



# **Put to the Test: Empowering Genomics to Improve Cancer Care and Patient Lives**

**Action Report**

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a. European Cancer Organisation's Policy Decision Making Process. <https://www.europecancer.org/2-un-categorised/24-policy-decision-making>

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## Executive Summary

The meeting brought together leading policy-makers, politicians, oncology experts and patient advocates to discuss the opportunities for improving the care and outcomes achieved for cancer patients by enhancing access to genomic tumour testing. The Roundtable aimed to stimulate consensus and promote better political understanding around current needs, in order to achieve better access for cancer patients to genomic tumour testing across Europe.

During this Roundtable misconceptions about genomic tumour testing were challenged, patient testimonials were captured, policy challenges such as inequalities in access, were explored, and recommendations for change were discussed.

Five key themes emerged in the policy recommendations discussed during the meeting:

1. **Networking between cancer centres** was often mentioned as an important means for resources to be pooled and the access of patients to genomic tumour testing to be improved. The formation of a new EU Network of Comprehensive Cancer Centres was raised as a potential opportunity in this respect.
2. **Greater consistency in approaches** across Europe in the area of genomic tumour testing was highlighted as desirable. This includes in respect of the fundamental terminologies used, means of communicating with patients, and approaches to reimbursement and approval.
3. **Data, in respect of genomic tumour testing, was identified as an area for policy attention.** This includes the collection and use of data relevant for cost-benefit considerations.

4. **Connected infrastructure needs, including those of the oncology workforce** must be addressed to ensure improved access to genomic tumour testing. This includes education and training needs for health professionals connected to the use of genomic tumour testing, investment in infrastructure and combatting relevant shortages in the workforce, including in pathology.
5. **A variety of present EU policy initiatives** were highlighted as connected. This includes:
  - a. The EU Network of Comprehensive Cancer Centres
  - b. The UNCAN.EU
  - c. The new 'Cancer Diagnostic and Treatment for All' of Europe's Beating Cancer Plan
  - d. The EU Cancer Inequalities Registry
  - e. The European Health Data Space

A suggestion was made that, to ensure action by Governments, national agencies and others on these issues, EU recommendations on Genomic Tumour Testing should be developed in order to forge the necessary areas of consensus, create political will and bring about accountability for implementation.

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# Glossary

**Actionable mutation:** Genetic mutation detected through single gene testing or genomic tumour testing, that is known to identify patients potentially responsive to a targeted therapy.

**Biobank:** A collection of human biological samples and associated information organised in a systematic way for research purposes. Molecular tumour diagnosis techniques, including genomic tumour testing, may use samples from biobanks for research.<sup>1</sup>

**Biomarker:** A biological molecule or change found in tissues or body fluids that is a sign of a normal or abnormal process, or of a condition or disease, such as cancer. Examples of biomarkers include genetic mutations and excessive/defective presence of certain RNAs or proteins.<sup>2</sup>

**Biomarker testing:** A laboratory method that uses a sample of tissue or body fluid to check for certain specific biomarkers that may be a sign of a disease or condition, such as cancer. May be used to help diagnose, select specific therapies, plan treatment, indicate prognosis, follow a treatment, make a prognosis, follow a treatment's efficacy or monitor long-term disease evolution. Part of molecular tumour diagnostics. Include single gene testing and companion diagnostic tests, opposed to whole genome sequencing.<sup>3</sup>

**Companion diagnostic test:** A test used to help match a patient to a specific drug or therapy, by checking for biomarkers known to predict efficacy for targeted therapies, such as actionable mutations. A category of biomarker testing designed specifically to help plan treatment. Companion diagnostic tests are therefore needed to 'accompany' targeted therapies by allowing to identify patients who may be responsive to it.<sup>4</sup>

**DNA:** Deoxyribonucleic acid. The molecule inside every cell that contains the genetic information responsible for the development and function of the cell and the individual. It is maintained in every cell's nucleus with the aim of protecting it from alterations, as it is transmitted to the descendance of the cell (via cell division) and the individual (via reproduction). DNA molecules are segmented into:

- Chromosomes: individual DNA molecules that play particular roles during cell division and reproduction; most human cells contain a total of 46 DNA molecules (23 pairs of chromosomes) in their nucleus; and
- Genes: portions of DNA molecules that code for the production of RNA molecules (transcription) and ultimately proteins (translation), via the process of gene expression, leading to a particular characteristic or function.<sup>5,6</sup>

**Genetic mutation:** A change, or rare variation, in a cell's DNA sequence. It can result from copying mistakes during the DNA replication/cell division process or from exposure to a mutagenic, DNA-damaging factor (e.g. UV or ionising radiation, chemicals, virus infection). Depending on its location and features (i.e. whether and how it affects the DNA sequence of, or around, a gene), a mutation can have functional consequences on the cell, such as contributing to cancer development. Importantly, a mutation may:

- be inherited from the individual's parents and present across all its cells (germline mutation – if present in their reproductive cells; possibly causing familial predisposition to develop cancer); or,
- arise during the individual's lifetime in some of its cells (somatic mutation; possibly initiating or accumulating during cancer development).<sup>7,8</sup>

**Genomic tumour testing:** A category of molecular tumour diagnostics. Analysis of a tumour sample's DNA to identify possible genetic alterations. Genetic tumour testing includes PCR (Polymerase Chain Reaction) and FISH (Fluorescence in situ hybridization) techniques, as well as multiplex (multiple genes and genetic alterations) approaches through the NGS (Next Generation Sequencing) technology; it may investigate mutations either:

- on a determined wide range of genes (biomarker testing approach); or,
- across all of the patient's tumour's DNA (whole genome sequencing approach).

Opposed to SGT (single gene testing). Importantly, identified mutations may be somatic (i.e. arisen

during the patient's lifetime, possibly specific to the tumour cells) or germline mutations (i.e. inherited from the patient's parents). It may identify actionable mutations and therefore help plan optimal patient treatment.

**Molecular tumour diagnostics:** The process of characterising a tumour by studying molecules, such as:

- DNA, providing an image of the tumour's genomic information, including possible genetic mutations (sequencing-based, such as single-gene testing or genomic tumour testing, or imaging-based techniques, such as fluorescence in situ hybridization (FISH)); but also,
- RNA, providing an image of the tumour's genomic activity, including overly or underly expressed genes (transcriptomic profiling); or,
- Proteins, providing an image of the tumour's biochemical and functional activity (e.g. immunohistochemistry).

Molecular tumour diagnostics may use samples from the patient's tissue (solid biopsy)<sup>9</sup> or fluid (liquid biopsy). Also called molecular tumour profiling or tumour subtyping, as it may allow to classify a tumour into a subtype based on its molecular features.

**MSI/MMR testing:** Microsatellite Instability/Mismatch repair testing. Microsatellite instability corresponds to a change that occurs in certain cells (such as some cancer cells) in which the length of microsatellites (which are repeated DNA sequences spread across the human genome) is abnormal. Microsatellite instability may be caused by mistakes that do not get corrected when DNA is copied in a cell, due to a deficiency in the mismatch repair system, the set of proteins responsible for correcting such DNA replication mistakes, caused by genetic mutations affecting genes coding for these proteins.

As such, MSI is therefore evidence for MMR deficiency, which in turn may have much broader consequences on the cell, such as contributing to cancer development by favouring the easier apparition of additional mutations through DNA replication mistakes. MMR deficiency may be inherited as part of hereditary cancer predisposition syndromes (e.g. Lynch syndrome), or acquired through somatic mutations during the cancer development process.

Testing for MSI or MMR deficiency through immunohistochemistry or PCR/DNA sequencing techniques is an established prognostic test associated with response to chemotherapy in certain cancers. It has also been recently shown to predict efficacy of certain immunotherapies in a tumour-agnostic manner, paving the way for it to be used as a companion diagnostics test in this setting.<sup>10-12</sup>

**NGS:** Next-Generation Sequencing. A high-throughput method used to determine the DNA sequence of a (portion of) a cell's or individual's genome. NGS may be used for genomic tumour testing, either to investigate mutations on a determined wide range of genes (biomarker testing approach), or on the entire patient's tumour's DNA (whole genome sequencing approach). Also called massively parallel sequencing and NGS. Opposed to SGT (single gene testing).<sup>13</sup>

**Protein:** A category of molecules inside every cell that are responsible for all functions of the cell and the individual. Proteins are the product of the gene expression process and are synthesised by complementarity with mRNA molecules (translation). Examples of functional sub-categories of proteins include antibodies, enzymes, receptors, and transporters.<sup>14</sup>

**RNA:** Ribonucleic acid. A category of molecules inside every cell that is produced by complementarity using portions of DNA molecules as a template, via the gene expression process. Cells make several different forms of RNA, each with a specific function; this includes messenger RNA (mRNA) which travel from inside to outside the cell's nucleus to serve as a template for the synthesis of proteins (translation).<sup>15</sup>

**SGT:** Single gene testing. A category of molecular tumour diagnostics and biomarker testing. Analysis of a tumour sample's DNA to identify possible genetic mutations on one single gene. Opposed to genomic tumour testing.

**Targeted therapy:** A type of therapy whose efficacy is evidenced among individuals with a specific biomarker, such as an actionable mutation identified through genomic tumour testing or single-gene testing. The aim of targeted therapies in cancer is that they would affect specifically certain types of cancer cells, causing less or no harm to other cells. This may be the case in a tumour-specific, or tumour-agnostic, manner.

Targeted therapies are an integral part of precision oncology.<sup>16</sup>

**Tumour-agnostic therapy:** A type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type. Tumour-agnostic therapies use the same drug to treat

all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy. Also called tissue-agnostic therapy.<sup>17</sup>

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# Introduction

**Matti Aapro, President of the European Cancer Organisation (2020–2021), and Mark Lawler, Board Member, European Cancer Organisation, and Chair in Translational Genomics, Queen’s University Belfast.**

This Roundtable brought together leading policymakers, oncology experts, patient advocates, and industry partners to discuss genomic tumour testing in Europe, and its implications for the delivery of precision oncology for European cancer patients. The Roundtable captured patient testimonials, promoted discussion on policy challenges, and produced a series of recommendations for genomic tumour testing to become part of the standard of cancer for European cancer patients, in the context of the implementation of Europe’s Beating Cancer Plan<sup>18</sup> and Horizon Europe’s EU Cancer Mission.<sup>19</sup>

The allied development of genomic tumour testing and tumour-agnostic therapies present challenges to the way we deliver cancer care, including in respect of the education, training and organisation of the oncology workforce. For example, we must address the commonly reported problem of a shortage of pathologists in many health systems, and ensure the provision of high-quality and independent up-to-date continuous medical education to healthcare professionals on genomic tumour testing. Supporting provision of optimal patient information, genomic counselling (where relevant), and shared decision-making, are also important policy needs to be addressed in connection with the implementation of genomic tumour testing across Europe.

There is a need to improve dissemination of the latest evidence and facilitate effective research on the benefits and costs of genomic tumour testing. Measuring and addressing inequalities in access to genomic tumour testing across European countries and social groups, as well as ensuring a connection with the emerging European digital health infrastructure, are also critical factors to be addressed. The terminology used in both clinical

practice and in interactions with patients also requires harmonisation, as for example, ‘genomic tumour testing’ is also sometimes referred to as ‘molecular tumour diagnostics.’

Collaborative actions from multiple stakeholders are required to address discrepancies in national processes and policies on genomic tumour testing, particularly in relation to next generation sequencing (NGS). We need to challenge misconceptions that may have become inferred around the reality of genomic tumour testing and capitalise on the increasing affordability and reliability of genomic tumour testing across Europe to ensure its widespread and robust implementation.

Looking to the policy context, patient-focused policy-making and ensuring consistency of communication about genomic tumour testing are essential. Stimulating consensus and promoting better political understanding about present policy needs will help to achieve better access for cancer patients to genomic tumour testing as a standard of care across Europe. Ensuring that genomic tumour testing is given due consideration as part of current EU policy initiatives on the monitoring, mitigation, and resolution of cancer inequalities, is an increasingly important element of improving the environment for the technology’s take-up across Europe. We need to embed genomic tumour testing as the standard of care for European cancer patients.



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# A Guide to Genomic Tumour Testing

**Richard Price, Head of Policy, European Cancer Organisation and Peter Schirmacher, President-Elect, European Society of Pathology (ESP), kicked-off the Roundtable with a 'fireside chat' interview explaining the basics of genomic tumour testing.**

Price opened by asking Schirmacher, (a leading expert in the field), what is meant by genomic tumour testing?

Schirmacher stated that this is a very innovative area of diagnostics and decision making, and whilst we often call it 'genomic tumour testing', it is often also called 'molecular tumour diagnostics'. This is the application of molecular technologies in clinical diagnostics for better diagnoses of tumours ('tumour typing'). This allows a more precise therapy decision via the use of predictive diagnostics in personalised / precision oncology, and improved detection of one's genetic predisposition. This ultimately leads to better cancer prevention. Molecular tumour diagnostics can guide better therapy to the right patients, improve patient survival, and provide a better quality of life with fewer side effects.

How is the landscape changing, for example, in relation to the development of targeted, and even in some cases, tumour-agnostic treatments?

Schirmacher replied stating that now that we have multiple biomarkers for several drug indications, the situation is becoming more complex. More tumour types can be tested, and we now also have 'across tumour' testing. There will be an increase in novel therapies, with testing guiding indications, with more complex biomarkers, and a 'second generation' of biomarkers. With the rise of these multiple complex technologies, we must have all the right tools at hand, and a high level of expertise. We should have 'competence centres' that can pool or join-up molecular diagnostic testing for personalised oncology.

What are the main challenges that we need to solve to leverage the full potential of genomic tumour testing to ensure it is effectively accessed by those who need it?

Schirmacher stated that a key challenge is ensuring sustainable financing and reimbursement for genomic tumour testing. There is also a need to ensure that testing does not evolve into a 'direct-to-consumer industry', and that data collected is used for patient care and future research. Establishing and supporting Centres of Excellence for personalised oncology, with both technology and human resources, and development of national and international networks, will be critical.

Schirmacher also stressed the need to ensure the availability of medicines connected to tumour testing (both in development and after approval), the translation of research into practice, molecular imaging for early response prediction, and molecular diagnostic testing for novel indications.

In the ensuing discussion, Gilly Spurrier-Bernard, Vice-Chair of the European Cancer Organisation's Patient Advisory Committee, asked: How can a patient, within the constraints of a public health system, make sure that their precious (sometimes only) piece of accessible tumour tissue gets tested and analysed for markers, that will cover all potential treatment options and management, in a timely way?

Schirmacher replied that the materials we get from normal biopsies are suitable for molecular testing, and usually do not degrade for the first five to seven years, if stored appropriately. Schirmacher also challenged whether the reimbursement rules in Europe are appropriate. For example, in Spain the pharmaceutical industry can pay for testing, whereas in Germany this is not permitted.

# The Advent of Tumour-Agnostic Therapies and Their Impact on the Need for Genomic Tumour Testing

The next session was chaired by **Gabriela Möslein**, Chair, European Hereditary Tumour Group (EHTG), and Past-General-Secretary, European Society of Coloproctology (ESCP), and **Amy Van Buskirk**, Global Product Strategy Oncology Head LASR (Lung, Agnostic, Skin & Rare Cancers), Roche.

Möslein opened by stating that as a surgeon, she is just one of the many specialists involved in genomic tumour testing, and that the EHTG is an ‘agnostic’ organisation in this sense, welcoming participation of oncology professionals from many different specialist domains. Möslein recalled the landmark case of pembrolizumab, the first ‘agnostically’ licensed drug. However, five years later, it is still not widely accessible. Möslein highlighted the work of John Burn et al on ‘Lynch syndrome’, and the link between aspirin and lower incidence of colorectal cancer.<sup>20</sup> Möslein stated that Burn and his team have also developed an NGS assay that can identify micro-satellite instability and all activating RAS mutations in colorectal tumour blocks, at very low cost, and in a single technology. Möslein informed the audience that EHTG aims to partner with industry to reduce costs and called for universal genomic testing to be performed alongside an algorithm for patient and family counselling.

*“If we don’t have access to the testing, we cannot help patients.”*

Van Buskirk proclaimed that if we don’t have access to the testing, we cannot help patients. The concept

of genomic tumour testing is not a well-known concept, yet it represents a significant revolution in care, with many more tests and treatments in the pipeline. One of the obstacles to overcome is the habit of health systems to ‘departmentalise’ care, meaning changes in practice and science that cross departments can be more challenging to act upon.

Van Buskirk stated that inherited mutations, multiple mutations, or specific mutations in one family member are known to pre-dispose other family members to other cancers, and therefore funding for broad molecular testing should be implemented. Regulatory and reimbursement systems need to evolve so precision oncology can become a reality.

The recommendations of the European Society of Medical Oncology (ESMO) on the use of next-generation sequencing (NGS) for patients with advanced cancers<sup>21</sup> represent an important first step, Van Buskirk stated, but they leave behind a substantial number of patients. Guidelines need to be rapidly adaptable, and we should move away from a histology-focused approach to a molecular tumour diagnostics approach. Molecular diagnostics should drive treatment. Van Buskirk cited the TAPISTRY<sup>22</sup> umbrella platform study for tumour-agnostic treatment, supporting the use of molecular tumour diagnostics.

Van Buskirk closed with five key take-aways:

**Figure 1. Pharma Perspective: Key Takeaways**



## The Need for Comprehensive Genomic Profiling

Fernando López-Ríos, Pathologist, “12 de Octubre” University Hospital, Madrid, opened by highlighting that there is a growing list of biomarkers that we can look for, and this should be done by comprehensive genomic profiling (not just by single gene approaches), an approach endorsed by ESMO.<sup>23</sup> López-Ríos stated that the arrival of pan-cancer biomarkers has assisted as it enables the performance of more NGS with larger panels.

López-Ríos highlighted the advantages of NGS, but stressed the need for a blend of analytics, with the longer turnaround time, higher costs, and other pitfalls of NGS. López-Ríos stated that we must define our relationship with liquid biopsies by using algorithms.<sup>24</sup> We should also define our relationship with digital pathology and explore the use of AI to identify very rare sub-groups of patients who can achieve very good clinical results.

López-Ríos closed by offering several take-away messages:

- The quantity of communication within intralaboratory tumour boards predicts quality
- Interlaboratory molecular tumour boards should integrate clinical, pathology, and biomarker data
- The use of real-world data from molecular tumour boards can improve outcomes in patients and in the clinical setting

## Ensuring We Address the Human Resources Needs of Testing

Fatima Carneiro, Past-President, European Society of Pathology; Professor of Pathology and Director of the Unit of Pathology and Oncology, Medical Faculty of the University of Porto, Portugal; and Head of Department of Anatomic Pathology, Centro Hospitalar São João, Porto, Portugal, began by providing the audience with the US National Cancer Institute’s definition of tumour-agnostic therapy.<sup>25</sup>

A type of therapy that uses drugs or other substances to treat cancer based on the cancer’s genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumour-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy. Also called tissue-agnostic therapy.

*“When how is better than where.”<sup>26</sup>*

Carneiro cited the first approval of an agnostic therapy (pembrolizumab) in 2017 in the US,<sup>27</sup> and the first EMA approval in 2019 (larotrectinib).<sup>28</sup>

Carneiro cited the Joint JSCO-ESMO-ASCO-JSMO-TOS guidelines on tumour-agnostic treatments in patients with solid tumours,<sup>29</sup> and the expert recommendation that patients with an incidence of microsatellite instability (MSI) / deficient Mismatch Repair (dMMR) proteins should be tested for their status. Carneiro reminded the audience that immunohistochemical staining (IHC) still plays a role all over the world in testing for MSI/MMR status, and that NGS is also allowing the identification of instability signatures, or even instability burdens. Carneiro stated that there is a very high concordance between endoscopic biopsies and surgical specimens, meaning MSI status can be determined confidently in biopsies before establishing the adequate treatment for patients.

Carneiro called for caution when planning the number of pathologists in a department, i.e., by considering all new technologies that are available, and the time it takes to use these technologies in practice.

Carneiro also raised a point concerning the possibility of detection of constitutional mutations linked to hereditary disorders in an NGS panel, and how this can be addressed. Carneiro stressed that patients have the right to know (or not to know) such information. She further challenged whether this is specified in the informed consent that patients sign upfront.

## Using Consistent Terminology for Practice and Communication with Patients

Natacha Bolaños, Member, Patient Advisory Committee, European Cancer Organisation, and Global Alliances Manager & Regional Manager, Lymphoma Coalition Europe, opened by saying that cancer patients are generally aware of the benefits of tumour testing, especially advanced cancer patients. For example, the potential benefits of an increase in efficacy whilst minimising side effects, either as treatment or within trials.

Bolaños stated that patients value the research use of their data, (secondary to their survival), but stressed that patients with non-European ancestry are often underrepresented in genetic research, thus widening disparities. Bolaños also highlighted

the need to address aspects of uncertainty during the testing process for patients, as testing itself can also raise its own concerns and impacts. For example, psychological risks such as becoming disappointed if there are no actionable results, or if there are, becoming disappointed because of inability to access treatment.

Bolaños highlighted the need to use consistent

terminology for both practice and patient communication. If patient-friendly terms are used, patients are empowered. Bolaños closed by stressing the need for patient empowerment, interoperable data infrastructures, consistent terminology, appropriate training of the workforce, addressing disparities in minorities, and the need to protect genetic data confidentiality.

### Policy Recommendations

- Competence centres' and use of networking solutions provide significant opportunity in respect to improving access to genomic tumour testing.
- In connection to EU policy in the area of health and cancer, connections should therefore be made with initiatives such as:
  - » The new EU Network of Comprehensive Cancer Centres
  - » The European Health Data Space
  - » UNCAN.EU
  - » The EU Cancer Inequalities Registry
- Universal molecular tumour diagnostics should be performed alongside an algorithm for patient and family counselling.
- Guidelines should be rapidly adapted according to progress in research and development.
- Beyond targeted and tumour-agnostic therapies, we need to recognise and leverage the potential of molecular tumour diagnostics to identify further germline / constitutional cancer-causing mutations, and ensure informed consent of patients.
- We should be using consistent terminology both in practice and when communicating with patients.

# Latest Evidence and Research Needs on Benefits and Costs of Genomic Tumour Testing

This session was chaired by Mark Lawler, Board Member, European Cancer Organisation and Chair in Translational Genomics, Queen’s University Belfast, and Brian Cuffel, Vice-President and Head of Market Access Oncology, Bayer.

Lawler opened by emphasising the primacy of cancer biomarkers and molecular tumour diagnostics in precision oncology, and asked:

“How do we embed this in practice?”

Lawler called for cancer biomarkers to be embedded into the real-world of oncology delivery and to be implemented across Europe.<sup>30</sup> Lawler coined the phrase ‘cancer biomarkers go mainstream’, when referring to the fact that in 2019, there were 70 approved drugs requiring tests,<sup>31</sup> and that we need to make sure these are available. Lawler raised the issue of cost and value, and stated that testing must be available and reimbursed. Lawler cited several studies providing evidence of the cost-effectiveness of ‘precision diagnostic testing’.<sup>32-34</sup>

Lawler also cited evidence that there are socio-economic inequalities in testing across Europe,<sup>35</sup> and that molecular tumour diagnostics should not widen existing inequality gaps, but should narrow them. Lawler stated that the cost of not testing equates to not being able to deliver the best care. Biomarkers need to be deployed as part of routine care.

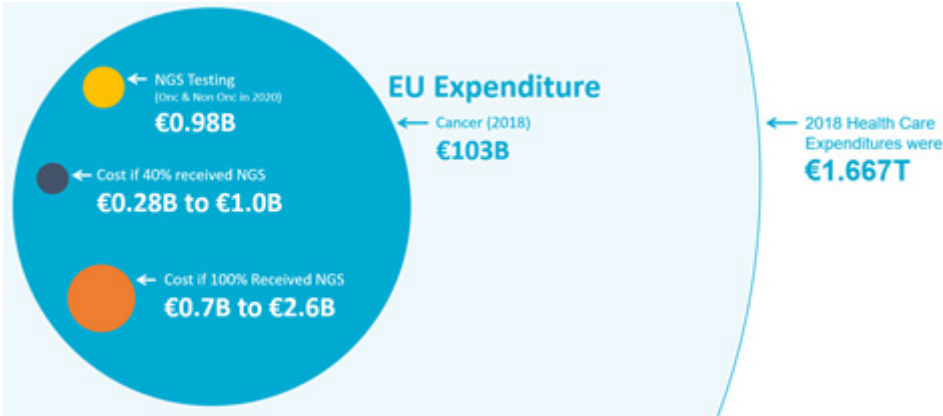
Cuffel opened by stating that more and more oncology medicines are being approved based on a genomic profile. However, policy discussions around access are almost always related to financial cost. Cuffel framed these discussions into two ‘buckets’:

- Is broad access to NGS a sustainable investment in the long term?
- Is broad access to NGS good ‘value for money?’

Cuffel proclaimed that the US and UK authorities have taken a stance on financial costs and benefits in their national coverage decisions. Cuffel stated that the data we have today may not be perfect, and more data on cost-benefit is needed, but the existing data does point in the right direction, and we should act upon this to inform policy today. Cuffel stated that the total cost of molecular tumour diagnostics has not been well documented, however it is likely to be a small percentage of the overall spend (5-6% of overall spend in EU).<sup>36</sup>

Cuffel highlighted that the cost effectiveness of large panel NGS represents good value for money relative to single gene testing (SGT) approaches, and that broad panel NGS testing indicated either a comparable, or in some cases, a substantially reduced cost (personal communication, publication in press, expected 2022). Cuffel described potential benefits to patients of around one additional year in survival time, and that there will also be a decrease in costs of NGS in the future due to advances in genomic science.<sup>37-41</sup>

**Figure 2. Total Cost of Genomic Testing in Cancer has Not Been Documented but is Likely to be Small Percentage of the Overall Spending**



## Collaborative Networks for Molecular Tumour Diagnostics

Giancarlo Pruneri, Head, Department of Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan; Full Professor of Pathology, University of Milan, School of Medicine; and President, Euro-Asian Mastology Association (EURAMA), opened by stating that the ESMO guidelines identify three types of tumours that should be 'broadly' tested: NSCLC (non-small cell lung cancer), prostate, and pancreatic cancer.

Pruneri called for NGS to be part of the standard practice for research centres and hospitals. In the past, Pruneri said, the costs have not been well evaluated, but cited a recent study comparing the costs of NGS and single-gene testing (SGT) in a NSCLC, and mCRC.<sup>42</sup> The study confirmed that NGS reduced costs compared to SGT, for instance, using NGS saves workforce time compared to SGT.

Pruneri stated that in his experience, the molecular tumour board addresses about 1500 cases per year and suggested that pooling resources in collaborative networks ('hub and spoke'), is the way forward. Pruneri concluded with the following take-home messages:

- Decreasing the use of SGT in favour of NGS can lead to a cost reduction
- Testing a minimum number of patients and molecular alterations may be necessary to generate savings
- Future analyses should clarify the cost of different NGS panels, including prevalence of actionable alterations and outcomes, as well as the impact of the molecular tumour board analysis

### A Series of Unfortunate Events

Bettina Ryll, Member, EU Cancer Mission Board, and Founder, Melanoma Patient Network Europe (MPNE), opened by emphasising the significant overtreatment of melanoma that takes place. This is of particular concern in respect to the long-term toxicities and side effects that may then occur. For example, a melanoma may be beaten by immunotherapy but the patient then develops diabetes as a result of the treatment. Patients with diabetes have, on average, a reduced life expectancy of 13 years. Therefore, a more precise way of identifying the patients who would benefit

from such therapies, (via molecular tumour diagnostics), would reduce the incidence of toxicity in patients who may not have benefitted from treatment in any case.

Ryll emphasised the difference in scale between treatment of large cancers (which is usually not personalised), versus treatment of smaller or rarer cancers, and that we should ensure we do not neglect the latter group. Ryll listed several barriers that we need to overcome, including collection of data, appropriate standards and protocols, harmonisation, cost of testing, the need for policy collaboration, and overcoming vested interests.

*"A series of unfortunate events."*

Ryll coined this phrase to describe how each step in the process of providing molecular tumour diagnostics has huge uncertainties.

*"Uncertainties that health technology assessment bodies really do not like."*

Ryll closed by stating that we have to think about how we minimise the uncertainty along this chain, and that we need to invest into a 'learning healthcare system'.

In the ensuing discussion, Lawler stated that precision diagnostics at an early stage of disease can save money, citing experience in Ireland. Ryll added that we should make better use of registries in areas where commercial interests are lacking.

Pruneri informed the audience that by using a molecular tumour board on a routine basis, and forming a partnership within a region, they are able to achieve a 'from-first-test-to-start-of-treatment' time of only 24 days. Pruneri reiterated the need to centralise laboratory operations, as the information and samples should travel, not patients. Pruneri also called for local oncologists to be involved in molecular tumour boards.

## Policy Recommendations

- Existing data should be better deployed to help inform policy changes. Simultaneously, efforts should be made to enhance collection and use of cost-benefit related data.
- In order to better manage cost and investment in the interim period, resource pooling should take place via collaborative networks of cancer centres to ensure a greater number of patients receiving access to genomic tumour testing. There is a role in this case for the EU Network of Comprehensive Cancer Centres, presently being constructed as part of Europe's Beating Cancer Plan.
- Using NGS over SGT can provide savings, but further analysis is needed.
- Molecular tumour diagnostics can reduce morbidity and toxicity in cancer survivors through targeted and rationalised treatment decisions.

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# Discrepancies in National Processes and Policies on Next Generation Sequencing

This session was chaired by **Matti Aapro, President (2020–2021), European Cancer Organisation, and John Longshore, Head of Scientific Affairs, Global Oncology Diagnostics, AstraZeneca.**

Longshore opened the session by stating his belief that molecular tumour diagnostics are key to achieving better care, and that the launch of Europe's Beating Cancer Plan is an excellent opportunity to highlight NGS and its benefits. For instance, the Beating Cancer Plan recognised the importance of molecular testing in Flagship 6, the 'Cancer Diagnostic and Treatment for All initiative', which is intended to leverage molecular testing and diagnostics to improve care and access and reduce inequalities.

Longshore also cited policy recommendations from The International Quality Network for Pathology (IQNPath), European Cancer Patient Coalition (ECPC), and European Federation of Pharmaceutical Industries and Associations (EFPIA) report titled 'Unlocking the potential of precision medicine in Europe'. This study demonstrates the unequal access to molecular diagnostic testing across Europe.<sup>43</sup> The study highlights challenges such as the lack of physician awareness of the benefits of testing, the absence of a framework demonstrating its value, and the relatively high investment required. The varying reimbursement frameworks across countries also contribute to the inequality gaps.

## Inequalities in Test Access and Test Quality

Nicola Normanno, President, International Quality Network for Pathology (IQNPath); Chief of the Cell Biology and Biotherapy-Unit, Istituto Nazionale Per Lo Studio E La Cura Dei Tumori Fondazione "G. Pascale", Naples, Italy; and President-Elect, Italian Cancer Society, opened by stating that the number of predictive biomarkers is increasing. It has been estimated that more than 25% of patients with advanced cancer may receive a treatment based on genomic profiling.<sup>23, 30, 44</sup>

Normanno referred to the aforementioned IQNPath-ECPC-EFPIA study<sup>43</sup> to evaluate the access to and

quality of biomarker testing across Europe. This study covered 12 biomarker tests, plus liquid biopsy. In total, 141 laboratory managers were surveyed representing 1.665 patients. 58 in-depth interviews with key stakeholders, and a literature review were performed as part of the study. Access metrics (medicine availability, laboratory access, test availability, test reimbursement, and test order rate) were applied.

Normanno stated that the study demonstrated significant variations in drug and test access, as well as test quality across Europe. For example, Italy, Spain, and Greece only have one to two percent of tumour types tested. In the majority of European countries, only a fraction of NSCLC patients receive a test, and the study found that tests are not ordered due to financial reasons, or because there is an uneven distribution of laboratory facilities.

As stated in a 2014 landmark article on molecular pathology for cancer patients, "internal quality control, regular internal audit of the whole testing process, laboratory accreditation, and continual participation in external quality assessment schemes are prerequisites for delivery of a reliable service".<sup>45</sup>

Normanno closed with the following calls to action:

- All cancer patients eligible for biomarker-linked therapy must undergo testing for all clinically relevant biomarkers that are indicated for precision medicine, with use of extended panels where appropriate
- The following actions are needed to improve short term access to biomarker testing:
  - » Parallel approval of the medicine and associated testing
  - » A national system for biomarker test value assessment
  - » Dedicated biomarker test budgets
  - » Mandatory ISO accreditation and EQA scheme participation
  - » Regional testing centres



- » Stakeholder education
- » Centralised national data collection
- » Horizon scanning for future testing needs
- In the near future, all patients with a cancer diagnosis should undergo comprehensive, ongoing tumour testing, throughout their care

## Ensuring the Payer and Prescriber Remain Aligned

Frédérique Penault-Llorca, Director-General, Jean Perrin Cancer Centre, Clermont-Ferrand, France, and Vice-President, Federation of French Cancer Centres (UNICANCER), provided a case study from France.

*“From a perfect model to mismanagement.”*

Penault-Llorca stated that until 2017, molecular tumour diagnostics were provided free of charge for patients in France, with 91% of those requiring test, benefitting from a test. However, in 2018 there was a change in reimbursement, with significant consequences. This change in reimbursement meant that the funding shifted directly to the hospital / prescriber, (with a maximum budget of €380 million per year, for all biological tests). Penault-Llorca stated, however, that this budget was insufficient, especially with more tests coming to the market, with the actual spend for 2017 being €694 million, with only around 50% of this covered by the budget.

Penault-Llorca cited other issues within the system, such as the reliability of the reporting system, an overestimation of the price / value of several acts, and an absence of ‘indication wording’ in the acts (leading to over testing).

Penault-Llorca stated that the ‘France Médecine Génomique 2025 Plan’ (FMG) was launched with the following three objectives:

- To implement the tools of the genomic care pathway
- To ensure operational implementation and ramp-up production
- To implement monitoring and steering tools

Penault-Llorca stated that the FMG 2025 is off to a slow start, with routine whole genome sequencing not yet performed. Penault-Llorca concluded by explaining that whilst French patients still have ‘equal access’, the cost has shifted to hospitals.

Additionally, despite the natural evolution toward prescription of NGS tests, the reimbursement system is geared for companion tests (i.e., single targets / SGT).

*“The early access to drugs is reimbursed, but where there may be a generic available, the test is only funded at 50%.”*

## Patients Expect Whole Genome Sequencing

Piarella Peralta, Patient Advocate, Inspire2Live, opened by stating that we are better equipped than ever to provide precision oncology care. Peralta stated that there is now an expectation that advanced cancer patients should have access to whole genome sequencing and other advanced technologies, such as NGS, the use of ex-vivo models, and leveraging the vast computational power now in our hands.

*“We need to bring the patient back to the equation.”*

Peralta expressed frustration that we do not apply knowledge and make technologies available to patients. Inspire2Live’s goal is to secure whole genome sequencing reimbursement in the Netherlands, and Peralta highlighted that the turnaround times for whole genome sequencing are clinically relevant.

Peralta proclaimed that it is time to act.

Peralta stressed the need to go broader with molecular tumour diagnostics, to avoid ‘post-code lotteries’ for testing, and to avoid disincentives for use of these innovative technologies. Peralta also called for patient self-determination, where the oncologist should be able to inform patients on which technologies are available. Peralta closed by calling for the use of FAIR data principles<sup>46</sup>, and the need to realise the potential of precision medicine for the individual patient. A patient, not product-centred approach.

In the ensuing discussion, Peter Schirmacher stated that sequencing costs are dropping. However, they are a minor part of the entire testing process, and we should keep in mind the other costs, (such as human resources and infrastructure), and thus these costs must also be incorporated into cost calculations.

For more information on a tool for costing molecular testing from the UK Royal College of Pathologists please see here.<sup>47</sup>

## Policy Recommendations

- Policies supporting whole genome sequencing should be developed.
- Policies addressing inequalities in access to, and quality of molecular tumour testing are needed.
- Workforce planning and infrastructure development costs should be included when planning for broader molecular tumour diagnostic services.

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## Where Next? The Policy Context

This session was chaired by Richard Price, Head of Policy, European Cancer Organisation.

### Patient-Focused Policy-making

Gilly Spurrier-Bernard, Vice-Chair of the Patient Advisory Committee, opened by emphasising the need to 'use tissue well', and provided a critique of the current operation of some biobanks in respect to issues such as patient communication. Spurrier-Bernard also stated that waiting times for molecular tumour diagnostics for paediatric patients has been reported to be as long as 55 days. In discussion, some of the delays experienced may be a result of practical issues such as sending large batches for testing. Spurrier-Bernard noted the role that liquid biopsies can play, highlighted the challenges to clinical trials concerning validation and collection of samples, and emphasised the power of cross-border networks.

### Personalised Medicine in All Policies

Jan-Willem van de Loo, Theme Lead cancer, Policy Officer cancer research and innovation, DG Research & Innovation, European Commission, stated that personalised medicine is not only research, as it is also public health implementation. Personalised medicine, stated van de Loo, is also not just about treatment, as it is also about prevention, and several DGs within the Commission are working on topics related to personalised medicine.

The EU Cancer Mission and Europe's Beating Cancer Plan are also opportunities to address molecular tumour diagnostics, for example, Flagship 7 on UNCAN.eu, as it will enable the connection of data within the EU and beyond. Research for data that is well beyond the 'health domain', for example, in geopositioning, agriculture, and urban planning, can also be leveraged in beating cancer, stated van de Loo.

The upcoming European Health Data Space (expected in 2022) will include a blueprint for an EU Cancer Patient Digital Centre to bring together data relevant for personalised medicine. In closing, van de Loo reminded the audience that DG RTD has been working on personalised medicine for a long time, for example, related to the ICPeMed definition.<sup>48</sup>

### Diagnostics at Diagnosis and Consistency of Communication

Zorana Maravic, Chief Executive of Digestive Cancers Europe (DiCE), opened by stating that such a complex topic requires comprehensive planning, and we have seen various successes by the EU in this space. Policies should enable timely access to testing for all patients, and all those tests that are approved should be made available, free of charge. There should be a dedicated budget for testing and associated resources to achieve this.

Maravic stated that molecular tumour diagnostics should happen at diagnosis of the cancer, or according to cancer progression. Guidelines should be regularly updated to avoid becoming a barrier.

Maravic proclaimed that comprehensive molecular tumour diagnostics are cost-effective, and that patients should have access to tumour boards to ensure cost-effective care. Data should be collected to facilitate development and provision of new treatments. Maravic closed by stressing the need for clear terminology, as patients need to understand what is being said.

*"We need to speak the same language."*

### A First in Lithuania, However Knowledge Gaps Remain

Sonata Jarmalaite, Acting Director at the National Cancer Institute of Lithuania, declared that this year, Lithuania celebrates the first reimbursement agreement of a molecular tumour diagnostic test, having previously only been funded by the pharmaceutical industry. Jarmalaite highlighted a knowledge gap in genetics for both healthcare professionals and politicians alike, something which is experienced often in other former Soviet countries. Jarmalaite described the difficulty in explaining to politicians that the developments in molecular tumour diagnostics are not for the benefit of science alone, but are for the benefit of patients and cost-effective care. Jarmalaite closed by stating that cost-effectiveness data is critical to policy-makers and decision-makers.

## Policy Recommendations

- A cultural change is required within political and health systems in respect of metastatic cancer. Hope is under-emphasised, yet treatment and care innovations often provide reason for it.
- Our oncology data approaches in Europe are deficient when it comes to metastatic cancer. A prime example relates to registries, which are not adequately recording metastatic cancer and cancer recurrence. In the context of Europe's Beating Cancer Plan, the EU Mission on Cancer and the establishment of the European Health Data Space, this deficiency should be addressed. The European Cancer Organisation's Digital Health Network has recommended political targets on registry interoperability as one means to support this.
- Treatment reimbursement strategies in Europe should better reflect patient preferences for their treatment, including reduced toxicities, shorter treatment and more convenient forms of treatment, such as treatment delivered at home.

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## Concluding Remarks

**The Roundtable was closed by Matti Aapro, President of the European Cancer Organisation, and Mark Lawler, Board Member, European Cancer Organisation, and Chair in Translational Genomics, Queen's University Belfast.**

From this Roundtable meeting, stakeholders clearly agreed that further work is needed to maximise the potential of molecular tumour diagnostics across Europe. Genomic testing / molecular tumour diagnostics must be provided to all eligible patients across European countries.

There was a concluding call for an EU Recommendation on Genomic Tumour Testing / Molecular Tumour Diagnostics to help take forward actions to overcome the variety of implementation challenges that persist.

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As the not-for-profit federation of member organisations working in cancer at a European level, the European Cancer Organisation convenes oncology professionals and patients to agree policy, advocate for positive change and speak up for the European cancer community.

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