Unlocking Access to Broad Molecular Profiling: Benefits, Barriers, and Policy Solutions

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Keywords

Personalized healthcare · Comprehensive genomic profiling · Genomics · Precision medicine · Targeted therapies · Oncology · Next-generation sequencing · Value assessment · Broad molecular profiling · Value of broad molecular profiling

Abstract

Objectives: “Personalized healthcare” is generating new approaches to disease management by considering inter-individual variability in genes, environment, and lifestyle. Technologies such as comprehensive genomic profiling (CGP) are drivers of this shift. Here, we address the significant hurdles to the equitable implementation of CGP into routine clinical practice. **Methods:** This article draws on published evidence on the value of genomic profiling, as well as interviews with nine academic and clinical experts from six different countries to validate findings and test policy proposals for reforms. **Results:** The potential benefits of CGP extend beyond direct patient outcomes, to healthcare systems with societal and economic impacts. Among key barriers impeding integration into routine clinical practice are the lack of infrastructure to ensure reliable clinical testing and the limited under-

standing of genomics among healthcare personnel. In addition, the absence of health economic evidence supporting broader use of CGP is creating concerns for payers regarding the systemic benefits and affordability of this technology. **Conclusion:** Policy proposals that aim to improve equitable patient access to CGP will need to consider new funding models, health technology assessment processes that capture both patient and systemic benefits, and appropriate regulatory standards to determine the quality of genomic profiling tests.

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Introduction

The new paradigm of “personalized healthcare” has enabled new approaches to treat diseases by considering variability in genes, environment, and lifestyle for each individual [1–3]. This new ecosystem has transformed healthcare systems and shifted care delivery towards greater patient centricity, as well as a greater engagement with digital health, molecular technologies, data sharing, and data science. Genomic insights are driving this transformation, especially in oncology where >200 clinically

	Multiple Genes	SNVs	Small Indels	CNAs	Gene fusions	Large SVs
Broad Molecular Profiling	yes	yes	yes	yes	yes	no
Sanger Sequencing	no	yes	yes	no	yes	no
Quantitative PCR (qPCR)	no	no	no	yes	no	no
Paralog-ratio testing (PRT)	no	no	no	yes	no	no
Molecular copy number counting (MCC)	no	no	no	no	yes	yes
Fluorescence in situ hybridization (FISH)	no	yes	no	no	yes	yes
Immunohistochemical staining (IHC)	no	yes	no	no	yes	no

Fig. 1. Technologies like CGP integrate multiple diagnostic tests in one assay. “Yes” means able to test for the column header, and “no” means not able to test for the column header. Source: CRA analysis. CGP, comprehensive genomic profiling; Indels, insertions and deletions; SVs, structural variants; SNVs, single nucleotide variants; CNAs, copy number alterations; qPCR, quantitative polymerase chain reaction; PRT, paralog-ratio testing; MCC, molecular copy number counting; FISH, fluorescence in situ hybridization; IHC, immunohistochemical staining.

Fig. 2. CGP is a type of targeted panel that uses NGS to test multiple genes at once. Source: CRA analysis. NGS, next-generation sequencing; CGP, comprehensive genomic profiling.

relevant genomic biomarkers have been identified across diverse cancer types, making each patient’s cancer unique [4, 5]. These biomarkers are changing cancer care, from the conventional organ-based approach to one that is increasingly based on genomics, especially in advanced cancers. These biomarkers can distinguish treatment responders from non-responders and avoid adverse event reactions [6]. The shift towards personalized health has the potential not only to deliver better outcomes for patients but also to reduce healthcare spending on ineffective care [7–12].

As the number of targeted therapies inexorably increases, so does the need to clinically investigate multiple genes [13]. Broad molecular profiling technologies such as comprehensive genomic profiling (CGP) address this need by using next-generation sequencing (NGS) to rapidly and broadly detect actionable DNA mutations, copy number variations, genomic signatures, and gene fusions across the genome (Fig. 1, 2) [14]. NGS technology covers a range of assays, from panels of selected genes to whole exome and whole genome sequencing. This article focuses on the use of panel-based technologies like CGP.

Despite the potential clinical benefits, the use of these technologies has not yet expanded much beyond the research setting or to a broader use outside specialized centres. Perhaps, one exception to this can be found in the USA and to some extent in Canada, where technological advancements have now enabled targeted genomic sequencing with faster turnaround times, reduced tumour specimen requirements, and increased ease of use which has made it possible to broaden access to many hospitals, including community-based hospitals where the majority of cancer patients are diagnosed and treated [15]. Despite this, the use of NGS in small community hospitals is often not fully capitalized upon due to significant challenges related to technical expertise, bioinformatics, computing infrastructure, laboratory practices, and integration into clinical decision-making [16].

The objective of this article is to review and outline the barriers and enablers of the routine and reliable use of NGS-based technologies like CGP and to make the case for accelerating investment decisions that would assist countries in the development of a comprehensive strategy for genomic profiling. This article not only reviews the existing evidence around the clinical benefits but also assesses the benefits beyond those directly related to the patient. It is important to consider the potential impact on the ecosystem including healthcare systems and the society, especially in countries with single-payer funding models.

Materials and Methods

Our approach consisted of two components: a review of the literature on the methodological and empirical benefits of CGP and a series of interviews with experts in fields related to investigating the challenges. From these, we determined the types of solutions and policy recommendation that are expected to emerge.

A comprehensive literature review of academic peer-reviewed articles, discussion articles, and white articles available in academic and open-source databases since 2014 (including PubMed, EconLit, and Google Scholar) that have examined CGP was undertaken. Databases using a variety of keywords, including: “precision medicines,” “broad molecular profiling,” “next generation sequencing,” “broad panel testing,” “comprehensive genomic profiling,” “challenges,” “barriers,” and “value of knowing” were searched. In total, over 65 academic articles have been reviewed and six industry-published or commissioned reports. A number of pragmatic decisions were made to limit record volume, including considering articles published over the past five years (between 2015 and 2020), and we used publication metrics, study design, and conduct rather than reporting to evaluate the validity and reliability of outcome measures as a component of detection bias. We used only highly relevant search terms, restricting search terms to the title field, searching for English-language publications only and excluding publica-

tion types unlikely to yield study reports (e.g., news items). Articles were included if they (i) presented some of the benefits of genomic testing, (ii) discussed the implications of new or emerging solutions around funding or coverage of funding diagnostics services such as NGS, and (iii) discussed value elements from a health ecosystem perspective.

To complement the literature review, a set of interviews with external stakeholders was undertaken to validate findings and test policy proposals for reform. A list of experts was compiled based on prior familiarity to the authors and preliminary literature searches. Each met one of two criteria: (i) research outputs relating to genomics technologies and their integration into clinical practice and (ii) membership of institutes and organizations involving the use of genomics technologies across different healthcare settings. Nine interviews were conducted from August to October 2019 with a variety of academic and clinical experts from six different countries (Australia, Brazil, Canada, New Zealand, Switzerland, and the UK). Semi-structured qualitative interviews lasting between 30 and 60 minutes were conducted via telephone. A discussion guide was distributed to experts prior to interviews (see online suppl. Appendix A; for all online suppl. material, see www.karger.com/doi/10.1159/000520000).

Results

Benefits of CGP for Patients, Physicians, Payers, and Healthcare Systems

The primary benefit of technologies like CGP is a combination of the breadth of diagnostic data that it unlocks and the speed of diagnosis, which allows for faster and greater diagnostic accuracy on a larger number of actionable targets. This ultimately helps to direct some patients to better suited and more effective therapies, whether available as part of routine care or through triaged access to suitable clinical trials [17]. In oncology, lung cancer exemplifies the need for multiple genes to be interrogated in order to guide treatment (i.e., BRAF, EGFR, MET, ROS1, NTRK, and ALK). As illustrated in Figure 3, technologies like CGP can detect more actionable mutations than those by other diagnostic tests [18]. The biomarker-based selection of targeted treatment improves patients' outcomes compared to alternative treatment selection algorithms [19–21]. Real-world outcomes have shown that the adoption of precision medicine can have a substantial effect on survival in patients with cancer and that molecularly guided treatments and the degree of matching are independent predictors of improved oncological outcomes including survival [22, 23]. It therefore offers a rational framework to identify and treat patients based on their likelihood to respond to existing targeted therapies (e.g., anti-EGFR therapy improves survival of the patient with metastatic colorectal cancer but provides no benefit

Fig. 3. Technologies like CGP detect actionable mutations in genes that other diagnostic tests failed to detect. Source: Sample of 31 patients with lung adenocarcinomas who harboured no evidence of a genomic alteration via focused non-NGS testing. CGP, comprehensive genomic profiling; NGS, next-generation sequencing.

and even causes harm in those with RAS-mutant tumours) [24, 25].

Based on the input from interviews, physicians and payers also highlighted that technologies like CGP can facilitate appropriate treatment selection (or clinical trial options), which in turn reduces wasteful healthcare spending [26]. This increases prescriber confidence in guiding treatment selection towards more effective therapies for patients based on their individual need, leading to improved patient outcomes. This can also help identify which treatment options to not use and thus reduce the use of ineffective treatment options.

Multiple gene testing also simplifies diagnostic routine (i.e., sample collection and processing) by replacing the need for repeat diagnostic procedures. It provides fast and accurate diagnosis even in cases when biopsy samples are limited [27]. Overall, this means that less effort and resources are engaged in the pathology laboratory. Implemented into routine practice, CGP could also increase diagnostic accuracy through the incidental identification of pathognomonic markers, suggesting a different pathological diagnosis, potentially changing treatment options. For the large group of rare cancers, such as sarcomas, misdiagnosis is a common and clinically important issue in cancer care [28].

The benefits of technologies like CGP can also have a broader societal impact. The benefits of knowing may also expand beyond the individuals being tested and treated as genetic information is shared between family members (e.g., hereditary cancers) [29, 30]. Knowing the risks and chances associated with a disease can enable informed decision-making, for example, family planning, treatment adherence, or preventative measures, thereby increasing quality of life for patients [31]. Lastly, tech-

nologies like CGP can guide the development of novel medicines and help direct future areas of research by quantifying how many patients harbour certain genomic alterations or do not respond to certain treatments [32].

Another benefit of technologies like CGP, and the wider personalized healthcare paradigm, is that it opens up treatment options for patients in underserved disease areas like rare cancers. Considering the growing clinical evidence of molecular-guided treatment options across tumour types and the increasing number of clinical development programmes targeting genomic drivers, cancer patients should have an opportunity to access these innovative treatments.

Rare cancer patients represent a fifth of all reported cases of cancers, and for them, access to biomarker-driven trials represents a transformation in therapeutic options compared to trials based on histotypes [33]. Everyone should have an equal opportunity to attain their full potential for health or for the use of healthcare. Especially, as regulatory bodies increasingly approve drugs on the basis of molecular biomarkers across multiple cancer types (e.g., larotrectinib, entrectinib, and pembrolizumab), universal access to testing becomes the major barrier to better clinical outcomes when associated with the right targeted treatment option.

Key Barriers to the Adoption of CGP

Despite the benefits set out above and the value that CGP delivers, there are significant barriers that impede its broader integration into clinical practice (Fig. 4).

Lack of Infrastructure

Unlike other diagnostic tests, technologies like CGP necessitate dedicated infrastructure and qualified person-

Fig. 4. Drivers and barriers to the broad use of technologies like CGP in oncology. Source: CRA analysis. CGP, comprehensive genomic profiling.

nel to ensure their reliable clinical execution and interpretation. In many countries, this translates into several distinct challenges:

- Lack of infrastructure to support this technology due to genomic testing being limited to research centres (often with a focus on cancer)
- Limited infrastructure in terms of data capture and electronic health records
- Limited laboratory and analytic services [34–36]

Limited Access to Personalized Therapies

There is a consensus, in the literature, that a broad adoption of technologies like CGP in routine diagnostic is often limited by the low number of on-label targeted treatment options and poor coverage of personalized treatment across geographies. Physicians embrace the concept of a future cancer agnostic care in oncology and acknowledge that today this vision is challenged by restrictions in the labels of targeted treatments in various countries [37]. This places an increasing reliance on clinical trials or self-funding.

Limited Clinical Experience of Genomics

There is a consensus among stakeholders that technologies like CGP are critical to accurate diagnosis, whose benefit would be optimally realized earlier during clinical management [38, 39]. However, CGP is not commonly embedded in routine clinical practice for multiple reasons. There is a major evidentiary workforce skill and knowledge gap that must be bridged to broaden the use of NGS-based technologies beyond specialized centres

[40]. This is also linked to limited access to the appropriate clinical trials or other treatment avenues which also creates a major barrier, creating a gap in the ability to interpret test results.

Health Technology Assessment in the Era of Genomics

Current health technology assessment pathways are only applicable to well-established biomarkers in a “companion diagnostic” paradigm. According to our interviews, classical payer evaluation frameworks have not been designed to evaluate diagnostic tests that are not coupled to a specific treatment algorithm. This poses challenges for technologies like CGP, where the value of the test at the population level resides in the net benefit from multiple matched treatments.

Payers must tackle the challenge of evaluating diagnostic tests that

- can be used for multiple indications
- are used to inform the selection of a range of treatment options with outcomes and benefits that may differ (i.e., from palliative care to targeted therapies) or are yet unknown (e.g., clinical trial option)

Additionally, the treatment options considered after a diagnosis from technologies like CGP can create a dynamic challenge. The benefit of the diagnostic test progressively evolves through time as new interventions emerge or resistance mutations are discovered, while the value assessment is only evaluated at a point in time. One interesting implication of this is that the net value of CGP is only likely to rise with time, and another is the burden

this potentially places on regulators overseeing health technology assessment. All these aspects contribute to the ongoing discussion, on which value elements should be included in a value framework for broad molecular profiling in the context of precision medicine [41, 42].

Need for Greater Economic Evidence about the Total Cost Impact

Technologies like CGP rarely have a clear evidence base that highlights the long-term benefits and potential cost savings when compared to current sequential single-gene tests (e.g., potential cost offset through reduced hospitalization and optimized sequencing of therapy) [43, 44]. This is in part due to the recent emergence of the technology and in part due to the co-dependence on constantly evolving drug development as well as evolving medical and scientific knowledge, that is, resistance marker, new cancer drivers, etc. As described above, while evidence of the clinical benefit of targeted therapies is mounting, evidence for the superiority of CGP over sequential single-gene tests remains to be collected.

The main drawback to the widespread use of CGP is arguably the cost of these technologies compared to single-gene testing [45]. The relatively low level of integration in clinical practice is in part due to the scepticism of healthcare system decision-makers regarding the improvement these technologies bring to resource optimization across a complex range of different care services (i.e., pathology services, oncology care, and pharmaceutical budgets). Outside direct health benefits, routine CGP has the potential to enhance the health economy through increased clinical trials activity, for example, payers need additional data demonstrating the full value proposition. To push forward personalized medicine and targeted treatments, the status quo needs to be challenged by adapting evidence requirements in order to improve the standard of care for oncology patients.

Discussion

Given the above challenges, it is recommended that evidence-based policies be proposed to better integrate technologies like CGP into clinical practice in order to improve equitable patient access and health outcomes.

Integrating Technologies like CGP into Clinical Practice

This will require a coherent personalized medicine strategy that is articulated around the approach to disease

profiling and consideration of integration into clinical practice. The strategy should consider the following components:

Education across Policy Makers, Payers, and HCPs

A structured multidisciplinary approach is needed across stakeholders (carers, pathologists, HCPs, regulators, and healthcare decision-makers) to fully understand the value of genomic information and integrate it into clinical practice. This should also include broadening access to clinical studies outside major research centres and into small community hospitals in order to improve clinicians' understanding of how specific genomic mutations match with anticancer drugs. A discussion of how to evolve the clinical trial design and roll-out strategies should become an important part of the policy discussion, for example, designing easier-to-access trials with more real-world design components, such as the TAPUR study [46].

Data Collection, Integration, and Linkage

The implementation of genomic testing will require better linkage between molecular data, clinical decisions, and health outcomes to support evidence generation. This will enable the acquisition of real-world evidence, the quantification of benefits, and the optimization of treatment protocols. Evidence-based policy engagement needs to be enabled to incentivize data sharing across health systems to unlock access to advanced diagnostics in oncology. This will require not only alignment on standards for genomic data generation, analysis, exchange, and privacy but also the development of agreed standards for interoperability of health informatics systems [47]. Because of the broader societal value of genomics, and the desire to extend this technology beyond centres of excellence, diverse sources and types of data need to be connected.

Consolidating Diagnostic Service into a Centralized Care Centre

There is mounting evidence that cancer centres can effectively bring together the required expertise and resources to support genomic integration into the standard of care [48]. Concentrating expertise and infrastructure investment in specific centres supports the availability of specialized testing units with sufficient analytical capabilities and the systematic collection of patient information but the sufficient number of experts to interpret genomic data appropriately and provides treatment guidance. Evidence demonstrates that specialized centres of

excellence improve outcomes for patients with rare cancers in particular [49]. It is however important to note that equity of access at the level of health systems will require transfer of complex technologies from academic settings into community practice.

Collaboration between Centres as well as across Countries

Collaboration between treatment centres can help streamline guidelines, collect data, and ensure a consistent approach to testing. Collaboration will facilitate the establishment of clinical decision-making processes and the access to advanced diagnostics and personalized treatment options. More importantly, the value of CGP hinges on a predictive capability, which is reliant on how much data are accumulating and being analysed. There is an economy of scale, which is best leveraged by collaboration between centres and across countries, to include data standardization and access arrangements. Importantly, the progressive fractionation of cancers into smaller categories defined by molecular signatures means that numbers are critical to understanding the diagnostic, prognostic, and therapeutic implications for translation into clinical practice. A separate issue is interconnectivity between genomic, clinical, and health systems databases. While many professional accreditation colleges are already merged between Australia and New Zealand, showing that collaboration and standardization is routine at one level, data collection, integration, and linkage remain challenging [50].

Integration in Clinical Guidelines

Guidelines must be updated as new technologies are introduced. In certain countries, timely update of guidelines remains a challenge. Updates are generally faster in countries where guidelines play a more important role in enabling access (i.e., Denmark). Coherent legislations on a national or EU level are needed to ensure citizens to have proper access to advanced diagnostics, facilitate the design of clinical decision-making processes, and access advanced diagnostics and personalized treatment options based on the use of genomic data.

Developing New Funding Models Tailored to Technologies like CGP

As genomic profiling techniques integrate into clinical practice, screening strategies using appropriate technologies should be optimized to ensure that greater numbers of patients are quickly identified and benefited from currently available treatments. Many national programmes

are driven from the research sector, and significant investment will be needed to scale up programmes to support integration into routine care, requiring a broader infrastructure development plan [51, 52].

Investments can take one of several forms depending on the market. In some countries, testing services are integrated into hospital budgets and are covered through a diagnosis-related group-type funding which shifts cost to the provider. Other countries have opted for disease-specific funding to ensure adequate financing for diagnostic services, as part of infrastructure investment in oncology care that allows for broad and equitable access [53].

Whilst the centralized funding model of some European systems may allow for infrastructure investment and high levels of access, a diagnosis-related group approach using competitive fee-for-service laboratories may increase competition and reduce prices, thereby improving general access to personalized medicine. Ensuring that funding for diagnostic tests is available in a timely manner is key. Both centralized funding and a tariff-based approach have a role. Funding models for technologies like CGP need to consider the required investment in infrastructure and capacity development, as well as the need to encourage competition between diagnostic providers. There are unique challenges related to healthcare technologies. Policymakers could look at alternative funding mechanisms for broad molecular profiling, perhaps considering novel payment mechanisms and funding models (e.g., “investigative infrastructure” or “Netflix” business model).

Rethinking Value Assessment for Technologies like CGP

Overall, a harmonized and transparent process will support evidence-based access to these technologies. This will require a closer dialogue between payers, regulators, physicians, patients, and industries to define requirements for advanced diagnostics in cancer care, develop common understanding and definition of value drivers, and to co-create cost-effective solutions for enabling access to personalized healthcare driven by medical need.

Several experts suggested that policymakers should develop a think tank tasked with creating a value assessment process for technologies like CGP. This vehicle could consider the broader societal and system benefits, including the value of reusing aggregated genomic data for future analysis and comparison, which could be used to optimize broader health strategy [54, 55]. Others suggested that the value assessment of more accurate pathological diagnosis should be distinct from the evaluation of

CGP as a test to define eligibility for associated targeted therapies. More accurate cancer diagnoses will improve health outcomes through more effective use of conventional therapies. Assessment of technologies like CGP should be considered as part of a broader clinical management strategy. While implementing technologies like CGP has large upfront costs, these costs are often offset by reduction in inpatient hospitalization and inappropriate treatments, biopsies, and end-of-life patient support costs brought about by the benefit of these technologies [56]. Technologies have large upfront costs, and limiting the cost of technologies like CGP to individual treatment assessments may lead to significant distortions. Moreover, routine implementation of CGP has a major potential to support the life sciences economy through engagement with and support by the industry of drug development. Sustainable models of healthcare are a major priority of governments.

There is a precedent for treating these technologies separately from the associated treatments. Imaging technologies, such as magnetic resonance imaging, do not pass through conventional value assessment and evaluation processes. Their implementation has been considered an investment in infrastructure as these technologies continuously find new use cases as they enter clinical practice [57]. It is important to draw parallels between this and the implementation of technologies like CGP. National healthcare strategies should set out clear road maps for capacity building, along with protocols to facilitate the uptake and appropriate use. Through scaling up these programmes across designated centres initially, they can support the broader needs of the population [58].

Quality Standards Help to Determine the Value of Genomic Profiling Tests

Technologies like CGP create the challenge of having reached a critical stage of clinical utility, while undergoing constant and rapid development. The translation of this clinical utility into a broad implementation throughout health systems is hampered by a data gap (i.e., need for more and better integrated data on quality and affordability) [59]. In many countries, the compliance requirement around implementation of quality reporting could be improved. There is currently a lack of information on testing methods and a lack of clear data on diagnostic uptake, as well as poor oversight of the performance of labs. Collecting and publicly sharing performance data through external quality assessments will help to ensure consistent testing quality throughout Europe.

Conclusion

In the context of a paradigm shift towards “personalized healthcare,” the uptake of broad molecular profiling technologies such as CGP has the potential to bring both significant clinical benefits for patients as well as economic benefits to healthcare systems. This can occur by optimizing diagnosis and disease management, streamlining and enhancing diagnosis, and contributing to more efficient use of healthcare system resources. However, there are multiple factors that have prevented these technologies from expanding beyond the research settings, and this has resulted in disparities in the standard of care. One of the limitations of this study is that given the technology is still very much in infancy, the number of clinical, policy, and economic experts on genomics technologies is currently very limited, and the experts who took part in the interview programme were also those producing much of the peer-reviewed literature. Most of these experts are amongst those who believe in the value of this technology, and there are therefore currently few studies contradicting its value creating a possible bias.

While the clinical use of these technologies is still maturing, we set out some policy proposals to better integrate CGP into clinical practice and improve equitable patient access to genomic testing. One of the greatest challenges in delivering broader access to genomic testing will be to develop evidence that demonstrates its clinical utility and analytical validity in clinical practice. A significant investment is needed to scale up programmes in order to increase diagnostic capacity to support the broader needs of the population. Policymakers could look at alternative funding mechanisms for broad molecular profiling and create a value assessment process for CGP that also considers the broader social and economic benefits of this technology.

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Statement of Ethics

The paper is exempt from Ethical Committee approval because our research methodology consisted of a review of the literature on the methodological and empirical benefits of CGP using informa-

tion freely available in the public domain, as well as a series of interviews with experts in fields related to investigating the challenges and therefore did not include research on human or animal subjects. The analysis of datasets was obtained from other researchers, where the data are properly anonymized, and informed consent was obtained at the time of original data collection.

Conflict of Interest Statement

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Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary files. Further enquiries can be directed to the corresponding author.

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