Investing in the future

Improving cancer biomarker testing and cancer diagnosis for sustainable healthcare

European Cancer Patient Coalition

Oncohealth Institute

fight bladder CANCER

A White Paper, by the following contributors:

Antonella Cardone, Director, European Cancer Patient Coalition (ECPC); **Professor Jesus Garcia-Foncillas**, MD, PHD, Director, Oncohealth Institute and University Hospital "Fundacion Jimenez Diaz" Autonomous University of Madrid, Spain; **Dr Lydia Makaroff**, CEO, Fight Bladder Cancer, UK, and Vice-President, World Bladder Cancer Patient Coalition, Belgium; **Dr Pietro Presti,** MBA, PHD, Vice-President European Cancer Patient Coalition (ECPC); **Dr Albrecht Stenzinger**, MD, Pathologist, Institute of Pathology, University Hospital Heidelberg, Germany; **Professor Gilles Vassal**, Pediatric Oncologist and Director of Clinical Research at Gustave Roussy, Villejuif, France

The development of this White Paper was funded by Bayer. Editorial control is retained by the authors.
MAC-VIT-ALL-0011-1

Local Approval Number: MA-LAR-BE-0067-2

BAYER

Contents

The development of this White Paper was initiated and fully funded by Bayer. Medical writing assistance was provided by communications agency FleishmanHillard, supported by Bayer. Bayer was also involved in the fact-checking of information. The named contributors provided input to the content and gave final editorial approval for the opinions and conclusions contained in this White Paper.

INVESTING IN THE FUTURE

Executive summary

Accurate and timely diagnosis is the foundation of good cancer medicine – diagnosis not only of a particular cancer, but diagnosis at a molecular level to help inform appropriate treatment selection for improved patient outcomes and health system sustainability. Advances in personalized healthcare in oncology, through the discovery of targeted therapies, have transformed the development of accompanying biomarker diagnostic tools that are changing the face of cancer treatment and patient survival.

As medical research continues to identify the genomic (biomarker) causes of tumors (the 'oncogenic drivers'), it follows that robust biomarker testing at the point of diagnosis is essential for identifying optimal, biomarker-directed treatment (or what is known as 'precision medicines') for patients across a broad spectrum of tumor types.

Based on these advances, a new era of cancer treatment is dawning that could offer radical improvements in outcomes for some patients and broader value to healthcare systems [1]. Treatment is moving away from traditional approaches based on a tumor's location (e.g., lung or colon), and towards a pan-tumor or tumor-agnostic approach that explores how a drug targets a particular genomic defect in the cancer. This allows the identification of effective therapies for cancers in different physical locations that share a common genomic alteration.

We clearly already have excellent cancer care facilities that many patients currently derive benefit from through improved diagnosis and long-term care. Biomarker testing is one part of this care, which is taking place to some extent within dedicated specialized centers of excellence and is conducted by multidisciplinary teams of experts.

However, many eligible patients are currently not benefiting from biomarker-directed care due to suboptimal testing practices and heterogeneity of available tests. As a result, some cancer patients spend substantial periods of time taking expensive medicines that just don't work, while other cancer patients lack access to effective treatments – an inefficient use of health system resources that negatively impacts patient outcomes, often resulting in unnecessary distress. We need to get the right treatment to the right patient at the right time.

Improving access to biomarker diagnostic testing is a crucial component of health system sustainability, driving efficiencies now and in the future. The biomarker diagnostic test itself is as important as the treatment selected – the two cannot be separated. As such, improved diagnostic testing should be a priority for payers and policy makers worldwide and considered as an investment in the future. In this paper we set out the background and the case for improved access to biomarker testing with the aim of empowering patient advocacy groups and patients to lead the 'call for action'. After all, it is the right of every patient to be able to choose the treatment that best supports their survivorship.

Introduction

How can we, patient advocates and policy makers, as guardians of good health, help to improve patient selection for transformative precision medicines (targeted treatment with a genomic biomarker target) to enhance patient outcomes, while respecting the variability in healthcare infrastructures and economies around the world? The answer could lie in greater access to biomarker diagnostic cancer testing, with sustainable healthcare and cost-efficiencies as a core value proposition.

The majority of healthcare systems globally are facing financial pressures that are undermining sustainability and the capability to innovate. The cancer community needs to ensure that access to important biomarker diagnostic testing is included in healthcare plans and budgeted for accordingly, either through budget increases and/or reallocation of resources. By doing so, healthcare systems, regardless of their sophistication, will realize economic and societal benefits by giving patients the opportunity for greater access to breakthrough therapies.

Healthcare professionals agree that biomarker diagnostic testing is a fundamental driver to improving treatment selection and better patient outcomes. Patients and their carers can return to work sooner and contribute to the economy, budgetary pressures on healthcare systems are relieved, and cost-savings can be reinvested into innovative research.

Due to population growth and ageing, more people are diagnosed each year with cancer, and demand for effective treatments is growing [2]. It is anticipated that there will be a 62% increase in cancer diagnosis by 2030, and it is predicted there will be 27.5 million new cancer cases worldwide each year by 2040 [3]. With this in mind, accurate diagnosis through biomarker testing is an important consideration to ensure that the right patient has the right treatment at the right time to increase the chance of cancer survivorship.

There is growing recognition within the cancer community of the need for improved access to biomarker testing. For example, the Innovative Partnership for Action Against Cancer (iPAAC) work stream on genomic testing acknowledges that genomics is viewed as “the harbinger of a brave new world in which healthcare is transformed”. The iPAAC states there is a critical need for an appropriate policy response on the inclusion of genomics and testing in healthcare discussions. It calls for improved education and training for all stakeholders [4].

The European Cancer Patient Coalition (ECPC) calls for increased access and decreased waiting times for high-quality biomarker testing in order to make personalized healthcare more of a reality across Europe; more information to educate and empower patients and caregivers around the potential and availability of biomarker testing; and a harmonized and more efficient regulatory framework across Europe that could increase access to, and potentially reduce the cost of, molecular testing [5]. Interestingly, up to 60% of patients in Europe are currently not offered biomarker testing according to a patient survey conducted by the ECPC, and 70% of respondents said that the importance of testing was not adequately explained to them [6].

In this paper, we will discuss the benefits of investing in better access to biomarker diagnostic testing, the case for sustainability, and how acting today could make this a reality tomorrow through a patient-centered ‘call for action’.

Biomarker diagnostic testing and healthcare sustainability

Good medical practice starts with early and accurate diagnostics and good treatment planning, of which biomarker testing, particularly in cancer, is an essential component. With improved access to biomarker diagnostic testing for cancer and personalized cancer therapy, there is real potential to increase the health quality of nations and improve patient outcomes, while lowering overall healthcare costs [7].

Personalized treatment is an attractive proposition, as in principle only those patients likely to benefit from treatment are identified.

Molecular diagnostic tests not only determine if a patient is eligible for a targeted medicine but can also be used to identify if a patient could be suitable to participate in clinical research. They can also be used as prognostic tools to determine how aggressive a cancer is and the potential outcomes for patients [8].

There is a need to promote technological evolution towards innovative testing methods that allow the identification of several markers for analysis in one upfront diagnostic test to inform treatment now and in the future [9]. The financial allocation for such a diagnostic test will be offset through greater cost benefits associated with precision therapeutics. The use of precision therapeutics is growing as many countries acknowledge the impact that biomarker testing has had on healthcare sustainability (Table 1).

In the UK in 2014, around 3,500 more patients may have benefited from treatment with a targeted medicine had they been tested [8].

The Organisation for Economic Co-operation and Development (OECD)

The OECD recognizes the importance of adopting policies on biomarker testing for a more sustainable future of healthcare. In a report ‘Policy Issues for the Development and Use of Biomarkers in Health’, the OECD notes that long-term investments in the development of sustainable initiatives and infrastructures are necessary to facilitate biomarker discovery and development. Education and communication among all stakeholders with a vested interest in improving healthcare sustainability is also of importance if access to improved biomarker testing is to be realized [11].

Cancer Control Joint Action (CanCon)

Improving access to optimal treatment is outlined in the Cancer Control Joint Action (CanCon) Policy Paper ‘Enhancing the value of cancer care through a more appropriate use of healthcare interventions’, which the ECPC co-authored. The paper includes recommendations on improving access to medicines, surgery, and radiotherapy by reducing waste and improving efficiency, as well as making use of technology to improve cancer care [12].

Patients enrolled in the National Cancer Institute’s Molecular Analysis for Therapy Choice (NCI-MATCH) phase 2 clinical trial all had biomarker testing to look for 143 genes associated with cancer. The study was done to determine whether targeted therapies for people whose tumors have certain gene mutations will be effective regardless of their cancer type. One of the goals of the trial was to find around 25% of patients with rare cancers.

Of the first 6,000 patients who had biomarker testing, 62.5% were seen to have less common or rare tumors, providing more opportunities for these rare cancers to be studied than expected. This was the first attempt to use Next-Generation Sequencing (NGS) to study several therapies at the same time and to potentially bring targeted treatments to patients with certain gene abnormalities, regardless of their cancer type [10].

TABLE 1:
EXAMPLES OF THE IMPACT OF BIOMARKER TESTING IN SELECTED COUNTRIES

Country	Impact of Biomarker Testing
France	• The French National Cancer Institute (INCa) and the French Ministry of Health has established a national network of 28 molecular genetics centers that perform molecular tests for all patients in their region, irrespective of the institution where they are being treated [13,14] • The development and use of targeted therapies has steadily increased over recent years, demonstrating the growing importance of precision medicine in the treatment of cancer, aside from other systemic treatments such as chemotherapy
Spain	• In order to address the need for improved access to personalized medicine, the Spanish Senate initiated sessions in 2018 on the 'Study of Genomics'. The government also recently launched the 'Spanish Strategy for Personalized Medicine', including an improved approach to biomarker testing • A study performed in Madrid showed that genomic testing increased quality-adjusted life years by 0.00787 per patient and saved costs from a national healthcare system perspective (by €13,867 per patient) and from a social perspective (by €32,678 per patient) [15]
United Kingdom (England)	• NHS England has a clear vision for genomic medicines with a dedicated national service, the NHS Genomic Medicine Service (NHS GMS). The NHS GMS is currently being implemented to enable timely and equitable access to the latest testing technologies and reimbursed treatments • The NHS Long Term Plan has committed to sequencing 500,000 whole genomes by 2023/24, including people with specific types of cancer for which there is likely to be the greatest patient benefit from using whole genome sequencing, as well as to extending access to molecular diagnostics to enable genomic testing to be routinely offered to all people with cancer [16]
U.S.A	• New research from CVS Health presented at the American Society of Clinical Oncology (ASCO) 2020 virtual congress, on access to diagnostic sequencing to detect more than one genomic driver mutation in lung cancer, concluded that broad panel sequencing (BPS) has been shown to optimize treatments in patients with lung cancer – Many payers are reluctant to pay for BPS as it is seen as more expensive than narrow panel sequencing (NPS). However, the authors concluded that BPS significantly reduces overall total costs of lung cancer care. The average 6-month per member per month total cost was $11,535 +/- $9,168 among those who underwent BPS compared to $20,039 +/-19,642 in those who underwent NPS. This difference of $8,504 was statistically significant, p = 0.0022 [17] • Despite the evidence of potential for improved outcomes, 55% of advanced non-small cell lung cancer (NSCLC) patients carrying targetable biomarkers did not receive a targeted therapy [18]

"The uptake of new diagnostic technologies will depend not only on regulatory approval, but also reimbursement and evidence both from trials and real-world studies. Improved access can facilitate faster diagnosis and treatment, and for this to become a reality, tests need to be integrated in the clinical setting and to be affordable and available to all patients" [19].

European Cancer Patient Coalition, 2017

SUCCESS OF BIOMARKERS IN CANCER AND IMPACT ON HEALTHCARE SUSTAINABILITY

Biomarker testing for cancer has been used for some years to identify molecular markers in patients to direct therapeutic approaches in organ-specific cancers. One of the first biomarkers to be discovered and reported in a peer review journal in 2001 was the HER2 protein in metastatic breast cancer (MBC) [20]. A biomarker test was developed to seek out HER2 overexpression, and only women with MBC who expressed HER2 were treated with the monoclonal antibody, trastuzumab.

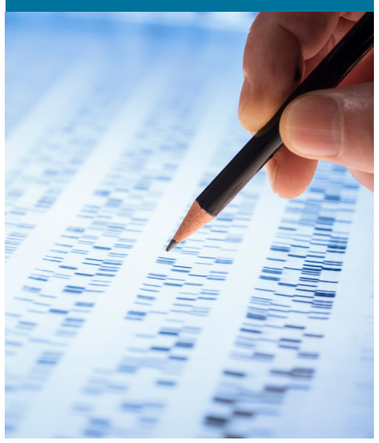
Biomarker testing can contribute to healthcare sustainability, and data show that use of an initial HercepTest that confirmed HER2-positive metastatic breast cancer had an incremental cost-effectiveness ratio (ICER) of $125,000 per quality-adjusted life year (QALY) gained, and the incremental cost-effectiveness was $145,000 per QALY gained [21]. Additionally, studies in the US and Europe indicate that there could be a 34% reduction in chemotherapy use if women with breast cancer received a genetic test of their tumor prior to treatment [14].

In NSCLC, ALK rearrangement and EGFR/KRAS mutations are the main biomarkers that are tested to determine if a patient is suitable for targeted therapies. When looking at the cost-effectiveness of biomarker testing for these mutations in NSCLC, it is more cost-effective to do this before a treatment decision is made. A review of costs associated with no biomarker testing compared with testing for at least one biomarker followed by appropriate treatment showed an incremental cost-effectiveness ratio of €13,230 per life-year saved. Furthermore, biomarker testing before first- or second-line treatment correlated with better survival and limited additional costs [22].

Many more biomarker tests are now available for multiple organ-specific tumors, and these tests have transformed patient outcomes over the years.

Pan-tumour research focus

Research has now moved on to another exciting field of research that focuses on using biomarkers for treatment selection across different tumors. This is called a pan-tumor approach to treatment, where tumors with a common genomic mutation can be targeted with a single treatment, regardless of the organ or tissue in question.



Unravelling the genomic fingerprint of tumors

New knowledge about the discovery of biomarkers has created a paradigm shift in patient treatment and led to widespread enthusiasm around personalized medicine. The term 'personalized medicine' is frequently used interchangeably with other terms such as 'precision medicine', 'genomic medicine', and 'precision oncology' [23]. They all describe the use of an individual patient's biomarker information to assist physicians in the diagnosis, prognosis, treatment and prevention of cancer for that patient [24].

FROM ORGAN-SPECIFIC TO BIOMARKER PROFILING

Traditionally, cancers have been classified and treated according to the tumor's type of tissue (histology) - that is, the type of tissue in which it originates or the location in the body in which the cancer first developed (primary tumor), such as lung, breast, and colon. This means that the diagnosis and treatment of different tumors varies according to tissue or organ type. Due to this historical approach to treatment, most established patient advocacy groups organize their efforts around a common feature such as the tissue or organ in which a tumor is found. Over the last two decades, significant progress and technological advances have contributed to the development of anticancer therapies that target molecular alterations in tumors with greater specificity than in the past. Biomarker tests are already available for many organ-specific cancers, and new therapies have emerged that have changed the treatment outlook for patients with these cancers.

A greater understanding of cancer biology has led to the discovery of various genomic causes of cancer that can act as targets for therapy. More recently, there has been a shift towards a pan-tumor approach, whereby therapies are targeted towards genetic mutations that are common across many cancers.

Pan-tumor genomics grounded in data

The field of pan-tumor genomics (tumor-agnostic or tumor-independent) is rapidly evolving and demonstrates the exciting potential of genomic and protein targets for cancer treatment. Researchers have already identified several tumor-agnostic biomarkers of potential clinical interest that continue to be examined further in order to determine their therapeutic benefit in the real world.

Genomic targets are identified by analyzing a tumor for different genomic markers (the drivers of cancer). In pan-tumor research, scientists look specifically for genomic targets that are common across many different tumor types, with the aim of finding effective therapies for cancers that share a common genomic alteration [23, 25]. Some clinical trials use this pan-tumor approach, to look at multiple different cell types, rather than an organ- or tissue-specific approach to identify several genomic markers in tumors [23].

Definition of tumor-agnostic treatments

Tumor-agnostic (tumor-independent) treatment is a treatment strategy that seeks out genomic markers for a tumor regardless of biological tissue origin (histology). This treatment typically fulfills the following criteria:

- 1+ Tumors have one oncogenic driver
- Alterations are likely to predict response to a therapy
- Alterations are found across a variety of cancers

Adapted from The European Society of Medical Oncology (ESMO) [26, 27]

The main genomic alterations – or tumor-agnostic markers – that have been identified as therapeutic targets to date include:

- **Microsatellite instability high/ deficient mismatch repair (MSI-H/ dMMR).** Associated with cellular repair mechanisms and the inability to repair mistakes in the DNA. Contribute to the development of a variety of cancers [28].
- **Neurotrophin tyrosine receptor kinase (NTRK).** Can cause several different types of cancer, including lung cancer, sarcoma, head and neck cancer, thyroid cancer and cancers of the central nervous system and others [29].
- **High tumor mutational burden (TMB-H).** Measures the number of gene mutations inside the cancer cells. High TMB is a biomarker of immunotherapy response and is expected be at the forefront of precision medicine in the foreseeable future [30].
- **Fibroblast growth factor receptor (FGFR).** Mutations in FGFR genes can drive urothelial, breast, endometrial, squamous lung, and ovarian cancers [31].

Extensive research into these and other genomic alterations continues.

Pan-tumor approach in the real world – approvals to date

The treatment landscape for patients living with cancer is evolving and the advent of precision oncology and a pan-tumor approach to treatment means that patients now have potential for greater access to treatments that can optimize outcomes based on their tumor biological make-up.

Measurements used to determine the value of pan-tumor therapies may include:

- **The efficacy and safety of the treatment.** The impact on survival and on tumor shrinkage, how long the treatment effect is seen, and if there are any adverse events.
- **Quality of life (QoL) parameters**, such as the impact of the treatment on a patient's life. QoL assessments can measure activities of daily living, returning to work, and other activities.
- **Cost and economic evaluations** can also be considered. Health economists may review treatments in line with standard of care to compare cost to society, usually over a longer time frame.
- **Ethical considerations.** Testing is as important as treatment, and the earlier the testing, the better, as it can change treatment outcomes.

Since 2017 three pan-tumor treatments have been approved (Table 2) by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These treatments target certain genetic abnormalities in tumor cells and are therefore not specific to any one particular cancer. In order for patients to have access to these treatments, they must undergo biomarker diagnostic testing of their tumors, but there is currently no universal genomic diagnostic test to determine if a patient is suitable for pan-tumor treatment. Patients must currently be tested for each of the known genomic mutational targets individually.

GLOBAL MILESTONES IN DEVELOPMENT OF PRECISION ONCOLOGY

1970s

DNA Sequencing to examine the building blocks of DNA

- Philadelphia chromosome genetic abnormality discovered in chronic myeloid leukemia (CML)
- HER2 overexpression in breast cancer discovered
- First gene therapy for cancer – chimeric antigen receptor-modified T cell (CAR-T)

1980s

A 21-gene-based test (Oncotype DX) predicts risk of recurrence and guides adjuvant therapy for women with certain types of breast cancer

- First immunotherapy atezolizumab / chemotherapy combination approved for extensive small-cell lung cancer
- PARP inhibitors represent a major treatment advance in BRCA-positive ovarian cancer

1990s

Human Genome Project commenced with aim of mapping all of the genes of the human genome

- Trastuzumab and IHC diagnostic test approved for HER-2 positive metastatic breast cancer – 20 years after discovery of the HER2 gene

2000s

Pan-tumor (tumor agnostic) research gains momentum – moving research from treating cancers based on the site of origin to molecular drivers

- Imatinib approved for CML – 30 years after discovery of Philadelphia chromosome abnormality

2010s

- Several targeted therapies approved with genetic targets, including pembrolizumab, larotrectinib and entrectinib (Table 2)
- Pembrolizumab becomes first drug to be approved with a tumor-agnostic indication in 2017 in the USA, and larotrectinib is the first to be approved in Europe in 2019

2020s

Research into other tumor agnostic targets continues (Table 3) with genomic targets TRK, ALK, ROS1, FGGR, RET 1, SRC, AXL kinase, FGFR and BRAF

Adapted from ASCO Cancer Progress Timeline [32]

TABLE 2: APPROVED PAN-TUMOR AGENTS

Agent	Biomarker	FDA Approval as of November 2020	EMA Marketing Authorization as of November 2020
Pembrolizumab	**MSI-H or dMMR** Microsatellite instability high/ deficient mismatch repair **PD-1** Programmed cell death protein 1	**23 May 2017** First-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC	
Larotrectinib	**NTRK gene fusions** Neurotrophin tyrosine receptor kinase	**26 Nov 2018** For adult and pediatric patients with solid tumors that have an NTRK gene fusion	**19 Sept 2019** Adult and pediatric patients with solid tumors that display a NTRK gene fusion
Entrectinib	**NTRK gene fusions** Neurotrophin tyrosine receptor kinase **ROS1** Receptor tyrosine kinase 1	**15 August 2019** Adult patients with metastatic NSCLC whose tumors are ROS1-positive	**28 May 2020** CHMP recommendation for marketing authorization as monotherapy for treatment of adult and pediatric patients 12 years of age and older, with solid tumors expressing a NTRK gene fusion

TABLE 3: SELECT PAN-TUMOR THERAPIES IN DEVELOPMENT [33]

Agent	Target
Selitrectinib	TRK
Repotrectinib	ALK, ROS1 and TRK
Debio 1347	FGFR
Erdafitinib	FGFR
Pralsetinib	RET
Selpercatinib	RET
TPX-0046	RET and SRC
Dubermatinib	AXL kinase
PLX8394	BRAF

Diagnostic tests for biomarkers explained

Standard testing for cancer to determine the type of tumor and stage of the disease includes tissue biopsies, which establish the biologic profile of the tumor at a cellular level at diagnosis. For example, a lung cancer sample may be classified as of small-cell origin or non-small cell origin, or may be squamous cell or adenocarcinoma. This is the 'histology' (the biological cellular make-up) of a tumor. These biopsies may also be tested in the laboratory using different methods for specific biomarkers that play a role in the development of that cancer, to help determine treatment choice.

Today, improvement in sequencing technologies of the human genome means that comprehensive genomic profiling (CGP) of tissues has become standard practice for sequencing the molecular profile across multiple tumors [28]. The latest sequencing methods, including NGS and whole genome sequencing (WGS) provide opportunities to study tumors at time of diagnosis and at defined intervals during treatment to determine efficacy and/or detect resistance to treatment.

As the number of clinically relevant predictive biomarkers for the treatment of solid tumors continues to increase, it is likely that NGS will become the key diagnostic tool to inform treatment decisions. This approach could be used to seek out genomic markers, regardless of biological tissue origin for a pan-tumor (tumor-agnostic) treatment strategy [34].

Different tests are used to identify suitable patients for the different types of tumor-agnostic treatments and their molecular targets (Table 4). For example, in order to determine which patients may benefit from treatment with TRK-inhibitor therapies, patients need to be tested for the NTRK gene fusion. Testing should account for all potential genomic alterations. For example, a diagnosis of NSCLC is just the beginning; a genomic deep-dive is required to determine the molecular make-up of the tumor (e.g., EGFR mutation) to guide effective ecision-making on what is the most appropriate treatment for that patient. The cost of the different testing techniques will be dependent on any given country's healthcare infrastructure.

CASE STUDY 1: MOLECULAR TESTING CAN BE LIFE-SAVING AND HELP OTHERS IN THE FUTURE – GERMANY

Patient

1. Female 30 years, never smoker presented with breathlessness and fluid on the lung lining
2. Metastatic adenocarcinoma of the right lung

The patient had extensive disease at diagnosis including bone metastases. After molecular testing there appeared to be no genomic abnormalities that justified treatment with a targeted therapy. She was treated with standard platinum-based chemotherapy, but after a year, unfortunately, she had progressive disease. In searching for alternative treatments, the patient had further investigations for molecular targets that may have been missed previously. RNA-based NGS was performed and detected a NTRK gene fusion.

After starting on a TRK-targeted therapy, she experienced marked improvements in her symptoms, a reduction in tumor size in both lung and bone, and a partial response to treatment. As of March 2020, the patient is free of symptoms and has resumed her regular daily activities, including work. Due to this case, in young never smokers, it is recommended that testing for the NTRK gene fusion should be routinely performed once a diagnosis of lung cancer is established.

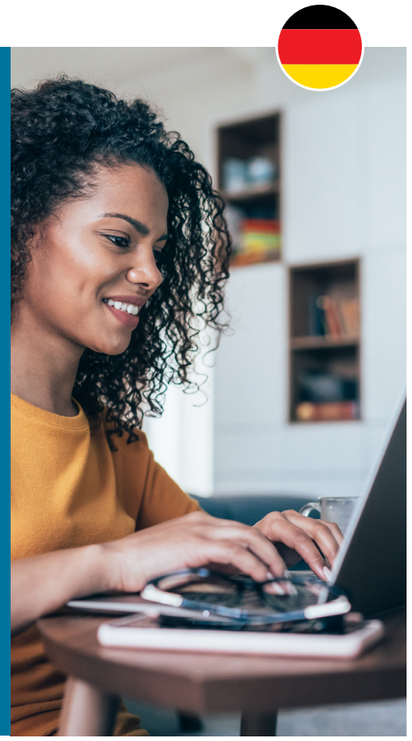


TABLE 4: TESTING APPROACHES FOR PAN-TUMOR MOLECULAR TARGETS

Test		Benefits and challenges
Next Generation Sequencing (NGS) [35, 36]		
Target: **DNA and/or RNA** Can detect: **genomic alterations**	• Detects alterations in the DNA and/or RNA (genetic material) • NGS can determine diagnostic biomarkers (if a person has cancer), prognostic biomarkers (is the tumor aggressive for example, and potential outcomes), and predictive biomarkers (a patient's potential response to treatment)	• Use of NGS has increased due to significant cost reductions and broader community acceptance • Potential for a significant positive impact on mutation detection, management and treatment of cancer • Effective at identifying mutations in cancer patients – in a review, 37% of diagnosed patients proceeded to receive therapy matching their genetic profile • Can detect multiple genomic alterations and mutations in a single test
Immunohistochemistry (IHC) [37]		
Target: **Cell** Can detect: **protein expression**	• Identifies proteins in cells of a tissue • In cancer diagnosis, there are specific proteins that are unique or over-expressed that IHC can detect	• Produces consistent specific and reproducible results • Can aid in distinguishing normal tissue from cancer tissue • Assesses whether a patient should receive or is responding to therapy
Reverse transcriptase polymerase chain reaction (RT-PCR) [38]		
Target: **RNA** Can detect: **gene expression**	• Detects RNA expression • RT-PCR is used to assess expression of genomic biomarkers in cancer	• The most sensitive technique for mRNA detection and analysis currently available • Used to quantify mRNA levels from much smaller samples
Fluorescence in situ hybridization (FISH) [39, 40]		
Target: **Chromosome** Can detect: **amplifications, deletions, fusions**	• Looks at the chromosomes (genetic material in a cell) • This test can be used to visualize specific genes or portions of genes in cancer	• Can be used to form a diagnosis, to evaluate prognosis, or to evaluate remission of cancer to then allow for tailored treatment • Does not require living cells for testing • Test results are ready in a few days

An opportunity to improve quality and efficiency within diverse healthcare systems

The heterogeneity of healthcare systems around the world, the available technologies, and infrastructure around testing at diagnosis all compound access to innovative medicines. This can result in a 'not my problem' attitude. The current treatment journey includes barriers or disincentives to upfront diagnostic testing, and treatment accessibility and reimbursement also presents a significant hurdle.

In 2010, the World Health Organization (WHO) commissioned a report on world health in response to a need 'expressed by rich and poor countries alike, for practical guidance on ways to finance healthcare'. According to the WHO, a universal healthcare system provides healthcare and financial protection to all residents of a particular country or region [41]. The WHO highlights the need to focus first on opportunities to improve efficiency, rather than ways to cut spending on healthcare. Improved access to biomarker diagnostic testing is one such way to embrace this principle, while acknowledging the diversities of resources available around the world within universal healthcare systems.

Heterogeneity of healthcare systems doesn't just exist around the world, but also within certain countries. In Spain, for example, the availability of molecular testing can vary significantly, depending on which healthcare system, public or private, a patient has access to (Case Study 2).

CASE STUDY 2: HETEROGENEITY IN BIOMARKER TESTING AVAILABILITIES IN SPAIN

Patient

1. Male 77 years, asymptomatic, non-smoker
2. Squamous lung cancer progressive disease

The patient was diagnosed and treated in a public health hospital, where NGS or other molecular tests aren't usually performed for squamous lung cancer, as it is often caused by smoking. However, given that the patient wasn't a smoker, the physician decided to run a PCR test to look for an EGFR mutation.

They were able to do this because it is a relatively inexpensive test that is also paid for by pharmaceutical companies. The test results didn't show an EGFR mutation.

In order to get a second opinion, the patient went to a private hospital and paid for an NGS-based diagnostic test, which revealed a NTRK2 gene fusion. At this point, the patient was able to receive a TRK-inhibitor, which, following recent data, has a median expectation of progression-free survival of more than three years.

Even among countries with a payer-based healthcare system, patients can experience variability in access to, and quality of, diagnostic testing. Under a payer-based system, a traditional approach to reimbursement of healthcare provision has focused on volume-based incentives, but this is now shifting more towards value-based incentives that are founded on quality and efficiency. Improved access to genomic diagnostic testing is one such method for improving efficiencies in diagnosis and delivery of quality treatments to those patients who are most suitable.

Due to variability of healthcare infrastructures, it follows that the best tests should be used based on resources available. There is also a need to ensure that diagnostics are consistently accurate from lab to lab and across a given territory.

The currently available diagnostic tools may vary in sensitivity, specificity, precision, and accuracy.

According to a European Cancer Patient Coalition (ECPC) report entitled 'Patients' Access to Precision Oncology', personalized medicine is the future of cancer treatment and should be standard practice. However, certain biomarker testing challenges persist due to variability from country to country, administrative barriers leading to delays in biomarker test results, and reimbursement and accessibility challenges related to country variations and resources available [42].

Some of the barriers for patient access to molecular testing include: low stakeholder awareness and prioritization, lack of diagnostic infrastructure, issues with Health Technology Assessment (HTA), and reimbursement and funding [1]. To overcome these challenges, there is a need to improve awareness levels among government and regulatory policy makers, clinicians and patient advocates of the concept of tumor-agnostic medicines and the value these bring to patients. Also, for HTA bodies and payers to consider tumor-agnostic therapies and genomic profiling in appraisals, to ensure that funding mechanisms are available for these innovative treatments.

There is also a need for more sophisticated centers of excellence, to invest in appropriate diagnostic and data infrastructures and to ensure testing protocols are in place and reimbursed across tumor types.

TABLE 5: CURRENT STATUS FROM SELECTED COUNTRIES ON TESTING, REIMBURSEMENT AND POLICIES IN PLACE

Country	Testing/biomarker reimbursement / policy approaches
Brazil	• The industry is striving to offer genomic tests as a way of facilitating improved treatment access • Biomarker tests used: IHC, PCR, NGS, FISH • Private healthcare: Reimbursement for biomarker testing is based on tumor type, following specific guidelines for each of the biomarkers: HER-2, K-RAS,N-RAS, EGFR, BRAF and ALK • Public healthcare: FISH for HER2 is recommended by the public healthcare guidelines, but the cost reimbursed is not enough to pay for the full test Adapted from references [43, 44]
France	• Testing is performed using the 28 INCa platforms. RNA sequencing can only be performed in selected platforms, and its availability is increasing with the arrival of new therapies targeting cancer with NTRK gene fusion • A specific assessment pathway for reimbursement of biomarker testing does exist, within HAS remits. However, it requires extensive evidence. Only a few tests are reimbursed through this formal reimbursement pathway such as HER2 in breast cancer (FISH), EBER in child neuroblastoma (FISH), and BCR-ABL • Newer tests are funded through an alternative pathway, RIHN, allowing broader access to testing. It requires data to be generated prospectively to then allow a formal HAS assessment • Access is guaranteed through RIHN funding, but the budget is capped. As the number of biomarkers is increasing, optimal funding of tests remains a topic high on the healthcare agenda
Italy	• Mutation tests used: EGFR and BRAF • Molecular Tumor Boards have been set up in some oncology centers in order to speed up decisions on testing and personalized therapies • A Manifesto of Rights to Personalized Medicine has recently been published by Cittadinanzattiva Adapted from references [45]
Spain	• There is no standardized procedure or specific regulatory framework for the evaluation, implementation and financing of biomarkers in clinical practice • Biomarker testing is managed at the regional level, by each hospital, but there is currently no national standardized testing process • Pharmaceutical companies fund some biomarker tests, while some are carried out within academic research programs Adapted from reference [46]
United Kingdom (England)	• Centrally reimbursed tests are listed in the national test directory: https://www.england.nhs.uk/publication/national-genomic-test-directories/ • NHS England has recognized the significance of tumor-agnostic therapies as part of strategic personalized medicine and genomics ambitions • Larotrectinib became the first tumor-agnostic treatment to gain NICE reimbursement approval in April 2020 via the Cancer Drugs Fund • The focus is now translating access into uptake by embedded NTRK testing within cancer pathways across the NHS to ensure the timely identification of eligible patients for treatment Adapted from references [47-49]

CASE STUDY 3: CLINICIANS LEAD DEMAND FOR GREATER ACCESS TO DIAGNOSTIC TESTING IN FRANCE [50]

Action

1. The availability of the 28 INCa platforms resulted from strong demand by clinicians to improve access to tests and ultimately to innovative treatments
2. A wide range of stakeholders mobilized to address risk of access inequalities due to capped funding

Medical call to action: Clinicians estimate the current allocated budget only covers 75% of the diagnostic tests requested, which means that some patients may be deprived of clinically relevant tests. This led to a demand by clinicians to accelerate access to approved reimbursement of tests. A specific committee was formed to ensure best practices for the application of testing, and the regular evaluation of outputs, so that cost efficiencies and healthcare sustainability were realized.

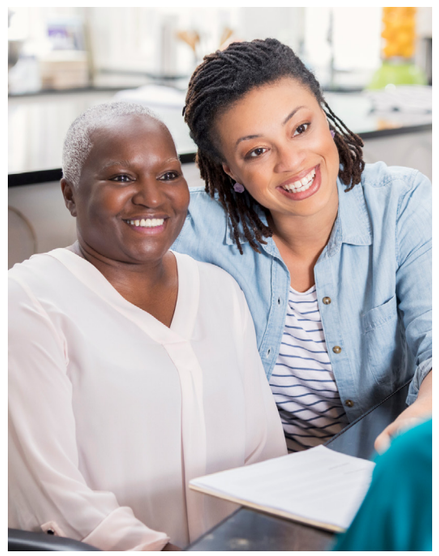
Political call to action: In a letter to the Minister of Health, parliamentarians raised awareness of the urgency to reform RIHN and the need to allocate specific funding for precision oncology and biomarker testing. As a measure of their commitment, an article was published on access to genomic testing and their intention to commit to an inter-ministerial mission on improved access to testing for the whole territory.

Patient advocacy call to action: 'Imagine for Margo', a patient association, is involved in sustaining research programs, such as the MAPPYACT trial aimed at characterizing the genetic profile of pediatric tumors refractory to standard of care.

Conclusion

There is no 'one-size-fits all' solution, but by working in concert, patients, healthcare professionals, advocates, policy makers, payers, and industry can find a path to a better future in which genomic profiling is a routine practice. The financial benefits are clear – if we find the right treatment for the right patient, and the right economic approach including addressing barriers to accessibility, we can improve healthcare sustainability, minimize impact on budgets, and most importantly, improve patient outcomes in a cost-effective manner.

An important caveat remains, that while there is definite room for improvement in access to genomic diagnostic testing worldwide, heterogeneity of infrastructure in different regions is an important factor that will influence what is possible. Change cannot happen overnight, but incremental steps can make a significant impact – through developing action plans that work for policy makers, through communication, and through listening to patients around the world.



Call to action

We can increase awareness about scientifically validated biomarker testing, to give patients the potential for suitable targeted cancer treatments, and drive better healthcare sustainability through increased biomarker diagnostic testing

1

Improve biomarker literacy – through educational activities about the economic and clinical value of testing; by sharing best practices across borders; ensuring patient inclusivity in informed decision making on testing and treatment, mindful of patient expectations.

2

Position diagnostic testing as integral to regulatory frameworks – champion the cause for improved access to diagnostic testing to be included in regulatory and healthcare frameworks; keep evaluating outputs to measure value and cost-effectiveness of testing to strengthen the case for more testing.

3

Listen to the science – utilize the new science, clinical research data and treatment advances as a bedrock of discussions; work with medical associations and medical regulators to include testing in clinical trial protocols; inform peers and partners about the dedicated specialized testing centers; call for standardized testing and best practices, and utilize resources with the best cost-benefit ratio.

4

Collaborate with professional and political experts – put biomarker testing high on political and scientific organization agendas; work with cancer centers of excellence and patient advocates to improve cross-talk among decision makers; be realistic as to what can be achieved, as small steps make a difference; petition for allocation of resources to fund more testing.

Appendix: Acronyms

Acronym	Meaning
ALK	Anaplastic Lymphoma Kinase
CGP	Comprehensive Genomic Profiling
CHMP	Committee for Medicinal Products for Human Use
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridisation
IHC	Immunohistochemistry
KRAS	Kirsten RAS oncogene

Acronym	Meaning
MBC	Metastatic Breast Cancer
MSI-H or dMMR	Microsatellite Instability High/Deficient Mismatch Repair
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotrophin Tyrosine Receptor Kinase
PCR	Polymerase Chain Reaction
RNA	Ribonucleic Acid
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
ROS1	Receptor Tyrosine Kinase 1
TMB-H	High Tumor Mutational Burden

References

1. A.T. Kearney. Preparing Health Systems for Tumor-Agnostic Treatment. 2019
2. International Agency for Research on Cancer. GLOBOCAN 2018. Available at: https://gco.iarc.fr
3. Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer/incidence#heading-One
4. Innovative Partnership for Action Against Cancer. Work Package 6 – Genomics in Cancer Control and Care. Available at: https://www.ipaac.eu/en/work-packages/wp6
5. European Cancer Patient Coalition. Molecular Testing & Personalised Medicine. Available at: https://ecpc.org/policy/molecular-testing-personalised-medicine/
6. European Cancer Patient Coalition/European Alliance for Personalised Medicine. Available at: https://ecpc.org/wp-content/uploads/2019/08/ECPC-patient-awareness-on-biomarkers-across-europe-2.pdf
7. Ciardello F, et al. Annals of Oncology 2014; 25: 1673-1678. Available at: https://core.ac.uk/display/33591330
8. Cancer Research UK. Available at: https://www.cancerresearchuk.org/sites/default/files/policy_august2015_mdx_final.pdf
9. European Cancer Patient Coalition. Available at: https://ecpc.org/wp-content/uploads/2019/08/ECPC-cancer-biomarkers-in-the-era-of-personalised-medicine.pdf
10. National Cancer Institute. Available at: https://www.cancer.gov/news-events/press-releases/2018/nci-match-first-results
11. Organisation for Economic Co-operation and Development. Available at: https://www.oecd.org/health/biotech/49023036.pdf
12. Grilli R, et al. Cancer Control Joint Action Policy Papers (Federici A, Nicoletti G and Van den Bulcke M, eds), pp. 29–67. National Institute of Public Health, Slovenia and Scientific Institute of Public Health, Belgium
13. Planchard D, et al. Available at: https://ascopubs.org/doi/full/10.1200/EDBK_100007
14. Wilsdon T, et al. Available at: http://www.crai.com/publication/benefits-personalised-medicines-patients-society-and-healthcare-systems
15. Ramirez SP, et al. Available at: https://pubmed.ncbi.nlm.nih.gov/31300934
16. NHS England. Available at: https://www.england.nhs.uk/wp-content/uploads/2020/10/BM2025Pu-item-5-diagnostics-recovery-and-renewal.pdf
17. Brito RA, et al. Available at: https://meetinglibrary.asco.org/record/190309/abstract
18. Gierman H, et al. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.1585
19. European Cancer Patient Coalition. https://ecpc.org/wp-content/uploads/2019/08/ecpc-white-paper-the-value-of-innovation-in-oncology.pdf
20. Slamon DJ, et al.N Engl J Med 2001; 344: 783–792.
21. Elkin EB, et al. Available at: https://ascopubs.org/doi/full/10.1200/jco.2004.04.158
22. Loubière S, et al. Available at: https://erj.ersjournals.com/content/51/3/1701467
23. Yates LR, et al. Annals of Oncology 2018; 29: 30-35.
24. Ciardello F, et al. Annals of Oncology 2014; 25: 1673-1678.
25. Martincorena I, et al. Cell 2017; 171: 1–13.
26. ESMO Oncology Pro. Available at: https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/overview-of-cancers-with-ntrk-gene-fusion/precision-medicine/tumour-agnostic-treatment
27. Offin M, Liu D, Drilon A. Am Soc Clin Oncol Educ Book. 2018; 38: 184–187.
28. Davis AA, et al. Am Soc Clin Oncol Educ Book 2018; 38: 998-1007.
29. Penault-Llorca F, et al. J Clin Pathol 2019; 72:460–467.
30. Buttner R et al. ESMO Open 2019;4:e000442. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6350758
31. Helsten T, et al. Clin Cancer Res. 2016 Jan 1;22(1):259-67.
32. American Society of Oncology. Available at: https://www.asco.org/research-guidelines/cancer-progress-timeline
33. Looney AM, Nawaz K, Webster RM. Nat Rev Drug Discov. 2020 Jun;19(6):383-384.
34. Yoshino T, et al. Ann Oncol. 2020 Jul;31(7):861-872.
35. Tan O, et al. Clin Genet. 2018 Mar;93(3):533-544.
36. Savelieff M. Available at: https://www.technologynetworks.com/diagnostics/articles/next-generation-sequencing-ngs-stimulating-the-next-generation-of-cancer-diagnostics-and-treatment-319649
37. Bueno R. Available at: https://cofactorgenomics.com/wk-6-2020-immunohistochemistry-in-cancer-diagnosis
38. Infogalactic. Available at: https://infogalactic.com/info/Reverse_transcription_polymerase_chain_reaction
39. Genome.gov. Fluorescence in situ hybridization (FISH). Available at: https://www.genome.gov/genetics-glossary/Fluorescence-In-Situ-Hybridization
40. Breastcancer.org. Available at: https://www.breastcancer.org/symptoms/testing/types/fish#:~:text=Fluorescence%20in%20situ%20hybridization%20%28FISH%29%20is%20a%20test,present%2C%20the%20more%20HER2%20receptors%20the%20cells%20have
41. World Health Organization. Available at: https://www.who.int/whr/2010/en
42. Florindi F, et al. Journal of Clinical Oncology35, no. 15_suppl. May 2017. Available at: https://www.researchgate.net/publication/327478533_Value_of_innovation_in_oncology_The_position_of_European_cancer_patients_on_access_to_innovative_treatments
43. Ferreira CG, Achatz MI, Ashton-Prolla P et al. BrLancet Oncol 2016; 17: e363–70.
44. Santos M, Coudry RA, Ferreira CG et al. Lancet Oncol 2019; 20: 20-23.
45. Cittadinanzattiva. Available at: https://www.cittadinanzattiva.it/comunicati/salute/13496-manifesto-for-the-right-to-personalized-medicine-for-cancerpatients-today-the-presentation.html
46. Sociedad Espanola de Oncologia Medica. Estudio SEOM sobre el Acceso a Fármacos y Biomarcadores en Oncología. Available at: https://seom.org/images/Estudio_SEOM_Acceso_2019_presentacion_resumen.pdf
47. NHS.uk. Available at: https://www.england.nhs.uk/2019/06/fast-track-game-changing-cancer-drugs
48. NHS.uk. Available at: https://www.england.nhs.uk/2020/04/nhs-strikes-deal-on-first-in-a-new-generation-of-cancer-busting-drugs
49. NICE larotrectinib technology appraisal guidance. Available at: https://www.nice.org.uk/guidance/ta630
50. Sénat. Available at: www.senat.fr/rap/r17-569/r17-5698.html

The development of this White Paper was initiated and fully funded by Bayer. Medical writing assistance was provided by communications agency FleishmanHillard, supported by Bayer. Bayer was also involved in the fact-checking of information. The named contributors provided input to the content and gave final editorial approval for the opinions and conclusions contained in this White Paper.

MAC-VIT-ALL-0011-1