., Braithwaite, J. & Taylor, N. Organizational perspectives on implementing complex health interventions: clinical genomics in Australia. *J. Health Organ. Manag.* **35**, 825–845 (2021).
115. Stark, Z. et al. Australian genomics: outcomes of a 5-year national program to accelerate the integration of genomics in healthcare. *Am. J. Hum. Genet.* **110**, 419–426 (2023).
116. Braithwaite, J., Glasziou, P. & Westbrook, J. The three numbers you need to know about healthcare: the 60-30-10 challenge. *BMC Med.* **18**, 102 (2020).
117. Khorshidi, H. A., Marshall, D., Goranitis, I., Schroeder, B. & IJzerman, M. System dynamics simulation for evaluating implementation strategies of genomic sequencing: tutorial and conceptual model. *Expert Rev. Pharmacoecon. Outcomes Res.* **24**, 37–47 (2024).
118. Investigators, G. P. P. et al. 100,000 genomes pilot on rare-disease diagnosis in health care - preliminary report. *N. Engl. J. Med.* **385**, 1868–1880 (2021).
119. Sosinsky, A. et al. Insights for precision oncology from the integration of genomic and clinical data of 13,880 tumors from the 100,000 Genomes Cancer Programme. *Nat. Med.* **30**, 279–289 (2024).
120. Howley, C. et al. The expanding global genomics landscape: converging priorities from national genomics programs. *Am. J. Hum. Genet.* **112**, 751–763 (2025).
121. Stark, Z. et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet. Med.* **18**, 1090–1096 (2016).
122. Lionel, A. C. et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet. Med.* **20**, 435–443 (2018).
123. Regier, D. A. et al. Real-world diagnostic outcomes and cost-effectiveness of genome-wide sequencing for developmental and seizure disorders: evidence from Canada. *Genet. Med.* **26**, 101069 (2024).
124. Dragojlovic, N. et al. The composition and capacity of the clinical genetics workforce in high-income countries: a scoping review. *Genet. Med.* **22**, 1437–1449 (2020).
125. Jenkins, B. D. et al. The 2019 US medical genetics workforce: a focus on clinical genetics. *Genet. Med.* **23**, 1458–1464 (2021).
126. Jayasinghe, K. et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genet. Med.* **23**, 183–191 (2021).
127. Yanes, T. et al. Evaluation and pilot testing of a multidisciplinary model of care to mainstream genomic testing for paediatric inborn errors of immunity. *Eur. J. Hum. Genet* **31**, 1125–1132 (2023).
128. Ma, A. et al. Genomic multidisciplinary teams: a model for navigating genetic mainstreaming and precision medicine. *J. Paediatr. Child Health* **60**, 118–124 (2024).
129. McCorkell, G. et al. A national education program for rapid genomics in pediatric acute care: Building workforce confidence, competence, and capability. *Genet. Med.* **26**, 101224 (2024).
130. Nisselle, A., Terrill, B., Janinski, M., Metcalfe, S. & Gaff, C. Ensuring best practice in genomics education: a scoping review of genomics education needs assessments and evaluations. *Am. J. Hum. Genet.* **111**, 1508–1523 (2024).
131. Nisselle, A. et al. Ensuring best practice in genomics education: a theory- and empirically informed evaluation framework. *Am. J. Hum. Genet.* **111**, 1497–1507 (2024).
132. Nightingale, K. P. et al. Evaluation of the Master's in Genomic Medicine framework: a national, multiprofessional program to educate health care professionals in NHS England. *Genet. Med.* **27**, 101277 (2025).
133. Pichini, A. & Bishop, M. A nationally agreed cross-professional competency framework to facilitate genomic testing. *Genet. Med.* **24**, 1743–1752 (2022).
134. Pichini, A., Tatton-Brown, K., Thomas, E. & Bishop, M. A cross-professional competency framework for communicating genomic results. *J. Genet. Couns.* **33**, 222–231 (2024).
135. Karthikeyan, A., McKee, S. & McKay, G. J. Integration of genomic medicine to mainstream patient care within the UK National Health Service. *Ulster Med. J.* **93**, 111–118 (2024).
136. Berkman, J. et al. Mainstreaming cancer genomic testing: a scoping review of the acceptability, efficacy, and impact. *Clin. Genet.* **107**, 123–135 (2025).
137. Mackley, M. P. et al. Mainstreaming of clinical genetic testing: a conceptual framework. *Genet. Med.* **27**, 101465 (2025).
138. Mordaunt, D. A. et al. The cost of proband and trio exome and genome analysis in rare disease: a micro-costing study. *Genet. Med.* **26**, 101058 (2024).
139. Best, S. et al. Teamwork in clinical genomics: a dynamic sociotechnical healthcare setting. *J. Eval. Clin. Pract.* **27**, 1369–1380 (2021).
140. Best, S. et al. The leadership behaviors needed to implement clinical genomics at scale: a qualitative study. *Genet. Med.* **22**, 1384–1390 (2020).
141. Friedrich, B. et al. A very big challenge": a qualitative study to explore the early barriers and enablers to implementing a national genomic medicine service in England. *Front. Genet.* **14**, 1282034 (2023).
142. Kirk, E. P. et al. Nationwide, couple-based genetic carrier screening. *N. Engl. J. Med.* **391**, 1877–1889 (2024).
143. Casalino, S. et al. Genome screening, reporting, and genetic counseling for healthy populations. *Hum. Genet.* **142**, 181–192 (2023).
144. Stark, Z. & Scott, R. H. Genomic newborn screening for rare diseases. *Nat. Rev. Genet.* **24**, 755–766 (2023).
145. McDermott, J. H., Tsakiroglou, M., Newman, W. G. & Pirmohamed, M. Pharmacogenomics in the UK National Health Service: progress towards implementation. *Br. J. Clin. Pharmacol.* **91**, 2241–2250 (2025).
146. Lennon, N. J. et al. Selection, optimization and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse US populations. *Nat. Med.* **30**, 480–487 (2024).
147. Rehm, H. L. et al. ClinGen–the Clinical Genome Resource. *N. Engl. J. Med.* **372**, 2235–2242 (2015).
148. Rehm, H. L., Harrison, S. M. & Martin, C. L. ClinVar is a critical resource to advance variant interpretation. *Oncologist* **22**, 1562 (2017).
149. Tudini, E. et al. Shariant platform: enabling evidence sharing across Australian clinical genetic-testing laboratories to support variant interpretation. *Am. J. Hum. Genet* **109**, 1960–1973 (2022).
150. Stark, Z. et al. Scaling national and international improvement in virtual gene panel curation via a collaborative approach to discordance resolution. *Am. J. Hum. Genet.* **108**, 1551–1557 (2021).

151. DiStefano, M. T. et al. The Gene Curation Coalition: a global effort to harmonize gene-disease evidence resources. *Genet. Med.* **24**, 1732–1742 (2022).
152. Stark, Z. et al. A call to action to scale up research and clinical genomic data sharing. *Nat. Rev. Genet.* **26**, 141–147 (2025).
153. Rehm, H. L. et al. GA4GH: international policies and standards for data sharing across genomic research and healthcare. *Cell. Genom.* **1**, 100029 (2021).
154. Roberts, M. C., Kennedy, A. E., Chambers, D. A. & Khoury, M. J. The current state of implementation science in genomic medicine: opportunities for improvement. *Genet. Med.* **19**, 858–863 (2017).
155. Chambers, D. A., Feero, W. G. & Khoury, M. J. Convergence of implementation science, precision medicine, and the learning health care system: a new model for biomedical research. *JAMA* **315**, 1941–1942 (2016).
156. Moullin, J. C. et al. Ten recommendations for using implementation frameworks in research and practice. *Implement. Sci. Commun.* **1**, 42 (2020).
157. Brown, H. L., Sherburn, I. A., Gaff, C., Taylor, N. & Best, S. Structured approaches to implementation of clinical genomics: a scoping review. *Genet Med* **24**, 1415–1424 (2022).
158. Curran, G. M., Bauer, M., Mittman, B., Pyne, J. M. & Stetler, C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med. Care* **50**, 217–226 (2012).
159. Taylor, N. et al. Aligning intuition and theory: a novel approach to identifying the determinants of behaviours necessary to support implementation of evidence into practice. *Implement. Sci.* **18**, 29 (2023).
160. Best, S. et al. Learning from scaling up ultra-rapid genomic testing for critically ill children to a national level. *NPJ Genom. Med.* **6**, 5 (2021).
161. Cheng, L. et al. Optimising the mainstreaming of renal genomics: Complementing empirical and theoretical strategies for implementation. *Eur. J. Hum. Genet.* **33**, 351–359 (2025).
162. Best, S. et al. Using a theory informed approach to design, execute, and evaluate implementation strategies to support offering reproductive genetic carrier screening in Australia. *BMC Health Serv. Res.* **23**, 1276 (2023).
163. Fehlberg, Z. et al. Scaling-up and future sustainability of a national reproductive genetic carrier screening program. *NPJ Genom. Med.* **8**, 18 (2023).
164. Best, S., Long, J. C., Braithwaite, J. & Taylor, N. Standardizing variation: Scaling up clinical genomics in Australia. *Genet. Med.* **25**, 100109 (2023).
165. Laskowski, N. M. et al. Variation exists in service delivery: similarities and differences in the provision of a whole genome sequencing service for paediatric rare disease patients in the National Health Service in England. *Public Health Genomics* **28**, 1–18 (2025).
166. Best, S., Vidic, N., An, K., Collins, F. & White, S. M. A systematic review of geographical inequities for accessing clinical genomic and genetic services for non-cancer related rare disease. *Eur. J. Hum. Genet.* **30**, 645–652 (2022).
167. Casauria, S. et al. Assessing the unmet needs of genomic testing in Australia: a geospatial exploration. *Eur. J. Hum. Genet.* 33, 496–503 (2024).
168. Pichler, F. B. et al. An operationalization framework for lifecycle health technology assessment: a Health Technology Assessment International Global Policy Forum Task Force report. *Int. J. Technol. Assess. Health Care* **40**, e45 (2024).
169. Makady, A., de Boer, A., Hillege, H., Klungel, O. & Goettsch, W. What is real-world data? A review of definitions based on literature and stakeholder interviews. *Value Health* **20**, 858–865 (2017).
170. Sterrantino, A. F. Observational studies: practical tips for avoiding common statistical pitfalls. *Lancet Reg. Health Southeast Asia* **25**, 100415 (2024).
171. Weymann, D., Krebs, E. & Regier, D. A. Addressing immortal time bias in precision medicine: practical guidance and methods development. *Health Serv. Res.* **60**, e14376 (2025).
172. Hernan, M. A., Sauer, B. C., Hernandez-Diaz, S., Platt, R. & Shrier, I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J. Clin. Epidemiol.* **79**, 70–75 (2016).
173. Pollard, S. et al. Defining a core data set for the economic evaluation of precision oncology. *Value Health* **25**, 1371–1380 (2022).
174. McPhail, M., McCabe, C., Regier, D. A. & Bubela, T. The importance of and challenges with adopting life-cycle regulation and reimbursement in Canada. *Health. Policy* **17**, 81–90 (2022).
175. Maggio, L. A., Villalba, K., German, D., Kanter, S. L. & Collard, H. R. Defining the learning health care system: an international health system leadership perspective. *Acad. Med.* **99**, 215–220 (2024).
176. Meghea, C. I. et al. An NIH investment in health equity - the economic impact of the Flint Center for Health Equity Solutions. *BMC Public Health* **21**, 1774 (2021).
177. Hock, D. H. et al. Untargeted proteomics enables ultra-rapid variant prioritisation in mitochondrial and other rare diseases. *Genome Med.* **17**, 58 (2025).
178. Tambuyzer, E. et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. *Nat. Rev. Drug Discov.* **19**, 93–111 (2020).
179. Chung, C. C. Y., Chu, A. T. W. & Chung, B. H. Y. A roadmap for genome projects to foster psychosocial and economic evidence to further policy and practice. *Commun. Med.* **5**, 198 (2025).

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Ilias Goranitis or Zornitza Stark.

Peer review information *Nature Medicine* thanks Elaine Mardis and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Karen O'Leary, in collaboration with the *Nature Medicine* team.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

© Springer Nature America, Inc. 2025

[1]Economics of Genomics and Precision Medicine Unit, Centre for Health Policy, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia. [2]Australian Genomics, Murdoch Children's Research Institute, Melbourne, Victoria, Australia. [3]Child Health Evaluative Sciences, Hospital for Sick Children Research Institute, Toronto, Ontario, Canada. [4]Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. [5]Precision Medicine Translational Research (PROMoTeR) Center, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA. [6]Center for Bioethics, Harvard Medical School, Boston, MA, USA. [7]Health Economics and Policy Research Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK. [8]National Institute for Health Research, Barts Biomedical Research Centre, Queen Mary University of London, London, UK. [9]Cancer Control Research, BC Cancer Research Institute, Vancouver, British Colombia, Canada. [10]Faculty of Health Sciences, Simon Fraser University, Burnaby, British Colombia, Canada. [11]School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, British Colombia, Canada. [12]Division of Clinical & Metabolic Genetics, Department of Paediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada. [13]Genomics England, London, UK. [14]Great Ormond Street Hospital for Children, London, UK. [15]UCL Great Ormond Street Institute of Child Health, London, UK. [16]National Health Service England, London, UK. [17]Hong Kong Genome Institute, Hong Kong, China. [18]Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. [19]Melbourne School of Health Sciences, University of Melbourne, Melbourne, Victoria, Australia. [20]RILD Wellcome Wolfson Centre, University of Exeter Medical School, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK. [21]Peninsula Clinical Genetics Service, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK. [22]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Victoria, Australia. [23]Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia. ✉e-mail: ilias.goranitis@unimelb.edu.au; zornitza.stark@vcgs.org.au