Commentary

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Challenges of Conducting Value Assessment for Comprehensive Genomic Profiling

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Abstract

Objectives: Clinical practice is shifting toward an era of precision medicine. The use of comprehensive genomic profiling (CGP) in oncology has broad potential as a universal companion diagnostic for targeted therapies which may significantly improve health outcomes while using healthcare resources more efficiently. Given the nature of this technology, assessing the value of CGP presents unique challenges.

Methods: This paper draws on evidence from the academic and policy literature in oncology, as well as stakeholder interviews (health economists, payers, clinicians, and public policy officials) in countries using incremental cost-effectiveness ratios (ICER) as part of health technology assessment (HTA).

Results: The degree to which CGP is subject to a value assessment varies significantly across healthcare systems. Current HTA processes focus on evaluating diagnostic testing through co-dependent assessment of diagnostic testing and associated therapeutic interventions. Diagnostic tests with multiple associated therapeutic interventions are rapidly evolving and poorly unsuited to current HTA approaches. Moreover, HTA approaches are limited in their ability to consider broader systemic benefits of the expanded diagnostic capabilities and enhanced opportunities for clinical trial participation offered by CGP.

Conclusions: The assessment of the overall value of CGP is limited by the current models of HTA. This paper suggests policy proposals for value assessment and funding reforms to help broaden patient access to CGP. These include investing in genomic testing infrastructure; decoupling the assessment of the value of CGP testing to identifying predetermined therapeutic interventions; tailoring evaluation methodology; and developing approaches to collecting evidence of clinical, healthcare system and societal benefit.

The emerging paradigm of precision medicine tailors clinical management to the individual characteristics of patients, reclassifying individuals into subpopulations based on predictive biomarkers for likely treatment response (1). In oncology, about 100 treatment options involve the consideration of genomic biomarkers, making oncology a leading field for precision medicine (2). In lung cancer alone, more than 12 genomic biomarkers have been identified that can be used to guide treatment selection (Figure 1). Broadly, comprehensive genomic profiling (CGP) is being used to guide the choice of therapy and is being recommended for somatic testing in oncology clinical management guidelines (3). CGP is based on next generation sequencing (NGS) and can consolidate multiple tests into a single assay (Table 1) (4). Compared to conventional single-gene testing, CGP detects a broad range of genomic alterations across multiple genes, covering known and exploratory biomarkers, from single variants to complex signatures such as tumor mutation burden in a single assay (5).

The integration of CGP into routine care in single payer systems is often dependent on the health technology assessment (HTA) processes. For four major reasons, it is arguable that HTA frameworks are not fit-for-purpose in evaluating technologies like CGP (6;7)

- Diagnostic tests are usually linked to therapeutic interventions. Most HTAs focus on evaluating single test-single process treatment class pairing. CGP links a single test to multiple interventions across treatment classes, increasing the complexity of the assessment of value.
- Beyond individual clinical benefit, CGP testing may also provide personal utility (e.g., prognosis and hope) and systems benefits (e.g., increased diagnostic accuracy), neither are formally considered in existing value frameworks (8).
- CGP can be used to guide patient participation in clinical trials. Enrolling patients in clinical trials is central to improving treatment for future patients, and participation in cancer trials
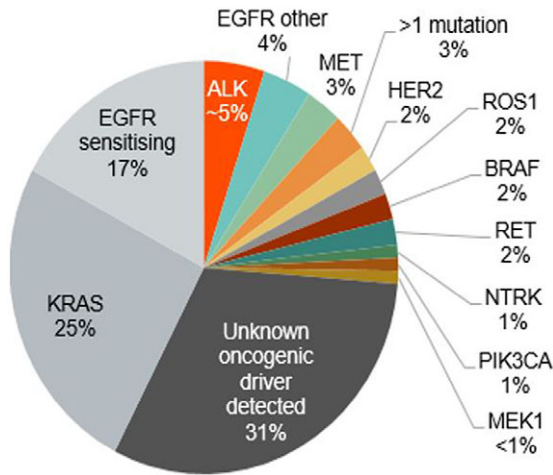
Figure 1. Common mutations in lung cancer.
Source: Adapted from Tsao et al. (9).

has been reported as being associated with improvements in survival (10). Spillover benefits such as this are not systematically considered within existing HTA frameworks.

- The value of genomic testing is dynamic and inexorably increases over time as more biomarkers, targeted therapies, and resistance mutations are identified. This creates challenges for the durability of current frameworks for value assessment.

This paper provides an overview of the current value frameworks in Australia, Canada, England, and New Zealand before identifying challenges and solutions for the evaluation of advanced diagnostic technologies like CGP.

Methods

To investigate the challenges in conducting value assessment and funding for CGP and to suggest policy proposals for reforming the access landscape to address them, a two-step methodology was adopted to develop a narrative review.

Table 1. Types of Genomic Test

Genomic test	Description
Single-gene test	Limited to specific genes (based on IHC or FISH analyses)
Multigene "hotspot" panels	Considers a small number of actionable genes in a region of interest "hotspot" panels (based on PCR or NGS analyses)
Comprehensive genomic profiling	Provides a greater depth of coverage, typically hundreds of genes within disease-associated regions of the exome (based on NGS analyses)
Whole genome or exome sequencing	Provide a fully comprehensive review of the entire genome or exome (complete coding region of the genome)
RNA sequencing	Uses targeted panels to select transcripts of clinical interest for gene expression profiling and fusion gene detection

NGS, next generation sequencing.
Source: Adapted from Yip et al. (4).

First, a literature review was undertaken from May to July 2019 to understand the current value assessment and funding mechanisms for genomic testing across four HTA countries (i.e., Australia, Canada, England, and New Zealand) and to identify the literature discussing the benefits, challenges, and potential policy solutions for assessing the value of CGP, with the objective to inform subsequent discussions with experts. The PubMed database and Google Scholar were searched using keywords, including: "precision medicine," "comprehensive genomic profiling," "next generation sequencing," "broad panel testing," "challenges," "barriers," "value assessment framework," "HTA," and "cost-effectiveness." The search was limited to English language articles. Additional records were identified through other sources, such as website searching, resulting in 130 studies to be screened. Articles were excluded if they did not focus on value assessment and/or funding of CGP. For the purpose of the paper, the literature search was updated in early 2021. Following the initial screening for eligibility, 75 peer-reviewed articles and 10 industry published or commissioned reports were retrieved for this analysis for a total of 85 unique citations (Supplementary Appendix A: PRISMA diagram).

To build on the insights from the literature review, an interview program was conducted to validate the literature findings, identify gaps in the literature, and test policy solutions for reform. Charles River Associates, an economic consultancy, was contracted to conduct the interviews. A total of 20 experts were initially identified across geographies (Supplementary Appendix B: List of experts contacted for interview). Eligible experts met at least one of three criteria: (i) research outputs relating to genomics technologies and their evaluation; (ii) experience with decision making in HTA; and (iii) membership of institutes and organizations involving the use or evaluation of genomic technologies. From this list, a total of nine experts agreed to take part in 30–60-min telephone interviews from August to September 2019. Experts included health economics and HTA experts ($n = 4$), former public payers ($n = 2$), and therapeutic area experts ($n = 3$) across Australia, Canada, England, and New Zealand. The interviews followed a semistructured discussion guide that focused on: characterizing the benefits of CGP; understanding the current process for value assessment and funding of genomic testing in each country; the associated challenges of current processes; and perceptions of future policy changes and potential solutions. The interview guide was developed drawing on insights from the literature review, and the findings were shared with the experts in these discussions for feedback (Supplementary Appendix C: Expert interview guide).

Due to the nature of the literature reviewed and the interviews, the evidence was summarized qualitatively by the four major themes covered in our interviews: (i) existing value assessment frameworks across Australia, Canada, England, and New Zealand; (ii) benefits of CGP across the care pathways; (iii) challenges in assessment of CGP using existing frameworks; and (iv) solutions to move forward to comprehensively evaluate the value of CGP. While the initial challenges and potential solutions for the value assessment of CGP were drawn from the literature and discussed in the interviews, the final recommendations proposed in this paper were not shared or validated with the experts who were interviewed. Although our search yielded 85 references, less than 40 references are only provided in the paper as per the journal requirements (Supplementary Appendix D: Full reference list).

Results

The results presented below are based on insights from both the literature review and interviews. In general, the interviews validated

the findings of the literature and there was no major disagreement noted in terms of the existing framework, clinical benefits of CGP, and challenges with evaluating CGP. However, in a few cases, the interviewees highlighted a few issues not covered in the literature. We first present the existing value frameworks and funding mechanisms for genomic testing across the four countries of interest, then highlight the benefits of CGP across the patient care pathway, and finally present the challenges identified in assessment of CGP using existing frameworks.

Existing Value Assessment Frameworks and Funding Mechanisms across Australia, Canada, England, and New Zealand

The frameworks for HTA are initially focused on medicines but now extend to all healthcare technologies, including diagnostics. Most HTA frameworks are based on an assessment of a metric called the incremental cost-effectiveness ratio (ICER) to assess the costs and benefits of introducing a new healthcare technology. Methodological guidelines published by decision-making authorities in Australia, Canada, England, and New Zealand outline preference for cost–utility analysis based on incremental cost per quality-adjusted life-year (QALY) gained (NICE 2014, PHARMAC 2015, CADTH 2019, MSAC 2021).

With the development of targeted medicines with regulatory approval as treatment for patients identified as harboring a specific genomic variant, value assessment frameworks in these four countries have expanded to consider the costs and consequences associated with funding the combined use of funding a diagnostic test and associated targeted treatment. This decision-making context directly links the value of a diagnostic with an associated treatment. For example, Australia uses a framework for reviewing co-dependent technologies (defined as combined biomarker, test, and drug reimbursement packages) (11). Concurrent evaluation is required by two independent committees (the Medical Services Advisory Committee [MSAC] and the Pharmaceutical Benefits Advisory Committee) before both the test and the associated therapy are recommended for reimbursement (12). Similarly, Canada has co-dependent technology evaluation process through the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) for oncology drugs. Standalone diagnostic value assessment processes are less common (see Table 2), limited here to the National Institute for Health and Care Excellence (NICE) in England and MSAC in Australia, which are required in order to obtain public funding. Methodological guidelines provide generalized advice to applicants to outline nonhealth benefits (if present) to supplement evidence of the direct health benefits of diagnostic tests. MSAC guidelines state that nonhealth benefits are to be considered alongside a cost–utility analysis but not within a cost–utility analysis and that conduct of cost–benefit analysis is unlikely to be helpful to the MSAC decision-making process. When applied to investigative diagnostics linked to multiple interventions, like CGP, current HTA processes based on the incremental cost per QALY metric do not capture the breadth of benefits associated with CGP (see Table 3). As discussed below, this has implications which may impact timely and equitable public access to new healthcare innovations such as CGP.

Benefits of CGP across the Patient Care Pathway

While evidence from randomized clinical trials is generally preferred by HTA bodies, there are limited large-scale, randomized controlled trials that assess clinical outcomes following treatment based on CGP compared with single-gene testing. Although a degree of uncertainty on the clinical utility of CGP remains, the clinical utility of screening for biomarker-based treatment options has been established by multiple clinical trials whose results were used to support regulatory approval of targeted treatments. The clinical utility of CGP is further recognized by several clinical guidelines including the NCCN (13) and ESMO (14) guidelines for metastatic non-small cell lung cancer which recommend panel testing for multiple biomarkers to identify patients suitable for targeted treatment. These guidelines acknowledge that multiplexed gene testing will be increasingly necessary as the number of targets increases. Several CGP assays have been approved for use as companion diagnostic assays by the FDA, including use to identify NSCLC patients who may benefit from treatment with targeted therapies (15). Given the uptake of biomarker screening using multigene panels in clinical practice (16), randomized studies of CGP are unlikely to be conducted for practical reasons.

Many benefits of CGP are not captured by HTA processes focusing on costs and benefits of single test: intervention pairings. These are summarized in Figure 2. The clinical value of CGP compared to sequential single-gene testing extends beyond the identification of predictive biomarkers. CGP can aid establishing an accurate diagnosis, provide prognostic information, as well as inform therapeutic decision-making including prioritization of subsequent treatment (17–20). Importantly, CGP can also identify patients who will not benefit from inadequate therapies (21), potentially reducing needless harm, as well as cost to the healthcare system (22). Beyond the clinical and systems benefits, CGP allows clinicians to make better-informed medical decisions in accordance with a patient's own values, interests, and preferences. In some situations, CGP may not change treatment but still provide personal or clinical utility for patients and their families (e.g., about prognosis and hope) (8).

Lastly, insights from widespread adaptation of CGP have the potential to accelerate development of novel medicines, by guiding strategic priorities for rational drug development and increasing the efficiency of clinical trials (23). Greater research and clinical trials efficiency in turn reduces the cost of drug development, the total costs of which are ultimately recouped in single payer systems by the taxpayer.

Challenges in Assessment of CGP Using Existing Frameworks

We next considered different elements of the assessment procedure identified through our literature review and interviews:

- Challenges imposed by coupling the value assessment of diagnostic testing to treatment decisions
- Challenges with HTA frameworks relying on ICER methodology
- Challenges with evidence requirements.

Codependent Assessment of Drug and Diagnostic

Current HTA is focused on comparing the costs and benefits associated with using a diagnostic test to identify patients suitable for treatment with a targeted treatment compared with no testing and use of standard treatment (24). Interviewees commented that, while feasible for a diagnostic linked to a single treatment or treatment class, this creates a significant challenge for a diagnostic linked to multiple and ever-expanding treatments. In addition, due to the breadth of targets captured on CGP panels, they may identify

Table 2. Value Assessment Process Applicable to Predictive Biomarker Testing

	Australia	Canada	England	New Zealand
Are predictive biomarker diagnostic tests subject to co-dependent evaluations?	Yes, under an integrated assessment framework for CDx	Yes, through CDR and the pCODR for oncology CDx	Yes, CDx are assessed under the NICE STA programme	No formal policy
Are there specific policies regarding value assessment of predictive biomarker tests?	No formal policy, however, a value assessment by MSAC is required in order to obtain public funding. These have been recently updated in the May 2021 MSAC guidelines	No formal policy at national level, however evidence of provincial HTA	Yes, but not mandatory. Genomic profiling cost for a new tumor agnostic drug was partially included into drug cost evaluation to share cost burden to build capacity needed between industry and healthcare system	No formal policy on HTA for diagnostics, however there is management of expenditure
Who is responsible for conducting the assessment?	The Medical Services Advisory Committee (MSAC) There is also potential for assessments at state level	Quebec—The INESSS Committee on Scientific Evaluation of Lab Tests Ontario—The Ontario Genetic Advisory Committee of the OHTAC Other Canadian provinces that have reviewed and funded oncology genetic test (e.g., Manitoba, Alberta)	The Medical Technologies Evaluation Programme (MTEP) at NICE	The Pharmaceutical Management Agency manages District Health Boards' hospital expenditures on pharmaceutical cancer treatments (PCTs)
What type of assessment is conducted?	Methodological guidelines provide generalized advice to applicants to outline nonhealth benefits (if present) to supplement evidence of the direct health benefits of diagnostic tests. MSAC guidelines state that nonhealth benefits are to be considered alongside a cost–utility analysis but not within a cost–utility analysis and that conduct of cost–benefit analysis is unlikely to be helpful to the MSAC decision-making process Formal guidance on how applicants should present evidence of nonhealth benefits and how MSAC incorporate nonhealth benefits as part of their decision making is not outlined	Cost-effectiveness evaluation based on cost/QALY and clinical validity	Cost consequence analysis on clinical and economic evidence	N/A
What is the timeline for assessment?	MSAC meets three times per year, each with an associated submission deadline	Quebec: 3–6 months under INESSS	63 weeks under MTEP	N/A
Is there an appeals process?	No evidence of an appeals process	No evidence of an appeals process	No	N/A
Other information	Only a small number of predictive biomarker tests have been approved so far through the MSAC process, with the remainder funded directly by other parties	Only Ontario has a specific mechanism for genomic tests, Quebec has developed a general evaluation methodology for molecular biology testing	NICE's Medical Technologies Advisory Committee selects products for evaluation and also recommends topics for Medtech innovation briefings, which support utilization by commissioners	

treatments still in development or under investigation in a clinical trial. This has two implications. First, trials-based therapies are an important ongoing source of therapeutic options for patients (1;25). Second, as trials-based therapies progress to reimbursed standard of care, the current single test:intervention pairing framework necessitates re-evaluation of diagnostic testing with each drug. Interviewees also added that CGP assays, which include testing of future drug targets, provide a common diagnostic platform for

Table 3. Implications of Value Assessment on Funding Predictive Biomarker Testing

	Australia	Canada	England	New Zealand
Is there mandatory funding following a positive HTA recommendation?	Yes, but only if a test has been recommended for funding by MSAC and the funding is approved by the Minister for Health	CADTH recommendations are generally not used for funding decision making. HTA recommendations in Quebec and Ontario guide provincial coverage	No	N/A
What funding mechanisms exist?	Can be included as part of the MBS	Funding decisions for genetic tests are made at provincial level, and decisions may vary across jurisdictions	The National Genomic Test Directory specifies genomic tests that are commissioned by NHS England	Regional health services open a multiyear tender for all hospital pathology services that would include a negotiated range of tests and diagnostic methodologies
Are there any conditions for funding?	Testing must be conducted entirely in Australia and in an accredited laboratory to receive funding through the MBS	Some block funding exists in Ontario and Quebec—the Ministry of Health provides some hospitals with funding for a certain volume of tests	Testing must be delivered through NHS England's network of seven GLHs	All pathology services are block-funded under an annual hospital budget
Is there evidence of reimbursement of panel testing/NGS?	There is some evidence—in 2016, the cost of Medicare-funded genetic and genomic tests was AU$43.5 million. This funding accounts for fewer than 30 genetic and genomic tests	NGS is currently available through academic medical centers in the more populated areas of British Columbia, Ontario, and Quebec but is only reimbursed in British Columbia and Ontario	The Directory has over 300 Rare Disease indications identified across 22 test technologies with ~75 panels/subpanels and 22 conditions identified for WGS	Currently, no general access to genomic testing in New Zealand, any access would be restricted to tertiary hospitals that provide specialized diagnostic services (e.g., Auckland or Christchurch)
Other information	Through this private system, there is no guarantee that any additional diagnostics and treatments are covered. Currently, there is no systematic data collection that identifies which tests are funded through these various source	The federal government has set up an annual $1 billion Healthcare Innovation Fund for new technologies, and the Ministry of Innovation is actively investing in infrastructure projects for novel healthcare technologies (including PHC and NGS)	There is no evidence of any HTA conducted by NICE on the panel testing included in the National Genomic Test Directory	Any new and expensive diagnostic technologies would likely be negotiated as out of scope of the pathology contract by the private pathology company

GLHs, Genomic Laboratory Hubs; HTA, health technology assessment; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee.

future drug approvals, bypassing the need for concurrent evaluation of a companion diagnostic test (26).

Another challenge highlighted in the interviews was designing a common value assessment that spans a broad range of rapidly evolving panel tests (27). Under the current value assessment frameworks, the value of CGP is critically dependent on the downstream benefits derived from matched therapies; thus, the constantly evolving nature of drug development creates challenges to ensuring a durable assessment of the value CGP within existing HTA approaches. Three general considerations are relevant. First, the capacity of CGP exceeds therapeutic actionability at any point of time. Second, drug development inevitably and progressively increases the net value of CGP to the patient and healthcare system. Third, drug development further induces the evolution of CGP platforms, sometimes in substantive ways. This creates the problem for the value assessment of CGP as thresholds generally accepted by HTA parties for determining cost-effectiveness will be dynamic as new patient populations and treatments reliant on genetic testing results are considered by regulatory agencies and reimbursement decision makers.

Challenges with Cost-Effectiveness Methodology

In "ICER" markets, the results of cost–utility analyses of introducing a new technology are central to funding decisions.

Implementing technologies like CGP is associated with large costs associated with equipment purchase; staff training and accreditation; bioinformatic processing, and data storage and management. These costs vary with in-house compared to send-out commercial profiling services. A Canadian analysis indicates that these range from $1,400/panel to $6,194 for a commercial send out test (28). Some costs can be offset by savings from replacing sequential/parallel single-gene testing. The value generated by CGP is both direct and indirect. Direct health benefits arising from treatment decisions based on a patients CGP results may be captured in suitably designed clinical trials incorporating assessments of health-related quality of life (e.g., through use of the EQ-5D instrument). However, the indirect benefits of CGP as a result of personal utility and the "value of knowing" (e.g., guiding future life decisions) are not routinely captured in existing quality-of-life instrument or clinical trials. As such, the incorporation of the indirect benefits of CGP as part of the overarching value assessment of CGP is limited within existing HTA frameworks with a stated preference for the conduct of cost–utility analysis based on the incremental cost/QALY gained. The important methodological challenge is to define and quantify the indirect value for patients and healthcare professionals for health technologies such as CGP which leads to multiple distinct outcomes (27;29).
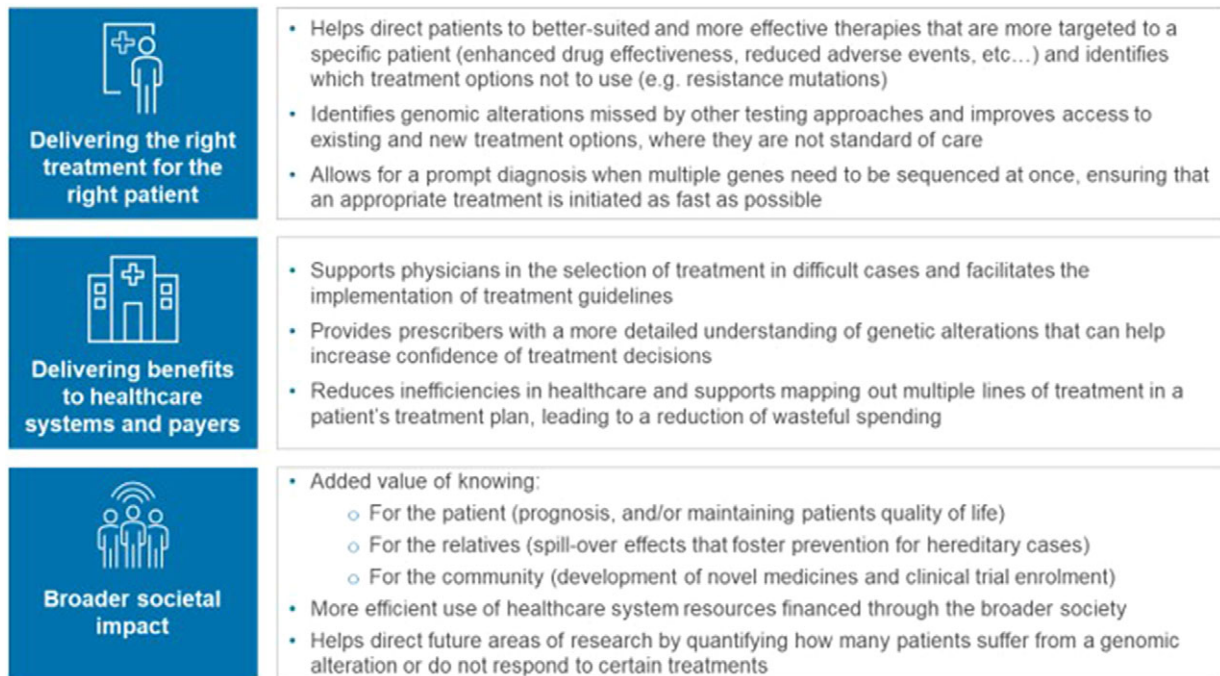
Figure 2. Summary of the potential benefits of comprehensive genomic profiling across the patient care pathway.

Challenges with Evidence Requirements

Interviews with payers highlighted that current HTA frameworks have been developed in response to well-established clinical development requirements supporting regulatory approval for new medicines and, more recently, the inclusion of diagnostics testing with a focus on evidence on the benefit of conducting specific biomarker testing in patients with only a small number of targeted treatments available (27). Interviews with health economics experts also identified that a key barrier in adopting CGP or other NGS-based technologies is the lack of payer-regulatory alignment on efficacy and effectiveness measures to guide evidence generation. For example, in Australia the Therapeutic Goods Administration (TGA) is introducing an updated regulatory framework for companion diagnostics to be fully implemented from 1 July 2022 (TGA 2020). Under this regulatory framework, the evidentiary requirements and processes to obtain regulatory approval for the use of companion diagnostic assays in Australia will differ for assays marketed by commercial manufacturers or assays developed by laboratories "in-house." The TGA is yet to publish the evidence requirements for commercial manufacturers to pursue approval of a diagnostic test as a companion diagnostic. Guidelines for preparing applications to MSAC seeking funding for diagnostic testing that would include companion diagnostics do not outline the role that the evidence used to support regulatory approval of companion diagnostic assays and their corresponding targeted treatment has in MSAC decision-making, nor how applicants should present this evidence to MSAC. This lack of payer-regulatory alignment in the evidence requirements for companion diagnostics assays, which will increasingly include CGP assays, limits that capacity for investigators (industry and academic) to design clinical trials generating evidence relating to the use of CGP that outlined as being applicable to addressing the needs of regulatory agencies and payers alike.

The complexity of benefits at the patient and healthcare system levels creates challenges in being able to collect evidence to accurately ascertain the full value that CGP delivers in a systematic fashion. Interviewees suggest that real-world evidence (RWE) is increasingly important as a means of capturing systems benefits (10). However, according to interviews with therapeutic area experts, this is challenging to acquire in public health systems and will remain limited so long as uptake of new technologies such as CGP remains low on the basis of lack of public funding (27). Overall, a fit-for-purpose framework for the collection and presentation of evidence for the broader value assessment of CGP is lacking.

Moving forward to comprehensively evaluate the value of CGP

Though CGP provides a number of benefits across the patient care pathway, challenges in the application of existing value assessment frameworks and funding mechanisms can limit impact. Here we outline policy proposals to policy makers and access decision-makers to adapt the value assessment in ICER markets and provide funding to improve patient access to CGP. As shown by the examples below, some of these policy proposals are not new although they may not have been widely applied to CGP.

Investment in Genomic Testing Infrastructure

CGP has clear potential to be clinically efficient and provides cost savings in comparison to sequential single-gene testing or hotspot testing (19). Decisions to access CGP should be part of a broader healthcare strategy to foster continuous improvement in healthcare infrastructure. Other imaging technologies in the diagnostic space, such as magnetic resonance imaging machines, have not been subject to conventional value assessment processes across markets and their implementation has been considered upgrading infrastructure (17). Decoupling the value assessment of diagnostic testing and treatments

would allow consideration of technologies such as CGP as part of investment in long-term healthcare infrastructure required for CGP (e.g., laboratories, sequencing machines).

A Flexible Approach to Value Assessment

Value assessment of CGP needs to take a broader and societal approach and consider benefits to patients and the healthcare system, as well as the economic value to the life sciences industry (7). Given the pace of change, a greater tolerance for uncertainty could be considered reasonable as part of the value assessment for CGP, that is, making the connection between the evidence available today and what that means in terms of downstream healthcare system impact and population health management impact (30). With an eye to likely future trends, the marginal cost of CGP is anticipated to reduce markedly over time as the upfront costs are spread over an increasing number of patients. Further, as the number of reimbursed targeted treatments increases, the incremental benefit for CGP underpinning those therapies should also improve. These factors result in CGP being likely to become increasingly more cost-effective over time (31). Acknowledging the scale of upfront investment requires a risk-sharing model involving governments and industry that may form a part of an overarching implementation plan for CGP. For example, the English HTA body, NICE, worked closely with NHS England and the manufacturer(s) of entrectinib and larotrectinib to address the cost of testing strategies. A "cost per patient" incorporated diagnostic testing costs into the economic model, sharing the burden between industry and the healthcare system to build capacity (32;33). An innovative approach leveraging both public and private sector co-investment in CGP and matching therapies has been announced recently in Australia (34). This public:private partnership will enable 20,000 Australians to access genome screening, coupled to expanded national trial capacity, improving health outcomes while creating more than 650 direct and indirect jobs and injecting $660 M in the Australian economy. Importantly, in this case funding for CGP has come from the Industry rather than Health Department, recognizing societal benefits beyond those considered by HTA bodies when evaluating CGP.

A Tailored Evaluation Methodology

Patient outcomes in terms of clinical benefit are central part of HTA, yet personal benefits such as the "value of knowing" are usually considered as additional factors, if at all. Downplaying societal or patient-preference measures in HTA can lead to inaccurate conclusions and funding decisions that do not truly reflect patient and societal preferences from healthcare services (35). The Professional Society for Health Economics and Outcomes Research (ISPOR) has been broadening its view on what constitutes value in health care and the benefits from new technologies (36). The ISPOR "Value Flower" indicates how different elements of value are relevant to fully assess the patient and societal gain from new technologies. Widely accepted methods for incorporating assessments of value beyond the core values of "QALYs gained" and "Net costs" in the ISPOR "Value Flower" during HTA processes are yet to be established. While current HTA processes most likely include qualitative consideration of the broader value of health technologies, ultimately a systemic approach to generating and assessing evidence pertaining to indirect benefits and patient preferences for complex technologies such as CGP should be considered as part of any HTA framework.

Funding Mechanisms that Do Not Act as a Barrier to Patient Access.

As existing HTA frameworks are limited in their ability to fully capture the value of CGP, policy makers should look to alternative funding mechanisms for CGP to minimize delays in patient access. Well-designed programs to provide block funding diagnostics services, exemplified by medical imaging technologies, address long-term funding sustainability and set clear funding pathways for these types of technologies as they are further adopted into clinical practice in the future (27). Several funding mechanisms may facilitate the adaptation of CGP into clinical practice. One example would be block funding the initial procurement of the platform infrastructure required to perform CGP in clinical practice. Given the longer-term revenue streams available to manufacturers of platform infrastructure through the sale of consumables required to perform CGP, there is an opportunity for governments to explore co-funding arrangements with commercial vendors which would offset some of the upfront cost to government cost. A further example would be for governments funding diagnostic testing through existing "fee for service" mechanisms to establish a separate program supporting laboratories with the costs associated with the procurement and maintenance of the platform infrastructure required to perform CGP. There is precedent for a program of this nature in the form of the Radiation Oncology Health Program Grants (ROHPG) operated by the Commonwealth government in Australia for the purposes of supporting capital equipment costs to service providers. Under a similar program to the ROHPG, government could pay eligible certified laboratories providing CGP with a separate payment for capital equipment costs for each CGP test performed on patients and funded through existing diagnostic testing mechanisms. Unlike block funding programs, establishing a separate funding mechanism to support laboratories to meet the capital equipment costs associated with CGP would not be associated with high upfront costs from government. Regardless of the funding mechanism applied the application of HTA principles, establishing a requirement for the collection of a minimum RWE dataset collected as part of initial funding arrangements used to establish CGP in broader clinical practice would facilitate assessments of the clinical and cost-effectiveness of CGP over time and inform the level of recurring funding provided to ensure CGP remains accessible to all indicated patients. Collecting a core dataset of real-world outcomes and developing a RWE national infrastructure is one of the key goals of the new Australian public/private partnership to create a precision oncology platform for large-scale genomic screening (36).

Conclusion

This paper identifies challenges in applying current approaches to value assessment using HTA frameworks to CGP. Governments and policy makers should consider alternative or complementary funding mechanisms to existing funding arrangement for diagnostic tests to ensure equitable access to CGP in all indicated patients. Policy proposals to address the challenges of assessing the value of CGP within an "ICER" framework include: considering costs associated with genomic testing as an infrastructure investment and exploring funding mechanisms which rely on a broader range of factors than just "cost-effectiveness" based on an assessment of incremental costs/QALY accordingly; developing a more flexible approach to value assessment including decoupling the assessment of the diagnostics to the value of subsequent treatment options;

tailoring HTA methodology to allow the inclusion of societal and patient preferences in a more robust and systematic fashion; and developing guidance to industry and academic investigators on the collection and presentation of RWE relating to the clinical, healthcare system and broader societal benefit of complex technologies such as CGP.

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