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Commentary

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Paving the path for implementation of clinical genomic sequencing globally: Are we ready?

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Abstract

Despite the emerging evidence in recent years, successful implementation of clinical genomic sequencing (CGS) remains limited and is challenged by a range of barriers. These include a lack of standardized practices, limited economic assessments for specific indications, limited meaningful patient engagement in health policy decision-making, and the associated costs and resource demand for implementation. Although CGS is gradually becoming more available and accessible worldwide, large variations and disparities remain, and reflections on the lessons learned for successful implementation are sparse. In this commentary, members of the Global Economics and Evaluation of Clinical Genomics Sequencing Working Group (GEECS) describe the global landscape of CGS in the context of health economics and policy and propose evidence-based solutions to address existing and future barriers to CGS implementation. The topics discussed are reflected as two overarching themes: (1) system readiness for CGS and (2) evidence, assessments, and approval processes. These themes highlight the need for health economics, public health, and infrastructure and operational considerations; a robust patient- and family-centered evidence base on CGS outcomes; and a comprehensive, collaborative, interdisciplinary approach.

Key words: clinical genomic sequencing; health economics; precision medicine; global health; genomic medicine; genetic testing.

Background

Clinical genomic sequencing (CGS) has significantly changed genomic medicine and garnered global interest, owing to its ability to process large amounts of genomic data rapidly and simultaneously.[1,2] As a diagnostic tool in oncology, immunology, and rare diseases, CGS could enhance clinical care by

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offering earlier detection and reduced diagnostic odysseys, tailored treatment options, and definitive and accurate genomic etiologies and prognoses.[3-8] However, efforts to evaluate and improve implementation and access to CGS are complicated by the variability in health systems and funding capacities across countries.[9,10]

This commentary is an international, collaborative contribution to illustrate the global landscape of CGS in clinical applications and to propose economic- and policy-focused solutions where appropriate. The authors are members of the Global Economics and Evaluation of Clinical Genomics Sequencing Working Group (GEECS), which aims to improve methodologies in assessing the value of CGS to facilitate its cost-effective and equitable implementation.[11] The topics covered in this commentary reflect two themes: (1) system readiness for CGS and (2) evidence, assessments, and approval processes. We discuss several key challenges and potential solutions for addressing the slow and limited uptake of CGS globally that reflect these two themes. These challenges and solutions include the lack of harmonization and standardization around genomic data and evidentiary uncertainty about CGS, which requires centralized practices and policies with collaboration among government bodies, laboratories, health and academic institutions, and patients to create robust evidence bases and to increase patient engagement. We also consider equity and both financial constraints and incentives to support implementation of CGS and ongoing sustainability. Although some of these topics are applicable to certain countries and types of health systems, particularly in the context of economic evaluation, the general considerations regarding challenges and solutions for implementing CGS are relevant in the broad context of health policy.

System readiness for CGS

Increasing trust in CGS through review, standardization, and transparency

It is a challenge for health systems to ensure that novel medical technologies, including CGS, are safe, effective, economically viable, and trusted by patients. In the United States, concerns have emerged due to conflicting information about the limitations of genomic tests in screening for rare diseases, such as a *New York Times* report on the frequency and consequences of false-positive findings from noninvasive prenatal genetic tests.[12] These reports contributed to calls for greater review, standardization, and transparency of genomic testing through regulation.

Transparency of CGS could be furthered through publicly accessible genetic and laboratory test registries and regulatory and delivery system infrastructures.[13,14] For example, the National Institutes of Health Genetic Testing Registry (GTR) was developed to document and standardize data on registered laboratories and genetic tests.[14] Although regulatory oversight of tests and laboratories typically falls under the jurisdiction of government agencies and professional bodies, registries such as the GTR could reveal gaps and issues in the registered tests that may prompt further inquiry and action.

However, increasing review and standardization of CGS can be complicated. Although the US Food and Drug Administration (FDA) regulates clinical tests, most genomic tests are laboratory-developed tests (LDTs) that often enter the market without regulatory review.[15] On September 29, 2023, the FDA announced its intent to provide greater oversight of LDTs through the rule-making process, with an expected final issuance in 2024.[15] Their rationale specifically notes that greater oversight is needed because of patient and provider mistrust about test safety and effectiveness.

The implications of the FDA proposal are complex and spark debate on balancing innovation and accessibility with trust in tests' safety and efficacy. Numerous responses to the proposed rules have emerged, with proponents and opponents arguing their perspectives.[16] These debates—and the implications if the rule is approved—are particularly relevant to CGS tests that are classified as LDTs. Regardless of the mechanisms used and actions taken, acceptance and trust by patients are critical aspects of CGS adoption.

Considerations of equity in CGS access and outcomes

Health inequity is embedded in genomic medicine. The exclusion of minoritized populations from genomics research has resulted in disparities in genomic data across ancestral groups and subsequent repercussions in clinical care, such as higher rates of inconclusive genetic results in patients from ancestral groups outside of Europe.[17,18] Compounding data disparities, individuals belonging to underserved populations, including racial and ethnic minority groups, socioeconomically vulnerable groups, and rural populations, face limited access to CGS.[19-22] When patients in underserved population groups do receive testing, disparities in outcome-based diagnostic value and accessibility to follow-up care further perpetuate cycles of health inequity.[21] If not addressed, these challenges and the greater medical distrust in these populations[23,24] could impede the successful implementation of CGS.

Policymakers and other relevant parties must consider the impact on health equity when developing policies to implement and support CGS. Health economists can advance understanding of empirical impacts on equity by using equity-informative approaches to economic evaluation of CGS interventions. One type of equity-informative analysis is the distributional cost-effectiveness analysis (DCEA). DCEA models the distribution of health benefits and opportunity costs across population subgroups and thus allows formal assessment of tradeoffs between efficiency and equity.[25,26] DCEA can inform health policy and implementation decisions, and by projecting the expected impact of CGS on total health and health equity, it can be used to monitor these outcomes as genomics research progresses. Future research is warranted to address the data and methodological challenges of using DCEA to evaluate CGS, and the acceptability and usefulness of DCEA output to policymakers. Results of DCEA should be considered alongside other social science research on attitudes and preferences for CGS among diverse and representative populations.

Centralized, regional sequencing and institutional-level informatics and results disclosure

Creating a diagnostic sequencing service requires significant investment in equipment and supplies, retooling of laboratories, staff training, and maintaining updated bioinformatics pipelines. Variations in services across institutions and laboratory partners, based on the patient's region of residence and insurance coverage, contribute to inconsistency and inefficiency.

Establishing a single, high-volume sequencing laboratory within a region or payer jurisdiction with cloud-based data storage can reduce procurement, supply, and contract costs, and enhance standardized procedures for staff training and

pipeline maintenance and updating.[27-29] An online regional accessioning system can be created where physicians can request sequencing for their eligible patients, allowing them to have blood drawn and shipped locally.[30] Raw results can be returned to bioinformaticians working locally with a requesting medical geneticist or specialist for clinical interpretation and reporting.[31] Alternatively, interpretation and reporting may be performed at a few academic health centers, and results returned to the ordering physician. Local solutions may be limited in terms of yielding economies of scale (eg, smaller sample throughput) and may potentially be more expensive compared with a centralized system. Decisions in managing sequencing informatics would need to be considered in the context of the specific health system.

Understanding features for system implementation and financial incentives to drive uptake in practice

System readiness for CGS in practice requires an understanding of operational and logistical considerations, including the technical platform, sample collection and preparation, and the testing site and methodologies. The future use of CGS in health systems requires the following: (1) infrastructure for a community of practice involving health professionals in various specialties; (2) operational resources for innovation, coordination, and evaluation of testing and reporting services; and (3) a health care environment integrating innovation and health care delivery with educational and training support.[32-36] The implications of these health system factors for CGS extend beyond individuals to collective societal values and needs.[35,37] Evidence of differential use of genetic tests among primary care physicians reveals lower rates of referral and testing for specific patient populations in the United States.[35] These findings reflect the potential for inequitable access and uptake of CGS among different populations and care systems that result in differential utilization of CGS. Consequently, inadequate consideration of the impacts of health system factors could affect the accessibility of CGS for specific population groups differentially. Engaging public health experts and health economists can support health care decision-making and develop systems for innovation and broader, more equitable use of CGS in care and preventive applications.[32]

Recognizing the financial structures of health systems and coverage policies is also necessary, as they incentivize hospital institutions to consider and negotiate price-volume arrangements to maintain revenues. The Medicare Benefits Schedule in Australia dictates a 75% rebate for fluorescence in situ hybridization testing for patients with epidermal growth factor receptor (EGFR)–negative, non–small cell lung cancer.[38] This test can be performed and claimed multiple times, which might encourage higher claims than actual testing costs. This fee structure, therefore, does not optimize clinical practice and necessitates routine review and adjustments. Conversely, the Netherlands introduced a payment bundle that covers genomic tests with a fixed rebate, encouraging health institutions to consider clinical utility–driven testing strategies in balancing off CGS tests against inexpensive alternatives.[39] As current health technology assessment (HTA) practices can overlook how health system incentives are associated with utilization and uptake, simulation models, particularly systems dynamics, can fill this gap by analyzing time-to-treatment and total cost of care episodes under varying conditions in clinical services.[40-44]

Evidence, assessments, and approval processes

Recommendations for CGS implementation need to be evaluated for impact

Professional societies and expert consortia have issued recommendations to guide CGS implementation, addressing processes such as test requisition, data management, and clinical follow-up.[45-49] However, evaluations of these recommendations are lacking due to implementation barriers, including a lack of confidence and knowledge among health care providers, concerns about infrastructure costs within health systems, and reluctance of payers to cover and reimburse services.[22,50-53] The lack of robust evaluations from multiple stakeholder perspectives can result in conflicting implementation approaches that increase risks of unintentional harm and reduce clinical utility while increasing costs to health systems.[54-56] For example, the American College of Medical Genetics and Genomics recommends opportunistic screening of existing genomic information for additional actionable information in a "minimum gene list" whenever whole-exome or genome sequencing is conducted.[57] In contrast, the European Society of Human Genetics discourages opportunity screening, except for the purposes of evidence generation to inform future policymaking.[58] Rigorous studies of CGS are needed to better ensure that implementation recommendations optimize benefits and minimize risks.

Demonstrating the value of CGS from multiple perspectives through a combination of economic modeling, prospective trials, and real-world data analyses may be particularly important to help different stakeholders prioritize needed infrastructure. Until then, health systems would likely be wary about adopting emerging applications, payers would be reserved about covering these services,[50,59-61] and regulators would be cautious about approving their use.[61-63]

Addressing uncertainty in decision-making —"daring to change" in systems and laboratories

Insurers and payers seek answers on the added value and cost-effectiveness of CGS, but estimating monetary and patient outcomes is challenging and relies on model-based economic evaluations.[64,65] Given the complexity and scope of implementation, fully and consistently capturing the added value is not always feasible, which may lead to uncertainty in decision-making for payers, hospitals, and laboratories. This uncertainty relates to the fact that choices need to be made without having complete insight into all added values compared with current technologies. A decision is needed, followed by more improvements and valuation of CGS in the patient journey with the data available.

Apart from impacts on costs and effects for society, the educational, technical, and material requirements to support CGS implementation are also substantial, and institutions may lack confidence in their financial and human resources to adopt and sustain recommendations provided by decision-makers fully.[66-68] To prevent further delays in patients' access to innovative technologies, discussions with payers and other relevant parties are therefore needed to transition towards more suitable assessment and adoption strategies in the face of this decision uncertainty.

Implementation and usage of CGS also require laboratories to transform their workforce and design. These changes can alleviate the financial burden to meet demand, enhance testing

scope and capacity, and support ordering institutions as a valuable resource. Laboratories should consult with other stakeholders to explore solutions to address the complexities of these adjustments. Implementing CGS depends on macrolevel (eg, design, equipment) and microlevel (eg, workforce, tasks) changes in the laboratory space, and the hope that these modifications can bring changes that cannot be empirically measured but can, nonetheless, offer significant value.

A unified HTA pathway and the need for life-cycle evidence

Traditional HTA processes, designed for "on/off" health system decisions and often for drug assessments, and the siloed nature of resource allocation decisions across and within systems may limit the optimization of CGS-related health and economic outcomes.[69,70] A unified HTA pathway with model- and data-sharing is crucial to avoid opportunity costs from uncoordinated, unstandardized, and delayed prioritization of HTA assessments. Neglecting these issues may result in structural inefficiencies, with a lack of consideration for technological changes, fiscal sustainability, and evidentiary uncertainty compromising the optimal and equitable adoption of genomic technologies.[71-74]

Establishing a unified, life-cycle HTA (LC-HTA) approach towards incremental evidence development, based on real-world data, could be one approach to facilitating CGS implementation.[69,72] Life-cycle HTA is defined as standardized data and methods that enable iterative and ongoing evidence appraisals throughout technology life-cycles as part of a learning health care system.[69] Its framework incorporates standard HTA concepts with on-market evidence that follows initial regulatory authorization and conditional health system reimbursement and risk-based pricing strategies based on the value of information analysis and payers' risk tolerance for increased flexibility.[72] Managed and time-limited access in reimbursing expensive therapies is central to LC-HTA and has been piloted in many countries worldwide, including publicly funded health care systems, such as the United Kingdom, Canada, and Australia, and primarily private systems such as the United States.[75-77] Oncology remains the most common indication for managed access, and to date, agreements have yet to consider CGS access.

Achieving LC-HTA in an international context requires capacity-building and investment in learning health care infrastructure to enable ongoing monitoring, evaluation, and deliberation. It also necessitates wide stakeholder engagement for endorsement, collaborative evidence generation, and cross-jurisdictional data sharing. Life-cycle HTA deliberation processes should be embedded into health systems to adapt to the evolving field of genomic medicine. With proper design, these efforts could mitigate uncertainty and ensure value-centered and cost-effective CGS implementation in clinical practice.

Building a robust patient-centered evidence base on CGS outcomes that integrates patient perspectives and preferences

Beyond system readiness is the need for high-quality genetic-testing services that value patient and family perspectives and preferences—with patients and families being informed, respected, and involved in their care in meaningful ways throughout their clinical journey.[78,79] This journey involves numerous relationships and interactions, spanning diagnostic assessments, genomic testing, and complex decision-making processes. Therefore, effective, efficient, and equitable CGS implementation requires meaningful engagement of patients and families that facilitates active involvement and improvement in their care.[80,81]

The current evidence base on CGS outcomes focuses on a narrow subset of measures, such as diagnostic yield, rather than outcomes recommended by HTA agencies, such as quality-adjusted life-years (QALYs).[82,83] Studies generating evidence on the health outcomes of CGS using metrics such as the QALY would significantly improve the evidence base for implementation. That said, preference-based, health-related quality-of-life instruments commonly used to generate QALY weights, such as EQ-5L, might not fully capture the patient-related benefits of CGS.[84] To date, few studies have utilized instruments that thoroughly assess psychosocial outcomes or investigated the broader impacts on patients' and families' well-being (eg, via nonclinical routes). However, evidence suggests that these outcomes are highly valued by patients and families, along with access to genomic testing and a timely diagnosis.[85,86] The complexity of genomic information and actionability creates challenges for its valuation, necessitating additional consideration for non-health outcomes.[87] The application of approaches, such as cost-consequences analysis or multicriteria decision analysis—which allow evidence on QALY outcomes to be considered alongside broader measures of patient benefit—should be encouraged.

Regardless of which measures are used to quantify the benefits of CGS for patients and their families, a coordinated global effort is required to ensure a multifaceted, robust evidence base on CGS outcomes. Data collection should be harmonized, where possible, to ensure sufficient data are collected, keeping in mind, for example, relatively small rare-disease populations.[82,88]

Supplementary material

Supplementary material is available at *Health Affairs Scholar* online.

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Conflicts of interest

Please see ICMJE form(s) for author conflicts of interest. These have been provided as supplementary materials.

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