Unlocking the potential of precision medicine in Europe

Improving cancer care through broader access to quality biomarker testing

Policy recommendations   February 2021

IQNPath
International Quality Network for Pathology

European Cancer
Patient Coalition

efpia

L.E.K.

A. About this report

This report represents the outcomes of the IQN Path, ECPC and EFPIA initiative to "improve cancer care through broader access to quality biomarker testing". The goal of this initiative is to identify barriers to biomarker testing in EU27 and the UK and to develop policy recommendations in order to ensure that all eligible cancer patients have access to the ideal testing paradigm: high-quality biomarker testing that is readily available to all cancer patients without compromising on the numbers of genes analysed, with new tests rapidly integrated into the standard of care.

The project was initiated and financed by IQN Path, ECPC and EFPIA together with a consortium of industry and academic partners. The project was supported by research and analysis conducted by L.E.K. Consulting.

About IQN Path

IQN Path is an international multi-stakeholder expert group focused on improving quality of clinical biomarker testing, bringing together organisations and key stakeholders involved in quality implementation of biomarker testing in pathology globally.   https://www.iqnpath.org

About ECPC

European Cancer Patient Coalition is the voice of cancer patients in Europe. With over 450 members, ECPC is Europe's largest umbrella cancer patients' association, covering all 27 EU member states and many other European and non-European countries. ECPC represents patients affected by all types of cancers, from the most common to the rarest.   https://ecpc.org/

About EFPIA

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the biopharmaceutical industry operating in Europe. Through its direct membership of 36 national associations, 39 leading pharmaceutical companies and a growing number of small and medium-sized enterprises (SMEs), EFPIA's mission is to create a collaborative environment that enables our members to innovate, discover, develop and deliver new therapies and vaccines for people across Europe, as well as contribute to the European economy.   https://www.efpia.eu/

This report was prepared with the support of L.E.K. Consulting. L.E.K. Consulting is a global management consulting firm. The firm advises and supports organizations that are leaders in their sectors, including the largest private- and public-sector organizations, private equity firms, and emerging entrepreneurial businesses. Founded in 1983, L.E.K. employs more than 1,600 professionals across the Americas, Asia-Pacific and Europe.   https://www.lek.com/

B. Executive summary

Inconsistent biomarker test access – a barrier to realising the promise of precision medicine

The advances in our understanding of cancer over the last two decades have been fundamental, highlighting huge variability between patients even within the same cancer type and emphasising the need for tailoring cancer care to individual patient characteristics. Precision medicine, a healthcare approach that systematically uses patient data to inform personalised treatment decisions, has emerged as potentially transformative – offering the promise of superior treatment outcomes for all cancer patients. Precision medicine is supported by significant advances in biomarker testing[1], with next generation sequencing[2] allowing the detection of genomic alterations which drive tumour development and providing critical insights into a patient's likely response to treatment. Yet, the promise of precision medicine cannot be realised if patients do not have access to the biomarker testing required to determine their eligibility for precision medicine treatments.

Access to high quality[3] oncology biomarker testing is inconsistent across Europe and contributes to an imbalance in health equity across the EU27 + UK.

Without immediate and concerted action to ensure the provision of adequate testing across countries, it is impossible to harness the full benefits of precision medicine.

Approach

This report presents the results of research conducted in 2020 to assess the current status of biomarker testing in the EU27 and the UK, identify country-specific shortcomings and develop policy recommendations to improve access to and quality of biomarker testing in oncology across Europe. The report assesses a selection of key biomarkers[4], both established and novel, according to four access metrics (laboratory access, test availability, test reimbursement, test order rate) and three quality metrics (quality scheme participation, laboratory accreditation, test turnaround time). It draws on a wide range of secondary sources, surveys of 141 laboratory managers and of 1,665 patients, and 58 in-depth interviews with laboratory managers, physicians, and payers. The findings were reviewed over a series of meetings with IQN Path, ECPC and EFPIA stakeholders and a consortium of pharmaceutical industry and academic partners, as well as a sounding board with key opinion leaders, in order to develop an unbiased view of existing test access barriers and to establish a consensus on critical policy recommendations for immediate, concerted action.

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[1] A biomarker is a biological characteristic that is objectively measured and evaluated as an indicator of biological processes. "Biomarker" refers to any molecule in the human body that can be measured to assess health. Molecules can be derived from blood, body fluids or tissue. A biomarker test is a biochemical measurement developed to quantitate one, or several, biomarkers for the screening, diagnosis and/or prognosis of cancer patients

[2] Next generation sequencing (NGS): large-scale DNA sequencing technology in which millions of nucleotide sequences are deciphered simultaneously. Allows for querying the entire genome (whole genome), the exons within all known genes (whole exome) or only exons for selected genes (target panel)

[3] Effective use of biomarker tests and applying high quality testing standards are fundamental to deliver on precision medicine. The clinical use of reliable biomarker tests to guide therapy selection depends on many related processes. A number of processes before and following clinical laboratory testing need to be considered (i.e. analytical validation, clinical validation, specimen handling, reproducibility, IT infrastructure), which can affect the accuracy and reliability of test results and patient safety. This is even more critical for advanced diagnostic technologies, such as next generation sequencing or digital pathology, which build on extensive bioinformatics and/or AI based algorithms. On top of this, External Quality Assurance (EQA) programmes are key to keep testing standards high and ensure patients can benefit from precision medicine [44-49]

[4] Single biomarker tests: PD-L1, HER2, ALK, MMR / MSI, BRCA, EGFR, NTRK, BRAF, KRAS / NRAS; multi-biomarker tests: NGS hotspot (up to 50 genes) / targeted panel, NGS comprehensive panel (>50 genes); liquid biopsy

Barriers to accessing high-quality biomarker testing

Six key barriers need to be overcome as a matter of urgency to allow patients, physicians and healthcare systems across the EU27 and the UK to realise the benefits of biomarker testing and to establish health equity across Europe.

- **Limited availability of precision medicine linked to biomarkers:** Reimbursed access to precision medicine is a prerequisite for biomarker testing, as tests are usually only ordered if they inform treatment decisions. Delays between medicine approval by the European Medicines Agency (EMA) and inclusion in national or regional reimbursement lists can be significant. EFPIA's Patients W.A.I.T. indicator Survey[5] shows that the average time to patients' treatment access across the EU and the European Economic Area is 504 days, but ranges from 127 days in Germany to over 823 days in Poland [10]. In addition, public funding of precision medicine is insufficient in some countries.

- **Unclear value assessment approaches for diagnostic tests** lead to delays in the integration of testing into clinical practice in many countries. Key challenges include:

  - Cost- or technology-based test reimbursement codes, with no appraisal in place to assign a value-based code towards a new diagnostic application, resulting in insufficient reimbursement value

  - Laboratory budgets or inpatient tariffs frequently not adjusted to cover new tests

  - Reimbursement approval of biomarker tests typically not linked to (or in time with) medicine reimbursement

- **Very diverse laboratory infrastructure, capabilities and referral pathways** can lead to slow integration of new biomarker tests into the standard of care. Challenges include regional variations in diagnostic laboratory coverage, with some countries lacking sufficient infrastructure or referral pathways to support equal access for all patients, and variations between laboratories in the availability of test technologies or the capability to perform specific biomarker tests.

- **Limited availability of public funding to support biomarker testing** acts as a barrier both to the development of testing capabilities and infrastructure as well as to driving widespread uptake and continued use of biomarker testing.

- **Limited stakeholder awareness and education:** Low physician awareness of available biomarker tests and their benefits as well as limited knowledge of referral pathways can hinder test uptake. Limited awareness can prevent patients from demanding testing proactively. In some countries, shortages of trained laboratory personnel might limit the ability to perform biomarker tests.

- **Inconsistent participation of laboratories in quality assurance schemes:** Even with good access to testing, test quality is varied and can limit the utility of test results. Key challenges

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[5] https://www.efpia.eu/publications/downloads/efpia/efpia-patients-wait-indicator-2019-survey/

[6] External quality assessment (EQA): challenge of the effectiveness of a laboratory's quality management system. In clinical laboratories, external quality assessment is a form of quality assurance to ensure the provision of precise and accurate analyses to support optimal patient care, through helping to minimise the variability, arising from biological or analytical sources, inherent in all quantitative measurements or qualitative examinations

include varying levels of participation in EQA[6] (external quality assessment) schemes (often due to budget constraints), limited ISO accreditation[7], as well as test turnaround times extending beyond clinically actionable windows, in part driven by high send-out rates.

Call for multi-disciplinary and concerted actions: 12 policy recommendations

To address these barriers, multi-disciplinary and concerted actions are needed. IQN Path, ECPC, EFPIA and pharmaceutical industry and academic representatives have jointly developed eight short-term and four long-term policy recommendations [8]

to address the identified shortcomings in biomarker test access and quality.

The short-term recommendations aim to achieve a vision of equitable access to biomarker testing to enable optimal treatment:

"All cancer patients eligible for biomarker-linked therapy should undergo testing for all clinically relevant biomarkers that are indicated for precision medicine, with use of extended panels where appropriate."

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[7] ISO: the International Organization for Standardization (ISO) is an international standard-setting body composed of representatives from various national standards organisations. Standards provided by ISO are internationally agreed by experts and aid in the creation of products and services that are safe, reliable and of good quality. ISO accreditation or ISO accredited certification refers to when a company or laboratory has achieved an ISO standard by a certification body that is accredited by one of the national accreditation bodies (e.g., UKAS in the UK)

[8] Short-term: coming to fruition in the next 2-3 years; long-term: coming to fruition in 5-10 years

Short-term recommendations

1. Parallel approval of the medicine and associated testing: Develop process for the parallel approval of the medicine and associated testing (both for regulatory and reimbursement approval)

▶ Processes need to be coordinated and synchronised in such a way that the associated biomarker test is available (approved and reimbursed) at the time when the medicine is made available in a given country

▶ Test approval requirements need to be flexible enough to allow for continuing test innovation and evolution (e.g., new biomarkers added to NGS panels)

2. Adopt a national system for biomarker test value assessment: develop an efficient value assessment process for new biomarker tests which defines clear criteria for determining value, considers the broader health system benefits of biomarker testing and allows for the incorporation of new data as it is generated (either in clinical trials or real-world evidence)

3. Dedicated biomarker test budgets: Introduce dedicated diagnostic budgets to support reimbursement of all biomarker tests, removing regional variation and inequality in access

▶ Diagnostic budgets should be sufficient to meet the growing needs for testing and future increases in volume and complexity of testing

4. Mandatory ISO accreditation and EQA scheme participation: Mandate that laboratories pursue ISO accreditation and participate in EQA schemes covering all predictive biomarker tests / test techniques, and provide dedicated budgets at the national level to fund participation in quality assurance measures

5. Regional testing centres: Encourage the creation of regional testing centres within countries to drive cost efficiencies, development of technical expertise and investment in test technologies, and allow for fast turnaround times due to high sample throughput and expertise, with standardised approaches to internal and external quality assurance

▶ Regional testing shall be pursued only if it achieves a clear efficiency and cost gain (e.g., single biomarker tests with sufficiently fast turnaround times at local testing facilities need not be centralised)

▶ Testing should be provided at regional expert centres, but treatment should be close to the patient's home

6. Stakeholder education: Ensure the availability of education for key stakeholders (i.e. physicians, pathologists, payers, patient advocacy groups, policy makers) on the utility of biomarker testing, testing pathways and reimbursement sources, with the ultimate aim of improving patient outcomes; this includes the active promotion of ESMO (European Society for Medical Oncology) / ESP (European Society of Pathology) guidelines by member states' cancer & medical societies

▶ Education and training should ensure that physicians and pathologists are equipped to operate in the evolving, and increasingly complex, precision medicine environment

7. Centralised data collection: Establish centralised national data collection to harness clinico-genomic data gathered during testing and thus advance the understanding of genomic alterations and their role in driving cancer

8. Horizon scanning: Establish processes for horizon scanning for future testing needs as well as emerging tests in order to better anticipate future demand and funding requirements

In the **long term**, country systems will need to evolve further to harness comprehensive testing[9] in order to drive additional improvements in patient outcomes.

This paper defines the long-term vision as:

"All patients with a cancer diagnosis undergo comprehensive and ongoing tumour testing throughout the episodes of care."

Long-term recommendations

1. Harmonised approaches along the test development continuum, including guidance on biomarker use during clinical trials and test value assessment: Create harmonised approaches across the EU and the UK for enabling the use of biomarker tests in clinical trials and for the value assessment of biomarker tests to inform reimbursement decisions, in order to drive equality in precision medicine and test access across the EU and the UK

2. Centralised testing infrastructure: Promote the development of networks of specialised labs / centres at the national level that carry out genomic / complex biomarker testing and interpretation of results to ensure consistent test access within the country and develop a shared knowledge base of patient outcomes

▶ Encourage the co-ordination of existing resources and supporting upgrades in capacity (as opposed to the establishment of new centres) – including greater co-ordination with and integration of private facilities

▶ Where there is a lack of existing infrastructure, centralisation of test volumes should help reduce the barrier posed by the high investment required in genomic / complex testing methods and capable centres

3. Data sharing: Encourage sharing of biomarker test data and collaboration between key stakeholders across Europe (in particular physicians and laboratories) to ensure that clinical insights are created by linking genomic data collected during biomarker testing with real-world clinical data[10]

▶ Leverage artificial intelligence to analyse the gathered data (e.g., on genomic profiles which do / do not respond well to treatments and new and validated biomarkers) and help inform treatment decisions

▶ Use gathered insights to modify treatment guidelines where appropriate

4. Guidelines on comprehensive testing: Work with ESMO / ESP to develop EU / UK-wide guidelines to promote the use of comprehensive testing at various stages of the disease journey and the implementation of best-practice methods

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[9] Comprehensive (multi-biomarker) testing defined as the use of genomic / complex testing (e.g., next-generation sequencing (NGS)) of tumour or blood samples to detect multiple alterations in genes that are known to drive cancer growth. In the context of this paper, comprehensive testing refers to ongoing tumour testing at each state of the diagnosis and treatment pathway (see longer-term vision laid out above) using genomic / complex testing and includes testing for ALL biomarkers linked to specific medicines, as well as testing for biomarkers not linked to specific medicines

[10] This recommendation is supportive of the "Cancer Diagnostic and Treatment for All" initiative as defined by the "Europe's Beating Cancer" plan, with the goal to facilitate the sharing of cancer profiles between cancer centres [40]

Implementation – task forces at the national and European level

This paper argues for the creation of country-level precision medicine task forces which bring together all country-level stakeholders involved in medicine and test reimbursement approval as well as in the organisation of testing. These task forces should be responsible for overseeing national initiatives: establishing comprehensive public reimbursement of testing, facilitated by a clear value assessment framework for biomarker testing; creating regional testing centres; investing in data collection; stakeholder education; and mandating the participation in quality assurance schemes. In addition, centralised action will be required to drive the implementation of biomarker testing across Europe. This paper therefore suggests the creation of a centralised task force at the European level to 1) monitor and guide national initiatives (with individual countries responsible for execution and reporting) and 2) to co-ordinate pan-European initiatives in line with the long-term recommendations: developing a standardised framework for test value assessments, driving pan-European data sharing and establishing pan-European guidelines for comprehensive testing.

Immediate action is paramount: medicine development in oncology is rapidly evolving, facilitated by a greatly improved understanding of cancer as a genetic disease. It is a therefore a matter of urgency to provide the biomarker testing infrastructures and processes required in order to deliver the benefits of these therapeutic advances to patients and to ensure that the pace of innovation can be sustained.

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C. Introduction and objectives

The burden of cancer continues to grow globally, creating substantial pressure on patients, their families, communities and healthcare systems. Cancer represents the second largest cause of death and morbidity in Europe, with more than 3.7 million new cases and 1.9 million deaths each year [11]. However, new therapeutic approaches are getting us closer to a future where cancer becomes a curable disease. Knowledge of cancer has improved vastly in the last two decades, revealing the huge variability not only between cancer types but also between patients of the same cancer type, and highlighting the need for – and the promise of – tailoring cancer care to individual patient characteristics. Fuelled by this knowledge, cancer treatment is increasingly shifting towards precision medicine, a healthcare approach that systematically utilises patient data to inform personalised treatment decisions. The vision for precision medicine in cancer is transformative: to deliver superior outcomes for all cancer patients and ultimately reduce the suffering caused by cancer.

Precision medicine has the potential to transform health outcomes in three key areas:

Firstly, it drives improved patient outcomes. Precision medicine has narrower indications, aiming to restrict their use to only those patient groups which are most likely to respond well to treatment. The prescription of medicines only to patients displaying specific biomarkers means that the optimal treatment is provided to each group, improving response rates and reducing the risk of adverse events. Meta-analysis of phase II trials looking at response, progression-free survival, and overall survival rates showed that patients treated with precision medicine had higher response rates vs. non-targeted arms and reported lower instances of adverse events [2]. An analysis of lung-cancer mortality in the U.S. demonstrated that incidence-based mortality from NSCLC among men decreased by 6.3% p.a. between 2013 and 2016, compared with a 3.1% p.a. decline in NSCLC incidence from 2008 to 2016. Corresponding lung cancer-specific survival improved from 26% among men diagnosed

Precision medicine (PM)

Precision medicine is a healthcare approach that utilises molecular information (genomic, transcriptomic, proteomic, metabolomic, etc.) phenotypic and health data from patients to generate care insights to prevent or treat human disease resulting in improved health outcomes [1]

[11] As reported by the WHO: https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics

Biomarker

A *biomarker* is a biological characteristic that is objectively measured and evaluated as an indicator of biological processes. *Biomarker* refers to any molecule in the human body that can be measured to assess health (e.g., haemoglobin A1c as a marker of diabetes). Molecules can be derived from blood, body fluids or tissue [7, 38]

Biomarker test

A *biomarker test* is a biochemical measurement developed to quantitate one, or several, biomarkers for the screening, diagnosis and/or prognosis of cancer patients. Tests can be divided into three groups: chromosome tests (looking for abnormal changes within chromosomes), gene tests (assessing either one gene or a short piece of DNA for changes such as extra gene copies, missing genes and mutations), and biochemical tests (assessing the presence of abnormal proteins or possible effects of cancer via the presence of specific chemicals in the blood) [7, 38]

in 2001 to 35% among men diagnosed in 2014. Similar patterns were found among women. This substantial improvement in survival was in part attributed to the approval and use of EGFR-targeting medicines [32].

Secondly, precision medicine, due to its targeted approach, can provide socio-economic benefits by reducing hospitalisation rates, slowing disease progression, and limiting the impact of disease on patient productivity, thus ultimately allowing a more efficient use of resources. For example, in the Netherlands, increased use of precision medicine has driven a decrease in the length of hospital stays for cancer patients, with an average stay of 3-4 days for precision medicine patients vs. 7 days for patients treated with chemotherapy [3].

Finally, increased uptake of precision medicine can reduce the impact of cancer treatment on healthcare budgets. While the cost of initial diagnosis and tests for treatment selection is higher, biomarker tests can help to identify patients most likely to respond to a given therapy, reducing unnecessary spending on treatments for patients who will not benefit. A study by the French Cancer Institute has highlighted the potential cost savings that molecular testing can provide due to reduced non-effective prescribing [4]. As an example, investing €1.7 million in EGFR mutation testing in France drove a cost saving of €70 million by only including NSCLC patients who would respond to treatment with gefitinib [5].

The shift towards precision medicine is supported by significant advances in biomarker testing, with next generation sequencing allowing the detection of genomic alterations which drive tumour development and providing critical insights into a patient's likely response to treatment and progression of disease.

A biomarker is a biological characteristic that is objectively measured and evaluated as an indicator of biological processes. For example, biomarker testing in oncology is used to identify clinically relevant genomic alterations or the levels of expression of proteins. Biomarkers are essential tools in the diagnosis and treatment of diseases, including cancer, for several reasons: they can be used to provide precise diagnoses and identify those patients who will not respond to treatment, therefore informing treatment selection. They can also help predict and monitor disease progression

Biomarker testing definitions

Single biomarker testing

Test evaluating the presence of a single gene mutation, gene or protein expression within a biopsy associated with a particular form of cancer (e.g., HER2 testing in breast cancer patients). Single biomarker testing methods include immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), and polymerase chain reaction (PCR) testing [7].

Comprehensive multi-biomarker testing

Use of genomic / complex biomarker testing (e.g., next-generation sequencing (NGS)) of tumour or blood samples to detect multiple alterations in genes that are known to drive cancer growth (i.e., base changes, insertions & deletions, and rearrangements or fusions). NGS can be used to sequence entire genomes or be constrained to specific areas of interest, effectively allowing multiple single gene tests to be run in parallel [7].

and identify patients at increased risk of developing a given condition. This paper focuses on the current and potential future use of biomarker testing – both single biomarker and comprehensive multi-biomarker testing – to inform treatment selection and improve patient care in oncology.

Significant progress has been made in the identification of biomarkers and the development of therapies linked to biomarkers, particularly in oncology, with around 55 percent of all oncology clinical trials in 2018 involving the use of biomarkers, as compared with around 15 percent in 2000 [6]. Ever increasing knowledge of biomarkers is driving the use of broader tests of hundreds of genetic variants allowing for precise treatment decisions and monitoring. In future, the use of comprehensive biomarker testing is expected to support a shift away from traditional "organ-of-origin" focused treatment paradigms towards the increased use of tumour-agnostic treatments based on patients' molecular signatures.

Effective use of biomarker testing and applying high quality testing standards play a fundamental role in fulfilling the potential of precision medicine to transform patient outcomes. The clinical use of reliable biomarker tests to guide therapy selection depends on many related processes. A number of processes before and following clinical laboratory testing need to be considered (i.e. analytical validation, clinical validation, specimen handling, reproducibility, IT infrastructure), which can affect the accuracy and reliability of test results and patient safety. This is even more critical for advanced diagnostic technologies, such as next generation sequencing or digital pathology, which build on extensive bioinformatics and/or AI based algorithms. On top of this, External Quality Assurance (EQA) programs are key to keep testing standards high and ensure patients can benefit from precision medicine [44-49]. **Yet, the current level of access to high quality oncology biomarker testing across Europe is inconsistent and contributes to an imbalance in health equity across the EU27 + UK. Without immediate and concerted action**

to ensure the provision of adequate testing across countries, it is impossible to harness the full benefits of precision medicine outlined above.

IQN Path, ECPC and EFPIA, together with a consortium of industry and academic partners, have conducted research across the EU27 and the UK in order to analyse the current status of biomarker testing in each country, identify country-specific shortcomings and develop a set of policy recommendations to improve access to and quality of biomarker testing in oncology. **The ultimate goal of these recommendations is to ensure that all eligible patients have access to the ideal testing paradigm: high-quality biomarker testing that is readily available to all cancer patients without compromising on the numbers of genes analysed, with new tests rapidly integrated into the standard of care.**

By laying out clear recommendations for optimising patient access to the ideal biomarker testing paradigm, this paper is contributing to achieving a vision of universal access to precision medicine in cancer care for all European cancer patients. This is in line with the European Commission's "Europe's Beating Cancer Plan" which details a new approach to cancer care, covering prevention, early detection, diagnosis and treatment, and quality of life for cancer patients and survivors. As one of its four key areas for action, the plan calls for optimised access to innovative cancer diagnosis and treatment. The plan foresees several initiatives to achieve this goal, including the "Partnership on Personalised Medicine" which will make recommendations for the roll-out of personalised medicine approaches in daily medical practice, as well as the "Cancer

Diagnostic and Treatment for All" initiative, to be launched by the end of 2021. The goal of this initiative is to establish NGS technology for quick and efficient genetic profiling of tumour cells, allowing cancer centres to share cancer profiles and applying the same or similar diagnostic and therapeutic approaches to patients with comparable cancer profiles [40].

The policy recommendations in this paper were developed based on an in-depth analysis of the conditions which have to be in place so that biomarker testing can play an active and effective role in cancer diagnosis. In order to provide a pathway for the improvement of biomarker testing in the EU27 + UK, this paper makes recommendations relating to both the short term (i.e., coming to fruition in the next 2-3 years) and the longer term (i.e., coming to fruition in 5-10 years).

The short-term recommendations proposed by this paper aim to achieve a vision of equitable access to biomarker testing to enable optimal treatment:

"All cancer patients eligible for biomarker-linked therapy should undergo testing for all clinically relevant biomarkers that are indicated for precision medicine, with use of extended panels where appropriate."

A number of steps must be taken to achieve this vision across Europe: it will be important to ensure that biomarker testing is supported by appropriate laboratory infrastructure, sufficient stakeholder education, policy (and guideline) support, public

reimbursement (including parallel reimbursement approval of the medicine and associated test), and appropriate quality control systems in all testing laboratories. Further, biomarker test results need to be reported and interpreted in a way that enables precise, personalised treatment decisions.

In the longer term, the goal is more ambitious, with increased emphasis on the use of comprehensive biomarker testing to enable continued improvements in patient care:

"All patients with a cancer diagnosis undergo comprehensive and ongoing tumour testing throughout the episodes of care."

Recommendations to achieve this longer term vision include a standardised medicine and biomarker test value assessment framework, in order to drive equality in precision medicine and test access across Europe, networks of specialised labs / centres to carry out genomic / complex biomarker testing, and biomarker data sharing and collaboration across Europe to ensure that value is extracted from biomarker test data.

This paper views the long-term vision as a continuation of the short-term goals, with different European countries at different levels of maturity along this continuum. In some countries, fundamental short-falls in access to and quality of single biomarker testing exist which the short-term recommendations aim to address as a matter of urgency, while other countries with more advanced testing provision can focus more of their efforts on expanding their comprehensive testing infrastructure and capabilities. The defined timeframes (2-3 years for short-term recommendations and 5-10 years for long-term recommendations) refer to the estimated time to "fruition" rather than the time point at which implementation is commenced and will vary by country depending on the country-specific status of biomarker testing along the continuum towards the long-term vision. It is important to stress that the implementation of long-term recommendations should not be delayed until the short-term recommendations have been addressed, but rather be pursued in parallel, in order to broaden access to comprehensive testing while ensuring that the provision of high-quality single biomarker testing is improved or maintained.

D. Methods

This paper is based on research conducted in 2020, aimed at assessing access to and quality of biomarker testing across all EU countries and the UK. The research covers a selection of key biomarkers[12], both established and novel, and aims to provide an accurate view of the testing landscape across different cancer types and testing technologies:

Illustration 1: biomarker tests covered as part of the research conducted for this paper

Single biomarker tests
Immunohistochemistry (IHC[13]) / Fluorescence in situ hybridisation (FISH[14])
PD-L1
HER2
ALK
MMR / MSI
Molecular (MDx[15]; includes Polymerase Chain Reaction (PCR[16]) and single biomarker next generation sequencing (NGS[17]))
BRCA
EGFR
NTRK
BRAF

Multi-biomarker test technologies
Complex genomic signatures
NGS hotspot (up to 50 genes) / targeted panel
NGS comprehensive panel

Other
Liquid biopsy (ctDNA / plasma)

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[12] Biomarker tests and test technologies considered in this paper were chosen based on feedback from IQN Path, ECPC, EFPIA and a consortium of industry and academic partners. The chosen biomarkers represent only a selection of biomarkers linked to currently approved medicines. Beyond these biomarkers and their corresponding medicines, an increasing number of precision medicines are under development, many of which follow a tumour-agnostic approach

[13] IHC: immunohistochemistry; technique to identify specific antigens within tissue sections utilising an antigen-specific antibody. Detection at the light microscopic level of antigen-antibody interactions can be achieved by labelling the antibody with a substance that can be visualised, either by conjugation to a fluorescent marker or enzyme followed by colorimetric detection

[14] FISH: fluorescence in situ hybridisation; technique that uses fluorescent probes to visualise and map the genetic material in an individual's cells, including specific genes or portions of genes; may be used for assessing a variety of chromosomal abnormalities and other genetic mutations

[15] MDx: molecular diagnostics; collection of techniques used to analyse biological markers in the genome and proteome, in order to diagnose and monitor disease, detect risk and aid therapy selection; examples include PCR (see below), DNA microarrays and NGS (see below)

[16] PCR: polymerase chain reaction; technique used to amplify small segments of DNA. Once amplified, the DNA produced by PCR can be used in many laboratory procedures, including DNA fingerprinting, detection of pathogens and diagnosis of genetic disorders

[17] NGS: next generation sequencing; large-scale DNA sequencing technology in which millions of nucleotide sequences are deciphered simultaneously. Allows for querying the entire genome (whole genome), the exons within all known genes (whole exome) or only exons for selected genes (target panel)

These tests were assessed according to key access and quality metrics in order to evaluate the current provision of precision medicine and biomarker testing as well as the key barriers to widespread adoption:

Illustration 2: metrics used to assess biomarker test access and quality

Test access metrics	
Drivers	Factors to consider
Laboratory access	• Laboratory capabilities & penetration • Infrastructure to support sample flow (e.g. sample origination)
Test availability	• % of laboratories with in-house capabilities or sending out tests to partner labs • Total time test has been available for
Test reimbursement	• Level of public reimbursement
Test order rate	• Patients tested / patients eligible

Test quality metrics	
Drivers	Factors to consider
Quality scheme participation	• EQA scheme participation
Laboratory accreditation	• Proportion of laboratories with ISO accreditation
Test turnaround time	• Time from test order to receipt of results

To generate the insights shared in this paper, a wide range of secondary sources were used, covering the cancer treatment and testing landscape across the EU and the UK. In addition, a survey of 141 laboratory managers and a survey of 1,665 patients were conducted to gather perspectives on current test access and quality by country and to identify key barriers. Survey results were supplemented by 58 in-depth interviews with key stakeholders (i.e., laboratory managers, physicians, and payers).[18]

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[18] Additional detail on research methodology and sources available in the appendix

E. Summary of findings and recommendations

a. Key barriers identified

The benefits of biomarker testing, both clinical and economic, are evident. Nonetheless, there are still significant shortcomings in testing provision in Europe. A survey of 141 laboratory managers conducted in June and July 2020 to inform this paper showed that in 15 out of 28 countries, it takes one year or more from the reimbursed launch of a precision medicine until the corresponding single biomarker test becomes available *(see Appendix: Supporting illustrations on biomarker access and quality findings, illustration D).* In 13 out of 28 countries, single biomarker testing is carried out in less than 75% of biopsies from patients who are theoretically eligible for the test *(see Appendix, illustration G).* And variability is significant: for example, order rates for PD-L1 testing in NSCLC biopsies range from around 10% in Hungary to around 95% in the UK[19] [8]. Even in countries with comparatively high biomarker test access, some challenges in enabling biomarker testing remain. For example, while testing is publicly reimbursed in Germany, funding sources may vary by biomarker (e.g., variations depending on treatment setting, prevalence rates and novelty of tests, with diagnosis related groups (DRGs) in the inpatient setting not keeping pace with the introduction of new technologies) [8].

Research performed for this paper has identified a number of barriers that must be overcome to allow patients, physicians and healthcare systems across the EU27 and the UK to realise the benefits of biomarker testing and to establish health equity across the region.

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[19] As reported in the lab manager survey conducted for this paper; measured as % share of total unique metastatic NSCLC biopsies for which PD-L1 test was performed out of the total unique metastatic NSCLC biopsies taken

Barriers to accessing high-quality biomarker testing

Limited availability of precision medicines linked to biomarkers

The availability of precision medicines linked to biomarkers is a pre-requisite for biomarker testing, as most physicians will not order tests unless the results can be used to inform treatment decisions. In many countries, there are significant delays before medicines approved by the European Medicines Agency (EMA) are launched and included on national or regional reimbursement lists. EFPIA's Patients W.A.I.T. indicator Survey shows that the average time to patient access to treatments across the EU and the European Economic Area is 504 days, but ranges from 127 days in Germany to over 823 days in Poland [10]. Additionally, in some countries public funding is not sufficient to support the prescription of precision medicines *(see Appendix, illustration B).* As pointed out by a study commissioned by EFPIA ("Every day counts"), the root causes of delayed patient access to medicines across Europe are reimbursement process challenges (late start, undefined timelines, multiple layers of decision-making); differences in and a lack of clarity on reimbursement criteria across Europe as well as evidence gaps and a misalignment on value and price between reimbursement decision-makers and pharmaceutical companies; and barriers to health system readiness (budget constraints, outdated clinical guidelines, suboptimal healthcare infrastructure) [39]. Addressing this challenge is one of the key priorities of the Pharmaceutical Strategy for Europe launched by the European Commission on 25 November 2020 [37].[20]

Unclear value assessment approaches for diagnostic tests

While reimbursement approval processes for medicines are in place in all EU countries and the UK, the value assessment for new diagnostic tests is unclear and inefficient, often leading to delays in the integration of testing into clinical practice *(see Appendix, illustration D, for delays between medicine availability and test availability).* In some markets (e.g., Germany, France, Belgium) new tests can tap into pre-defined reimbursement codes. However, these codes are typically cost- or technology-based, with no value appraisal or HTA in place to assign a value-based code towards a new diagnostic application. As a result, the reimbursement value is often insufficient to cover the cost of testing, or there is no code for specific biomarkers (e.g., PD-L1 in Belgium). In other markets, tests are included in the DRG tariff and laboratories are funded using a global budget principle, with budgets frequently not adjusted to cover new test launches. In addition, the reimbursement approval of biomarker tests is typically not linked to (or in time with) medicine reimbursement.

Very diverse laboratory infrastructure, capabilities and referral pathways

There is a significant degree of regional variation in diagnostic laboratory coverage, with some countries lacking sufficient laboratory infrastructure or established referral pathways to support equal access for all patients *(see Appendix, illustration C, for variability in laboratory access between countries).*

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[20] The Pharmaceutical Strategy for Europe aims to ensure greater access to and availability of pharmaceuticals by reviewing incentives and obligations for innovation, market launch / entry and continuous supply of products [37]

There is also variation between laboratories regarding the availability of test technologies or the capability to perform specific biomarker tests, especially multi-biomarker testing, or the IT / bioinformatics infrastructure and capabilities to make sequencing outputs viable. In many cases variations in infrastructure and capabilities lead to slow integration of new biomarker tests into the standard of care *(see Appendix, illustration D, for the availability of single biomarker tests by country; illustration H, for the availability of multi-biomarker tests by country).*

Limited availability of public funding to support biomarker testing

A lack of dedicated funding is a key contributor to limited access to biomarker testing. Insufficient funding acts as a barrier both to the development of testing capabilities and infrastructure as well as to driving widespread uptake and continued use of biomarker testing *(see Appendix, illustration F, for single biomarker test reimbursement; illustration K for multi-biomarker test reimbursement).*

Limited stakeholder awareness and education

Access to biomarker testing can be hindered by low awareness among physicians of the availability of biomarker tests as well as limited knowledge of referral pathways. Initial uptake of tests can also be delayed by insufficient physician education about the benefits of new tests. Similarly, awareness among patients can be lacking, as a patient survey by ECPC showed [33]. Finally, in some countries, shortages of trained laboratory personnel might limit the ability to perform biomarker tests.

Inconsistent participation of laboratories in quality assurance schemes

Currently, even in the event of good access to testing, test quality is varied and can limit the utility of test results. Standardisation in quality assurance across laboratories is limited, driven by low levels of participation in EQA (external quality assessment) schemes (often due to budget constraints) and limited ISO accreditation in a number of countries. Test turnaround times can also extend beyond clinically actionable windows, in part driven by high send-out rates *(see Appendix, illustrations M-P).*

B. Key country findings

The identified barriers act across countries to varying degrees to impede patient access to high quality biomarker testing. In the context of this paper, patient access is defined as the actual prescription and use of medicines and associated biomarker testing, which is dependent on three milestones: 1) regulatory approval, 2) reimbursement by public payers, and 3) prescription by physicians and use by patients [39].

Medicines access

Medicines access in a given country was assessed based on the availability (commercial launch) and reimbursement by public payers of 37 EMA approved therapies that are linked with the biomarkers in scope.[21]

Countries with high medicines access generally have national reimbursement processes in place. For example, in Germany, medicine approval by the EMA leads to reimbursement of the medicine by the statutory health insurance, with free pricing in the first year. For countries with high medicines access, incremental improvements could be driven by more regular updates to treatment guidelines following the approval of new medicines [8]. However, national decision-making does not guarantee high medicine availability: in France, for example, 34 out of 37 EMA-approved precision medicines are available, but there is a delay between the addition of the medicines to the reimbursement list and the inclusion in guidelines, in turn leading to delays in medicine uptake. In Sweden, reimbursement decisions are made quickly at a national level, but availability of medicines is moderate, with only 27 of 37 EMA-approved precision medicines available and publicly reimbursed [8].

| High | Medium | Low | N/A |
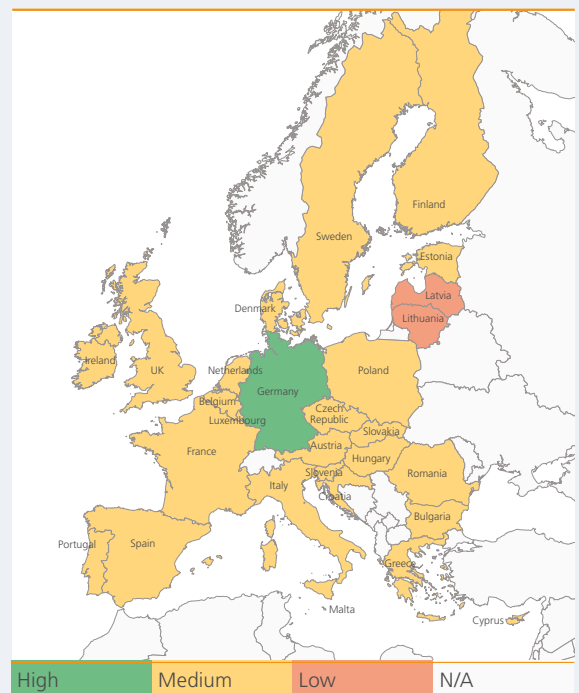
In some Western European countries, for example Spain and Italy, medicines are funded via regional or hospital budgets. This contributes to delays in reimbursement approval due to the need for sequential decision-making processes by national, regional and hospital stakeholders.

Several Eastern European and Baltic countries have low medicines access (e.g., Latvia with 10/37 EMA approved medicines available and publicly reimbursed

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[21] The colour grading is a function of both medicine availability (i.e., commercial launch of a medicine) and public reimbursement. E.g., in France, where 34 out of the 37 medicines in scope of this report are available, but only 27 of these 34 are reimbursed, the medicines access was rated as "medium". Thresholds for medicine availability are: >30 (high), 26-30 (medium), <26 (low). Thresholds for medicine reimbursement are: >30 (high), 16-30 (medium), <16 (low)

Single biomarker test access

Single biomarker test access was analysed based on the average of scores across all test access metrics [22].

These include:

• Laboratory access: regional availability of diagnostic labs and the efficiency of referral pathways

• Availability of single biomarker testing: composite score based on average proportion of labs offering single biomarker tests in scope, either in-house or via referral, and average time from medicine availability to test availability

• Single biomarker test reimbursement: average proportion of tests reported to be covered by public reimbursement

• Single biomarker test order rate: average order rate across biomarkers in scope

Due to the critical importance of public reimbursement for sustainable test access, single biomarker test access was scored as no better than medium in countries where >25% of single biomarker tests were funded by pharmaceutical companies.

| High | Medium | Low | N/A |
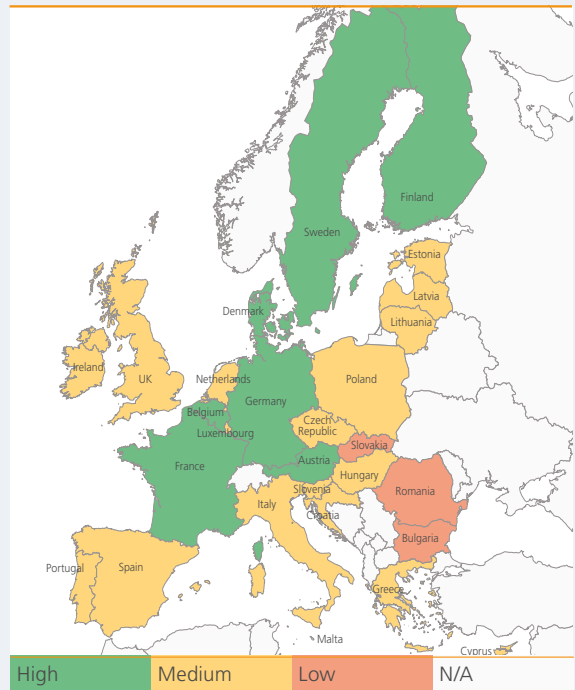
[8, 19]). These countries are characterised by long delays from EMA approval to medicine reimbursement and limited availability of public funding [10].

For additional detail on medicines access please refer to Appendix, illustrations A and B.

In the countries with the lowest performance on single biomarker test access (i.e., Slovakia, Romania, Bulgaria), diagnostic laboratory infrastructure remains underdeveloped or not efficiently organised, providing insufficient laboratory coverage and limiting patient access *(see Appendix, illustration C).*

Regarding the availability of single biomarker tests, there are significant variations between countries

in the proportion of laboratories with the required capabilities as well as in the time to widespread introduction of a new biomarker test, driving disparities in access. Generally, countries in Western and Northern Europe show rapid and widespread integration of tests into clinical practice, while in Eastern Europe integration is slower and narrower, reflecting lower levels of investment and more disconnected processes for the reimbursement of medicines and tests *(see Appendix, illustration D and E).*

Single biomarker test access is also impeded in Southern and Eastern Europe due to lower levels of public reimbursement for testing, meaning that patients must pay out-of-pocket (e.g., in Slovakia,

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[22] The single biomarker test access score is a function of the individual scores of composite metrics. Laboratory access score was based on regional availability of diagnostic labs (i.e., number of labs per capita) and the efficiency of referral pathways. Availability of single biomarker testing score was based on the average proportion of labs offering each single biomarker test in-house or through referral [>75% (high), 50-75% (medium), <50% (low)], and the time from drug to test availability [<1 year delay (high), >1 year delay (low)]. Single biomarker test reimbursement was calculated based on the average proportion of tests reported to be covered by public reimbursement [>90% (high), 75-90% (medium), <75% (low)]. Single biomarker test order rate was calculated based on the average order rates across focus biomarkers [>75% (high), 50-75% (medium), <50% (low)]
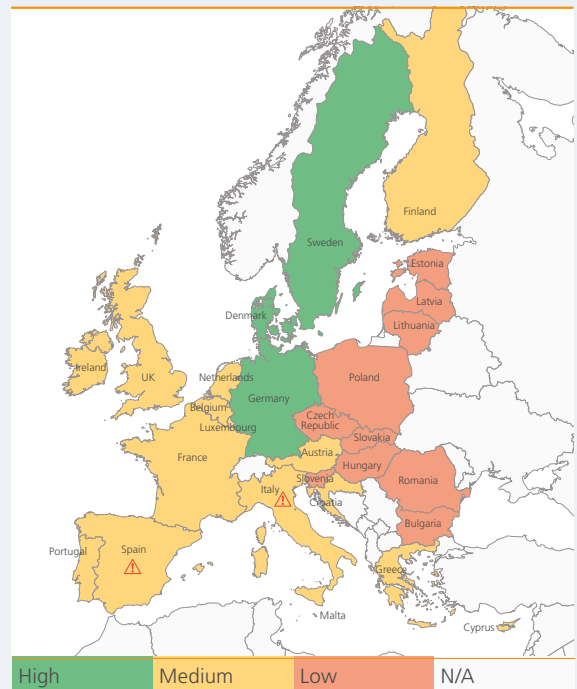
Multi-biomarker test access

Multi-biomarker test access was analysed based on the average of scores across all test access metrics [23].

These include:

- Laboratory access: regional availability of diagnostic labs and the efficiency of referral pathways

- Availability of NGS testing: composite score based on availability of different NGS modalities (hotspot, panel, comprehensive) within a given country, and proportion of labs offering any NGS modality in-house or via referral

- Integration of testing into clinical practice: average score for time available (time since introduction of any NGS modality) and NGS uptake (average % of all biopsies analysed using NGS)

- NGS test reimbursement: average proportion of tests reported to be covered by public reimbursement

- NGS test order rate: % share of total unique lung biopsies for which a given NGS test was performed (NSCLC used as an example)

As for single biomarker test access, multi-biomarker test access was scored as no better than medium in countries where >25% of tests were funded by pharmaceutical companies.

| High | Medium | Low | N/A |

⚠ Significant regional variation in test access

Greece) or rely on pharmaceutical funding (e.g., in Bulgaria, Spain, Hungary, Romania) *(see Appendix, illustration F) [43]*.

Countries with better single biomarker test access (e.g. Belgium, France) are characterised by policy support and functioning referral pathways. For example, Belgium has regular testing guideline reviews to encourage the uptake of new tests, as well as organised laboratory networks supported by well-established referral pathways. Similarly, there are clear and well-established referral pathways in France and Denmark, to ensure that patients have

access to centres with the required testing capabilities *(see Appendix, illustration C, for laboratory access by country)*.

Access to NGS testing is generally lower and more varied than access to single biomarker testing, given NGS is a newer technology and requires higher capital investment. Further, multi-biomarker testing has not been required to inform appropriate treatment selection in most cancer types to date. However, this is changing as more biomarkers are approved, with multi-biomarker testing via NGS allowing the analysis of large biomarker panels while

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[23] The multi-biomarker test access score is a function of the individual scores of composite metrics. Laboratory access score was based on regional availability of diagnostic labs and the efficiency of referral pathways. Availability of NGS testing was based on the capability to perform different NGS testing [all 3 test technologies (high), 2 of the 3 (medium), or 1 or no NGS test technologies (low)] and the availability of different NGS modalities in-house or through referral [>90% (high), 75-90% (medium), <75% (low)]. Integration of testing was evaluated based on time from introduction [>5 years (high), 3-5 years (medium), <3 years (low)] and level of uptake which was calculated as the % of all biopsies analysed

using limited sample volumes, and with molecular guided clinical development programmes gathering pace. NSCLC is at the forefront of this development, with a range of biomarkers (e.g., PD-L1, EGFR, NTRK) available to inform treatment selection.

Multi-biomarker test uptake tends to be higher in countries with centralised systems as economies of scale justify the initial infrastructure investment. Examples of a centralised model are Denmark, Portugal, France and the UK, where NGS test capability has been developed in regional reference hubs supported by efficient referral pathways[24]. However, even in countries with developed NGS infrastructure, reimbursement of NGS testing is not assured: while some countries, e.g., Germany, offer national reimbursement via the public payer system, pharmaceutical sponsorship can be required in others (e.g., Italy, Spain, Greece). The lack of a clear framework for demonstrating the value of multi-biomarker testing is a key barrier to access as it leads to uncertainty about what constitutes convincing evidence to secure reimbursement. Further, a lack of physician awareness of the benefits of multi-biomarker testing negatively affects order rates, even when infrastructure and reimbursement might be in place.

Southern European countries display regional variations in NGS access. For example, in Spain and Italy, this is due to a combination of limited infrastructure and variable public funding by region. In Greece, public funding constraints and limited public policy advocacy in favour of multi-biomarker testing significantly limit NGS uptake. However, access limitations are being mitigated through the pro-active integration of private NGS-equipped testing facilities into the public sector [8].

In Eastern Europe and the Baltics, uptake of NGS is either limited by a lack of public capabilities or a lack of public reimbursement for testing. For example, there are limits on the amount reimbursed by public payers in Hungary, meaning that additional funding from pharmaceutical companies is required [8]. In Bulgaria there is no public funding for NGS. Incentives for improving access to NGS are lacking as NGS is not integrated into the current standard of care and political pressure to drive wider use is limited.

Multi-biomarker test reimbursement

| High | Medium | Low | N/A |

⚠ Significant regional variation in test reimbursement
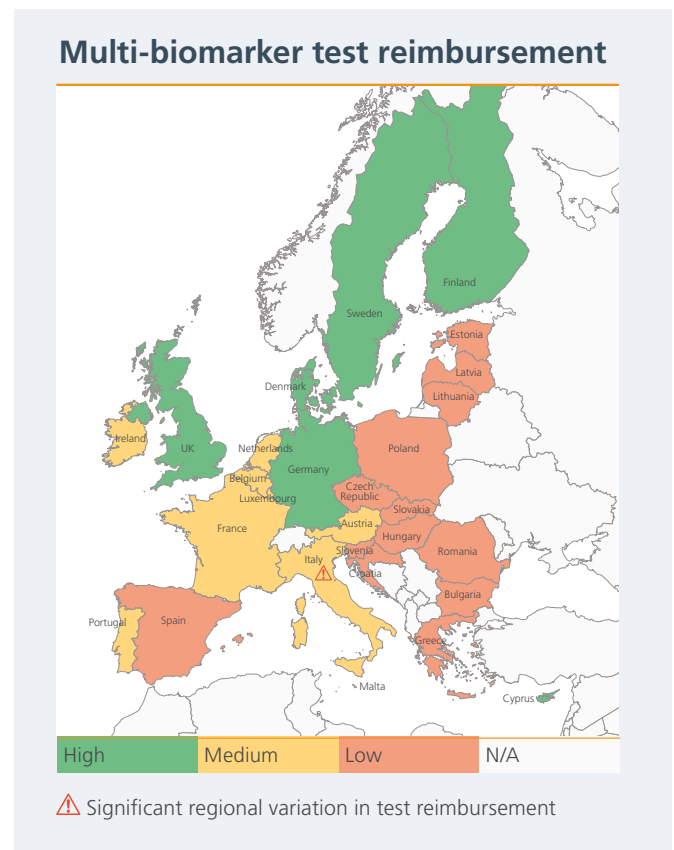
Overall, the lack of sufficient public reimbursement for multi-biomarker testing is a key barrier to multi-biomarker test access in a large number of European countries.

with NGS technology [>75% (high), 50-75% (medium), <50% (low)]. Multi-biomarker test reimbursement was calculated based on the average proportion of tests reported to be covered by public reimbursement [>90% (high), 75-90% (medium), <75% (low)]. Multi-biomarker test order rate was calculated based on the maximum order rate for NSCLC across available NGS platforms [>75% (high), 50-75% (medium), <50% (low)]

[24] UK rated as "medium" on multi-biomarker test access despite the creation of Genomic Laboratory Hubs (GHLs), given these are still in the process of ramping up [42]. The positive responses on multi-biomarker test reimbursement received during the laboratory survey for this report therefore reflect a future view when the GHLs are fully operational
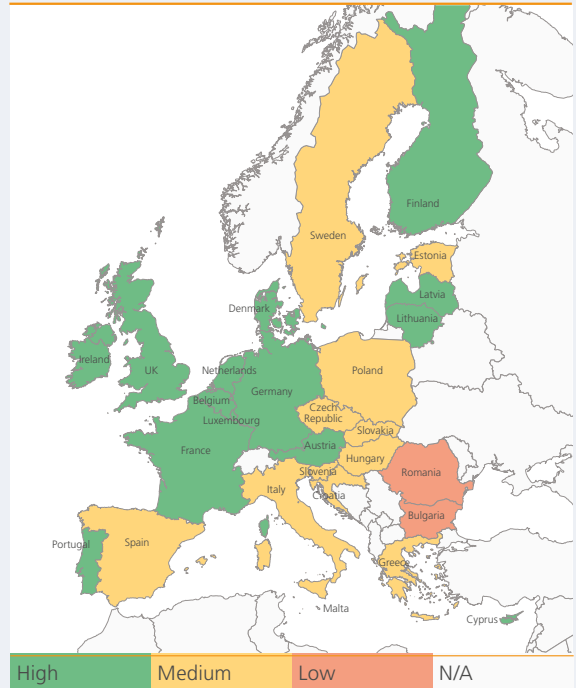
Biomarker test quality

Test quality[25] was assessed based on the average of scores across all test quality metrics.

These include:

• Participation in EQA (external quality assessment) schemes: proportion of laboratories participating in at least one EQA scheme

• ISO accreditation: proportion of laboratories that are ISO accredited

• Turnaround times: average time from test order to receipt of the result by the physician across biomarkers in scope

The quality of biomarker testing is highest in Western and Northern Europe, in part driven by increased incentivisation of laboratories to participate in quality assurance schemes. For example, in the UK, EQA participation is mandated, and in Belgium, all molecular diagnostic laboratories must be ISO accredited for around 80% of all molecular testing procedures performed in-house [12]. The situation is different in some Eastern European countries: for example, in Slovenia, neither EQA participation nor ISO accreditation are required for public funding or clinical trial participation *(see Appendix, illustrations M and N).*

| High | Medium | Low | N/A |

See Appendix, illustration H, for multi-biomarker test capabilities and availability by country; illustration I and J for multi-biomarker test uptake; and illustration K for multi-biomarker test reimbursement.

Another key driver of quality assurance is the provision of dedicated funding to support scheme participation. In the Netherlands for example, funding for mandatory EQA participation and ISO accreditation is provided via the central diagnostic budget, while in Finland and Austria, public funds are set aside specifically for quality assurance. In contrast, laboratory managers in Romania, the Czech Republic and Hungary have highlighted a lack

of available funds as a key barrier to EQA scheme participation *(see Appendix, illustration N).*

Centralisation of testing can facilitate scheme participation. For example, in Denmark centralisation of most testing to large regional centres ensures that test volumes are sufficient to justify the cost and effort of EQA scheme participation [8, 13, 14, 15].

In summary, the research conducted for this paper highlights the regional disparity in biomarker test access and quality across the EU27 and the UK: Northern and Western European countries generally perform the highest on the metrics covered, reflecting their higher investment in healthcare.

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[25] Composite score; EQA participation: high = >90% of labs participating in at least one EQA scheme; medium = 75-90%; low = <75%; ISO accreditation: based on proportion of labs that are ISO accredited within each country; test turnaround times: high = <2 weeks; medium = 2-3 weeks; low = 3+ weeks

Illustration 3:

Aggregate performance on precision medicine availability vs. biomarker testing by country
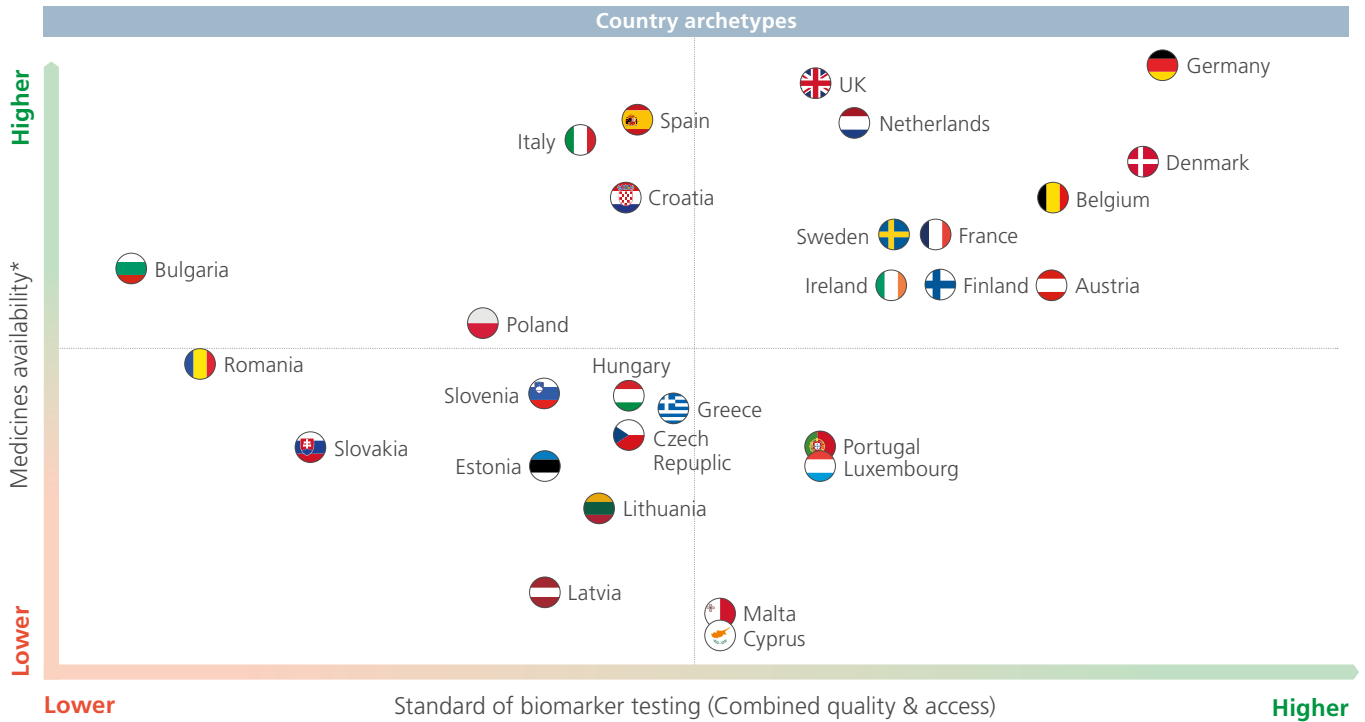
Note: * Focused on precision medicines; high score defined as being commercially launched and publicly reimbursed
Source: L.E.K. research and analysis

Southern and Central European countries as well as the Baltic states tend to have moderate availability of precision medicine and a reasonable standard of biomarker testing, with common limitations including regional variability in access to test infrastructure and funding (e.g., in Italy and Spain). More substantial barriers to uniform biomarker test access and quality were identified for Eastern European countries, requiring more significant structural changes to achieve equity in access to precision medicine across Europe.

c. Policy recommendations – short-term

IQN Path, ECPC, EFPIA, and pharmaceutical industry and academic representatives have jointly developed a number of policy recommendations to address the identified shortcomings in biomarker test access and quality.

Across the short and the long term, the policy recommendations target four key areas:

- Comprehensive public reimbursement of testing, facilitated by a clear value assessment framework for biomarker testing (both single- and multi-biomarker), detailing the evidence requirements and considering the full value of advanced testing

- Infrastructure investments, including investment into centralised clinico-genomic data collection across countries

- Stakeholder education

• Universal and consistent participation in quality assurance schemes

In the **short term**, steps must be taken to standardise access to and quality of biomarker testing across the EU and UK, guaranteeing a minimum standard of testing everywhere. This paper defines this minimum standard as:

"All cancer patients eligible for biomarker-linked therapy should undergo testing for all clinically relevant biomarkers that are indicated for precision medicine, with use of extended panels where appropriate."

Six supporting access goals and two quality goals need to be met to realise this vision:

Access goals

1. Precision medicine is available and reimbursed

2. Biomarker tests are broadly available at the time of, or soon after, relevant medicine launch

3. Laboratories have the required capabilities to perform the full range of biomarker test technologies

4. Biomarker tests are available at accessible costs, total cost effectiveness is in line with acceptable thresholds and tests are consistently and nationally reimbursed by public payers

5. Biomarker tests are ordered for all eligible patients *(requiring high physician awareness of testing pathways)*

6. All key stakeholders have access to policies and

high quality, continuous education promoting biomarker testing

Quality goals

7. Quality assessments and validation processes are in place to drive best practice

8. Biomarker test results are delivered within a clinically actionable timeline

We outline eight recommendations to achieve these access and quality goals over the short term (next 2-3 years), supported by in-depth analysis of existing barriers to biomarker access and quality in EU27 and the UK.

> **1. Develop process for the parallel approval of the PM and associated testing (both for regulatory and reimbursement approval). Processes need to be coordinated in such a way that the biomarker test is available (approved and reimbursed) at the time when a PM is made available in a given country**

The recent EFPIA paper "The root cause of unavailability and delay to innovative medicines" (published in June 2020) highlights that significant delays between the EMA approval of novel precision medicines and patient access can occur. EFPIA identifies five key contributing factors to delays in access to, or unavailability of, precision medicine [16]:

1. Time prior to market authorisation

2. The pricing and reimbursement process

3. The value assessment process

4. Health system readiness

5. Delay from national to regional approval

While the focus of this paper is not on potential improvements to the medicine approval and reimbursement process, diagnostic testing plays a role in ensuring prompt availability of innovative medicines as a component of health system readiness. Biomarker testing acts as a gateway to accessing precision medicine, with patients requiring tests to receive prescriptions. Hence, delays in implementation of testing will lead to further restrictions on precision medicine access. In fact, in many countries tests are the key limiting factor, with variable medicine availability and limits on test order rates, particularly for newer biomarkers. This is in part a result of the separation between reimbursement approval of the medicine versus the test: In many countries there are two different committees, one that approves reimbursement of the medicine and another that approves reimbursement of the test, a separation which often leads to significant delays in the reimbursement approval and introduction of new tests. In some markets (e.g., Germany, France, Belgium) reimbursement approval of new tests is circumvented as new tests can use pre-defined reimbursement codes. However, these codes are typically cost- or technology-based, with no value appraisal in place to assign a value-based code towards a new diagnostic indication. As a result, the reimbursement value is often insufficient to cover the cost of testing.

While this paper does not advocate for a joint health technology assessment (HTA) process for the medicine and the test, the two processes should be coordinated and conducted in parallel. The current lack of co-ordination means that even though a medicine may be available and theoretically reimbursed, patients must pay for the corresponding biomarker test out-of-pocket or receive sponsorship from the pharmaceutical company until public

funding of the test has been established. For example, in Belgium there was a delay of 6 years between the reimbursement approval of Xalkori in 2013 and the reimbursement approval of the companion diagnostic [17].

Additionally, in many countries, testing guidelines are not regularly updated and publicised, meaning that physician awareness of the availability of new biomarker tests and test technologies is delayed.

Best practice case studies

In Scotland, the key stakeholders involved in reimbursement approval decisions for tests also participate in reimbursement approval for medicines, ensuring alignment between the two processes

In Belgium, regular review and updating of testing guidelines ensures a dynamic biomarker test reimbursement approval process [8]

Two key learnings related to reimbursement approval should be highlighted: a) There is a need for co-ordination between medicine and test reimbursement approval processes to ensure that they occur in parallel, thus reducing the time from medicine to test availability and access. b) Testing guidelines should be updated regularly to keep pace with the speed of innovation in testing and ensure that key stakeholders (i.e., physicians, payers, patients) are aware of the availability of new tests

In the context of regulatory approval for the test, it will be important to ensure that adherence to the EU's In Vitro Diagnostic Medical Device Regulation 2017/746 (IVDR), which introduced more stringent requirements for regulatory approval of diagnostic

tests, does not constrain and delay access to test innovation (e.g., addition of new biomarkers to NGS panels).[26]

2. Adopt a national system for value assessment of new biomarker tests: develop an efficient value assessment process for new biomarker tests which defines clear criteria for determining value, considers the broader health system benefits of biomarker testing and allows for the incorporation of new data as it is generated (either in clinical trials or real-world evidence)

Streamlined and co-ordinated reimbursement of testing (as outlined above) needs to be supported by an efficient value assessment process for new biomarker tests. In order to drive efficiencies in national test reimbursement approval, standardised systems need to be adopted for assessment at the country level. Currently the value assessment and reimbursement process for new tests acts as a significant barrier to accessing new biomarker tests. In some countries, e.g., Spain, national and regional stakeholders conduct separate processes with often differing outcomes.

There is a lack of alignment on the assessment of clinical utility and cost-effectiveness of genetic diagnostics which impacts the value assessment of new tests in Europe [18, 19]. This is driven largely by differences in criteria used in the value assessment process for biomarker tests across, and even within, countries (e.g., in Spain where reimbursement

decisions are made at the regional level). This can result in inequalities in HTA outcomes and hence in reimbursed access to different biomarker tests.

Additionally, payer awareness of the long-term benefits of biomarker testing is limited. In many cases payer expectations are based on historical experience with medicines, and hence can be narrow in their focus and limited in the timeframe they consider. The value assessment process for biomarker testing therefore requires re-examination, with the goal of developing an alternative framework that is more inclusive of the broader benefits provided (including health system efficiencies through improved targeting of precision medicine to patients most likely to respond). The revised value framework should be adaptable and dynamic to allow the incorporation of new data as it is generated, either in clinical trials or real-world evidence (RWE).

This change is particularly crucial due to the movement from single biomarker to multi-biomarker testing using NGS panels. Due to this shift, the link between a given test and the use of a specific medicine is being eroded. Single biomarker tests corresponding to a specific medicine directly inform the treatment decision, and as such the test's contribution to improving treatment outcomes is evident. However, given the broader data that NGS panels provide, it is more difficult to establish a clearly defined connection between a specific medicine and a corresponding test. Broader value arguments around improved patient outcomes and health system efficiencies are hence becoming more

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[26] Entered into force on 26 May 2017, with transitional period to May 2022. Replaces EU's current directive on in vitro diagnostic medical devices (98/79/EC) and aims to improve quality and safety of medical devices approved for the EU market. Key changes include: product scope expansion (to cover diagnostic services, genetic testing and other tests that provide information about a patient's predisposition to a specific disease or susceptibility to medical treatment), reclassification of devices according to risk, need for more rigorous clinical evidence, need for premarket approval for self-testing and near-patient testing devices, more stringent documentation requirements, more rigorous surveillance by Notified Bodies and improved traceability and recall procedures (see https://eur-lex.europa.eu/eli/reg/2017/746/oj)

central. It will be crucial to develop a pragmatic value assessment framework which considers the full spectrum of the value of diagnostics, including value in guiding care decisions, economic efficiencies, public health benefits, operational efficiencies and the value of patient empowerment in order to incentivise diagnostic uptake and innovation [41].

3. Introduce dedicated diagnostic budgets to support reimbursement of all biomarker tests, removing regional variation and inequality in access

A common barrier to biomarker testing across countries is the lack of, or variation in, availability of public funds to support use. This can either manifest regionally between laboratories, or within laboratories, with varied public reimbursement by biomarker or test technology.

Regional variation in test funding is prevalent in countries with decentralised healthcare budgets (e.g., Spain, Italy, and Austria) [8]. In these countries, while tests are approved for use and integrated into treatment guidelines at the national level, regional bodies can be involved in decisions on test reimbursement and the allocation of laboratory budgets. The lack of funding co-ordination can lead

to disparities in test access, with different regional governments allocating different amounts to support diagnostics. This means that in some areas out of pocket payments or pharmaceutical sponsorship are required.

Where public reimbursement exists, it is often derived from a "patchwork" of funding sources (e.g., a combination of laboratory budgets, hospital budgets, and academic grants) which can lead to inconsistent reimbursement across different biomarker tests and test technologies. This can trigger delays in performing tests and necessitate patient out of pocket spend. The dependence on multiple sources of funding can also act as a barrier to further test adoption and integration as it is difficult for laboratories to manage the various funding sources required. For example, public reimbursement, derived from a number of different sources, is currently sufficient to serve demand for NGS testing in Ireland; however, the lack of a national funding policy is likely to limit further uptake in future *(see Appendix, illustrations F and K).*

As a consequence of funding deficiencies, pharmaceutical funding is often a key source, particularly to support the introduction and uptake of new tests, before public funding becomes available.

Best practice case studies

Single biomarker testing

Public reimbursement for single biomarker testing is guaranteed through hospital budgets, covering testing which is performed in-house or sent out [8]

In Denmark, dedicated diagnostics budgets exist as part of hospital budgets, with formalised, regular budgetary review – ensuring that there is sufficient budget ahead of the adoption of further testing (e.g., new biomarker tests)

In the UK, regular reviews of regional budgets governed by Clinical Commissioning Groups (CCGs[27]) ensure that funding is adjusted, and is therefore sufficient to cover local biomarker testing demand

Multi-biomarker testing

Dedicated funding at the national level supports NGS testing, driving uniform uptake and access within the country [8]

In the UK, NGS testing is reimbursed by the NHS at the national level

In Denmark, a specific diagnostic budget, co-ordinated at the national level, is allocated to major regional diagnostic centres, supporting multi-biomarker panel testing

In Finland, in cases where public institutions lack in-house NGS capabilities, private laboratories are integrated into the testing network, and are reimbursed by public funds [8]

Based on an analysis of the identified barriers and observations from the best practice examples, two funding models emerge:

1. Biomarker test reimbursement is ensured through hospital budgets (regardless of whether testing is performed in-house, or whether patients are referred to centralised facilities for testing)

2. Dedicated national funding is allocated to biomarker testing via a code-based system

Dedicated national funding is likely to be more suitable as it is centrally controlled and hence ensures equality in access across regions. It is important that budgets be reviewed regularly to ensure that they cover current testing demand and are able to meet the growing needs and complexity of testing in future.

> **4. Mandate that laboratories pursue ISO accreditation and participate in EQA schemes covering all predictive biomarker tests / test techniques, and provide dedicated budgets at the national level to fund participation in quality assurance measures**

To ensure that test data is reliable and actionable, test quality and standards need to be improved across most European countries. The methods for test analysis and reporting are often different between laboratory groups, due to a lack of technical expertise that, in the absence of internal and external validation of testing, can lead to high variability in test quality. This is detrimental both to informing treatment decisions and to supporting wider uptake of biomarker testing.

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[27] Groups of general practices which convene in their local area to commission services on behalf of their patients

Variability in test quality is to a large extent driven by insufficient quality assurance and test validation. Incentives for laboratories to participate in external quality assurance (EQA) schemes or to pursue ISO accreditation are currently low in many countries, with no or insufficient funding allocated to support scheme participation and laboratory accreditation *(see Appendix, illustrations M and N).*

For example, in most Eastern European countries, limited EQA scheme participation is due to insufficient laboratory budgets, forcing managers to prioritise essential costs over scheme participation. However, in other countries, the key barrier to participation is a lack of proper incentivisation. In Greece, Slovenia, and Sweden for example, EQA participation and ISO accreditation are neither a requirement for public funding nor for clinical trial participation. The degree of centralisation of testing can also play a role in the standard of quality assurance. For example, in Bulgaria, participation in schemes is low partly due to the decentralised nature of testing. Different laboratories typically handle testing for specific biomarkers which means that sample volumes are often insufficient to justify the cost of EQA participation [8].

In order to address these issues, strong incentives must be created, with policies mandating ongoing EQA participation for all approved tests as well as ISO accreditation as a gateway to performing biomarker testing. Comprehensive and dedicated public funding should be in place at the country level to support laboratories in this pursuit. In several countries, this model is already in place and has been proven to work well. For example, in the UK, Belgium and the Netherlands, laboratory funding for biomarker testing is tied to accreditation *(see examples below).*

Best practice case studies

EQA participation and / or ISO accreditation is a legal requirement to be eligible for public reimbursement of testing, ensuring that all facilities meet minimum quality standards [8]

In Belgium, a Royal Decree mandates that molecular diagnostic laboratories are accredited for most activities

EQA participation is a legal requirement for diagnostic laboratories in the Netherlands, with funding linked to compliance

Centralisation of testing to large regional centres in Denmark ensures that test volumes are sufficient to justify EQA participation

Comprehensive funding of EQA participation and / or ISO accreditation ensures high quality testing [8]

In Austria and Finland, some public funding (e.g., as part of hospital or laboratory budgets) is dedicated to quality assurance; pharmaceutical funding is not allowed in order to ensure impartiality

A few key learnings should be highlighted from our analysis of current quality assurance practices: Firstly, EQA scheme participation for all relevant biomarker tests and test technologies should be mandated as a requirement to qualify for public funding. To enable this, the funding structure should be revised to include coverage of EQA schemes, as in many cases laboratory funding can be a limiting factor for participation. Therefore, diagnostic budgets should include a specific allocation for quality scheme participation. In the shorter term, existing public funding sources and pharmaceutical sponsorship

could be used while dedicated budgets are being established. Secondly, some degree of centralisation of testing should be encouraged to ensure that laboratories are handling sufficient test volumes in order to justify the implementation of the optimal quality assurance framework.

> **5. Encourage the creation of regional testing centres within countries to drive cost efficiencies, development of technical expertise and investment in test technologies, and allow for fast turnaround times due to high sample throughput and expertise, with standardised approaches to internal and external quality assurance**

For biomarker testing to be widely adopted, it is necessary that patients have access to laboratories with the required capabilities to perform the full range of biomarker tests. This means that there must either be sufficient laboratory density that ensures coverage of all patients, or efficient referral pathways to support access.

Particularly in Western and Northern Europe, the level of laboratory access tends to be relatively high, mirroring generally higher rates of public health expenditure; however, across Southern and Eastern Europe, it is not uncommon for diagnostic capabilities to be concentrated in capital cities. Therefore, patients must travel to these centres, making access more cumbersome, or samples must be sent out, leading to inefficiencies and delays in the turnaround of results. Another key difference between better and worse performing countries is the level of organisation and co-ordination of available laboratories – specifically the existence, and efficiency of, the patient referral pathways from primary care to suitably equipped diagnostic facilities. For example, in Bulgaria, the laboratory infrastructure is disparate, with significant regional variations in referral. Laboratories often perform only a single type of biomarker test, requiring oncologists to send several biopsy samples out to different laboratories and resulting in significant delays in receiving results. Patients may also have to transport their samples to the laboratory *(see Appendix, illustration C).*

Best practice case studies

High density of testing facilities within a country (e.g., laboratories, in-house hospital testing facilities, private laboratories) – with some centralisation of more complex testing methodology [8]

In Germany, molecular diagnostics, including NGS testing, is centralised by region to key testing centres, generally large and / or university hospitals acting as de facto centres of excellence (CoEs); access is ensured through established referral pathways

Lower density of laboratories but good access to testing through referral pathways to regional referral centres or centres of excellence – including collaboration with private laboratories [8]

In the UK and Denmark, all biomarker testing (including single biomarker and NGS) is centralised to regional or national hubs

In France, all molecular diagnostic testing is centralised to the regional reference laboratory network, ensuring that hospitals lacking in-house capabilities also have access to testing via referral pathways

In Greece, where public institutions may lack in-house capabilities, private facilities are integrated into the testing referral pathway to ensure access

Given the capital investment required to increase the number of laboratory facilities in a given country, the second of the two best practice models, aimed at developing good referral to regional test centres, is the most adaptable and easiest to implement in countries with insufficient or inconsistent patient access to testing.

This regional consolidation of testing to a smaller number of centres has several benefits. Firstly, streamlining the laboratory network should provide additional clarity on referral pathways, increasing awareness among physicians of the test capabilities available to them. Secondly, centralisation of testing will drive cost efficiencies through volume, hence the cost of introducing new test technologies (e.g., instruments and NGS panel tests) can be more easily justified. It will also reduce required laboratory technician headcount and promote the development of technical expertise. A shortage of trained laboratory technicians has been highlighted by laboratory managers in several Eastern European countries (e.g., Croatia) as a bottleneck for test implementation as well as a limiter on the sample volume that can be processed [8].

Consolidation of testing to a highly organised network of laboratories can also have benefits in terms of test quality. As mentioned previously, it drives consistency in technical expertise but also allows for the implementation of standardised quality assurance measures. A key issue in many countries is that there is little consistency in internal and external validation of testing. This is in part due to limited alignment on the pre-requisites to performing biomarker testing, but also due to the cost associated with participating in external quality assurance (EQA) schemes or with pursuing ISO accreditation (see Appendix, illustrations M and N). Adoption of a network model would allow increased oversight on the quality assurance measures

employed across laboratories, driving improvements in quality. Meanwhile, increased consolidation of test volumes would help to justify the cost of quality scheme participation.

However, this paper only recommends regional testing if it achieves a clear efficiency and cost gain (e.g., single biomarker tests with sufficiently fast turnaround times at local testing facilities need not be centralised). While testing should be performed regionally where appropriate, treatment should remain close to the patient's home.

> **6. Ensure the availability of education for key stakeholders (i.e. physicians, pathologists, payers, patient advocacy groups, policy makers) on the utility of biomarker testing, testing pathways and reimbursement sources, with the ultimate aim of improving patient outcomes; includes the active promotion of ESMO / ESP guidelines by member states' cancer & medical societies**

In addition to developing infrastructure that will support the provision of testing and providing funding to facilitate biomarker test reimbursement, it is important to ensure that key stakeholders are aware of the benefits of biomarker testing and are clear on the pathways for access.

Across countries, surveyed laboratory managers highlighted a lack of test orders as a key barrier *(see Appendix, illustrations G and L).* In a minority of cases this is driven by low awareness of the benefits of testing among key stakeholders. In Lithuania for example, uptake of biomarker testing has historically been low due to a lack of education about the clinical and economic benefits of precision medicine and low physician awareness of available

biomarker tests [8, 25]. In order to address this, more focus should be put on precision medicine in physician training and postgraduate education. More commonly, however, low test orders are a result of low or delayed visibility of available tests. While theoretically available, physicians may not be aware that new tests have been integrated into diagnostic guidelines due to poorly publicised updates, or national approval and reimbursement guidelines are not updated frequently enough. This should be addressed as a matter of urgency. ESMO provides diagnostic guidelines but it is essential that these are actively disseminated and used across Europe [26]. This will help to address the current lag in physician awareness which can be significant, especially beyond academic centres, and which can contribute to low order rates for eligible patients.

Improving health literacy among patients is also an important goal, as patients who are more knowledgeable about test and treatment options can actively demand these. In a survey of 1,665 patients conducted to inform this paper, patients in 15 out of 16 surveyed countries rated their satisfaction with information received about the test procedure, test results and implications for treatment as low to medium [33]. Patient advocacy groups can play a key role in patient education by developing and distributing information on the purpose and benefits of biomarker testing and the specific test options available (e.g., online materials produced by ECPC) [26].

In order to improve stakeholder education, it is important for national cancer and medical societies to disseminate materials which highlight the importance of biomarker testing in improving patient outcomes in oncology. Societies should also be tasked with updating diagnostic guidelines and providing clarity to physicians and pathologists about referral pathways [8].

Best practice case studies

Single biomarker testing

In France and Denmark, referral pathways are well established; patient access benefits from centralisation of testing which ensures that referral centres have the capability to perform all relevant biomarker tests [8]

High awareness of the benefits and availability of biomarker testing is ensured through regular and well-publicised guideline updates and a focus on educating the clinical community. Belgium, for example, has multiple rounds of guideline review per year, including clear communication of national regulatory body approval and reimbursement decisions [8]

Multi-biomarker testing

In the UK, high awareness of referral pathways to centralised NGS laboratories coupled with policy support facilitate the integration of NGS into the standard of care [8]

In Germany, a national programme (nNGM Lungenkrebs) offers NGS testing for lung cancer patients via a network of 15 university cancer centres. The objectives of the network are to offer access to uniform multiplex testing for all lung cancer patients, ensure uniform quality standards, further develop regional referral networks, harmonise therapy recommendations based on the data collected, develop a joint data collection and evaluation structure, work closely with payers to develop a reimbursement pathway and coordinate clinical study approaches [34]

Government programmes and initiatives drive high awareness of the benefits of NGS, supporting uptake. However, as initiatives are recent, order rates

may still be medium or low[28] in some countries listed below (e.g., Austria, Lithuania) [8]

In Belgium, a pilot programme (The Cancer Prevention Roadmap) promotes the use of multi-biomarker methods

One of the key aims of the National Cancer Framework in Austria is the promotion of molecular diagnostic testing, emphasising the importance of access to comprehensive testing early in the disease journey

The Lithuanian Ministry of Health has sought to increase NGS awareness through centralised policy implementation; education around the benefits of NGS testing and the introduction of a panel tailored to common mutations in Lithuania is driving a shift away from single biomarker testing

Based on these examples of best practice, this paper recommends two key actions: firstly, new biomarker tests should be promptly included in clinical guidelines, with regular review cycles ensuring timely guideline updates. Secondly, dedicated national policies should be introduced which support the implementation of biomarker testing and education of stakeholders.

7. Establish centralised national data collection to harness clinico-genomic data gathered during testing and thus advance the understanding of genomic alterations and their role in driving cancer

Changes are required to the way in which biomarker test data is collected, collated and analysed in order to improve treatment selection and patient outcomes, and ultimately to advance precision medicine. Currently, there is little to no co-ordinated data collection across Europe, and in countries where data is collected, the quality and consistency of data collection processes varies between laboratory organisations. This makes it difficult to compare data and to identify actionable trends in patients' response to therapies. These factors combine to act as a barrier to the evolution of clinical decision-making and improved patient outcomes.

Establishing centralised national data collection (e.g., academic centre / national centre biobanks) will require investment and policy support. Systems need to be put in place to optimise the collection and analysis of biomarker data. The key findings of these analyses should be shared regularly, in order to promote the use of comprehensive testing and support improvements in treatment approaches. Interoperability between systems will be crucial in order to facilitate data sharing.

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[28] Test order rate is calculated based on the maximum test order rate for NSCLC across available NGS platforms; medium: 50-75% of total unique lung biopsies for which NGS test was performed; low: <50%

Best practice case studies

Initiatives are underway in several countries aimed at developing national databases or biobanks to collect and analyse biomarker data.

In Greece, the National Network of Precision Medicine was established in 2018 with the goal of identifying predisposition to cancer and suitability for personalised treatment regimens [27]

- 4 Precision Medicine Units are expected to be opened based on initial funding of >€5.4m, with the addition of further units planned in the future

- In the longer term, the initiative plans to establish accredited biobanks and computing infrastructure for data storage and interpretation

In Finland, long-term investments have been made to support the establishment of biobanks and to co-ordinate cancer treatment across regions. The majority of biomarker testing is carried out in 6 main diagnostic centres, to which patients are referred for testing and treatment [28]

The Swedish government invested €5M in 2018-20 in the country's biobanks and cancer registries which collect samples and data to benefit research and patient care [8]

In recent years, the UK has put increased emphasis on molecular testing as a key pillar of cancer care

- In 2016, the 100,000 Genomes Project was launched, seeing the establishment of 13 NHS Genomic Medicine Centres and aiming to consolidate precision medicine knowledge, including the analysis of NGS and biomarker data gathered to-date [29]

France plans to invest €670m into the Genomic Medicine Plan 2025 to enhance genomic medicine capabilities and sequence around 235k genomes annually [30]

There are also a number of EU-wide initiatives in place aiming to centralise genomic data, for example the European Commission project to sequence **1+ million genomes** by 2022, with participation from more than 20 countries [31].

> **8. Establish processes for horizon scanning for future testing needs as well as emerging tests in order to better anticipate future demand and funding requirements**

In a rapidly evolving precision medicine environment, characterised by new precision medicine launches, the development of new biomarker tests as well as the advancement of test modalities, it is crucial to establish horizon scanning processes. The objective of horizon scanning is to anticipate future requirements for infrastructure, capabilities and funding resulting from precision medicine innovation, in order to be prepared to meet testing demand when it arises.

In this context, it will be important to anticipate workforce needs, including future skills needed to perform testing and analyse the resulting data, and develop workforce and training plans to ensure that the current workforce keeps pace with demands.

d. Policy recommendations – long-term

In the long term, country systems that have developed to deliver the "minimum standard of testing" will need to evolve further to harness comprehensive testing[29] in order to enable personalised treatments for every patient and drive additional improvements in patient outcomes.

This paper defines the long-term vision as:

"All patients with a cancer diagnosis undergo comprehensive and ongoing tumour testing throughout the episodes of care."

The long-term vision encompasses comprehensive testing of both tissue and ctDNA samples.

We argue for a more ambitious long-term vision beyond the short-term optimisation of biomarker access and quality for three reasons:

1) Advanced diagnostics (i.e., comprehensive testing[30]) should be used to capture the increasing number of biomarkers and define the tumour throughout the treatment pathway, including at initial diagnosis, treatment selection, and ongoing patient monitoring.

2) The data generated through comprehensive testing will improve personalised treatment decisions for individual patients. As more targeted treatments emerge, treatment decisions are becoming more complex. It is important that all appropriate treatment options are considered by physicians. Comprehensive testing will ensure that biomarker results are not a limiting factor in therapy selection and that they can be leveraged to guide optimal care. Universal, publicly reimbursed access to approved precision medicines is a pre-requisite.

3) Testing acts as a platform for data generation. This data can be used to develop insights that will optimise future personalised treatment decisions. Evolution of biomarker testing must keep pace with developments in patient care and the underlying science. Care is evolving quickly, with the accelerating development of tumour-agnostic treatments driving the need for comprehensive testing. Hence it is critical to lay the foundation for a new system over the next 5 years. Once this system is in place, data consolidation and sharing should be encouraged to accelerate insight generation, shortening the timeline to improved patient outcomes and public health benefits.

The long-term vision represents a continuation from short-term goals towards an optimal testing paradigm and drives greater consistency in testing provision across Europe.

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[29] Comprehensive (multi-biomarker) testing defined as the use of genomic / complex testing (e.g., next-generation sequencing (NGS)) of tumour or blood samples to detect multiple alterations in genes that are known to drive cancer growth. In the context of this paper, comprehensive testing refers to ongoing tumour testing at each state of the diagnosis and treatment pathway (see longer-term vision laid out above) using genomic / complex testing and includes testing for ALL biomarkers linked to specific medicines, as well as testing for biomarkers not linked to specific medicines

[30] Use of genomic / complex testing (e.g., next-generation sequencing (NGS)) of tumour or blood samples to detect multiple alterations in genes that are known to drive cancer growth (i.e., base changes, insertions & deletions, and rearrangements or fusions)

Illustration 4: evolution of biomarker testing goals towards the long-term vision

	Current situation	Short-term goals	Long-term vision
Test frequency	Mainly at initial diagnosis	At initial diagnosis, and on progression	Ongoing, at initial diagnosis, for treatment selection and monitoring
Test breadth	Some biomarkers linked to specific medicines are tested	All biomarkers linked to specific medicines are tested	Comprehensive testing Includes testing for ALL biomarkers linked to specific medicines, and testing for biomarkers not linked to specific medicines
Test modality	Primarily single biomarker Limited complex biomarker testing (e.g., NGS)	Single biomarker in cancers with limited PM options Growing complex biomarker testing	Complex testing (e.g., NGS) standard but supplemented with singe biomarker tests as needed (i.e., in cases where biomarker not available on panel, or where single biomarker provides quicker results) Non-complex modalities used as required
Consistency across countries	Variable access and quality by country / region	Consistent access to quality testing within countries Some variability across EU / UK	Consistent access to high quality complex testing (e.g., NGS) across EU member states / UK

Source: L.E.K. research and analysis

Four key pillars must be in place to support achievement of the long-term vision of comprehensive and ongoing biomarker testing. Establishment of these pillars will be enabled by structured dialogue and collaboration between key stakeholders (i.e., physicians, payers, regulators, pathologists, pharmaceutical industry, patients and policy-makers).

Funding
Funding must be in place, across all countries, to support initial (i.e. at diagnosis) and on-going access and reimbursement of comprehensive biomarker testing as well as linked PMs

Testing infrastructure and capability
Across all countries and regions, patients must have access to comprehensive, high quality, genomic / complex testing (e.g., NGS). All clinical laboratories should use validated and verified panels, and tests should be performed by laboratories that are ISO accredited

Education & guidelines
Key stakeholders should be educated about the benefits of comprehensive testing, driving uptake and the shift away from the existing "test on demand" model. Test results must be correctly communicated, interpreted, and incorporated into treatment decision processes. This will allow all appropriate treatment options to be

considered at each therapeutic intervention point, with the goal of enabling personalised treatment for every patient

Diagnostic guidelines must be continuously updated to promote the use of comprehensive testing at various stages of the disease journey

Processes to support data collection & sharing
Systems must be in place to collect and analyse data and to maximise the value of the data generated

Key findings of data analysis should be shared regularly, supporting sustained value and use of comprehensive testing

Investing in these pillars will create a virtuous cycle that will further support uptake of comprehensive testing in future.

This paper defines a set of long-term recommendations that should support the development of these pillars and drive the achievement of the long-term vision. The recommendations target an aspirational testing landscape. While we anticipate that uniform implementation of comprehensive testing will take 5-10 years in practice, the recommendations set out in this paper describe actions that should be taken now to lay the foundations for comprehensive testing in the longer term.

Long-term recommendations

1. Harmonised approaches along the test development continuum, including guidance on biomarker use during clinical trials and test value assessment: Create harmonised approaches across the EU and the UK for enabling the use of biomarker tests in clinical trials and for the value assessment of biomarker tests to inform reimbursement decisions, in order to drive equality in precision medicine and test access across the EU and the UK

▶ Differing national requirements for using a diagnostic test in clinical trials (e.g., related to patient screening, enrolling, stratification) present a challenge for trial sponsors and might hinder the user of biomarker tests in clinical trials. This should be addressed by developing a harmonised process and clear expectations for sponsors to meet

▶ Inconsistencies in endpoints and relative focus (e.g., on clinical benefits vs. cost-effectiveness) can present challenges for the development of new biomarker tests. The heterogeneity in approaches

can mean that clinical and economic evidence of utility must be adapted to meet the requirements of different national stakeholders, slowing the reimbursement approval and integration of new tests. It also acts as a disincentive to innovation, making it more difficult to introduce a new test across multiple countries

2. Centralised testing infrastructure: Promote the development of networks of specialised labs / centres at the national level that carry out genomic / complex biomarker testing and interpretation of results to ensure consistent test access within the country and develop a shared knowledge base of patient outcomes

▶ Encourage the co-ordination of existing resources and supporting upgrades in capacity (as opposed to the establishment of new centres) – including greater co-ordination with and integration of private facilities

▶ Where there is a lack of existing infrastructure, centralisation of test volumes should help reduce the barrier posed by the high investment required in genomic / complex testing methods and capable centres

3. Data sharing: Encourage sharing of biomarker test data and collaboration between key stakeholders across Europe (in particular physicians and laboratories) to ensure that clinical insights are created by linking genomic data collected during biomarker testing with real-world clinical data

▶ Leverage artificial intelligence to analyse the gathered data (e.g., on genomic profiles which do / do not respond well to treatments, new and validated biomarkers) and help inform treatment decisions

▶ Data and insights generated should be used to support the ongoing monitoring and updating of guidelines in line with new medicine and test developments, as well as supporting stakeholder education on the need for comprehensive testing

▶ This recommendation is supportive of the "Cancer Diagnostic and Treatment for All" initiative as defined by the "Europe's Beating Cancer" plan, with the goal to facilitate the sharing of cancer profiles between cancer centres [40]

4. Guidelines on comprehensive testing: Work with ESMO / ESP to develop EU and UK-wide guidelines to promote the use of comprehensive testing at various stages of the disease journey and the implementation of best-practice methods

e. Suggestions for implementation

In order to ensure that the recommendations are consistently and uniformly implemented across EU member states and the UK, oversight at the European level may be required. This paper suggests the creation of a centralised special task force to drive the implementation of biomarker testing across the EU and the UK. This special task force should co-ordinate with key stakeholder groups (physicians, payers, regulators, pathologists, pharmaceutical industry, patients, policy-makers) to ensure agreement on the plan for implementation. It will be particularly important to gain support from the European Commission in order to help drive acceptance of the policy recommendations and make the case for implementation.

The task force will be required to play an active role in driving efficient and uniform patient access to biomarker tests, with little to no delay in test availability following the regulatory approval and introduction of a new medicine. In order to achieve this, the task force should encourage countries to coordinate medicine and test reimbursement approval processes to allow for the simultaneous assessment of medicines and tests. Tied to the establishment of a streamlined medicine and test reimbursement approval process, the task force should provide guidance to countries on developing a system for the value assessment of new biomarker tests, including clarity on desired data / endpoints for value assessments. Finally, the task force should convince governments to provide additional funding for the public reimbursement of all biomarker tests, removing the need for coverage by pharmaceutical companies or patient out of pocket payments.

The task force should also monitor the progress of implementation initiatives at the national level. National initiatives include:

- encouraging efficiency in testing through consolidation of a network of large laboratories / reference centres

- mandating that laboratories pursue ISO accreditation and participate in EQA schemes covering all biomarker tests / test techniques being carried out and providing dedicated budgets to cover the cost of quality assurance

- establishing centralised national data collection (e.g., academic centre / national centre biobanks)

- educating key stakeholders (i.e., physicians, payers, patients) on the utility of biomarker testing, including the active promotion of ESMO / ESP and national guidelines regarding biomarker testing by member states' cancer & medical societies

- driving improved awareness of pathways to secure access to, and reimbursement of, biomarker testing through stakeholder education

In addition to a central European taskforce, this paper argues for the creation of country-level precision medicine task forces which bring together all existing country-level stakeholders involved in medicine and test reimbursement approval as well as in the organisation of testing. The key responsibility of these task forces is to provide funding, execute initiatives at the national level, and report on progress.

F. Conclusion

The outlined short- and long-term recommendations will drive coordinated improvements in the provision of cancer care across Europe and will result in benefits for all key stakeholder groups: patients, physicians, pathologists, payers, and policy makers. They will drive improvements in access to and quality of biomarker testing, aid the development and introduction of new tests and increase confidence in the value of ongoing investments in this space.

The recommendations will ensure consistency in biomarker testing across Europe, thus facilitating equality in access to precision medicine and driving improvements in patient outcomes. In addition, greater access to precision medicine will allow for the more effective use of healthcare budgets by reducing the prescription of therapies to non-responsive patients and will deliver socio-economic improvements due to reduced hospitalisation rates and delayed disease progression.

The large volume of data that increased biomarker testing will generate, especially following a shift towards comprehensive testing, will allow researchers and physicians to tailor medical interventions, thus improving the efficiency of clinical trials and optimising treatment along the disease journey. Routine use of genomic / complex testing (e.g., NGS) and increased data consolidation and sharing between countries should facilitate the dynamic identification of correlations between patient characteristics and treatment response, establishing and strengthening clinical pathways. Increased use of genomic / complex testing will also remove current limitations on sample analysis with single biomarker methods (e.g., biopsy size and availability).

The recommendations will further trigger a review and redefinition of value assessments of new tests, providing increased scope for the inclusion of real-world evidence and clearly defining the endpoints which innovative diagnostics need to be measured against, thus incentivising increased investment and innovation in oncology diagnostics.

It is important to act quickly: molecular and genomic profiling has significantly improved our understanding of cancer as a genetic disease as well as of the molecular sub-types of cancer against which precision medicine can be developed. The discovery of oncogenic drivers across multiple tumour types facilitates the exploration of molecular signatures across cancers and the development of tumour-agnostic treatments. This has triggered a rapid evolution of medicine development in oncology. It is therefore a matter of urgency to provide comprehensive testing infrastructures and processes in order to identify patients who will benefit from these therapeutic advances and to ensure that the pace of innovation can be sustained.

The benefits of this paper's recommendations are clear; however there are significant barriers to achieving the outlined vision. It is therefore crucial that the implementation of these recommendations is supported by a coordinated effort from policy makers, payers, pathologists, physicians, industry participants and patient advocacy groups.

G. Appendix

a. Best practice case study: laboratory infrastructure in France

France has a higher number of molecular diagnostics laboratories per capita than the EU and UK average, with the French Cancer Institute (FCI) having established 27 molecular genetic centres to improve access to biomarker testing [23].

Illustration 5: Regional diagnostic laboratory network in France

Molecular genetic centre
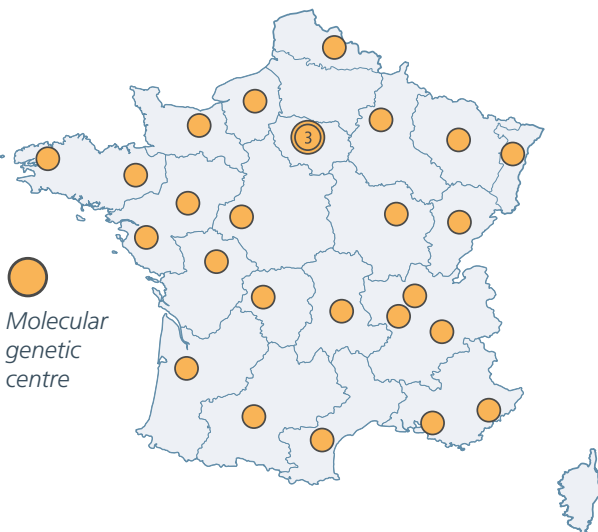
France - Regional dianostic laboratory network

Single biomarker testing

Access to established technologies – IHC, FISH, PCR – is broad throughout the network of regional centres. Most histopathology and single biomarker molecular tests are referred to these public regional reference centres (often university hospitals). The

centres are distributed evenly across France, ensuring regional consistency in testing provision. Patients are actively referred to these publicly funded centres from local hospitals which often lack advanced testing capabilities [8].

Multi-biomarker testing

23 out of 27 publicly funded molecular diagnostic centres in France have NGS capabilities, evenly distributed across the country. These ensure consistent access to NGS testing across France.

b. Supporting illustrations on biomarker access and quality findings

Note: all illustrations are based on secondary and primary research conducted by L.E.K. Consulting on behalf of IQN Path, ECPC, EFPIA and a consortium of industry and academic partners. Primary research included qualitative interviews with 58 laboratory managers / pathologists, oncologists, and payers, an online survey with 141 laboratory managers and an online survey with 1,665 cancer patients in the EU and the UK.

Illustration A: Medicines access

Rank	👤		Number Reimbursed	Number Available	Percent Reimbursed	Cumulative % of pop.
1		DE	35	37	95%	16%
2		NED	35**	36	95%	20%
3		UK	29+5*	36	95%	33%
4		SPA	31**	33	95%	42%
5		ITA	30**	33	90%	53%
6		DEN	29	29	100%	55%
7		BEL	28	29	95%	57%
8		CRO	28	28	100%	58%
9		SWE	27	35	75%	60%
10		FR	27	34	80%	73%
11		BUL	26^	29	90%	74%
12		AUT	25^^	33	75%	76%
13		FIN	24	34	70%	77%
14		IRE	24	33	75%	78%
15		POL	23	27	85%	23%
16		ROM	22	27	80%	22%
17		SLV	20	33	60%	20%
18		HUN	20	25	80%	20%
19		GRE	19	26	75%	19%
20		CZE	19	25	75%	19%
21		SLK	18	31	60%	18%
22		POR	18	26	70%	18%
23		LUX	17	26	65%	17%
24		EST	17	23	75%	17%
25		LIT	15	24	65%	15%
26		LAT	10	24	40%	10%
27		CYP	7	27	25%	7%
28		MLT	7	7	100%	7%

37 EMA approved therapies

Reimbursed	>30	16-30	<16
Available	>30	26-30	<26
% Reimbursed	>90%	75-90%	<75%

Note: Ranking based on # of medicines publicly reimbursed; * 5 medicines available only through the cancer drug fund (CDF); ** Downgraded as some variation in reimbursement by region / hospital reported; ^ Downgraded as actual availability of these medicines may be unstable, with several reports of regular medicine shortages; ^^ Some medicines may only be reimbursed on a case-by-case basis following physician request (e.g., larotrectinib)

Source: EFPIA; L.E.K. research and analysis

Illustration B: Medicines access

Western Europe

UK	FRA	DE	IRE	BEL	NED	LUX	AUT
Reimbursed following NICE assessment; 5 medicines only available through cancer drug fund (CDF), with some variation in availability between constituent nations	High availability but lag from addition to reimbursement list to inclusion in guidelines	Medicine approval and inclusion into SHI formulary is linked to EMA decision	Good availability, but system for inclusion on reimbursement list is disorganised driving delays	Moderate availability, high awareness driven by publication of updates in national journal	Short time to PM launch and national reimbursement but delayed patient access due to contract negotiations at hospital level; long time to guideline inclusion	Moderate availability, reimbursement through statutory national insurance	High rates of availability but reimbursement is more limited, some requiring case-by-case approval

Nordics & Baltic

DEN	SWE	FIN	LIT	LAT	EST
Good availability and comprehensive reimbursement of PM medicines. Guideline updates could be more regular	Moderate availability of therapies. Reimbursement decisions made at national level driving fast introduction	Moderate availability of therapies. Reimbursement decisions made at national level driving fast introduction	Lag to reimbursement, limited public reimbursement but revision to HTA process may improve this	Slow time to approval for reimbursement, limited public reimbursement	Reasonable availability, but slow time to approval for reimbursement & limited drivers of uptake

Southern Europe

ITA	SPA	GRE	POR	MLT	CYP
Medicines funded via regional budget, creating variations in reimbursement	Medicines funded via regional budget, creating variations in reimbursement	Funding at national level but often insufficient	Slow time to medicines reimbursement vs. EU average	Limited reimbursement; some additional funding via Community Chest Fund	Many medicines require prior authorisation. In most cases, reimbursement is granted

Central Europe

POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
Reasonable access, although long lag from EMA approval to reimbursement	National approval structure in place; access to reimbursed therapies reported to be limited due to low testing	Delays in access following inclusion on reimbursement list driven by slow introduction of testing	Reasonable availability but patient OoP sometime required for new medicines	Regional variation in availability of reimbursement	Recent but reasonable availability; medicine shortages are reported	Strict access criteria common; lag to public reimbursement from EMA approval	While theoretical access is good (if delayed), there are limited drivers of uptake (e.g., guideline inclusion

Reimbursed	>30	16-30	<16
Available	>30	26-30	<26
% Reimbursed	>90%	75-90%	<75%

Source: L.E.K. research and analysis; ESMO country profile Romania; EFPIA: Every day counts (2020)

Illustration C: laboratory access

Western Europe							
🇬🇧 UK	🇫🇷 FRA	DE	🇮🇪 IRE	🇧🇪 BEL	NED	LUX	AUT
National network of regional testing hubs, with clear referral pathways	Centralisation of testing to regional reference labs	Regional centralisation to CoEs through referral pathways	Established regional hubs, with clear referral pathways	Dense & accessible lab network	Referral pathways not optimised due to lack of cooperation between labs; some spontaneous network formation, but no centralisation at national level	One central lab, with some tests sent abroad	Good lab coverage provided by high number of hospital pathology labs

Nordics & Baltic					
DEN	SWE	FIN	LIT	LAT	EST
Uniform access through co-ordinated network of regional hubs	Uniform access through co-ordinated network of regional hubs, good awareness of referral paths	Highly centralised landscape, patient travel to regional hubs may be required for NGS	Regional variability in access due to low awareness of referral pathways	Good access to centralised labs, but some testing sent abroad	Relatively small number of facilities, reasonable referral pathways

Southern Europe					
ITA	SPA	GRE	POR	MLT	CYP
Regional (North vs. South) variability in number and capability of labs	Dense availability of single biomarker capable labs; one NGS lab per major region	Good access ensured through collaboration between public & private labs	Good access through centralised referral centres and pathology labs	One central lab, with some tests sent abroad	Handful of labs provide access to testing, with some specialisation by indication

Central Europe							
POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
Good lab coverage, though regionally variable referral pathways; patient travel may be required	Centralisation of most testing to oncology centres; limited capabilities outside of hubs	Centralisation of testing to main treatment and testing facilities	Centralisation of testing to oncology and diagnostic labs	Limited and disparate lab infrastructure, with frequent reports of staff shortages	Limited public lab infrastructure, testing performed in private lab network to which patients are required to travel for testing	Established regional hubs, with clear referral pathways	Disparate and complex lab infrastructure, with regional variation in referral

High	Medium	Low

Lab access score based on regional availability of diagnostic labs and the efficiency of referral pathways

Note: Countries with regional variation in ability can drive a lower score (even if the overall number of labs is high)
Source: L.E.K. research and analysis

Illustration D: single biomarker test availability

Western Europe	Availability	Timing
UK	75-100%	Late
FRA	75-100%	On time
DE	80%	On time
IRE	76%	Late
BEL	100%	On time
NED	50-75%	On time
LUX	80%	Late
AUT	75-100%	Late

Southern Europe	Availability	Timing
ITA	75%	On time
SPA	82%	On time
GRE	66%	Late
POR	90%	On time
MLT	50-75%	Late
CYP	70%	Late

Nordics & Baltic	Availability	Timing
DEN	75-100%	Late
SWE	85%	Late
FIN	75-100%	On time
LIT	60%	On time
LAT	40%	On time
EST	50-75%	Late

Central Europe	Availability	Timing
POL	64%	On time
CRO	50-75%	On time
HUN	90%	On time
SLV	50-75%	Late
SLK	70%	Late
ROM	50-75%	Late
CZE	50-75%	Late
BUL	50-75%	Late

Availability of biomarker testing is calculated based on the scores for test availability and timing for each country

Single biomarker test availability:

Single biomarker: Average proportion of labs offering each single biomarker test* in-house or through referral

High > 75%	Medium 50-75%	Low <50%

Timing:

Single biomarker Average time from medicine availability to test availability

■ On time – Test available around time of medicine launch

■ Late – Lag from medicine availability to test availability (i.e. >1 year)

Note: * Average across all biomarkers considered in this study
Source: IQN Path / EFPIA lab manager survey (2020); L.E.K. research and analysis

Illustration E: single biomarker test availability

Western Europe							
UK	FRA	DE	IRE	BEL	NED	LUX	AUT
Broad availability, but reimbursement approval for test slowed by NICE review process	Test approval prompted by therapy introduction	EU-Leader in test availability following medicine approval, ensuring prompt & generally uniform test availability	Generally high post-medicine approval availability, although some tests experience delays	Good availability across labs, with dynamic review ensuring up-to-date, though sometimes variable, availability	Significant differences between academic and local labs; slow clinical uptake of tests in local labs	Established send-out process abroad where national capabilities are lacking; slow time to introduction	Pre-authorisation lab preparation process aims to reduce time to test availability

Nordics & Baltic					
DEN	SWE	FIN	LIT	LAT	EST
Good availability in centralised testing centres, though some lag in test availability following medicine approval	Good availability in regional testing centres, though some lag in test availability following medicine approval	Good availability in centralised testing centres, prompt availability driven by inclusion of novel therapies into clinical guidelines	Limited availability of tests linked to newer medicines due to limited reimbursement; generally prompt availability following medicine approval	Limited / no availability of tests linked to newer PM medicines; access often significantly delayed	Limited / no availability of tests linked to newer PM medicines; time to test availability can vary significantly

Southern Europe					
ITA	SPA	GRE	POR	MLT	CYP
Regional variability (North vs. South) in both availability & timing - linked to funding disparities	Good availability of testing. Time to availability generally amongst fastest in EU28	Variable availability in public facilities due to funding restrictions; variable timing of test availability for newer tests	Generally fast and comprehensive adopter of tests, though some delays in medicine reimbursement delay test access	Send-out process abroad / private labs where national public capabilities are lacking	Though improving, some delays in availability reported owing to a lag in reimbursement approval & HCP awareness

Central Europe							
POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
Some delay in the establishment of testing infrastructure following medicine approval	Theoretically broad & prompt availability limited by hospital guidelines & quotas	Established across hospitals and pathology labs; some lag due to lab funding adjustments required	Test availability restricted by limited test reimbursement; tests available upon medicine reimbursement	Significant urban / rural disparity, linked to variable personnel and infrastructure required to run tests	Reasonable availability of tests via private labs; significant delays in availability	Test availability restricted by limited medicine availability; tests available upon medicine reimbursement	Variable availability due to disparate lab landscape, labs often limited to single biomarker testing

Single biomarker: Average proportion of labs offering each single biomarker test in-house or through referral

Single biomarker test availability:
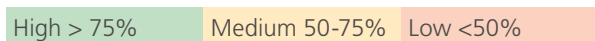
High > 75%	Medium 50-75%	Low <50%

Availability of biomarker testing is calculated based on the scores for test availability and timing for each country

Timing:

Single biomarker

■ On time – Test available around time of medicine launch

■ Late – Lag from medicine availability to test availability (i.e. >1 year)

Source: L.E.K. research and analysis

Illustration F: Single biomarker test reimbursement

Western Europe							
🇬🇧 UK	🇫🇷 FRA	⚫ DE	🇮🇪 IRE	🇧🇪 BEL	🇳🇱 NED	🇱🇺 LUX	🇦🇹 AUT
93%	**96%**	**90-100%**	**75-90%**	**82%**	**75-90%**	**100%**	**75-90%**
Comprehensive public funding, with dynamic regional adjustment	Good public funding, through tariff system / academic grants	Some variability in funding for in-patient setting due to different sources	Lack of clarity in reimbursement pathways, some patient OoP	Public reimbursement subject to delays and caps, resulting in pharma co-sponsorship or OoP	New tests can exceed the budget ceiling agreements between hospitals and health insurers	Centralised LNS budget covers all single biomarker tests	Some regional variation in reimbursement driven by different funding sources by region

Nordics & Baltic					
🇩🇰 DEN	🇸🇪 SWE	🇫🇮 FIN	🇱🇹 LIT	🇱🇻 LAT	🇪🇪 EST
100%	**100%**	**96%**	**<75%**	**<75%**	**75-90%**
Specific budget allocated to major Dx centres that supports biomarker testing	Testing reimbursed at regional level via hospital budgets	Testing reimbursed via specific regional diagnostic budget	MDx tests are generally pharma sponsored. Government review of funding underway	Mixture of public and Pharma funding	Established tests covered by public reimbursement via hospital budgets

Southern Europe					
🇮🇹 ITA	🇪🇸 SPA	🇬🇷 GRE	🇵🇹 POR	🇲🇹 MLT	🇨🇾 CYP
84%	**79%**	**<75%**	**75-90%**	**75-90%**	**86%**
Variable reimbursement driven by regional discrepancies in funding. Lack of national co-ordination	Variable public reimbursement driven by regional discrepancies in funding. Some pharma involvement	Public coverage of certain biomarker / indication combinations. Significant OoP burden	Hospital budgets and pharma cover in-house & sent out tests	All testing is covered under lab budget provide by National Heath Fund, though some pharma funding is required	Testing is reimbursed nationally via specific codes, though some pharma funding is required

Central Europe							
🇵🇱 POL	🇭🇷 CRO	🇭🇺 HUN	🇸🇮 SLV	🇸🇰 SLK	🇷🇴 ROM	🇨🇿 CZE	🇧🇬 BUL
89%	**65%**	**75-90%**	**75-90%**	**<75%**	**<75%**	**100%**	**<75%**
Some biomarker tests reimbursed by MoH via specific codes, but large proportion of pharma funding	Most testing reimbursed via DRG-type system; some pharma sponsorship	Testing reimbursed but Dx funding is capped, leading to some reliance on Pharma	Testing reimbursed via SHI budget; some pharma sponsorship	Cheaper biomarker tests reimbursed, more expensive paid OoP	Tests are often not reimbursed due to lack of public funding; heavy reliance on Pharma funding	Testing reimbursed via SHI budget	No public funding; testing is sponsored by Pharma

High > 90%   Medium 75-90%   Low <75%

Test reimbursement calculated based on the average proportion of tests reported to be covered by public reimbursement **based on both patient and lab survey results**

Source: IQN Path / EFPIA lab manager survey (2020); KPMG: Versnellen van implementatie van biomarker diagnostiek (February 2020); L.E.K. research and analysis

Illustration G: Single biomarker test order rates

Western Europe							
UK	FRA	DE	IRE	BEL	NED	LUX	AUT
66%	**78%**	**78%**	**75-100%**	**92%**	**50-75%**	**50-75%**	**75-100%**
Strict testing paradigms may reduce order rates for some biomarkers	Clear referral pathways to MDx centres; good public funding	High order rates driven by good access to testing	High order rates for established tests driven by referral process	High awareness of available tests driven by regular and well publicised guideline updates	Significant differences between academic and local labs; unclear referral can hinder order rates	Introduction of reflex testing is expected to continue to drive order rate increases	Some patient leakage, but initiatives in place to address this

Nordics & Baltic					
DEN	SWE	FIN	LIT	LAT	EST
83%	**65%**	**87%**	**62%**	**30%**	**50-75%**
High order rates for all tests due to good reimbursement and high awareness of referral pathways	Order rates lag for newer tests	High order rates for all tests due to good reimbursement and high awareness of referral pathways	Historically limited by lack of education and awareness of PM. Both are increasing as PM uptake improves	Order rates limited by the severe lack of availability of linked therapies	Order rates limited by the lack of availability of linked therapies

Southern Europe					
ITA	SPA	GRE	POR	MLT	CYP
78%	**75%**	**81%**	**78%**	**80%**	**77%**
High order rates, although some regional variation in funding and guidelines	Order rates are high driven by prominence of biomarker testing in guidelines	Good referral pathways, and Pharma sponsorship for certain tests	Order rates higher for lung cancer driven by increased awareness	Established initial referral system, centralised care and testing and good funding	Established initial referral system, centralised care and testing and good funding

Central Europe							
POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
68%	**75-100%**	**43%**	**50-75%**	**<50%**	**<50%**	**38%**	**<50%**
High awareness driven by recent educational effort; some newer tests not performed	Order rates are high for established tests; newer tests limited by medicine availability	Lack of reimbursed linked medicines, limited awareness of tests & budgetary caps	Good awareness of guidelines, as well as established referral pathways	Limits on reimbursement by patient profile and indication	Order rates limited by the severe lack of availability of linked therapies	Order rates for limited by low availability / use of linked therapies	Order rates limited by lack of availability of linked therapies & availability of funding

High > 75%   Medium 50-75%   Low <50%

Test order rate is calculated based on the average order rates across focus biomarkers*

Note: * Test **order rate** is defined as % share of total unique biopsies for which a given biomarker test was performed; e.g., in the case of PD-L1, the order rate is defined as the number of unique metastatic NSCLC biopsies on which a PD-L1 test was performed out of the total unique metastatic NSCLC biopsies takenib)

Source: IQN Path / EFPIA lab manager survey (2020); L.E.K. research and analysis

Illustration H: Multi-biomarker test availability

Western Europe	Capability	Availability
UK	**High**	**100%**
FRA	**High**	**100%**
DE	**High**	**100%**
IRE	**High**	**100%**
BEL	**Medium**	**100%**
NED	**Medium**	**75-90%**
LUX	**Medium**	**67%**
AUT	**High**	**100%**

Southern Europe	Capability	Availability
ITA	**High**	**67%**
SPA	**Medium**	**83%**
GRE	**High**	**60%**
POR	**High**	**100%**
MLT	**N/A***	**N/A***
CYP	**Low**	**100%**

Nordics & Baltic	Capability	Availability
DEN	**Medium**	**100%**
SWE	**High**	**100%**
FIN	**High**	**100%**
LIT	**Medium**	**<75%**
LAT	**Low**	**<75%**
EST	**Low**	**<75%**

Central Europe	Capability	Availability
POL	**High**	**60%**
CRO	**Medium**	**75-90%**
HUN	**Medium**	**75-90%**
SLV	**Low**	**<75%**
SLK	**Low**	**<75%**
ROM	**Low**	**<75%**
CZE	**High**	**75-90%**
BUL	**Low**	**<75%**

Availability is calculated based on the scores for NGS test capability and the availability of NGS testing

Capability:

NGS: Availability of different NGS test technologies (i.e. hotspot / panel / comprehensive) within a given country (available in 1+ lab)

- 🟩 High - All 3 test technologies
- 🟨 Medium - 2 of the 3 technologies
- 🟥 Low - 1 or no test technologies

Availability of NGS testing:

NGS: Proportion of labs offering any NGS modality in-house or through referral

- 🟩 High - 90%
- 🟨 Medium - 75-90%
- 🟥 Low - <75%

Note: * Not scored as currently in transition period, with NGS capabilities being established but not available yet

Source: IQN Path / EFPIA lab manager survey (2020); L.E.K. research and analysis

Illustration I: Multi-biomarker test integration

Western Europe	Timing	Uptake
UK	**Average**	**9%**
FRA	**Average**	**21%**
DE	**Leader**	**12%**
IRE	**Average**	**8%**
BEL	**Average**	**22%**
NED	**Average**	**52%**
LUX	**Follower**	**<50%**
AUT	**Average**	**25%**

Southern Europe	Timing	Uptake
ITA	**Leader**	**2%**
SPA	**Average**	**2%**
GRE	**Average**	**1%**
POR	**Leader**	**31%**
MLT	**Follower**	**N/A***
CYP	**Follower**	**31%**

Nordics & Baltic	Timing	Uptake
DEN	**Average**	**50-75%**
SWE	**Leader**	**33%**
FIN	**Follower**	**17%**
LIT	**Follower**	**18%**
LAT	**Follower**	**3%**
EST	**Follower**	**<50%**

Central Europe	Timing	Uptake
POL	**Leader**	**10%**
CRO	**Average**	**3%**
HUN	**Average**	**14%**
SLV	**Follower**	**<50%**
SLK	**Follower**	**0%**
ROM	**Follower**	**<50%**
CZE	**Average**	**0%**
BUL	**Follower**	**<50%**

Integration is calculated based on the average scores for NGS timing and uptake of NGS testing

Time available:

NGS: Time from introduction of any NGS test modality

■ Leader – Mostly >5 years

■ Average - Mostly 3-5 years

■ Follower – Mostly <3 years

Uptake:

NGS uptake: Average % of all biopsies currently analysed using NGS technology

■ High - >75%%

■ Medium - 50-75%

■ Low - <50%

Note: * Not scored as currently in transition period, with NGS capabilities being established but not available yet
Source: IQN Path / EFPIA lab manager survey (2020); L.E.K. research and analysis

Illustration J: multi-biomarker test availability and integration by country – additional detail

Western Europe							
🇬🇧 UK	🇫🇷 FRA	🇩🇪 DE	🇮🇪 IRE	🇧🇪 BEL	🇳🇱 NED	🇱🇺 LUX	🇦🇹 AUT
Available through centralised genomic network; although genomic hubs not yet fully operational yet	Slight delay in adoption, but good availability through regional reference centres	Early & comprehensive adopter of full-suite of NGS test technologies	Recent, but comprehensive adoption of all NGS test technologies – available in regional hubs	Good, but recent availability of hotspot and panel technologies; comp. panels only in private labs	Significant differences in availability between academic and local labs	Recent introduction of hotspot and panel testing; progressive integration of NGS into clinical SoC	Limited to diagnostic facilities with variable referral pathways

Nordics & Baltic					
🇩🇰 DEN	🇸🇪 SWE	🇫🇮 FIN	🇱🇹 LIT	🇱🇻 LAT	🇪🇪 EST
Established availability of hotspot and comprehensive panels in regional referral centres	Established availability of hotspot and comprehensive panels in regional referral centres and dedicated NGS facilities	Recent availability of full NGS test technology suite across regional hubs	No public sector availability as part of clinical SoC, access only possible through private labs and research centres	No public sector availability access only possible through private labs	No public sector availability access only possible through private labs

Southern Europe					
🇮🇹 ITA	🇪🇸 SPA	🇬🇷 GRE	🇵🇹 POR	🇲🇹 MLT	🇨🇾 CYP
Contrastingly variable availability by region (North vs. South), introduction delayed by funding restrictions	Regional variability in NGS availability, with large hospitals equipped but limited availability outside of them	Available in academic / private facilities, broader uptake limited by significant funding restrictions	Early adoption of NGS testing in centralised referral centres	Currently unavailable, but target panels to be implemented start-2021	Recent but strong drive towards comprehensive pan-cancer NGS panels

Central Europe							
🇵🇱 POL	🇭🇷 CRO	🇭🇺 HUN	🇸🇮 SLV	🇸🇰 SLK	🇷🇴 ROM	🇨🇿 CZE	🇧🇬 BUL
Availability limited to hotspot testing in specialised centres; larger panels unavailable	Drive towards broader use in specialised centre in partnership with phama	Available only in major research centres & private facilities	Lack of integration into SoC limits availability, despite established testing infrastructure	Only available in private & research facilities	No public availability limited by lack of in-house capability	Established availability in University hospital labs; uptake limited by funding	No public availability limited by lack of in-house capability

High	Medium	Low

Score calculated based on the average scores for availability (NGS test capability and availability of NGS testing) and integration (timings and uptake of NGS testing)

Source: L.E.K. research and analysis; KPMG: Versnellen van implementatie van biomarker diagnostiek (February 2020)

Illustration K: Multi-biomarker test reimbursement

Western Europe							
UK	FRA	DE	IRE	BEL	NED	LUX	AUT
100%	**86%**	**100%**	**75-90%**	**75-90%**	**75-90%**	**75-90%**	**75-90%**
Funding at the national level for genomic hubs, although some pharma contribution to tests relating to medicines funded by CDF; some delays in transitioning to genomic hubs	Public funding via hospital budgets for hotspot panels. Larger panels funded by RIHN (academic budget)	Good level of public reimbursement in out-patient setting. In-patient DRG system limits reimbursement of new panels	Public reimbursement sufficient but lack of national funding policy limits further uptake	Good funding for small panels, though Pharma sponsorship or patient OoP required for larger panels	New tests can exceed the budget ceiling agreements between hospitals and health insurers	Centralised LNS budget covers small panel tests. Patient OoP for large panels	Reimbursed via hospital budgets or national sickness fund

Nordics & Baltic					
DEN	SWE	FIN	LIT	LAT	EST
100%	**90-100%**	**100%**	**20%**	**<75%**	**<75%**
High order rates for all tests due to good reimbursement and high awareness of referral pathways	Order rates lag for newer tests	High order rates for all tests due to good reimbursement and high awareness of referral pathways	Historically limited by lack of education and awareness of PM. Both are increasing as PM uptake improves	Order rates limited by the severe lack of availability of linked therapies	Order rates limited by the lack of availability of linked therapies

Southern Europe					
ITA	SPA	GRE	POR	MLT	CYP
75-90%	**<75%**	**<75%**	**75-90%**	**N/A**	**90-100%**
High order rates, although some regional variation in funding and guidelines	Order rates are high driven by prominence of biomarker testing in guidelines	Good referral pathways, and Pharma sponsorship for certain tests	Order rates higher for lung cancer driven by increased awareness	Established initial referral system, centralised care and testing and good funding	Established initial referral system, centralised care and testing and good funding

Central Europe							
POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
50%	**<75%**	**<75%**	**<75%**	**<75%**	**<75%**	**<75%**	**<75%**
Patchy funding necessitates pharma co-sponsorship	NGS testing is nascent, with most (esp. large panels) currently Pharma funded	Limits on reimbursement amount leads to pharma co-sponsorship. Expected to limit uptake	NGS tests must be funded by the reference labs themselves, with no National Health contribution	Variable reimbursement by statutory public insurers	Not reimbursed due to lack of public funding	Only available via academic / government grants or patient OoP	No public funding; testing is paid for by patients

High > 90%   Medium 75-90%   Low <75%

Test reimbursement calculated based on the average proportion of tests reported to be covered by public reimbursement

Source: IQN Path / EFPIA lab manager survey (2020); KPMG: Versnellen van implementatie van biomarker diagnostiek (February 2020); L.E.K. research and analysis

Illustration L: Multi-biomarker test order rate

Western Europe							
UK	FRA	DE	IRE	BEL	NED	LUX	AUT
50-75%	**80%**	**50-75%**	**2%**	**80%**	**50%**	**50-75%**	**55%**
High awareness of referral pathways to centralised NGS labs, drive towards NGS testing	Centralised system drives high NGS uptake	Policy ensuring reimbursement of tests performed elsewhere in lab network contributes to high order rates	Funding remains a barrier to increased uptake of NGS	High use of hotspot panels, driven by pilot programme promoting multi-biomarker methods	Significant differences between academic and local labs; unclear referral can reduce order rates	Moderate but pilot assessing value and feasibility of expanded NGS could drive uptick	Focus of the National Cancer Framework to promote NGS use

Nordics & Baltic					
DEN	SWE	FIN	LIT	LAT	EST
100%	**80%**	**50-75%**	**30%**	**<50%**	**<50%**
Good education of benefits, high awareness of test availability and good reimbursement	High use of NGS driven by regional programmes and initiatives promoting its use	Moderate NGS order rates, with lab managers / physicians preferring cheaper single biom. tests	Increasing use of NGS driven by "Lithuania panel" and perceived benefits and supported by Pharma	Only available through private sector at patients' expense	Only available through private sector at patients' expense

Southern Europe					
ITA	SPA	GRE	POR	MLT	CYP
50-75%	**50-75%**	**50-75%**	**79%**	**N/A**	**100%**
Order rates for hotspot testing high in NSCLC; comprehensive panel use limited by scarcity of funding	Some regional variation in uptake of NGS driven by differing levels of awareness but order rates are generally high	Use restricted to lung cancer where order rates are high	Early adopter; good referral and reimbursement drives high use of small / medium panels	N/A – NGS testing not yet available	Centralised NGS facility ensures volumes justify cost of NGS platform

Central Europe							
POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
50-75%	**12%**	**30%**	**<50%**	**<50%**	**<50%**	**<50%**	**<50%**
Drive towards NGS (hotspot) resulted in high physician awareness in large volume centres	NGS use low but increasingly supported by government policies	Centralisation of NGS drives volumes to support growing uptake	Lab managers cite a lack of political pressure as a barrier to wider NGS testing	Limited drivers of use of NGS	Only available through private sector at patients' expense	Limited policy drive to integrate NGS into SoC; funding only via grants and for childhood cancers	Only available through private sector at patients' expense

High > 75% Medium 50-75% Low <50%

Test order rate is calculated based on the max. order rate for NSCLC across available NGS platforms

Note: Test **order rate** is defined as % share of total unique biopsies for which a given NGS test was performed; e.g., in the case of hotspot, the order rate is defined as the number of unique metastatic NSCLC biopsies on which a hotspot test was performed out of the total unique metastatic NSCLC biopsies taken

Source: IQN Path / EFPIA lab manager survey (2020); KPMG: Versnellen van implementatie van biomarker diagnostiek (February 2020); L.E.K. research and analysis

Illustration M: Test quality

EQA participation

Lab (ISO) accreditation

Directional

Key – average proportion of labs participating in at least one EQA scheme:

- 🟩 High - >90%
- 🟨 Medium - 75-90%
- 🟥 Low - <75%

EQA participation calculated based on the average proportion of labs participating in at least one EQA scheme

ISO accreditation determined based on the proportion of labs that are ISO accredited within each country

Source: IQN Path / EFPIA lab manager survey (2020); L.E.K. research and analysis

Illustration N: Test quality – EQA scheme participation & ISO accreditation

Western Europe							
UK	FRA	DE	IRE	BEL	NED	LUX	AUT
EQA participation mandated, many labs ISO accredited	Most clinical labs are ISO accredited, participation & performance in EQA is high	EQA participation very common, supported by lab funding. Internal validation routinely assessed	EQA participation a requirement for pubic reimbursement	Royal Decree mandates MDx labs ISO accreditation for 80% of activities. EQA funded by hospital budgets	EQA participation & ISO accreditation mandated, with funding provided by lab budgets	LNS participates in EQA supported by lab budget but is not ISO accredited	Funding for EQA scheme participation from lab budget or associated hospital budget. Pharma funding prohibited

Nordics & Baltic					
DEN	SWE	FIN	LIT	LAT	EST
High in large centres, supported by regional diagnostic budgets. May be lower in smaller labs	While pass rates are high, lack of mandatory participation may limit EQA participation beyond university hospitals	Labs are typically ISO accredited and participation & performance in EQA schemes is high. Funding from hospital Dx budgets	Only a few of the largest centres participate, pass rates are low. Funding is the limiting factor for smaller labs	EQA participation and ISO accreditation is a legal requirement for Dx labs. Funding from lab budgets	All main labs participate in EQA schemes but pass rates are very low

Southern Europe					
ITA	SPA	GRE	POR	MLT	CYP
High pass rates in EQA schemes, minority ISO accredited. Funding is varied, with some Pharma reliance	Reasonable participation in EQA schemes, minority ISO accredited. Funding is varied, with some Pharma reliance	Funding constraints limit EQA participation and ISO accreditation. Not a legal requirement, often driven and supported by Pharma	Most labs participate. Labs usually fund EQA, with sporadic support from Pharma for certain schemes	Central lab participates in EQA supported by lab budget. Currently pursuing ISO accreditation	Both main labs are ISO accredited & participate in EQA schemes, supported by lab budgets

Central Europe							
POL	CRO	HUN	SLV	SLK	ROM	CZE	BUL
Most public labs self-fund participation in EQA schemes. Few ISO accredited	Centralisation of testing ensures good EQA participation. Limited ISO accred.	Quality thresholds on reimbursement drive reasonable part. & accred.	Good EQA but low pass rates. Accreditation not a requirement for funding or trial participation	Reasonable participation in EQA schemes, minority ISO accredited. Funding is varied, with Pharma reliance	Funding shortages and lack of drivers limits quality assurance for public labs; Private labs commonly participate in EQA	Reasonable EQA participation but low pass rates. Some labs are ISO accredited	Lack of centralisation & limited funding restricts participation. No ISO accreditation

EQA participation calculated based on the average proportion of labs participating in at least one EQA scheme

ISO accreditation determined based on the proportion of labs that are ISO accredited within each country

High	Medium	Low
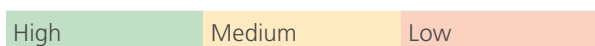
Source: L.E.K. research and analysis

Illustration O

Single biomarker testing TAT

Multi-biomarker testing TAT
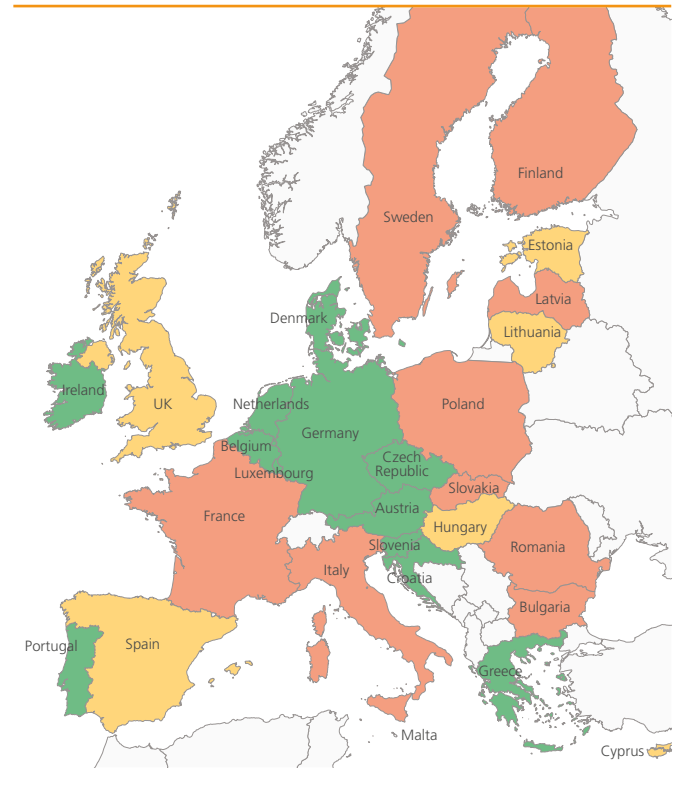
Single:	<2 wks	2-3 wks	3+ wks
NGS:	<2 wks	2-3 wks	3+ wks

Testing TAT is calculated based on the average turnaround times (i.e. time from test order to receipt of the result by the physician) across focus biomarkers / NGS platforms

Note: Malta and Luxembourg: indicated TATs for locally performed tests

Source: IQN Path / EFPIA lab manager survey (2020); L.E.K. research and analysis

Illustration P: Test quality

Western Europe

🇬🇧 UK	🇫🇷 FRA	🇩🇪 DE	🇮🇪 IRE	🇧🇪 BEL	🇳🇱 NED	🇱🇺 LUX	🇦🇹 AUT
Though timely in-house testing, variable send-out efficiency may push TAT outside of guidelines	Communication inefficiencies add significant delay to NGS TAT	Efficient referral to centralised testing labs, though some reports to delays induced by a shift to NGS testing	Efficient referral to centralised testing labs ensure consistent TAT	TAT within 2 weeks for all tests. Efficiency gains possible in the communication of test results	Guideline-stipulated TAT ensure consistent performance across labs	Established and efficient external referral ensure fast TAT even when international send-out is required	Variability between internal and send-out TAT, though generally within guidelines

Nordics & Baltic

🇩🇰 DEN	🇸🇪 SWE	🇫🇮 FIN	🇱🇹 LIT	🇱🇻 LAT	🇪🇪 EST
Testing centralisation to regional hubs ensures consistently good TAT	Decentralised nature of testing leads to variability in practice and slows TAT	Testing centralisation to regional hubs ensures consistently good TAT , though NGS may be slower	Actionable TAT driven by efficient centralisation -though BRCA testing can be significantly delayed	Inefficient private & international send-out	Centralisation of testing and treatment ensures actionable TAT

Southern Europe

🇮🇹 ITA	🇪🇸 SPA	🇬🇷 GRE	🇵🇹 POR	🇲🇹 MLT	🇨🇾 CYP
Common reports of testing delays – particularly for NGS – driven by variable access and referral	Pro-active communication pathways between lab managers and prescribing physicians; NGS TAT may be subject to delays	Efficient referral process to private labs where required	Consistent TAT driven by centralisation – with capacity to expedite testing upon request	Established and efficient external referral ensure fast TAT despite international send-out; NGS may be subject to some delays	Variable single biomarker TAT by test technology despite centralisation, though consistent fast TAT for NGS

Central Europe

🇵🇱 POL	🇭🇷 CRO	🇭🇺 HUN	🇸🇮 SLV	🇸🇰 SLK	🇷🇴 ROM	🇨🇿 CZE	🇧🇬 BUL
Additional pre-analytical referral adds significant delay to send-out TAT	Centralisation ensures actionable TAT with limited regional variation	Pro-active drive towards standardised testing ensures TAT are within guidelines	Centralisation ensures batch runs are sufficiently frequent for actionable TAT	Generally slow TAT, exacerbated by regional disparities in access to testing facilities	High proportion of samples handled by private labs acts to reduce TATs	Though currently fast, a lack of skilled personnel pose long-term risk of deterioration	Complex, sequential test referral process further delayed by patient involvement in sample transport

High	Medium	Low

Single:	<2 wks	<2-3 wks	3+ wks
NGS:	<2 wks	<2-3 wks	3+ wks

Testing TAT is calculated based on the average turnaround times (*i.e. time from test order to receipt of the result by the physician*) across focus biomarkers / NGS platforms

Source: L.E.K. research and analysis

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d. Members of working group behind policy recommendations

Steering Committee

- AIOM
- AstraZeneca
- DGP
- EFPIA
- ECPC
- ESP QA
- Gen&Tiss
- GSK
- IQN Path
- MSD
- NordiQC
- Novartis
- Roche
- SEAP
- UK NEQAS

Advisory Committee

- Bayer
- BMS
- Guardant Health
- Lilly
- Merck Group

e. Methods

The findings of this paper are based on research conducted by L.E.K. Consulting between October 2019 and August 2020, on behalf of IQN Path, ECPC, EFPIA and a consortium of industry and academic participants, aimed at understanding the access to, and quality of biomarker testing across all EU countries and the UK.

The research covered key biomarkers, as defined by IQN Path, ECPC and EFPIA, with increased focus 10 core countries.

Biomarker tests

Tier 1 in every country
Single biomarker IHC / FISH
PD-L1
Single biomarker molecular
BRCA
EGFR
NTRK
Complex genomic signatures
NGS hotspot (up to 50 genes) / targeted panel
NGS comprehensive panel

Tier 2 only in the core countries
Single biomarker IHC / FISH
HER2
ALK
MMR / MSI
ROS1
Single biomarker molecular
BRAF
KRAS / NRAS
Other (application)

Geographical coverage

10 Core countries			
EU4 / UK		Ex-EU4 / UK	
Germany	Spain	Belgium	Poland
France	Italy	Netherlands	Greece
UK		Sweden	

Scope: coverage of Tier 1 & 2 tests

18 Remaining countries		
Western Europe	Central Europe	Southern Europe
Austria	Bulgaria	Cyprus
Ireland	Croatia	Malta
Luxembourg	Czech Republic	Portugal
	Hungary	
Nordics	Romania	Baltics
Denmark	Slovenia	Estonia
Finland	Slovakia	Latvia
		Lithuania

Scope: coverage of Tier 1 tests *only*

Phase 1 – Secondary research

As a first step, existing data inputs from pharmaceutical / laboratory project partners on the biomarker testing landscape were gathered and supplemented by extensive country-specific research. Through this research we aimed to develop a preliminary view of the biomarker testing situation in each country, characterising the access and quality landscape, and to define hypotheses on barriers to testing. Over the course of the research we leveraged a wide range of secondary sources, investigating the laboratory landscape (number of laboratories, distribution, and capabilities), reimbursement and access policies and status, test availability and usage, and level of quality scheme participation:

Academic papers

- Christensen, et al., 2017
- Basu et al., 2018
- Ryska, et al. 2018
- Pennell, et al., 2019
- Verderio et al., 2018
- Castel, et al., 2019
- Helsper et al., 2017
- Jedrejewski, et al., 2015
- Valckenbourg et al., 2018
- Robertson et al., 2017
- Wurcel et al., 2016
- Deticek et al., 2018
- Normanno et al., 2017
- Colomer, et al., 2017
- Paradiso et al., 2009
- Oberst et al., 2015
- Whitten et al., 2016
- Nowak et al., 2012
- Epskamp-Kuijpers, et al., 2019
- Normanno et al., 2015
- Fokkema et al., 2019
- Charles et al., 2017
- Jedrzejewski et al., 2015
- Anell et al., 2012

Cancer networks and institutes

- French National Cancer Institute (INCa)
- Dutch Association of Genetic Labs (VKGL)
- Belgium Health Care Knowledge Centre (KCE)
- Hungarian National Institute of Oncology (NIO)
- Austrian Comprehensive Cancer Centre (CCC)
- Portuguese Institute of Oncology (IPO)

Government bodies

- **National Health Funds and Services**
  e.g. NHS (UK, Luxembourg); SV; VLK; DIMDI; Bundesministerium für Gesundheit; HSE; CNS; Ministry of Health (France, Greece, Poland)

- **National Drug Reimbursement Lists**
  e.g. Cyprus Pharmaceutical Services; VLK; BNF; INFRAMED; GKV-Spitzenverband; G-BA; Kela; Danish Medicines Agency; Polish Ministry of Health; State Institute for Drug Control; Italian Medicines Agency; Maltese Government Formulary List; Croatian Health Insurance Fund; Greek Ministry of Health; Pharmaceutical Service Cyprus; Agency of Medicines; Ministry of Social Affairs and Health

Quality assurance bodies

National accreditation bodies			Quality schemes
BMWA	ENAC	NAT	IQN Path
BELAC	SEWDAC	HAA	AIOM
DANAK	CYS-CYSAB	PCA	Nordic QC
INAB	CAI	SNA	DGP
ILNAS	EAK	ESYD	SEAP
IPAC	FINAS	BAS	EMQN
PCA	NAB-Malta		
SA	LATAK		
UKAS	LA		

Other sources

- Cancer Drug Development Form
- Cancer Control
- CDDF
- Charles River Associates
- eCancer
- The Economist
- ECPC
- EFPIA
- EMSO
- EPAAC
- Eunethta
- Eurostat
- European Commission
- DataMonitor
- Diaceutics
- Galinos
- Infarma
- Inami
- IPAAC
- ICCP
- LSE
- Lung Cancer Europe
- NCCN
- News and press articles
- NICE
- Norden
- Nordic Medical Research Councils
- OECD
- Personalized Medicine Coalition
- WHO

Phase 2 – Qualitative stakeholder interviews

We then conducted qualitative interviews in every EU country and the UK to fill gaps identified based on secondary research and pressure test hypotheses on barriers. We interviewed 58 laboratory managers / pathologists, oncologists, and payers. Through these discussions, we developed a more detailed understanding of the testing environment in each country, validated our view of country performance against access and quality metrics, identified access and quality drivers and barriers as well as potential initiatives to achieve the vision of rapid and widespread access to biomarker testing.

Phase 3 – Quantitative surveys of laboratory managers and patients

We designed and fielded a survey of laboratory managers to further test hypotheses on testing barriers and quantify country performance against key access and quality metrics. This allowed us to pressure test our hypotheses and add specificity and robustness to our findings.

Over the course of the summer of 2020 we distributed the survey, receiving 141 completed responses across the EU27 and UK:

Country	Completed responses
Austria	2
Belgium	**4**
Bulgaria	-
Croatia	2
Cyprus	2
Czech Republic	5
Denmark	1
Estonia	1
Finland	2
France	**13**
Germany	**12**
Greece	**9**
Hungary	4
Ireland	7
Italy	**18**
Latvia	1
Lithuania	1
Luxembourg	-
Malta	1
Netherlands	**6**
Poland	**12**
Portugal	2
Romania	1
Slovakia	2
Slovenia	1
Spain	**13**
Sweden	**5**
UK	**14**
Other	-

Note: Countries listed in **bold** defined as priority countries

Unlocking the potential of precision medicine in Europe

We also designed and fielded a survey of cancer patients to better understand patient concerns on cancer diagnosis and care and further test hypotheses on testing barriers, receiving 1,665 responses across 16 target countries within Europe.

Country	Total responses	"n" patients having received a biomarker test(s)	"n" patients not having received a biomarker test(s)	% of patients having received a biomarker test(s)
Belgium	16	5	11	31%
Bulgaria	18	3	15	17%
Croatia	50	12	38	24%
Czech Republic	27	7	20	26%
Denmark	26	2	24	8%
France	16	3	13	19%
Germany	90	16	74	18%
Greece	163	65	98	40%
Ireland	19	5	14	26%
Italy	208	102	106	49%
Lithuania	516	165	351	32%
Netherlands	174	35	139	20%
Poland	21	6	15	29%
Romania	23	9	14	39%
Spain	161	61	100	38%
UK	59	7	52	12%
Others	78	25	53	32%
Total	**1,665**	**528**	**1,137**	**32%**

f. Glossary

ALK: a gene that makes a protein involved in cell growth. Mutated forms of the ALK gene and protein have been found in some types of cancer, including neuroblastoma, non-small cell lung cancer, and anaplastic large cell lymphoma. These changes may increase the growth of cancer cells. Checking for changes in the ALK gene in tumour tissue may help to make cancer treatment decisions. Also called anaplastic lymphoma kinase gene [35]

Biomarker: biological characteristic that is objectively measured and evaluated as an indicator of biological processes. Biomarker refers to any molecule in the human body that can be measured to assess health (e.g., haemoglobin A1c as a marker of diabetes). Molecules can be derived from blood, body fluids or tissue [7, 38]

Biomarker-linked therapy: therapy for which a biomarker test is specified in the medicine label; the presence or absence of the biomarker determines whether the patient is eligible to receive the therapy

Biomarker testing: biochemical measurement developed to quantitate one, or several, biomarkers for the screening, diagnosis and/or prognosis of cancer patients. Tests can be divided into three groups: chromosome tests (looking for abnormal changes within chromosomes), gene tests (assessing either one gene or a short piece of DNA for changes such as extra gene copies, missing genes and mutations), and biochemical tests (assessing the presence of abnormal proteins or possible effects of cancer via the presence of specific chemicals in the blood) [7, 38]

BRAF: gene that makes a protein involved in sending signals in cells and in cell growth. Mutated forms of the BRAF gene and protein have been found in many types of cancer including melanoma and colorectal cancer. These changes can increase the growth and spread of cancer cells. Checking for this BRAF mutation in tumour tissue may help to plan cancer treatment [35]

BRCA: genes on chromosome 17 (BRCA1) or on chromosome 13 (BRCA2) that normally help to suppress cell growth. A person who inherits certain mutations in a BRCA1 or BRCA2 gene has a higher risk of developing breast, ovarian, prostate, and other types of cancer [35]

Companion diagnostic: medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding medicine or biological product

Comprehensive testing: use of genomic / complex testing (e.g., next-generation sequencing (NGS)) of tumour or blood samples to detect multiple alterations in genes that are known to drive cancer growth (i.e., base changes, insertions & deletions, and rearrangements or fusions). NGS can be used to sequence entire genomes or be constrained to specific areas of interest, effectively allowing multiple single biomarker tests to be run in parallel

Circulating tumour DNA (ctDNA): tumour-derived fragmented DNA in the bloodstream that is not associated with cells. ctDNA are small pieces of DNA, usually comprising fewer than 200 building blocks (nucleotides) in length. The quantity of ctDNA varies among individuals and depends on the type of tumour, its location, and for cancerous tumours, the cancer stage. Examination of ctDNA from a blood sample, also called liquid biopsy, can detect and identify cancer-related mutations. ctDNA has gained significance as a biomarker for cancer as they are released into the bloodstream by delocalised tumour cells, thus having the potential to provide a more accurate representation of tumour heterogeneity compared to tissue samples.

Clinical commissioning groups (CCG): groups of general practices in England which convene in their local area to commission services on behalf of their patients

Diagnosis related group (DRG): patient classification system that standardises prospective payment to hospitals; in general, covers all charges associated with an inpatient stay from the time of admission to discharge

EGFR: protein found on certain types of cells that binds to a substance called epidermal growth factor. The EGFR protein is involved in cell signaling pathways that control cell division and survival. Sometimes, mutations in the EGFR gene cause EGFR proteins to be made in higher than normal amounts on some types of cancer cells. This causes cancer cells to divide more rapidly. Medicines that block EGFR proteins are being used in the treatment of some types of cancer. EGFRs are a type of receptor tyrosine kinase. Also called epidermal growth factor receptor [35]

European Network for Health Technology Assessment (EUnetHTA): supports collaboration between European HTA (health technology assessment) organisations through facilitation of efficient HTA resource use, creation of a sustainable system of HTA knowledge sharing and the promotion of good practice in HTA methods and processes; consists of a total of 68 organisations from 26 EU member states plus Norway, Switzerland, Ukraine and the UK

External quality assessment (EQA) schemes: challenge of the effectiveness of a laboratory's quality management system. In clinical laboratories, external quality assessment is a form of quality assurance to ensure the provision of precise and accurate analyses to support optimal patient care, through helping to minimise the variability, arising from biological or analytical sources, inherent in all quantitative measurements or qualitative examinations. Laboratories undertake two separate but complementary QA activities:

- Internal quality control (IQC) assesses, in real time, whether the performance of an individual laboratory or testing site is sufficiently similar to its previous performance for results to be usable; it controls reproducibility or precision, and facilitates continuity of patient care over time. Most IQC procedures employ analysis of a control material and compare the result with predetermined limits of acceptability - unsatisfactory sets of results may thereby be suppressed

- External quality assessment (EQA) looks at differences between different sites testing the same analyte. This usually involves the analysis of identical specimens at many laboratories, and the comparison of results with those of other sites and with a 'correct' answer

Fluorescence in situ hybridisation (FISH): technique that uses fluorescent probes to visualise and map the genetic material in an individual's cells, including specific genes or portions of genes; may be used for assessing a variety of chromosomal abnormalities and other genetic mutations

HER2: a protein involved in normal cell growth. HER2 may be made in larger than normal amounts by some types of cancer cells, including breast, ovarian, bladder, pancreatic, and stomach cancers. This may cause cancer cells to grow more quickly and spread to other parts of the body. Checking the amount of HER2 on some types of cancer cells may help select treatment. Also called c-erbB-2, HER2/neu, human EGF receptor 2, and human epidermal growth factor receptor [35]

Health technology assessment (HTA): systematic evaluation of the properties, effects and / or impact of a health technology. Multidisciplinary process to evaluate the social, economic, organisational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making [36]

Immunohistochemistry (IHC): technique to identify specific antigens within tissue sections utilising an antigen-specific antibody. Detection at the light microscopic level of antigen-antibody

interactions can be achieved by labelling the antibody with a substance that can be visualised, either by conjugation to a fluorescent marker or enzyme followed by colorimetric detection

ISO accreditation: the International Organization for Standardization (ISO) is an international standard-setting body composed of representatives from various national standards organisations. Standards provided by ISO are internationally agreed by experts and aid in the creation of products and services that are safe, reliable and of good quality. ISO accreditation or ISO accredited certification refers to when a company or laboratory has achieved an ISO standard by a certification body that is accredited by one of the national accreditation bodies (e.g., UKAS in the UK)

KRAS: gene that makes a protein involved in cell signalling pathways that control cell growth, cell maturation, and cell death. The natural, unchanged form of the gene is called wild-type KRAS. Mutated forms of the KRAS gene have been found in some types of cancer, including non-small cell lung cancer, colorectal cancer, and pancreatic cancer. These changes may cause cancer cells to grow and spread in the body. Knowing whether a patient's tumour has a wild-type or mutated KRAS gene may help plan cancer treatment. Belongs to the Ras family of oncogenes (genes with the potential to cause normal cells to become cancerous), which also includes NRAS and HRAS [35]

Liquid biopsy: sampling and analysis of non-solid biological tissue, primarily blood. Also known as fluid biopsy or fluid phase biopsy. Like traditional biopsy this type of technique is mainly used as a diagnostic and monitoring tool for diseases such as cancer, with the added benefit of being largely non-invasive. The term "liquid biopsy" encompasses circulating tumour DNA (ctDNA – *see separate glossary entry*) / cell-free DNA (cfDNA), circulating tumour cells (CTCs), circulating miRNAs, and exosomes

Mismatch repair deficiency (MMR): describes cells that have mutations in certain genes that are involved in correcting mistakes made when DNA is copied in a cell. Mismatch repair (MMR) deficient cells usually have many DNA mutations, which may lead to cancer. MMR deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in cancers of the breast, prostate, bladder, and thyroid. Knowing if a tumour is MMR deficient may help plan treatment or predict how well the tumour will respond to treatment [35]

Molecular diagnostics (MDx): collection of techniques used to analyse biological markers in the genome and proteome, in order to diagnose and monitor disease, detect risk and aid therapy selection; examples include PCR (*see separate glossary entry*), DNA microarrays and NGS (*see separate glossary entry*)

MSI: a change that occurs in certain cells (such as cancer cells) in which the number of repeated DNA bases in a microsatellite (a short, repeated sequence of DNA) is different from what it was when the microsatellite was inherited. MSI may be caused by mistakes that do not get corrected when DNA is copied in a cell. It is found most often in colorectal cancer, gastric cancer, and endometrial cancer. Knowing whether a cancer has MSI may help plan the best treatment. Also called microsatellite instability [35]

Next generation sequencing (NGS): large-scale DNA sequencing technology in which millions of nucleotide sequences are deciphered simultaneously. Allows for querying the entire genome (whole genome), the exons within all known genes (whole exome) or only exons for selected genes (target panel)

NGS comprehensive panel: multi-biomarker test using next generation sequencing; defined for this paper as covering more than 50 genes

NGS hotspot: multi-biomarker test using next generation sequencing; defined for this paper as covering up to 50 genes

NGS targeted panel: multi-biomarker test using next generation sequencing; defined for this paper as covering up to 50 genes for a specific tumour biopsy (e.g., lung)

NTRK gene fusion: mutation that occurs when a piece of the chromosome containing a gene called NTRK breaks off and joins with a gene on another chromosome. NTRK gene fusions lead to abnormal proteins called TRK fusion proteins, which may cause cancer cells to grow. NTRK gene fusions may be found in some types of cancer, including cancers of the brain, head and neck, thyroid, soft tissue, lung, and colon. Also called neurotrophic tyrosine receptor kinase gene fusion [35]

PD-L1: programmed death-ligand 1 is a protein that in humans is encoded by the CD274 gene and acts as a "brake" to keep the body's immune responses under control. PD-L1 may be found on some normal cells and in higher-than-normal amounts on some types of cancer cells. When PD-L1 binds to another protein called PD-1 (programmed cell death-1, a receptor found on the surface of activated T cells), it keeps T cells from killing the PD-L1-containing cells, including the cancer cells. Anticancer medicines called immune checkpoint inhibitors bind to PD-L1 and block its binding to PD-1. This releases the "brakes" on the immune system and leaves T cells free to kill cancer cells. Monoclonal antibody therapies against PD-1 and PD-L1 are routinely used in clinical practice. Examples include Nivolumab and Pembrolizumab [35]

Polymerase chain reaction (PCR): technique used to amplify small segments of DNA. Once amplified, the DNA produced by PCR can be used in many laboratory procedures, including DNA fingerprinting, detection of pathogens and diagnosis of genetic disorders

Precision medicine (PM): healthcare approach that systematically utilises multiomic (genomic, transcriptomic, proteomic, metabolomic, etc.), phenotypic and health data from patients to generate care insights to prevent or treat human disease resulting in improved health outcomes [1]

Single biomarker testing: Test evaluating the presence of a single gene mutation, gene or protein expression within a biopsy associated with a particular form of cancer (e.g., BRCA1 or BRCA2 gene testing in breast cancer patients). Single biomarker testing methods include immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), and polymerase chain reaction (PCR) testing [7] – *for definitions see relevant glossary entries*

Test technologies: methods used to perform biomarker tests; for the biomarkers in scope of this paper, these include immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), polymerase chain reaction (PCR), single biomarker next generation sequencing (NGS), NGS hotspot, NGS targeted panels, NGS comprehensive panels – *for definitions see other glossary entries*