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A roadmap for genome projects to foster psychosocial and economic evidence to further policy and practice

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Advances in genomic sequencing (GS) have transformed personalised treatment strategies for genetic diseases across a diverse array of clinical indications, resulting in notable public health progress. However, limited evidence on the broader psychosocial and economic impacts hinders its widespread adoption in healthcare systems. The launch of genome projects offers an opportunity to address the unmet needs of a wide range of genetic diseases. This Perspective examines the multi-dimensional effectiveness of GS and summarises indicators and measurement tools for psychosocial and economic outcomes. It highlights priority areas identified by the Clinical Sequencing Exploratory Research Consortium. Drawing on initiatives such as the Genomics England 100,000 Genomes Project and Australian Genomics initiative, this article showcases best practices in selecting outcome measures for assessing the effectiveness of GS in policy and practice. This Perspective intends to equip future studies with a strategic and sustainable approach for outcome-oriented research within genome projects, facilitating evidence-based clinical implementation of GS in an appropriate, equitable and efficient manner.

Genomic sequencing (GS) has revolutionised the diagnostic journey of patients with genetic diseases across a diverse array of clinical indications, driving significant advances in public health, including a major shift towards precision medicine[1,2]. The existing literature primarily focuses on the clinical effectiveness of GS, evaluating endpoints related to diagnostics and clinical utility. These include clinical benefits such as indication and contra-indication of medications and procedures, referral to specialists for surveillance, follow-up screening recommendations, and decreased morbidity and mortality[3,4]. Recognising the clinical benefits of GS, recent studies have increasingly highlighted its translational value in clinical practice, and emphasised the importance of equitable and scalable access to address the unmet needs of marginalised populations, including families affected by rare diseases (RDs) and cancers[1]. Nevertheless, a key challenge to its widespread adoption in national healthcare systems lies in the lack of evidence regarding its broader psychosocial and economic impact on individuals, health systems, and society as a whole. This knowledge gap poses potential risks, such as unequal access and increased psychological and economic burden for individuals and healthcare systems. A lack of comprehensive understanding of the non-clinical implications of GS and its associated clinical genetic services, including genetic counselling, may lead to widening health disparities, potentially favouring certain socioeconomic or demographic groups access to this technology. Such unequal access could further exacerbate existing inequities, limiting the benefits of personalised medicine enabled by GS to only a privileged few. Additionally, the absence of evidence of long-term psychological impact, such as increased anxiety or perceived stigma associated with genetic information, may result in substantial mental health challenges for individuals undergoing GS. From an economic perspective, the lack of data on the cost-effectiveness and budgetary impact of implementing genetics services at scale could lead to unsustainable implementation strategies, burdening healthcare systems and imposing unnecessary financial strains on patients and their families. To advance the appropriate integration of GS into healthcare systems and prioritise the implementation of its broader genetic services as part of universal health coverage and global health priorities, it is imperative to generate evidence and measure the psychosocial and economic outcomes of genomic medicine. In the era of precision medicine that integrates personalised treatment and individual preferences, it is important to comprehensively evaluate the outcomes beyond clinical parameters, encompassing non-health and societal dimensions, such as participant's perceived utility and economic impact on healthcare systems and society. Such evaluations will contribute to informed decision-making processes, equitable access, and sustainable and appropriate implementation strategies that benefit individuals, healthcare

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systems, and society as a whole. By addressing broader implications, stakeholders can work towards realising the full transformative potential of GS while mitigating potential risks and barriers to its widespread adoption.

Framework for evaluating outcomes for genomic medicine

The six-tiered model of efficacy of GS was elucidated by Hayeems et al. based on the Fryback and Thornbury framework[5,6]. The hierarchical model delineates the outcome effectiveness of GS across six different levels, including technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, patient outcome efficacy, and societal efficacy related to GS and its associated genetic services (Fig. 1). Achieving levels 1 to 4 is considered pivotal in genomic medicine, with the laboratory-based components at levels 1 and 2 serving as fundamental elements that underpin clinical utility[6]. These domains have been well documented in many of the published literature and guidelines[7–9]. In contrast to Hayeems et al.'s focus on a measurement toolkit encompassing the six efficacy levels of GS, this Perspective offers a comprehensive overview of outcome indicators and measurement strategies on the psychosocial and economic dimensions, with a specific emphasis on levels 5 (patient outcome efficacy) and 6 (societal efficacy) within the six-tiered efficacy model (Supplementary Table 1). Furthermore, it presents a detailed list of psychosocial domains for consideration. Drawing on insights from initiatives such as the Genomics England 100,000 Genomes Project and Australian Genomics initiative, this Perspective highlights best practices for selecting outcome measures in ongoing large-scale genome projects. Additionally, it offers guidance on research methods and data collection time points to facilitate an organised approach to planning outcome-oriented studies.

Clinical outcomes of genomic sequencing

GS is emerging as one of the most robust diagnostic strategies for achieving timely diagnosis for patients with genetic diseases, including undiagnosed diseases and RDs. Diagnostic thinking efficacy (level 3) and therapeutic efficacy (level 4) are recognised as the core dimensions of value for GS in clinical and research studies, with multiple published meta-analyses and systematic reviews summarising the evidence in the literature[3,4].

Diagnostic thinking efficacy. Diagnostic thinking efficacy refers to the impact of GS on a clinician's decision-making for a patient's differential diagnosis[6]. Assessment at this level includes diagnostic classification, prognostic clarity, indication or avoidance of additional diagnostic investigations, and timeliness of diagnosis. Traditionally, chromosomal microarray has been widely applied as a genetic diagnostic tool, in which chromosomes are analysed to detect aneuploidies as well as structural variations in the genome. Advances in next-generation sequencing technologies such as exome and genome sequencing have enabled more comprehensive genomic analysis. Exome sequencing focuses on the protein-coding regions of the genome, while GS analyses the entire genome. The diagnostic capability of exome and genome sequencing over conventional diagnostic testing strategies has been well demonstrated in literature, with studies combined as meta-analyses to illustrate the magnitudes across countries and regions[3,4,10–12].

In a meta-analysis[3] that included 37 studies and included 20,068 children with RDs, GS was found to achieve a higher diagnostic yield than chromosomal microarray. The diagnostic capability of GS was further supported by a more recent meta-analysis[4] which included 161 studies across 31 countries/regions and comprising 50,417 probands. This highlights the diagnostic benefits for RD diagnosis across clinical settings and provides additional support for GS as an untargeted diagnostic test. Recent studies have also illustrated the vast potential of rapid GS in shortening or averting the diagnostic trajectories for patients with urgent needs. In critically ill patients needing a genetic diagnosis, the diagnostic and clinical implication of GS were corroborated by findings from multiple meta-analyses and reviews, with median results turnaround time found to be as short as 0.8 days[10,13–15]. The introduction of ultra-rapid GS has enabled a significant reduction in time to diagnosis, possibly within 90 min[14,16]. In addition to ending the diagnostic odyssey and uncertainties, an early and rapid genetic diagnosis could potentially impact a patient's clinical management, achieving outcomes at the level of therapeutic efficacy (level 4).

Therapeutic efficacy. Therapeutic efficacy refers to the impact of GS on a patient's clinical management, which is often referred to as clinical utility in published literature. Clinical utility includes implications for medication and therapy management, surgical or interventional procedures, specialist referrals, surveillance plans, lifestyle changes, reproductive-risk counselling, etc[6]. In a systematic review that reviewed evidence of clinical utility in GS, the rate of clinical utility ranged from 4 to 100% of diagnosed patients across 24 studies, reporting a total of 613 management changes, and providing evidence that GS has a greater potential to improve patient clinical outcomes than conventional genetic testing[17]. Similar conclusions were reached in two other meta-analyses[3,4]. Rapid GS was also found to achieve a significantly higher clinical utility than non-rapid GS ($p < 0.01$), illustrating the power of shorter results turnaround time for rapid management changes in critically ill patients[4]. These clinical implications are typically assessed by the clinical geneticists or clinicians and documented in patient's clinical notes, with more recent evaluations utilising the validated Clinician-reported Genetic testing Utility InDEx (C-GUIDE).

Findings from these meta-analyses and systematic reviews shed light on the considerations when implementing GS into clinical workflows to enable precision medicine. Nevertheless, the integration of genomic medicine in public healthcare raises a lot of ethical and psychosocial challenges, particularly in terms of its accessibility and affordability. Genomic medicine is a complex intervention and has broader objectives than just health gain[18]. The transformative potential of genomic medicine will only be fully realised by identifying and applying evidence-based approaches from a population perspective. It is important to consider individual personal values and socio-economic outcomes in conjunction with patient's clinical needs to inform decisions on implementation.

Psychosocial and economic outcomes of genomic medicine

In contrast to the clinical outcomes of GS, its psychosocial and economic landscape remain underexplored. These aspects typically involve a broader and more complex intervention within clinical genetic services. It often encompasses measures of process attributes and their associated outcomes through the provision of GS and genetic counselling[18]. To comprehensively harness the potential of GS, it is imperative to evaluate outcomes of GS beyond the diagnostic and clinical perspective, targeting the patient outcome efficacy (level 5) and societal efficacy (level 6) domains. Funded by the National Human Genome Research Institute (NHGRI), members of the Clinical Sequencing Exploratory Research (CSER) Consortium formed the Outcomes and Measures Working Group to highlight the priority areas in evaluating the psychosocial and behavioural outcomes of GS for clinical integration[19]. Six conceptual domains were identified by the Outcomes and Measures Working Group, including preferences for disclosure of sequencing findings, understanding, psychosocial impact, behavioural impact, healthcare utilisation, and decisional satisfaction and regret[19]. These domains were in line with the constructs indicated in the levels of patient outcome efficacy (level 5) and societal efficacy (level 6) of the Fryback and Thornbury model. Supplementary Table 1 summarises the indicators across psychosocial and economic outcomes in these two levels, which can be assessed using quantitative and/or qualitative methods. Some patient-centred outcomes may require both quantitative and qualitative data to fully elucidate their multifaceted nature. A complementary mixed-method approach may benefit in capturing the depth and breadth of its impact. Several patient-reported outcome measures (PROMs) have been validated for use in outcome research in genomic medicine and are discussed with a description and suggested timepoint of administration for consideration of adaption in future large-scale outcome evaluation studies.

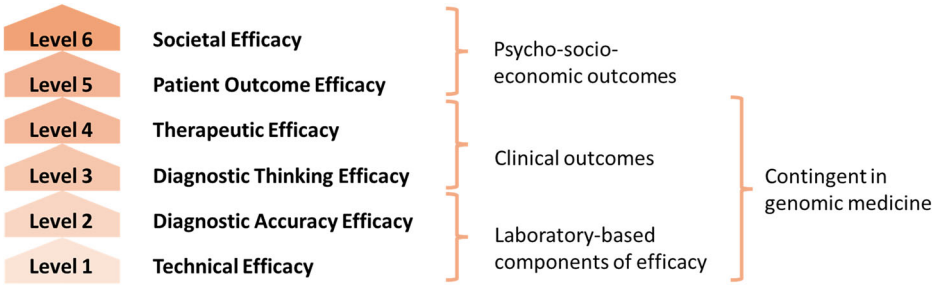

Fig. 1 | Six levels of efficacy offered by genomic sequencing. The hierarchical model delineates the outcome effectiveness of GS across six different levels,including technical efficacy, diagnostic accuracy efficacy, diagnostic thinking efficacy, therapeutic efficacy, patient outcome efficacy, and societal efficacy related to GS and its associated genetic services.

Patient outcome efficacy. Patient outcome efficacy (level 5) refers to patient outcomes that are broadly categorised into health-related outcomes and non-health-related outcomes[6]. Health-related outcomes refer to indicators associated with utilisation of healthcare services, disease burden, morbidity, mortality, and quality of life. These are important indicators to monitor health-related outcomes at a national level and generally require information from electronic patient records (ePR) or survey/interview data from patients and caregivers. Existing genomic medicine networks have illustrated the value of ePRs for genomic discovery and outcomes evaluation within a genomic medicine implementation across large populations[20]. Previous studies have estimated the disease burden and healthcare resource utilisation pattern for RDs using ePR and administrative datasets, demonstrating the disproportionately high service and resource needs, as well as the higher mortality rate as compared to other common conditions and the general population[21–23]. Standard quality of life measures are PROMs that assess the perceived patient's health-related quality of life (HRQoL) from the individual's or caregiver's perspective. They are increasingly recognised in outcome research, particularly in observational studies and clinical trials. Studies have also highlighted the importance of including preference-based HRQoL instruments in the planning of outcome evaluation studies for large-scale sequencing projects, as they can provide valuable evidence on the impact of GS on patient's overall well-being. This in turn could facilitate clinicians and policy makers to identify unmet needs and prioritise services and resources[24]. Numerous well-validated instruments have been used in research in genomic medicine, such as the EuroQol five-dimension (EQ-5D) and Medical Outcomes Study Short Form (SF-36) questionnaires[25–27]. The use of preference-based HRQoL instruments to generate quality-adjusted life years (QALYs) also provides valuable evidence, especially when used in conjunction with cost measures, which is recommended by health technology assessment (HTA) agencies to inform value-based healthcare initiatives.

Measuring the non-health-related outcomes for genomic medicine, such as psychosocial well-being, is equally important in providing evidence for its integration into public healthcare systems. The term psychosocial outcomes is used inconsistently in the genomics literature. For this work, we define psychosocial outcomes as encompassing both psychological and social aspects related to the impact of genomic medicine. This includes outcomes spanning psychological/emotional well-being, social functioning and relationships, patient empowerment, perceived values and concerns, social consequences and stigma, as well as coping and adjustment to genetic and genomic information. These psychosocial outcomes are broadly categorised into two key indicators: psychological impact and patient-oriented utility.

Concerning the psychological impact, various single-dimensional and multi-dimensional instruments have been developed and validated to evaluate psychological responses to genetic information. A meta-analysis of seven studies from the CSER Consortium assessed pre-test and post-test anxiety, depressive symptoms, and multi-dimensional psychological impact using validated single-dimensional and multi-dimensional scales, including the 7-item General Anxiety Disorder scale (GAD-7)[28], 9-item Patient Health Questionnaire (PHQ-9)[29], the Hospital Anxiety and Depression Scale (HADS)[30], Multidimensional Impact of Cancer Risk Assessment (MICRA)[31], and the Feelings About genomiC Testing Results (FACToR)[32,33]. Findings suggested that there was no clinically significant psychological harm from the return of genomic testing results, and an overall decreased trend of anxiety from pre- to post-disclosure of genomic results[32]. Another commonly assessed outcome in genomics is patient empowerment, a set of beliefs among individuals to feel that they have a degree of control over, and hope for, the future. It focuses on equipping individuals with the knowledge, skills, and resources to take control of their health. The 24-item Genetic Counselling Outcome Scale (GCOS-24) and its shorter version, Genomic Outcome Scale (GOS), both assess patient empowerment in clinical genetics and genetic counselling, while the Genome Empowerment Scale (GEmS) evaluates parental empowerment in genomics[34–36]. Although single-dimensional instruments might be more sensitive in measuring specific psychological responses to GS, incorporating multiple single-dimensional scales in the same questionnaire could increase the risk of respondent burden, which is the degree to which the participant perceives the completion of the survey to be time-consuming, difficult, or emotionally stressful, potentially leading to poor compliance rates[37]. Going forward, experts recommend a multi-dimensional evaluation approach rather than a test-dependent state psychological measure[32,38]. Qualitative research methods are also likely to be beneficial for providing a more in-depth understanding of the multi-dimensional psychological impact of GS and its associated genomic services.

Evaluating what matters to patients and families is central to improving patient care and service delivery. Patient-oriented utility, often referred to as perceived or personal utility, has emerged as a core non-health-related construct that reflects patient's subjective values and concerns regarding genomic medicine[39]. It encompasses both positive and negative effects of GS and its entire process, including genetic counselling, and is indirectly associated with health outcomes, which can influence an individual's well-being. The GENEtic Utility (GENE-U) scale was recently developed and validated through the CSER Consortium[40]. This scale is grounded in a conceptual model encompassing five domains designed to assess patient-centred perceived utility to capture the positive and negative effects of GS: clinical, affective, cognitive, behavioural, and social[40]. The paediatric diagnostic version of the GENE-U scale features two subscales: the informational utility subscale, which includes items related to the impact of GS findings on the child's clinical care and various aspects of life, drawing from all five conceptual domains; and the emotional utility subscale, which emphasises the emotional responses and psychological impacts associated with GS, incorporating items from the affective and social domains. The subscales were demonstrated to be strongly associated with relevant domains of other outcome measures, with the information utility subscale covering elements from the GOS[35], the meaning of diagnosis, seeking information and support, and implications and planning subscales of the GEmS[36], as well as the primary child gains and parent control factors of the Parent Personal Utility (PrU) scale[41]. On the other hand, the emotional utility subscale includes elements from the 4-item PHQ for anxiety and depression, as well as the negative emotions and uncertainty subscales of

FACToR[33]. The total GENE-U score provides valuable quantitative evidence to assess parents' overall perceived utility of GS for their child, complementing assessments of clinical utility, such as changes in clinical management and health outcomes.

Another validated PROM that has emerged from the CSER Consortium is the PrU scale, developed to quantify adults' perceptions of utility in genomic medicine[41]. The PrU has a somewhat different factor structure, but also reflects elements of these conceptual domains. The three-factor structure of PrU centred on self-knowledge, reproductive planning, and practical benefits. Self-knowledge represents the benefits of learning about oneself from undergoing GS, which covers elements from the cognitive and affective domains conceptualised previously[40,42]. In contrast, reproductive planning is specific to family planning, and practical benefits refers to outcomes related to future planning, involving elements within the behaviour domain, such as access to programs and resources, as well as communication with family members. The PrU is also available in the parent version, which assesses perceived utility regarding their child[43]. Use of the two PrU scales may enable clinicians or researchers to anticipate the overall benefits perceived by their patients from GS, informing decision-making discussions.

Several other PROMs have been validated to measure specific domains of perceived utility[39,40]. Measurement tools that target the clinical domain were discussed earlier in this Perspective. With respect to the affective domain of GS, it refers to an individual's emotional state such as enhanced coping, mental preparation, and feeling of responsibility. Well-validated PROMs such as the GCOS-24 and Psychosocial Aspects of Hereditary Cancer (PAHC) questionnaires capture these affective elements, including mental preparation and feeling of responsibility[34,44]. The Psychological Adaptation Scale (PAS) also measures affective elements related to adaptation[38]. The affective domain was highlighted as one of the priority areas by the CSER Working Group, with a number of CSER studies evaluating affective outcomes including tolerance of uncertainty and anticipated regret[19].

The cognitive domain emphasises the importance of information and knowledge gained from GS, which is essential for informed consent and decision making. Assessing participants' understanding and knowledge at different timepoints will be beneficial in evaluating the value of GS over the process of clinical genetics and genetic counselling, reflecting the belief that informed choices would lead to better decision outcomes and thus motivate change for better clinical and psychological outcomes[20]. A systematic review found that patients with higher knowledge scores were more likely to actively participate in decision-making for their treatment, and were associated with higher decisional satisfaction and fewer concerns about genomic testing[45]. The importance of evaluating patient's cognitive outcomes was acknowledged by the CSER Consortium, and they have set up projects to measure participants' understanding, knowledge, and information processing using a variety of validated outcome measures, including the Genome Sequencing Knowledge Scale and an adapted version of the Quality of Informed Consent (QuIC) questionnaire[19,46,47].

The behavioural domain encompasses the practical application of genomic information to influence future planning, including lifestyle, education, career, financial, reproduction, and long-term care, etc[39,42]. Routine use of GS in clinical practice has the potential to drastically impact behaviours, this concept overlaps slightly with the level of therapeutic efficacy of the Fryback and Thornbury model. Studies showed that participants with positive results are more likely to make use of their genetic findings in decision-making, including the sharing of cancer risk results with family members to promote risk management[45]. The majority of the previous studies have evaluated behavioural outcomes through mixed research methods or qualitative interviews to develop an in-depth understanding of participant's behavioural responses to GS. While no specific instrument focuses solely on behavioural aspects, several validated tools include relevant subscales and questions that capture behavioural experiences, such as GCOS-24, and the Psychological Adaptation to Genetic Information Scale (PAGIS)[34,41,48]. Some projects from the CSER Consortium have also attempted to quantitatively assess behavioural responses by adopting questions from large national studies, including the Health Information National Trends Survey (HINTS) by the National Cancer Institute[19,49]. Other studies have developed novel questions or measures to assess behavioural responses tailored to specific research questions and study objectives.

Lastly, the social domain addresses changes in social support or status of the individual, family, or society. This conceptual domain focuses on the social constructs of GS through the individual's support groups and its effect on social values, potentially affecting social relationships in different social environments[39,42]. A systematic review highlighted considerable concerns related to genetic discrimination, particularly regarding insurance, which was shown to hinder participation in genetic testing[50]. Most published studies have assessed the social domain using a qualitative or mixed research method, aiming to provide a nuanced understanding of individual responses[42]. PROMs specifically measuring stigma, such as the Stigma Scale for Chronic Illnesses 8-item version (SSCI-8) for individuals with neurological conditions[51], and broader questionnaires, such as the PAHC questionnaire[44], capture elements of the social domain, while large-scale projects often adapt and develop their survey questions to assess perceived social impacts of GS[52].

Societal efficacy. Finally, societal efficacy (level 6) of the Fryback and Thornbury model refers to the societal acceptability of GS beyond the index case, particularly focusing on values and preferences as well as the value of GS relative to its cost (e.g. economic evaluation)[6]. To inform appropriate decision-making regarding the integration of GS into routine clinical workflows, stakeholders must consider a variety of factors such as benefits, harms, costs, and uncertainties. The uptake of GS depends upon the value individuals place on GS (i.e. perceived utility), often reflected through an individual's willingness to pay. The stated preference discrete choice experiment has been successfully used to elicit preferences and values about genomics, and is increasingly applied in the study of RDs and cancers[53–55]. The cost of GS and its economic impact on patients, families, the healthcare system, and society, also play an important role in its clinical implementation. In particular, the validated Client Service Receipt Inventory for the rare disease population (CSRI-Ra) survey was developed to collect direct and indirect cost-related data associated with RDs[56,57]. Using the CSRI-Ra, the total annual cost of RDs was estimated to be HK$484,256 (US$62,084)/patient in Hong Kong, with direct non-healthcare costs and indirect costs accountable for over 61% of the total costs[58]. Other studies have also developed their own set of questionnaires to collect cost data related to RDs[59,60]. Alongside clinical benefits of GS, robust economic evaluations that encompass both the technology component (e.g. GS) and the service component (e.g. genetic counselling) are essential for successful implementation within healthcare systems[18]. Cost-effectiveness evidence has been identified as a critical factor in the effective delivery of genomic medicine services, as demonstrated by the National Health Service (NHS) England[61]. The cost-per-QALY approach in economic evaluation is recommended by HTA agencies to inform value-based healthcare initiatives. Nevertheless, genetic services and GS comprise both health and non-health aspects. Maximising health is insufficient when valuing the economic benefits of genomic medicine[18]. While non-health-related outcomes require further validation and standardisation, their incorporation into economic evaluations may be beneficial, especially in the context of genomic medicine, where outcome effectiveness is multi-dimensional.

The application of PROMs in large-scale longitudinal studies is directly relevant to researchers, clinicians, and policymakers, as they could potentially inform public service delivery, including the implementation of GS in clinical workflows, thereby improving patient-centred care. As highlighted by multiple studies, the landscape of GS encompasses various dimensions, which may require qualitative research methods to complement quantitative analyses, further exploring the breadth and depth of the interactions between individual, families, healthcare system, and social context, and

providing a more comprehensive understanding of the implications in public health.

Establishing genome projects for evidence-based implementation

The implementation of healthcare innovations typically spans an average of 17 years, during which time the chosen approach not only determines the adoption of evidence-based interventions but also influences their ability to deliver the expected benefits[15,62]. The paucity of psychosocial and economic evidence has been identified as a factor hindering the uptake and long-term viability of genomic medicine in national healthcare systems. Building evidence for genomic medicine with outcome-oriented studies has the potential to inform service delivery, HTA, health and social care policies, and allocation of resources. Acknowledging the diagnostic capability and clinical utility of GS, governments around the world have started to launch large-scale genome projects, aiming to benefit patients and families with more precise diagnosis-predicted clinical management, and laying the groundwork for the implementation of GS in routine clinical care within a national genomic medicine service. A large sample size is advantageous but necessitates efficient, low-cost strategies for collecting multi-dimensional outcomes, targeting evidence-based delineation of domains and elements of effectiveness through the application of different PROMs[63].

Outcome-oriented studies should be planned as part of a pipeline from discovery to implementation within genome projects. Few genome projects have reported outcomes to date, with the 100,000 Genomes Projects by Genomics England and the flagship studies by Australian Genomics acting as exemplars in driving the transformation process of clinical implementation of GS.

The 100,000 Genomes Projects by Genomics England reported preliminary findings from its pilot study involving 4,660 participants from 2183 families, demonstrating the diagnostic capability of GS across 161 RDs, achieving a diagnostic yield of 25%, and further leading to immediate clinical actionability in 25% of the diagnosed patients (134 of 533 genetic diagnoses)[64]. The Cancer Programme of the 100,000 Genomes Project has also recently reported genomic and clinical data of 13,880 tumours across 33 cancer types, providing evidence of the diagnostic value of GS data in characterising clinically actionable variants in a tumour, and evaluating treatment outcomes for patients based on pangenomic markers[65]. In addition to the clinical outcomes of GS, Genomics England has also conducted quantitative and qualitative research to evaluate the psychosocial outcomes of GS, with a particular focus on the patient outcome efficacy domain of the Fryback and Thornbury framework[52,66–70]. In particular, Genomics England has developed cross-sectional surveys to collect outcome data related to participant's attitudes, knowledge, decision-making, and psychological impact at the time of testing (T1) and 12-18 months post-consent (T2) by adopting and adapting multiple validated PROMs, as well as developing new items specifically for the Project (Supplementary Table 1)[52,66]. T1 survey findings indicated high perceived benefits, low concerns, and low decisional conflict; whereas T2 results showed low decisional regret and generally minimal negative psychological impact of receiving GS results among participants. The Scottish Genomes Partnership (SGP) within the 100,000 Genomes Project has also developed a survey to understand participants' health status and views in the NHS Scotland context, focusing on the HRQoL and value of GS[59]. Qualitative interviews were also conducted with participants as well as with the general public to understand the experiences, views, and concerns towards the Project[55,57–59]. The combination of the quantitative and qualitative findings has provided a richer understanding of people's experiences, and offered implications for policy and practice as GS is integrated into the NHS. Empirical evidence generated from the 100,000 Genomes Project has driven the transformation process of establishing the new Genomic Medicine Service under NHS England to offer GS for patients with RDs and cancers as part of their routine clinical care. The Scottish Government has also announced a £4.2 million bridge funding package for NHS Scotland's genetics services to support future service delivery.

Australian Genomics has published the results of its first five-year national program, summarising the outcomes of genomic testing across 19 RD and cancer flagship studies[71]. GS was offered to 5273 patients with RDs and cancers and 2399 relatives to evaluate diagnostic and clinical outcomes across a broad range of clinical indications. They have achieved an average diagnostic rate of 33% in the RD flagships and have demonstrated that 48% of the findings in the cancer flagships were clinically actionable. Beyond the diagnostic and clinical implications, Australian Genomics has also set out to evaluate the psychosocial and economic outcomes for patients, families, and the healthcare system by adopting well-validated PROMs and developing their survey questions (Supplementary Table 1). In particular, they have illustrated the significant parental spillover effects of RDs by assessing the HRQoL data[72]. Another key research priority for Australian Genomics has been to evaluate the economic value of GS, including societal preferences and values, as well as its cost-effectiveness, which targets the societal efficacy domain of the Fryback and Thornbury framework. Multiple preference-elicitation studies have been conducted with the Australian general public and participants of the flagship studies using discrete choice experiment, with the value of GS estimated at AUD$1,570 to AUD$11,500 per test depending on clinical context, demonstrating the high economic value placed on GS[53,73–75]. Furthermore, GS was shown to be cost-effective and cost-saving compared to conventional diagnostic methods in multiple cohorts, providing evidence that the implementation of GS in the Australian healthcare system would be economically beneficial[76–78]. Comprehensive analyses of the socio-economic implications of incorporating genomics in the Australian context have informed evidence-based change in policy and practice, particularly in terms of increased national government funding for the transition of genomic testing to healthcare systems.

Other genome projects from China, Denmark, France, Hong Kong, Saudi Arabia, Thailand, and Turkey are expected to complete the sequence of 50,000 – 100 million participants by 2030[1,79]. Alongside the primary outcomes of diagnostic yield and clinical utility of GS in the majority of these projects, evaluating broader psychosocial and economic outcomes using quantitative and qualitative research methods may provide empirical evidence to guide health- and social-care decision making. For instance, the Hong Kong Genome Project (HKGP) established by the Hong Kong Genome Institute is the first large-scale GS project in Hong Kong, implemented to spearhead the important work of integrating genomic medicine into mainstream healthcare. Qualitative studies have been conducted to harness insights into stakeholders' views, concerns, and aspirations on issues related to GS, providing a basis for the smooth launch of the HKGP Pilot Phase in 2021[80,81]. The Pilot Phase focuses on undiagnosed diseases and hereditary cancers and has now been completed[82]. Lessons learnt from the Pilot Phase have laid the foundation for the Main Phase of HKGP and have provided further insights into the evaluation of broader psychosocial and economic outcomes using quantitative and qualitative research methods. With HKGP being the first and the largest local clinical genomic database, it creates new research opportunities for studying multi-dimensional outcomes for various diseases. The specific indicators and measurement strategies we discussed built on the six-tiered model by Fryback and Thornbury will facilitate the planning of outcome-oriented studies, aiming to inform evidence-based service delivery.

Challenges and future directions

While many studies have demonstrated the clinical benefits of genomic medicine, building evidence for psychosocial and economic outcomes is rather challenging and involves a vast array of considerations. The current approach of quantitative and qualitative outcome data collection in genomic medicine is fragmented and suboptimal, with participant-reported outcomes often lacking standardised definitions and measurement tools. This makes it difficult to compare and interpret results across different studies and healthcare settings. This is especially the case for the study of genomic medicine in underserved groups such as the RD population, where reliable and valid PROMs specifically tailored to these individuals are scarce. While generic PROMS have been applied to the RD population, a recent study

evaluating the responsiveness of SF-6D, EQ-5D-5L, and AQoL-8D in the context of genomic testing suggests that these instruments may lack responsiveness to the diagnostic, clinical and personal outcomes of genomics[83]. This highlights the need for further research to establish the measurement properties and relevant evaluative space of PROMs specifically within the context of RDs, particularly considering the unique challenges and experiences of this population. Individuals from the underserved population may also encounter more challenges in completing PROMs due to physical or mental limitations, socio-economic barriers, or literacy challenges, leading to potential exclusion from studies. Thus, PROMs need to be designed and selected in a way to capture relevant psychosocial and economic data while remaining accessible and comprehensible for patients. Tools available in both self-complete and proxy-versions may be considered more suitable to address these needs. The development of standardised outcome approaches in the foreseeable future is warranted for aggregating outcome data across study populations.

Very often, a single PROM may not provide all the necessary indicators to capture all the elements of interest to address complex research questions[84]. Most of the published studies evaluating the outcomes of GS have focused on specific domains and elements of effectiveness using various PROMs. In many studies, such as in the cases of the Genomics England 100,000 Genomes Project and the Australian Genomics initiative, more than one PROM is used to study the outcomes of GS. However, the application of multiple PROMs will increase the time for completion and potentially increase respondent burden, which will eventually lead to low compliance and data validity issues. Some previous studies suggest minimising survey length without compromising reliability and validity, especially in contexts where patients' conditions may hinder their ability to interpret and complete questions[37,85]. Failure to address issues of respondent burden risks exacerbating health inequalities and unequal access to services and resources[86].

To comprehensively assess the outcomes of GS, it is important to carefully select relevant measurement tools that address different efficacy levels, particularly for patient outcome efficacy and societal efficacy domains, where assessment of these elements could be measured in numerous ways. A standardised tool with the same constructs may not always be feasible, therefore, it is essential to balance the needs and priorities of the project with the respondent burden. We recommend that the selection of measurement tools be informed by the study population, research question and outcomes of interest, study design and cultural and contextual factors.

The specific needs and experiences of the target population should guide the selection of relevant constructs and measurement tools. This includes considering whether the focus is on patients, family members, healthcare providers, or the general population. For example, a tool designed for healthcare providers may not adequately capture the unique challenges and benefits experienced by individuals with RDs. The research question and the specific outcomes will inform the choice of measurement tools. Each outcome measure assesses unique aspects, as illustrated in this Perspective. It is important to carefully select tools that contains items necessary to address specific hypotheses.

The intended study design, whether qualitative or quantitative, cross-sectional or longitudinal, or the timing of administration (e.g. pre-test or post-test), will influence the measurement strategies and survey length. Additionally, the amount of time allotted for respondents to complete the survey is an important consideration.

Cultural differences can impact how patients perceive and report outcomes. Tools that consider cultural relevance and are available in multiple languages can enhance data quality and applicability.

Similar to the CSER consortium and the systematic review by Payne et al.[84,87], we suggest using existing validated outcome measures and minimising changes to established tools whenever possible to facilitate comparisons across studies. However, adapting materials across settings and populations for literacy and cultural sensitivity is essential. In some cases, novel measures may be necessary to assess outcomes not captured by existing tools, as demonstrated by the 100,000 Genomes Project and Australian Genomics initiative. While a universal approach may not be practical, transparency in reporting is crucial. Researchers should justify their choice of measurement tools, including the rationale for any novel measures.

Building evidence for GS to individualise treatment plans and care strategies for patients and families, as well as to guide clinical integration, requires an extensive international effort to recruit and follow large and diverse study populations. To accelerate the adoption of evidence-based service delivery, there must be an increased emphasis on implementation research, particularly regarding the psychosocial and economic impacts of GS.

The launch of genome projects worldwide will necessitate efficient methods for simultaneously collecting multi-dimensional outcomes. Future large-scale psychosocial and economic outcome studies should adopt a strategic, sustainable, and integrated evidence-based approach to create a non-burdensome data collection pathway, minimising respondent burden for patients and families.

The selection of measurement constructs and tools will largely be driven by pragmatic considerations based on what is anticipated to be most successful within the project's design and target population. For each project, we recommend establishing a Working Group to identify consensus measures based on the factors discussed. For instance, the CSER consortium formed six working groups, including the Measures and Outcomes Working Group (MOWG), to facilitate discussions aimed at harmonising measures across CSER projects[87].

Conclusions

Our approach begins with identifying outcome indicators and selecting PROMs that correspond to stakeholders' needs, encouraging collaborative multi-stakeholder efforts among patients, healthcare providers, researchers, and policymakers. In this Perspective, we highlight key factors to consider when selecting outcome measures and provide examples of outcomes selected by genome projects. This organised approach aims to equip future studies with effective strategies for planning outcome-oriented research across selected psychosocial and economic outcomes. An integrated approach facilitates the efficient collection of patient-centred psychosocial and economic outcomes alongside clinical outcomes, addressing unmet challenges at scale, harnessing the power of GS, and providing evidence to inform health- and social-care decision-making appropriately and equitably.

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Author contributions

All authors contributed to the conception of the manuscript. CCYC drafted the article. ATWC and BHYC critically reviewed and revised the manuscript. All authors contributed to the overall data interpretation, reviewed, and approved the final draft for submission.

Competing interests
The authors declare no competing interests.

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