THE UNTAPPED POTENTIAL OF COMPREHENSIVE GENOMIC PROFILING

WHY POLICYMAKERS MUST TAKE ACTION TO OVERCOME BARRIERS TO PATIENT ACCESS FOR COMPREHENSIVE GENOMIC PROFILING

RECOMMENDATIONS PROVIDED BY THE EUROPEAN COALITION FOR COMPREHENSIVE GENOMIC PROFILING

ECGP

EUROPEAN COALITION FOR ACCESS TO COMPREHENSIVE GENOMIC PROFILING

This position paper was prepared by the European coalition for access to Comprehensive Genomic Profiling (ECGP), Vintura and EUCOPE in consultation with ECGP's Steering Group.

Colophon

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EUROPEAN COALITION FOR ACCESS TO COMPREHENSIVE GENOMIC PROFILING

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EXECUTIVE SUMMARY

The introduction of biomarkers and genomically matched therapies has revolutionised our approach to cancer treatment. In addition, focus on the molecular aspects of tumours, combined with advances in high computing power and the rise of artificial intelligence (AI), will continue to drive several paradigm shifts in cancer care. Soon, it may be the tumour's molecular profile, in addition to its origin, that defines the cancer's categorisation and associated optimal treatments.

Comprehensive Genomic Profiling (CGP) – a single test for all cancer types – is highly effective for this purpose. Recent ESMO guidelines also recommend the use of broad molecular diagnostics to identify appropriate therapies.

Tumour profiling using CGP offers substantial advantages in managing molecularly complex cancers. The use of CGP enables the timely identification and administration of genomically matched therapies, which, when available, offers health-economic benefits by providing substantial clinical improvements and significantly better patient outcomes at only minor additional costs. Furthermore, CGP offers societal benefits by accelerating treatment pathways, enabling patients to rejoin the workforce more quickly and reducing the burden on caregivers.

Although significant steps have been taken in recent years to improve patient access to CGP in Europe, the full benefits are not realized today due to limited patient access. There are various preconditions for the widespread adoption of CGP in clinical practice.

- **Awareness** - Awareness of the true value of CGP compared to other iterative molecular diagnostic technologies among policymakers and other stakeholders to ensure action.
- **Appropriate assessment** - Use of health technology assessment, including cost-effectiveness analysis, for new diagnostic technologies is needed to enable policy-makers, Health Technology Assessment (HTA) Agencies and payers to compare CGP with the current standard of diagnostics.
- **Investment costs** - Understanding the need of upfront investment and the return on investment when implementing CGP in clinical practice.
- **Infrastructure needs** - The large-scale implementation of CGP requires a proper organisational and data infrastructure, including high-quality facilities and coordination between centres.
- **Capacity and capability** - Implementing CGP demands sufficient capacity and capability, specific skills in data interpretation and integration of clinical bioinformaticians and molecular biologists into healthcare teams, with discussions best conducted within a molecular tumour board.
- **Clinician-friendly data reports** - To improve the adoption of CGP, data reports need to be easier to understand and more actionable for clinicians.

Members of the European Coalition for Comprehensive Genomic Profiling (ECGP), and its Steering Group, intend to engage in constructive dialogue with European Parliament and European Commission, policy makers of European countries, Ministries of Health, HTA-agencies, and payers across Europe.

The goal is to unlock the enormous potential of CGP and to discuss **ECGP's recommendations** to stakeholders on improving patient access to CGP.

ECGP recommendations

1 **Comprehensive Genomic Profiling (CGP) enables the selection of appropriate treatment options for patients when available, thereby avoiding the use of less suitable treatments.**

A. **Engagement programmes:** Engage with policymakers about the true value of CGP compared to other diagnostics techniques, including hotspot panels, in collaboration with medical societies and patient advocacy groups.

B. **Awareness campaigns:** Develop and launch public awareness campaigns to inform patients and the general public about the availability and benefits of CGP, in collaboration with patient advocacy groups.

C. **Information campaigns:** Develop and launch information campaigns to inform healthcare practitioners on how to utilise CGP and understand the clinical data report, in collaboration with medical societies.

2 **Swift adoption of CGP requires clear funding and reimbursement pathways, both of which are currently lacking.**

A. **Assessment framework:** Develop standardized assessment frameworks for CGP across Europe in line with HTA standards, with clear and transparent evaluation criteria that focus on the timely evaluation of the benefits of CGP in indications where this is not yet established.

B. **Flexible reimbursement methods:** For indications where current evidence is sufficient e.g., cancer of unknown primary (CUP) and non-small cell lung cancer (NSCLC), evaluate the use of CGP in clinical practice for coverage in public health insurance.

C. **Funding:** For indications where more evidence is needed, allocate EU and national funds to support CGP utilisation in pilot programmes and studies for gathering evidence. Funding can be facilitated through innovative solutions such as co-financing with research funding for temporary coverage. This approach aims to kick-start the use of GCP which enables data collection without promising full funding. The collected evidence can then be used for a thorough evaluation to support long-term reimbursement.

3 **Optimal implementation of CGP requires inclusion in guidelines, enhanced (data) infrastructure, sufficient qualified rofessionals and fair procurement policies.**

A. Guidelines: Advocate for the inclusion of CGP in national treatment guidelines of medical societies and install Molecular Tumour Boards (MTBs).

B. Infrastructure and data integration: Invest in enhancing existing infrastructures and support the European Health Data Space to facilitate CGP data integration into clinical workflows.

C. Data standards: Develop and implement standardized protocols for CGP data collection across EU member states, for effective cross-country comparison.

D. People: Attract and retain professionals in the genomic health sector, initiate training development by IVD providers and professional societies, and evolve reporting and analytics tools to ensure they are easy to use.

E. Procurement Policies: Develop fair and transparent procurement policies that foster long-term competition among In Vitro Diagnostics (IVD) suppliers and laboratories, prioritizing quality and value for money.

4 **Cancer care outcomes can improve rapidly through enhanced collaboration among policymakers, industry, healthcare professionals, and patient advocacy groups, with CGP as a key enabler.**

A. Policy forums and joint initiatives: Establish regular policy forums and launch joint initiatives that bring together policymakers, industry leaders, healthcare professionals, and patient advocacy groups to discuss and develop CGP strategies.

B. Performance metrics and funding mechanisms: Enhance pan-European policy frameworks with improved metrics for implementation, linking financial resources and operational strength to project acceleration in personalized cancer care.

C. Collaborative networks: Establish collaborative networks (between academia, industry, suppliers) at national and regional levels to collaboratively work on implementation of CGP in clinical practice, facilitate knowledge sharing and rapid dissemination of best practices.

D. Inclusive design: Involve all relevant stakeholders (e.g. policy-makers, payers, HTA agencies, industry stakeholders, healthcare professionals and societies, and patients) in designing and implementing optimal care pathways.

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FOREWORD

The ECGP is a multi-stakeholder initiative that aims **to improve cancer care through increased routine clinical access and reimbursement of Comprehensive Genomic Profiling (CGP)** across Europe. The Coalition identifies and shares best practice and develops evidence-based policy recommendations on the benefits of CGP for patients, healthcare systems and society, based on multi-stakeholder and multi-disciplinary perspectives. ECGP's objective is to create multi-stakeholder consensus **to support wider CGP coverage and reimbursement** in view of the development of personalised medicine to unlock value for patients and healthcare systems.

ECGP works with a **wide range of stakeholders** to ensure that all perspectives are considered. Our Steering Group includes **patient representatives, clinical, academic and health economic experts** from key markets **across Europe.**

ECGP develops and drives the implementation of **European-level recommendations** that address the **untapped potential of CGP and provide actionable guidance for policymakers to overcome barriers to patient access to CGP**. This position paper focuses on European-level recommendations. In addition to activities at the European level, the coalition is also focusing on national-level initiatives. In Italy and Spain, the coalition is collaborating with national policymakers to **overcome barriers in patient access.** Aligned with the EU Beating Cancer Plan and Cancer Mission's call to **"leave no**

stone unturned to take action against cancer”, ECGP considers **CGP adoption essential for advancing personalised medicine.**

This **position paper** is written with support of ECGP’s Steering Group members. The Steering Group (patient representatives, clinical, academic, and health economic experts) is uniquely qualified to provide guidance on formulating the value of CGP due to their roles and expertise, which allow them to access the latest insights.

The scope of this document covers the **oncology diagnostics testing landscape in Europe** and is intended for policymakers, including members of the European Parliament and European Commission, national policy makers from European countries, Ministries of Health, HTA agencies, and payers across Europe.

“As members of pathology departments, we recognize the critical role of comprehensive genomic profiling in identifying molecular alterations and biomarkers that guide targeted therapies, ultimately improving patient outcomes. The integration of genomic data into routine diagnostics not only enhances our understanding of disease mechanisms but also paves the way for innovative therapeutic approaches.”

Dr. Beatriz Bellosillo Paricio (Hospital del Mar Barcelona)
Dr. Raed Al Dieri (European Society of Pathology (ESP))

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CONTEXT

Cancer continues to significantly impact patients, healthcare systems, and society. Europe has outlined a plan to reduce the cancer burden, incorporating clinical and technological advancements along with a clear strategy and political commitment. Yet, the full value of these advancements remains untapped, which calls for immediate action to realize the commitments from Europe's Beating Cancer Plan, EU Cancer Mission and other national initiatives.

Cancer continues to have a profound impact on patients, healthcare systems and societies across Europe. In 2022, 4.5 million people were newly diagnosed with cancer, and 2.0 million people died from the disease.[1] Cancer not only impacts patients, but also their families, caregivers, workplaces, and communities. The burden of cancer is expected to increase, with annual incidence projected to rise to 5.6 million and annual mortality to 2.8 million by 2050.[1] This will result in an estimated global economic impact of $25.2 trillion between 2020 and 2050[2], with cancer potentially surpassing cardiovascular disease as the leading cause of premature death[3]. Decisive action is needed now to reduce this significant burden on patients, healthcare systems and societies worldwide.

Europe is lagging in cancer care compared to other regions, with patients experiencing long delays in accessing newly registered cancer drugs and significant variation in the availability of essential diagnostic testing needed to match them to the right drug. On average, marketing approval for these drugs occurs 242 days later in Europe than in the United

States.[4] Once approval of a targeted therapy is granted, there is no standardised mechanism across European countries to provide access to the genomic diagnostic tests to match the drug with the right patient. The infrastructure and access to molecular diagnostic testing with Next-Generation Sequencing (NGS) are far more advanced in the United States compared to the EU.[5] In the U.S., NGS testing is widely supported by ASCO guidelines, reimbursement is covered by Medicare and, for several indications, by private insurance, and physicians report high utilizations rates.[5,6,7]

In the EU, access to and utilization of NGS are limited, with significant disparities both within and between countries[8]. In chapter 4.3 access to molecular diagnostic testing in Europe will be discussed in further detail.

Europe's Beating Cancer Plan and the EU Cancer Mission are the EU's response to this need for change and its commitment to leave no stone unturned in taking action. In 2021 the European Commission launched their political commitment aimed at reversing the cancer trend, contributing to a robust European Health Union, and ensuring a more resilient and prepared EU.[9] The plan includes more than €4 billion of funding for flagship initiatives which focus on research, innovation and digitalisation; prevention; early detection; good quality diagnosis and cancer care for all; quality of life for people with cancer and care givers; inequalities in cancer care; and specifically paediatric cancer care.[10]

It's important to recognize that this ambitious plan complements numerous national initiatives

"By integrating advanced molecular diagnostics, we can tailor therapies to the unique genetic makeup of each patient's cancer, thereby enhancing treatment efficacy and improving patient outcomes. This precision medicine approach not only offers hope for more effective interventions but also paves the way for a future where cancer treatment is increasingly personalized and data-driven."

Prof. Albrecht Stenzinger (University Hospital Heidelberg)

across Europe, each contributing to the collective effort to combat cancer. These national programs play a crucial role in addressing specific local needs.

Great advancements have changed cancer care drastically in the last decades, enabling more targeted treatment options for patients. The introduction of biomarkers and genomically matched therapies has revolutionised our approach to cancer treatment by enabling more specific treatment options for patients.[11] In 2022, a quarter of patients with advanced cancer had a specific malignant subtype eligible for genomically matched therapy. As of 2019, 70 approved cancer drugs required or recommended predictive biomarker tests, with 5-10 new approvals annually since.

The number of relevant biomarkers and molecular-guided therapies is expected to increase significantly in the coming decades due to a rich pipeline of innovations. The proportion of patients treated with genomically matched therapy is expected to exceed a third based on promising therapies in clinical development.[12]

The focus on the molecular aspects of tumours, combined with advances in high computing power and the rise of artificial intelligence (AI), is leading to a paradigm shift in cancer diagnosis. Currently, cancer treatment pathways are still highly dependent on the tumour's origin (the organ), in approximately 75% of patients this determines the treatment options[11]. In the future, it may be the tumour's molecular profile, in addition to its origin, that determines the cancer's categorisation and associated treatment options. This will further encourage the shift from using single gene or hotspot analysis for specific treatments to employing standalone broad diagnostic tools at the start of the treatment pathway. Broad molecular diagnostic tools, such as Comprehensive Genomic Profiling (CGP) – a single test for all cancer types – is highly effective for this new approach to selecting the right treatment option. With this paradigm shift, cancer care becomes more and more targeted. This evolution will also drive a shift towards the centralisation of care, creating a network of cancer centres that refer patients to specialised centres. In addition, the rise of artificial intelligence, computational power, and innovation will result in more sensitive and advanced diagnostic tools in oncology, enabling earlier and more targeted care for cancer patients.

The European Society for Medical Oncology (ESMO) supports the use of broad molecular diagnostics and has included it in its recommendations for advanced and metastatic cancer. Recent guidelines from the European Society for Medical Oncology (ESMO) indicate that the European medical community is also embracing the use of broad molecular diagnostics to identify appropriate therapies for patients with advanced or metastatic cancer. Box 1 shows the 2020 recommendations, which already included the use of NGS for patients with metastatic Non-Small Cell Lung Carcinoma (NSCLC), cholangiocarcinoma, prostate, and ovarian cancer[13]. The more recent 2024 recommendations expand this to include other advanced cancers and a wider range of cancer types, even recommending NGS for all metastatic patients where targeted treatments are available.[14]

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group (2020)

"ESMO recommends the use of tumour multigene NGS in NSCLC, cholangiocarcinoma, prostate and ovarian cancers. It is recommended to test TMB in well- and moderately-differentiated neuroendocrine tumours (NETs), cervical, salivary, thyroid and vulvar cancers. Academic research centres should perform multigene NGS as part of their missions to enable access to innovative treatments."

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group (2024)

"In this updated report, the consensus within the group has led to an expansion of the recommendations to encompass patients with advanced breast cancer and rare tumours such as gastrointestinal stromal tumours, sarcoma, thyroid cancer, and cancer of unknown primary. Finally, ESMO recommends carrying out tumour NGS to detect tumour-agnostic alterations in patients with metastatic cancers where access to matched therapies is available."

Box 1

Medical guideline recommendation for the European Society for Medical Oncology (ESMO) for the use of broad molecular diagnostics in patient with metastatic or advancer cancer.

2.1 Limited Access to CGP in Europe

Despite ESMO's recommendations, access to broad molecular diagnostics, including CGP, remains inconsistent and limited across Europe, highlighting a critical gap in equitable cancer care. While significant progress has been made in single biomarker and hotspot gene panel testing, access to comprehensive diagnostics like CGP, remains low and uneven across countries.[15,16,17,18] Recent studies highlight the uneven availability of multi-biomarker test access across the continent. In several Eastern European nations, including Bulgaria, Estonia, Latvia, Lithuania, Romania, Slovakia, and Slovenia, less than 75% of laboratories possess the capability to perform NGS in-house or through external referrals. Conversely, in countries such as Denmark, France, Germany, and the United Kingdom (UK), the availability reaches 100%, with Spain and Italy following at 83% and 67%, respectively.[15] However, a high availability of NGS does not automatically translate into greater clinical use. Utilization rates (of all biopsies analysed with NGS) vary significantly, with Denmark reporting a 50-75% uptake, France at 21%, Germany and the UK at a mere 12% and 9% respectively, and both Italy and Spain at a low 2%.[15] While specific data on CGP are lacking, they are expected to mirror or fall below current NGS utilization rates, underscoring the need for action. It highlights the intricate relationship between the availability of advanced genomic diagnostics and their integration into clinical practice, indicating that factors beyond mere accessibility play a role in their adoption.

This paper will examine the specific barriers and opportunities to improve patient access to CGP and ensure its full potential is realised.

“The integration of comprehensive genomic profiling (CGP) into routine clinical practice represents a transformative step forward in oncology, enabling more precise treatment decisions and better outcomes for patients with complex cancers.”

Prof. Antoine Italiano (Institut Bergionié, Bordeaux)

“CGP (>300 genes) is particulary useful in certain clinical situations in oncology, as for example in my routine practice in lung cancer. CGP is used to identify if patients can be included in a clinical trial. Before this could only be done via targetd NGS (~50 genes). In addition, since recently we use CGP for molecular diagnosis in never smoker patients or young patients (<45 years) with tumor progression after one or two lines of treatment. An extra benefit is that CGP can also be done in liquid biopsies.”

Prof. Paul Hofman (University Côte d’Azur, Nice)

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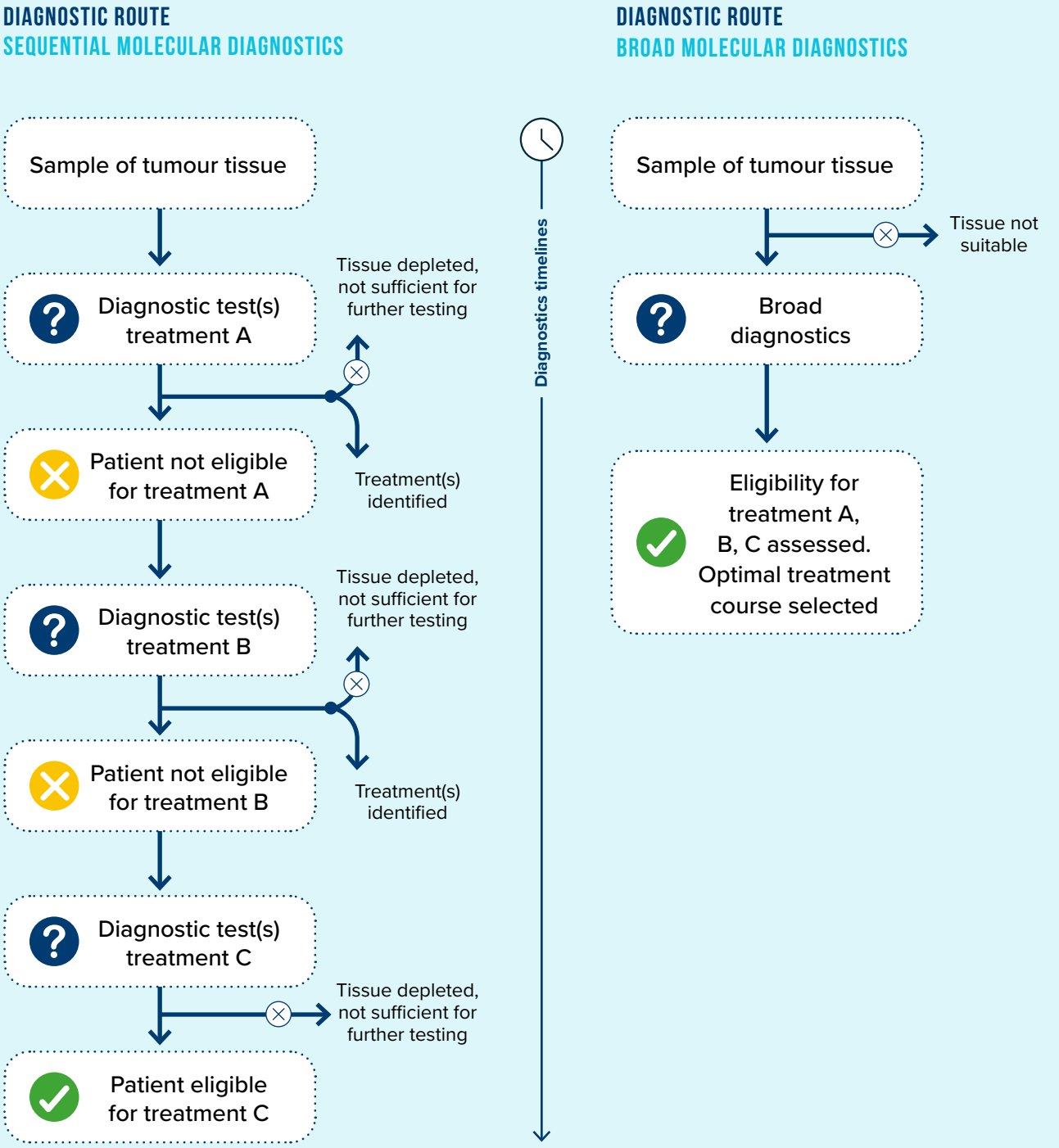
CASE FOR CHANGE

Comprehensive Genomic Profiling (CGP) is revolutionizing tumour diagnostics by consolidating multiple tests into a single, comprehensive next-generation sequencing (NGS) assay, uncovering a wide range of genomic alterations and signatures that drive cancer growth. CGP covers a wide range of tumour types and stages. Furthermore, the collection of these extensive datasets aids in identifying new biomarkers, thereby enhancing cancer care for future patients. In addition to clinical value, CGP also provides specific economic and societal benefits.

3.1 The unique value of Comprehensive Genomic Profiling

The use of CGP also changes the treatment selection route from a stepwise process involving multiple tests performed sequentially to a single test at the beginning of the diagnostic pathway. When single-gene tests (SGT) or multiple gene (hotspot panel) tests are used, they are often employed in a stepwise approach, testing first for one or a few genes changes, followed by additional tests if the initial round yields no results, as shown in Figure 1. CGP is advantageous compared to conventional tests as it requires less specimen material[19], shortens the turnaround time when multiple biomarkers need to be assessed[19], and simplifies diagnostic routine (i.e., sample collection and processing) by eliminating the need for repeat diagnostic procedures.[22] It provides fast and accurate diagnoses even when biopsy samples are limited, besides tissues samples blood samples can also be used for CGP in some indications. This approach minimizes resource demand in pathology laboratories, enhancing efficiency across diagnostics workflows.[20]

Numerous studies published over the last two decades provide strong evidence of the benefits of integrating CGP into routine care procedures, compared to the current oncological standard of care.[21]



Time to finding the optimal eligible treatment is faster because one test is performed, and the probability of finding an eligible treatment is increased because there is less tissue waste.

Figure 1

Different routes of finding the right therapy for the patient, sequential molecular diagnostics until the right treatment is found and broad molecular diagnostics with one test for all potential treatments.

Definition of Comprehensive Genomic Profiling (CGP)

CGP is a broad molecular diagnostics test, uncovering all known genomic alterations and signatures that drive cancer growth. Currently over 700 genes are known to drive cancer and this number will continue to grow in the future. A unique aspect of CGP is that it not only detects genomic alterations, but also uncovers critical genomic signatures such as tumour mutational burden (TMB), microsatellite instability (MSI) and homologous recombination deficiency (HRD), see Figure 2.

TMB measures the number of mutations in cancer cells, MSI indicates how well the DNA repair system is working, and HRD shows if the cells can effectively repair DNA breaks; all serve as important pan-oncologic biomarkers. CGP can simultaneously identify single base changes, chromosomal rearrangements, small insertions or deletions, potential fusions, and copy number variation across numerous genes with a single test. This is achieved through a combination of probes against specific targets and innovative bioinformatics applications. This simultaneous provision of comprehensive molecular data empowers healthcare providers to make the most impactful treatment decisions immediately.

Tissue biopsies are currently the predominant method for CGP. In some European countries, blood-based biopsies are currently used in clinical practice for patients unable to undergo tissue biopsy, when rapid results are needed, or when tissue quality or quantity is insufficient. In addition, NCCN guidelines in the US now include blood-based genomic profiling for 17 cancer types, demonstrating the growing acceptance of this approach.

Beyond matching the right patient to the right treatment, CGP also has potential in other clinical applications, such as the detection of Minimal Residual Disease (MRD). This enables better patient monitoring and management of disease outcomes. While applications like these are still in the clinical research phase, they hold promise for the future.

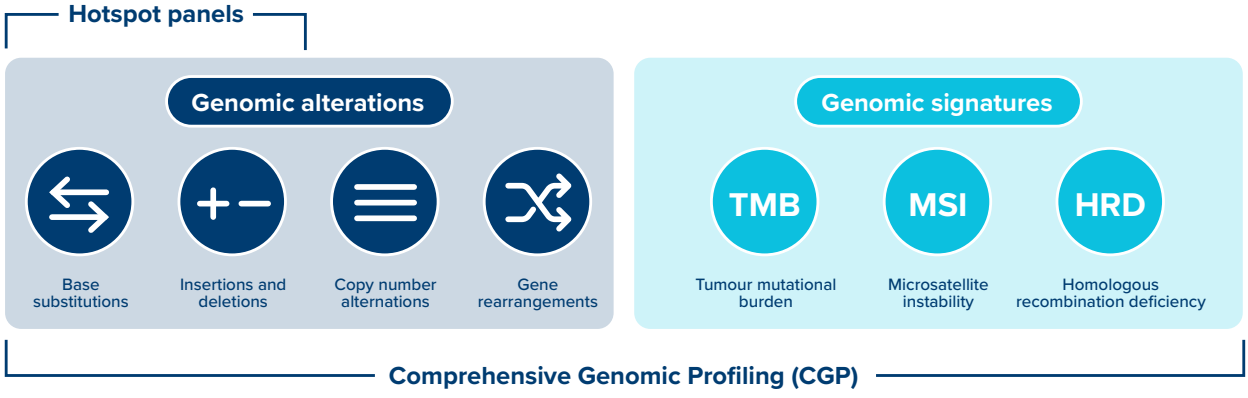


Figure 2

Comprehensive Genomic Profiling vs. hotspot panels, two types of next generation sequencing assays with different scopes

Box 2

Definition of Comprehensive Genomic Profiling (CGP)

3.2 Understanding the Benefits of Comprehensive Genomic Profiling

CGP surpasses standard diagnostic tests for cancer, offering extensive clinical, health-economic, and societal advantages. Integrating CGP into routine care is essential for advancing cancer treatment and improving patient outcomes.

3.2.1 Benefits to patients

As the development of targeted treatments accelerates, the benefits of CGP for patients will grow and become increasingly evident. Already today, CGP offers substantial advantages in managing Non-Small NSCLC, Cancer of Unknown Primary (CUP), and shows promising results in other areas, such as breast cancer brain metastasis and rare, poor-prognosis cancers, by facilitating the earlier identification and administration of appropriate molecular treatments.

CGP benefit 1 - CGP enables the selection of appropriate treatment options for cancer patients, markedly improving patient outcomes when these options are available.

For example in NSCLC, clinical studies indicate that patients undergoing CGP, as opposed to small panel testing, have more actionable alterations detected[22,23,24,25] resulting in a significantly higher proportion of patients receiving the most beneficial genomically matched targeted therapy or immunotherapy,[22,25,26] having a substantial impact on treatment options in patients with lung cancer[22]. Additionally, those treated with matched therapies exhibit improved survival rates compared to patients who did not receive matched therapies.[22,25] In the study of Scott et al., treatment initiation with genomically matched therapy after CGP showed an overall survival of 13 months, compared to 6.4 months in patients who received a non-genomically matched therapy and 5.5 months in patients who initially received early immunotherapy but had their treatment interrupted and switched to a genomically matched therapy.[27] Also the studies of Al-Ahmadi et al. and Aggarwal et al., show that tumour profiling of NSCLC using CGP significantly improves patient outcomes, by an average of 10 months[28] and up to 18 months when CGP results are obtained before first-line treatment[29]. This suggests that CGP tests are clinically helpful for making the right treatment decisions from the start in people with NSCLC.[22,27]

CGP benefit 2 - CGP offers significant advantages in the management of Cancer of Unknown Primary (CUP), a diverse group of metastatic cancers where the primary site remains unidentified despite thorough diagnostic efforts.

CUP accounts for 2-5% of all malignancies, with 80-85% falling into an unfavourable subset.[30] A recent study highlighted that genomically matched therapy, informed by CGP at diagnosis, offers a survival advantage over traditional platinum-based chemotherapy, which has been the standard of care for three decades. Patients treated with genomically matched therapies had a median progression-free survival of 6.1 months, compared to 4.4 months for those on

chemotherapy. These findings underscore the clinical utility of CGP in identifying actionable targets, thereby enabling targeted treatment strategies that improve patient outcomes. Consequently, CGP should be considered at the initial diagnosis of patients with unfavourable CUP to optimize therapeutic decisions and enhance survival rates.[30]

CGP benefit 3 - In other indications, such as breast cancer brain metastasis and rare and poor-prognosis cancers, CGP also shows promising results by ensuring the (earlier) identification and administration of the appropriate molecular treatments.

Clinical studies indicate that CGP testing and early administration of genomically matched therapies prior to standard care in untreated metastatic or recurrent tumours (including gastrointestinal, pancreatic, biliary tract, lung, breast, gynaecologic, and melanoma) provides significant clinical benefits.[31] In rare and poor-prognosis cancers where standard therapies have been exhausted, CGP testing was successful in 92% of patients and led to changes in clinical management in 31% of patients by implementing genomically guided therapy.[32] Additionally, patients with rare cancers preferentially benefited from tumour mutation profiling by increasing the chances of therapeutic response to matched therapies, and early-line treatments after profiling increase the therapeutic benefit irrespective of tumour types.[33] Additionally, patients with rare cancers preferentially benefited from tumour mutation profiling by increasing the chances of therapeutic response to matched therapies, and early-line treatments after profiling increase the therapeutic benefit irrespective of tumour types. In addition, in people with breast cancer brain metastasis (BCBM), CGP testing discovered actionable genomic alterations in 94% of the patients and actionable genomic alterations undetected in in the matched samples (primary tumour) in 31% of the patients.[34] Lastly, a study on the routine implementation of in-house comprehensive genomic profiling (CGP) for

"Rather than the cost of genomic profiling, we should focus on the cost of not profiling. Ensuring that patients are genomically profiled not only ensures they are given access to the best available therapy for their specific cancer, it also helps deliver significant economic benefit for health systems and society."

Prof. Mark Lawler (Queens University Belfast)

patients with advanced-stage solid tumours (30+ subtypes identified) found that 67% of tumours harboured actionable alterations when assessed with CGP, compared to 33% with an in silico 50-gene panel. These alterations included alterations relevant to clinical trials.[35] More studies are needed to generate additional evidence on the improvement in survival rates for these patients.

3.2.2 Benefits to the healthcare system

CGP Benefit 4 - CGP is often less costly than sequential SGT, has only a modest impact on the budget when considering other healthcare expenses as well, and is cost-effective across several indications.

Comparing the direct costs (e.g., personnel, consumables, equipment) of broad NGS-based molecular diagnostic tests, like CGP, with a sequential SGT strategy reveals that the NGS-based approach is less expensive in many cases.[36,37,38] The cost savings generated by the NGS-based approach arise from its ability to test many genes simultaneously. Consequently, as the number of alterations increases, the cost savings also rise. For example, an Italian study demonstrated that the NGS-based strategy was a cost-saving alternative to the SGT-based strategy in 94% of the cases studied (15 out of 16 cases) involving advanced non-small cell lung cancer (aNSCLC) and unresectable metastatic colorectal cancer (mCRC). The savings achieved using the NGS-based approach ranged from €30 to €1249 per patient. In the single instance where NGS was more costly, the additional expense per patient was €25.[37]

Another study, which evaluated the cost per correctly identified patient (CCIP), found that multiplex NGS was less costly compared to sequential SGT in advanced/metastatic non-squamous NSCLC, breast, colorectal, gastric cancers, and cholangiocarcinoma. In small panels, NGS is more costly.[36]

When considering not only the direct costs of the diagnostic test but also other healthcare expenses, the budget impact of CGP is not significantly higher than that of conventional testing[39]. This modest increase in cost is primarily due to the positive effect on survival and improved clinical outcomes associated with longer use of more effective treatments identified through CGP.[39] For instance, a study from a US commercial health plan perspective found that increasing CGP usage from 20% to 30% among patients with advanced NSCLC (aNSCLC) resulted in only a modest budget impact.[39] In the Canadian context, adopting CGP for aNSCLC would have a minimal budget impact.[40] Similarly, a Japanese study highlighted that CGP testing before standard of care (SoC) may improve patient outcomes in various cancer types with a limited and controllable increase in medical costs.[41]

Analysing cost effectiveness, taking into account both the budget impact and the effectiveness, CGP proves to be highly advantageous. Health-economic research comparing large-panel next-generation sequencing (LP-NGS) with SGT for first-line treatment decisions in aNSCLC patients indicated that LP-NGS lead to greater or similar quality-adjusted life years (QALYs) at a lower

cost, from a US commercial payer perspective.[42] This makes LP-NGS a dominant strategy in terms of cost-effectiveness. Additionally, multigene panel sequencing (MGPS) has proven to be more cost-effective than single-marker genetic testing (SMGT) in the US, identifying more patients who could benefit from targeted therapies.[43] These studies show that broad molecular diagnostic tests, like CGP, are cost-effective over SGT in aNSCLC.

Moreover, CGP has the potential to offer similar cost-effectiveness in other cancer indications, further enhancing its value in oncology. As the number of mutations in genes and genomic signatures tested in oncology increases, sequential single-gene testing will become more expensive. While it is uncertain when or if this will happen, the potential is significant.

CGP benefit 5 - CGP helps identify and reduce the use of ineffective treatments.

CGP has the potential to reduce waste by facilitating appropriate treatment selection or clinical trial options, thereby minimizing wasteful healthcare spending.[44] CGP not only enables the prediction of response to treatment but also identifies resistance, thereby avoiding unnecessary therapies. Furthermore, traditional treatments can be just as, if not more, burdensome due to the higher likelihood of hospital admissions.[45]

CGP benefit 6 - Widespread adoption of CGP in clinical practice contributes to a growing database of valuable cancer-related information, expanding treatment options and accelerating the development of new therapies.

This wealth of information will enhance our understanding of cancers and aid in the identification of new biomarkers.[19] Detailed genomic information from a CGP test also enables the alignment of patients with molecular-based therapies still in clinical development. By doing so, CGP expands treatment options for patients whose tumours may not respond to registered therapies, extends access to non-registered medicines, and accelerates the clinical trial process.[19] Patients may gain access to cutting-edge treatments, while principal clinical investigators gather valuable data on the efficacy of new drugs, ultimately advancing the field of oncology and improving patient outcomes.

3.2.3 Benefits to society

CGP benefit 7 - CGP contributes to societal well-being by improving labour participation among people with cancer and caregivers, driven by better treatment outcomes.

Healthier populations contribute to a more productive workforce, reducing economic burdens associated with chronic illnesses and long-term care. In the context of cancer, patients often face higher unemployment rates compared to healthy people, with disease progression and severity being key factors[46]. However, many survivors are eager and able to return to work after diagnosis and treatment, viewing employment as a sign of recovery and normalcy[47]. Employment is also linked to a higher quality of life.[47] CGP, by enabling more precise

and effective treatments, can improve survival rates and health outcomes for patients. This, in turn, can enhance their ability to return to work and maintain productivity.[40]

For instance, cancer survivors are generally more likely to face unemployment compared to healthy individuals, but effective treatments that mitigate disease progression and severity can reduce this risk. In Australia, cancer survivors aged 45–64 continue to participate in the workforce, although at lower rates than those without cancer, particularly around the time of diagnosis and treatment. By improving treatment outcomes, CGP can help mitigate these productivity losses.[48] Additionally, the labour participation of caregivers is also affected, as they often experience reduced productivity due to the time and expenses required for caregiving.[46] Effective cancer treatments facilitated by CGP can alleviate some of this burden, allowing caregivers to maintain better workforce participation. Thus, the integration of CGP into cancer care not only enhances clinical outcomes but also supports labour participation, contributing to economic stability and reducing the societal burden of cancer.

CGP benefit 8 – Lastly, the benefits of CGP extend beyond individual patients, offering societal impact through genetic insights that empower families.

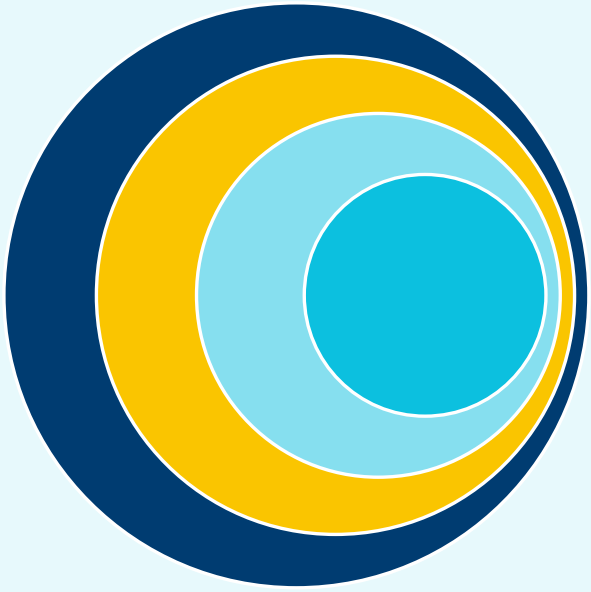
The genetic information obtained through CGP can be shared with family members, in cases of hereditary cancers, providing them with crucial insights into their own health risks. This knowledge empowers families to make

"Ensuring equitable access to comprehensive genomic profiling is crucial for the advancement of precision medicine. These diagnostics enable precise and timely identification of cancer types, allowing for tailored treatment plans that significantly improve patient outcomes. At Cancer Patients Europe, we advocate for policies that remove barriers to these essential technologies, ensuring all patients, regardless of their location or socio-economic status, can benefit from the latest advancements in cancer care."

Antonella Cardone (Cancer Patients Europe)

informed decisions regarding, for example, family planning, treatment adherence, and risk reduction measures.[30] By understanding their genetic predispositions through genetic counselling, family members can take proactive steps to manage their health, thereby improving their overall quality of life. Thus, CGP not only enhances patient outcomes but also contributes to the well-being and resilience of their families and friends.

Despite the significant benefits of CGP for patients, both now and in the future, as well as for healthcare systems and society, access to CGP testing remains limited. The next chapter discusses the preconditions for access and presents case studies.



1 **Value for current patients**
CGP brings value to patients via early identification of the right therapy

2 **Value for future patients**
CGP enables rapid knowledge development via growing database of valuable cancer-related information

3 **Value for the healthcare system**
CGP offers substantial clinical benefits and significantly improves patient outcomes, while incurring only minor additional costs compared to conventional testing strategies (like panels)

4 **Value for the society**
CGP enables patients to receive treatment more promptly, allowing both patients and caregivers to return to their work sooner

Figure 3

The multiple dimensions of benefit that the use of CGP offers

4

PRECONDITIONS FOR IMPLEMENTATION AND CASE EXAMPLES

The widespread adoption of CGP in clinical practice requires meeting several critical preconditions to ensure successful implementation and equitable access. Key preconditions include increasing awareness, clarifying evaluation pathways and criteria, managing upfront investment costs effectively, establishing robust organisational and data infrastructures, ensuring sufficient capacity and capability, and improving the user-friendliness of data reports. While several improvements to these preconditions are still needed to achieve successful implementation of CGP, there are already numerous successful examples of country pilots and projects that have made CGP available to patients. This demonstrates the potential for widespread adoption of CGP and the positive impact this will have.

4.1 Preconditions

Awareness of the true value of CGP compared to other molecular diagnostic technologies among policymakers and other stakeholders to ensure action. The lack of awareness of the true value of CGP prevents policymakers from prioritising CGP implementation in clinical practice. Additionally, uncertainty about the appropriate patient population and place in the treatment pathway complicates implementation strategies. Beyond policymakers, unequal awareness among healthcare professionals (HCPs) and patients also poses significant

challenges. Not all HCPs work in environments where the latest clinical developments are regularly discussed. If they are unaware of or uncomfortable with using CGP due to the complexity of interpreting results[49], this leads to unequal patient access. Similarly, inequity in patient awareness is problematic, especially as patient input becomes increasingly important in determining treatment pathways. Please read recommendations 1A-B in Chapter 5.1 for ECGP's proposed solutions to this issue.

Clear evaluation processes for new diagnostic technologies are needed to enable policymakers to compare CGP with the current standard of diagnostics. Molecular diagnostics is a rapidly evolving field, and many studies have highlighted the difficulties policymakers face in evaluating diagnostic technologies. Key challenges include how to view the technology in the context of the treatment pathway and how to assess the benefits at an early stage in the treatment pathway. A recent review article analysed 42 value frameworks and distilled a robust list of evidence-based criteria and sub-criteria to evaluate CGP. This set can inform policymakers on how to best evaluate diagnostic technologies and overcome their challenges.[50] In addition to difficulties in determining an appropriate evaluation framework, a lack of sufficient data to perform the evaluation could be problematic. This issue can be overcome by initiating CGP access pilots where data collection is mandatory. Finally, policymakers might also decide not to evaluate CGP due to a lack of available treatment options following the identification of biomarkers in certain types of cancer. Please read recommendations 2A-B in Chapter 5.1 for ECGP's proposed solutions to this issue.

Recognizing the need for upfront investment and understanding the return on investment when implementing CGP in clinical practice is crucial. Establishing the necessary CGP infrastructure poses a significant challenge for healthcare systems due to the initial costs. However, these expenditures can be viewed as an investment in the healthcare system. These investments will lead to value for patients, the healthcare system and society, as elaborated in Chapter 3.2. Furthermore, as the use of CGP is expected to grow in the future, the costs per test will decrease due to economies of scale, thereby increasing the return on investment. An alternative approach to upfront investment in infrastructure is to outsource molecular diagnostics to external services that provide all necessary components. Although outsourcing involves costs, it eliminates the need for investment in public sector infrastructure. Please read recommendations 2C, 3A-E and 4A-D in Chapter 5.1 for ECGP's proposed solutions to this issue.

The large-scale implementation of CGP necessitates the establishment of a proper organisational and data infrastructure. Implementing CGP for all relevant patients requires extensive infrastructure to ensure the quality and timely delivery of the diagnostic technology. This necessitates sufficient high-quality facilities and clear coordination between centres for patient referrals. This can be arranged via existing cancer networks. However, in some European countries, these infrastructures

are not present and therefore need to be created, making it challenging for policymakers to determine the appropriate organisational set-up. The optimal set-up highly depends on the size and structure of the local healthcare system. Besides an organisational infrastructure, a robust and scalable data infrastructure should also be implemented to handle the large volumes of data. When implementing new infrastructures or utilising existing structures, it is important to consider that creating an open market for diagnostic providers is necessary to ensure competition, resulting in price reductions and quality improvements. Please read recommendations 2C, 3A-E and 4A-D in Chapter 5.1 for ECGP's proposed solutions to this issue.

The large-scale implementation of CGP requires sufficient capacity and capability. The use of broad molecular diagnostics necessitates specific skills, particularly in data interpretation. This means that more bioinformaticians and molecular biologists need to be integrated into the team of healthcare professionals. The data should not only be interpreted but also discussed in a multidisciplinary setting. The best approach for discussing the results and making treatment decisions for the patient is within a molecular tumour board (MTB).[51] The process of molecular diagnostics, from requesting the technology to discussing the data in the MTB, along with the required healthcare professionals involved, is shown in Figure 4.[51] Please read

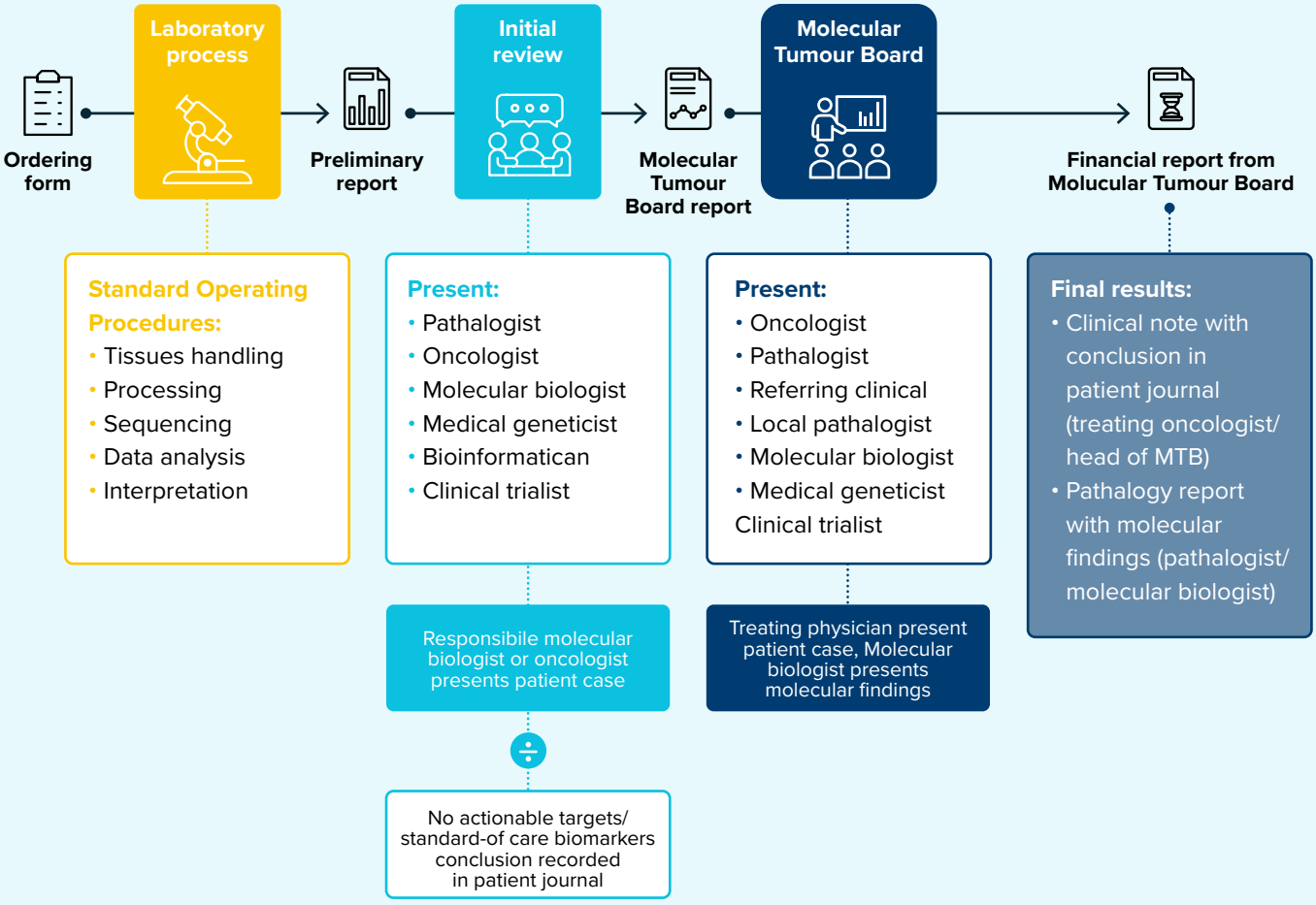


Figure 4

Blueprint of CGP workflow including HCPs involved, developed by PCM4EU[51]

recommendations 1C and 3D in Chapter 5.1 for ECGP's proposed solutions to this issue.

Data reports of broad molecular diagnostics, including CGP, need to be improved in terms of understandability and clear actionability for clinics to ensure they do not pose a barrier to adoption. There are clear signals in the field that the complexity of data reports is currently preventing oncologists from requesting CGP. To address this barrier, ESMO has developed recommendations on clinical reporting for genomic test results[52]. With a working group of international experts, van de Haar et al. have developed guidelines aimed at improving the quality and consistency of genomic reports and fostering best practices in integrating genomic testing within clinical settings.

It is important to recognise that supplementing or replacing traditional diagnostic pathways with CGP represents a significant change. Implementation requires long-term planning and investment to ensure a smooth transition, adoption among healthcare professionals, and successful integration.

4.2 Case studies on country-level and public EU-level initiatives to realise these preconditions

Across Europe, pilot programs have been launched to integrate CGP into clinical practice. These initiatives aim to address critical challenges such as data availability and uniformity, which impede the efficient evaluation and adoption of CGP and other broad molecular diagnostic tests. These programs demonstrate the feasibility of use and potential benefits of CGP, offering valuable lessons for scaling implementation across Europe.

For example, the 100,000 Genomes Project provided patients with access to Whole Genome Sequencing (WGS) to explore opportunities for precision cancer care within the UK National Health Service (NHS). The project established the infrastructure and resources necessary for linking genomic data with longitudinal clinical outcome data. It supported the commissioning of clinical WGS to detect various mutations, including pangenomic markers, with a single test to inform clinical treatment decisions for sarcoma, glioblastoma, ovarian high-grade serous carcinoma, and triple-negative breast cancers.[53] In France, a similar pilot programme, Plan France Genomique 2025, was launched, providing free access to WGS, transcriptomic and whole exome sequencing for multiple rare indications where standard diagnostic pathways did not offer solutions for patients.[54]

This programme had a significant impact on patients with otherwise difficult-to-treat diseases. Another project, Référentiel des actes Innovants Hors Nomenclature (RIHN), was initiated in France. This ongoing programme provides

temporary reimbursement for new innovative diagnostic techniques outside the standard reimbursement scheme to facilitate molecular diagnostic data collection.[55] However, the project encountered several challenges regarding data collection due to the lack of mandatory requirements.

As a result, a second programme, RIHN 2.0, was launched with clearer guidelines and frameworks for data collection. Additionally, this programme allows industry to apply for temporary reimbursement of testing, not just medical centres. A key learning for other pilot programmes is that mandatory uniform data collection should be included as a precondition for reimbursement to ensure learning opportunities. Both programmes made a significant impact in France, where the reimbursement of NGS for specific biomarkers in NSCLC received a positive recommendation.

The exact details about the reimbursement code are currently under evaluation and are expected early 2025. A pilot program, with InPreD[56] and the DRUP-like clinical trial IMPRESS-Norway[57], is successful and a renewed reimbursement scheme for broad molecular diagnostics, using large gene panels, has been implemented in the country.[58] The effective collaboration between hospitals and the centralization of care were key to the success of this reimbursement decision. Additional examples of pilot programs aimed at ensuring sufficient data to evaluate the (cost-)effectiveness of molecular diagnostics include GeNeo and BALLETT in Belgium[59], IMPaCT and the 5P Plan in Spain[60], and the recently started program GenomeDE in Germany[61]. At the European level, there are pilot programmes aimed at creating a uniform data infrastructure, such as the European Genomic Data Infrastructure project.[62] Collecting uniform data points across Europe can save time and resources for individual countries, enabling more efficient use of resources.

“CGP is transforming cancer care by broadening access to innovative treatments and clinical trials. The BALLETT study underscores this potential, calling on policymakers to ensure its accessibility for all patients.”

Dr. Brigitte Maes (Jessa Hospital, Hasselt)

Pilot programs were also launched to address the implementation challenges that arise when deploying CGP as an oncology diagnostic tool for patients on a large scale. At the European level, a project was launched in January 2023, involving a collaboration of 15 partners across 17 European countries, named the PCM4EU consortium. The consortium aims to enhance knowledge and accessibility to cutting-edge cancer diagnostics and treatments, ultimately improving the quality of life and survival rates for people with cancer. To realise this, the consortium is specifically focussing on Flagship No. 6, "Cancer Diagnostic and Treatment for All," of the EU Beating Cancer Plan.[63]

The consortium shares their insights via scientific publications. The most recent publication, set to be released at the end of 2024, discusses the need for Molecular Tumour Boards (MTBs) to review diagnostic results and select the appropriate genomically matched therapy.[51]

Country specific pilot programs focused on implementation challenges include InPreD[56] & CONNECT[64] in Norway, and Genomic Medicine Sweden[65].

Policymakers and national health systems do not have to tackle these challenges alone. It is important to recognise that partnerships can add significant value, particularly in addressing implementation challenges. There are various well-functioning diagnostic networks that can be utilised in partnerships or reviewed for insights and best practices.

These diverse European and local initiatives underscore the commitment of policymakers to expanding patient access to diagnostic technologies such as CGP. In the following chapter, we will provide recommendations on how patient access to CGP can be further improved.

5

ENGAGEMENT IN CONSTRUCTIVE DIALOGUE TO CREATE PATIENT IMPACT AND STRENGTHEN THE EUROPEAN LIFE SCIENCE SECTOR

Cancer remains a critical and escalating challenge in Europe, demanding urgent action to reduce further burden on patients and healthcare systems. Technological advancements – such as CGP – offer promising solutions to combat cancer, improving patient outcomes and holding substantial potential for impact. However, due to the limited availability of CGP for patients this potential is not fully realized. Policymakers face several barriers for the widespread adoption of CGP in clinical practice. Still, the specific country examples demonstrate the great willingness of policymakers to make changes for improved patient access to CGP.

Members of the European Coalition for Comprehensive Genomic Profiling (ECGP), along with the Steering Group, aim to engage in constructive dialogue and collaborate with key stakeholders and policymakers across Europe. This includes Members of the European Parliament and European Commission, national politicians, Ministries of Health, HTA agencies, and payers. The goal is to unlock the enormous potential of the wider introduction of CGP and to discuss the ECGP statements and recommendations.

Realising the ECGP recommendations will strengthen Europe's innovation landscape and enhance the competitiveness of its Life Science sector. Incorporating patient access to CGP as a core objective of the EU's new European Life Sciences Strategy and establishing CGP as a cornerstone of precision medicine will solidify Europe's leadership in Life Science on the global stage. In addition, now it is important to leverage the European Commission's initiative to pass a European Biotech Act to boost biotechnology and biomanufacturing in the EU by collaborating with involved stakeholders.

5.1 ECGP recommendations

The ECGP recommendations are linked to the preconditions discussed earlier in this paper. The awareness precondition is addressed by recommendations 1A-B. The evaluation methodology precondition is addressed by recommendations 2A-B. The investment costs as well as the infrastructure needs preconditions are addressed by recommendations 2C, 3A-E and 4A-D. The capacity and capability precondition is addressed by recommendation 1C and 3D. The clinical-friendly data report is addressed by recommendation 1C.

1 **Comprehensive Genomic Profiling (CGP) enables the selection of appropriate treatment options for patients when available, thereby avoiding the use of less suitable treatments.**

A. Engagement programmes: Engage with policymakers about the true value of CGP compared to other diagnostics techniques, including hotspot panels, in collaboration with medical societies and patient advocacy groups.

B. Awareness campaigns: Develop and launch public awareness campaigns to inform patients and the general public about the availability and benefits of CGP, in collaboration with patient advocacy groups.

C. Information campaigns: Develop and launch information campaigns to inform healthcare practitioners on how to utilise CGP and understand the clinical data report, in collaboration with medical societies.

2 **Swift adoption of CGP requires clear funding and reimbursement pathways, both of which are currently lacking.**

A. Assessment framework: Develop standardized assessment frameworks for CGP across Europe in line with HTA standards, with clear and transparent evaluation criteria that focus on the timely evaluation of the benefits of CGP in indications where this is not yet established.

B. Flexible reimbursement methods: For indications where current evidence is sufficient e.g., cancer of unknown primary (CUP) and non-small cell lung cancer (NSCLC), evaluate the use of CGP in clinical practice for coverage in public health insurance.

C. Funding: For indications where more evidence is needed, allocate EU and national funds to support CGP utilisation in pilot programmes and studies for gathering evidence. Funding can be facilitated through innovative solutions such as co-financing with research funding for temporary coverage. This approach aims to kick-start the use of GCP which enables data collection without promising full funding. The collected evidence can then be used for a thorough evaluation to support long-term reimbursement.

3 **Optimal implementation of CGP requires inclusion in guidelines, enhanced (data) infrastructure, sufficient qualified rofessionals and fair procurement policies.**

A. Guidelines: Advocate for the inclusion of CGP in national treatment guidelines of medical societies and install Molecular Tumour Boards (MTBs).

B. Infrastructure and data integration: Invest in enhancing existing infrastructures and support the European Health Data Space to facilitate CGP data integration into clinical workflows.

C. Data standards: Develop and implement standardized protocols for CGP data collection across EU member states, for effective cross-country comparison.

D. People: Attract and retain professionals in the genomic health sector, initiate training development by IVD providers and professional societies, and evolve reporting and analytics tools to ensure they are easy to use.

E. Procurement Policies: Develop fair and transparent procurement policies that foster long-term competition among In Vitro Diagnostics (IVD) suppliers and laboratories, prioritizing quality and value for money.

4 **Cancer care outcomes can improve rapidly through enhanced collaboration among policymakers, industry, healthcare professionals, and patient advocacy groups, with CGP as a key enabler.**

A. Policy forums and joint initiatives: Establish regular policy forums and launch joint initiatives that bring together policymakers, industry leaders, healthcare professionals, and patient advocacy groups to discuss and develop CGP strategies.

B. Performance metrics and funding mechanisms: Enhance pan-European policy frameworks with improved metrics for implementation, linking financial resources and operational strength to project acceleration in personalized cancer care.

C. Collaborative networks: Establish collaborative networks (between academia, industry, suppliers) at national and regional levels to collaboratively work on implementation of CGP in clinical practice, facilitate knowledge sharing and rapid dissemination of best practices.

D. Inclusive design: Involve all relevant stakeholders (e.g. policy-makers, payers, HTA agencies, industry stakeholders, healthcare professionals and societies, and patients) in designing and implementing optimal care pathways.

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