At the crossroads of tumour-agnostic innovation

How can Europe keep up with advances in cancer treatment?

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Working group members

Sahar Barjesteh van Waalwijk van Doorn-Khosrovani, Prime-Rose Consortium and Leiden University Medical Centre, Netherlands

Jean-Yves Blay, Centre Léon Bérard, France

Yvonne-Beatrice Böhler, TH Köln, University of Applied Sciences, Germany

Antonella Cardone, Cancer Patients Europe, Belgium

Ilaria Colombo, Oncology Institute of Southern Switzerland, Switzerland

Jan Geissler, Patvocates, Germany

Viktor Grünwald, University Hospital Essen, Germany

Ebba Hallersjö Hult, Vision Zero Cancer, Stockholm School of Economics, Sweden

Garbiñe Lizeaga, Hospital Universitario Donostia, Spain

Domenica Lorusso, Humanitas University and Humanitas San Pio X Hospital, Italy

Lavinia Magee, Lung Cancer Europe

Warnyta Minnaard, World CUP Alliance, Netherlands

Frédérique Penault-Llorca, University of Clermont-Auvergne, France

Russell Petty, University of Dundee, United Kingdom

Javier Puente, Hospital Clinico San Carlos, Madrid, Spain

Jade Putzolu, Neovidence, France

Naureen Starling, The Royal Marsden NHS Foundation Trust, United Kingdom

Albrecht Stenzinger, University Hospital Heidelberg, Germany

Vivek Subbiah, Sarah Cannon Research Institute, United States

Benedikt Westphalen, Comprehensive Cancer Centre, LMU University Hospital Munich, Germany

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Foreword

Recent decades have brought significant advancements in addressing cancer as one of Europe's biggest health challenges. However, much is left to do to make sure that every patient across Europe receives the best care and treatment to ensure the best possible outcomes. As representatives of the patient community, we are acutely aware of the difference that timely access to effective therapies can make and how crucial every single day can be for those living with cancer.

Tumour-agnostic therapies are treatments that target a specific biomarker irrespective of tumour location or origin. This emerging approach could represent a significant step forward in cancer care, one that brings new possibilities to people living with cancer and in areas of high unmet medical need. However, this requires more than scientific progress alone. It calls for healthcare systems that are prepared to assess, integrate and deliver these therapies in ways that are both evidence-based and responsive to patients' needs.

This white paper brings together the insights of a multidisciplinary group committed to improving how novel approaches such as tumour-agnostic therapies are evaluated and introduced into care. We identified the barriers that need to be addressed and proposed practical steps to support workable solutions and responsible adoption across Europe. Patients, clinicians, policymakers, payers and industry now must work together across the healthcare environment to create the conditions in which new innovative tumour-agnostic treatment approaches reach those who may benefit most from them and continue advancing our shared goal of better outcomes for people affected by cancer.

Antonella Cardone, Cancer Patients Europe, Belgium

Jan Geissler, Patvocates, Germany

Warnyta Minnaard, World CUP Alliance, Netherlands

Executive summary

Tumour-agnostic therapies target the molecular markers of a cancer, regardless of where the cancer is in the body or where it started.[1] As these therapies work across all cancer types that share a specific molecular alteration, they can deliver precision medicine to patients whose cancers may have previously lacked such options. While only a few such therapies are currently approved in Europe, more are in development, making this a fast-growing area of precision oncology.[2,3]

The characteristics of tumour-agnostic therapies present specific challenges to existing evidence, access and clinical practice frameworks.[4] These processes are designed around tumour-specific treatments and have previously centred on randomised controlled trials (RCTs). However, RCTs present several challenges to tumour-agnostic drug development;[3] only relying on RCTs would hamper the development of tumour-agnostic therapies and deny patients with cancer timely access to potentially effective treatments.[5]

Alternative trial designs, such as single-arm basket trials, have been identified as a key approach in enabling therapies to be assessed across different tumour types.[4,6] However, regulators and health technology assessment (HTA) bodies have frequently rejected this evidence based on a lack of randomisation and a comparator arm.[5] Real-world evidence (RWE) used to complement these trials has also been rejected.[7] This has led to delays in getting therapies approved, reimbursed and to patients.[8]

Finally, Europe needs to be prepared for the clinical adoption of future tumour-agnostic therapies. Availability of biomarker testing remains uneven and such disparities limit patient identification and reinforce geographic inequalities.[9] Clear clinical guidelines on the role of different therapies will also be needed. Support tools such as molecular tumour boards can help, but their availability is limited and integration into routine care remains inconsistent.[10,11]

Health systems are still adjusting to the shift that tumour-agnostic therapies represent, but addressing the barriers outlined above will require coordinated, system-wide change. By acting now, European countries can close the gap between scientific potential and real-world benefit, accelerating access for today's patients and laying the groundwork for a more agile, evidence-led future. Working collaboratively with multidisciplinary stakeholders and maximising patient involvement is key to ensuring that tumour-agnostic innovation is translated into care that genuinely meets patients' needs.

To support the timely, **equitable and effective integration of tumour-agnostic therapies in Europe**, the following actions are recommended:

1. Regulators and HTA bodies should publish guidance outlining requirements for the acceptance of alternative trial designs and RWE in the assessment of tumour-agnostic therapies.
2. Structured engagement is needed on evidence requirements, conditional reimbursement and real-world data collection to enable timely access to tumour-agnostic therapies, involving patients, regulators, HTA bodies, healthcare professionals and developers.
3. Regulators and HTA bodies should be ready to evolve guidance, policy and practice in response to new insights from pilot programmes, regulatory sandboxes and real-world experience.
4. Healthcare decision-makers must ensure clinical practice keeps pace with tumour-agnostic therapies through guidelines, workflows and testing infrastructure.

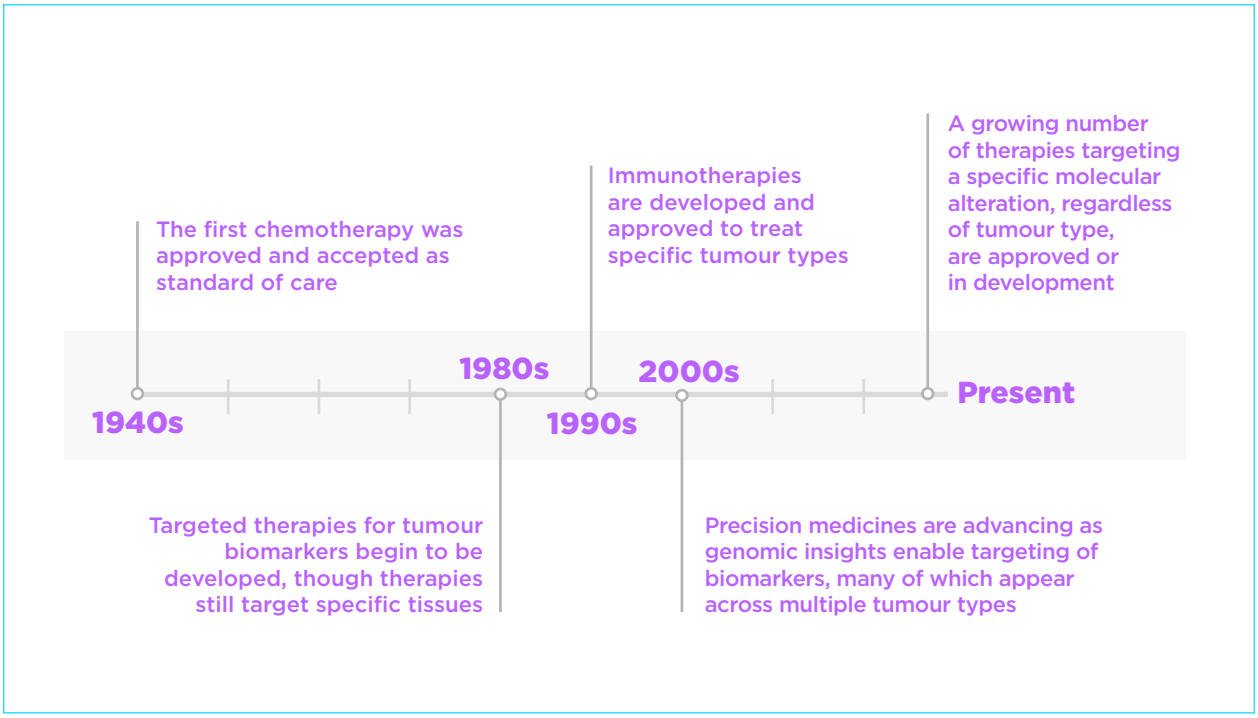
The next advancement in cancer therapy is here

Cancer outcomes in Europe have improved significantly in recent decades – across countries in the European Union (EU), premature mortality due to cancer fell by almost 20% between 2012 and 2022.[12] This trend reflects advances in early diagnosis, care delivery and, importantly, treatment innovation.[12] Biomarker-driven treatments targeting molecular alterations found in tumour cells have played a significant role in this.[13,14]

Despite this progress, there remains a significant unmet need. Several cancer types, such as lung, colorectal and liver, still have markedly high mortality rates, and improvements in outcomes across cancers have been uneven.[15,16] Even in tumour sites where overall outcomes have improved, cancers with particular molecular alterations may still lack treatment options due to less research and fewer approved therapies.[17] Additionally, many advanced-stage cancers, rare cancers and cancers of unknown primary also continue to pose a significant challenge with limited treatment options and poor clinical outcomes.[18–20]

Accelerating or even maintaining this improvement in outcomes for patients with cancers will require continued treatment innovation. Tumour-agnostic therapies are one such major advance in precision oncology (Figure 1). **Tumour-agnostic therapies are treatments that work by targeting a specific molecular alteration, regardless of where the cancer started or is located.[1] They can be used to treat all patients with cancer where the specific molecular alteration is present.** In theory, these therapies work across all cancer types that share a specific molecular alteration, making it possible to deliver precision medicine to patients whose cancers may have previously lacked effective options.[1] Currently, only a small number of tumour-agnostic therapies have been approved and reimbursed in Europe, but with many more in development, there is a clear need to ensure health systems are ready to provide equitable access for patients.[2,3]

Figure 1: Evolution of cancer treatments over time[21–23]



Health systems will only realise the potential of tumour-agnostic therapies for patients if both innovation and policy evolve together. At both European and national levels, creating an environment that supports innovation is already a stated policy priority. For example, the Draghi report calls for coordinated action to modernise clinical trial design and evidence standards, while the European Commission has committed to a 'forward-looking framework conducive to innovation in areas like health technology assessment (HTA) and clinical trials'.[24,25]

Patients and patient groups have consistently played a lead role in policy change – whether advocating for top-level political commitment, engaging with research and clinical trials or through support, advocacy and information for individual patients.[26] Their perspectives must shape how evidence is generated and how access decisions are made. Recent initiatives, such as HTA4Patients, an EU-funded advanced training programme to increase patient involvement in HTAs led by European Patients' Academy on Therapeutic Innovation (EUPATI), highlight a growing recognition by policymakers that embedding patient voices in such processes is essential.[27] Policymakers across Europe must now stand by these commitments to enable the research, access and adoption needed to deliver on the potential of tumour-agnostic therapies for those living with cancer.

A need to deliver change for patients with cancer in Europe

Tumour-agnostic therapies represent a significant advancement in cancer treatment.[17] By their very nature, tumour-agnostic therapies challenge traditional models of evidence generation, assessment and care delivery, which are built around tumour-specific treatments.[4] These approaches must evolve to fully realise the potential of innovation. If they remain unchanged, access to tumour-agnostic therapies is likely to remain inconsistent, uptake will be slow and patients who could benefit today may miss out on potentially effective treatment options.

Rethinking evidence generation: The case for evolution

Evidence generation refers to gathering data to understand how well a treatment works, how safe it is and whether it offers good value. Tumour-agnostic therapies present specific challenges for this process. These therapies target shared molecular alterations that occur across multiple cancer types, which means patient populations are typically small and unevenly distributed across tumour sites with varying standards of care in current clinical practice.[5] As a result, conventional trial designs are often difficult to apply, requiring alternative approaches to demonstrate effectiveness and value.[28]

Randomised controlled trials present ethical and practical challenges for tumour-agnostic therapies.

Randomised controlled trials (RCTs), where patients are randomly assigned to a treatment or a control group (which receives either a placebo or standard of care), are central for clinical evidence generation.[29] RCTs require a large number of patients with the same key characteristics, such as tumour type and cancer stage, to produce reliable and meaningful results.[30] In the case of tumour-agnostic therapies, patient populations

are defined by specific biomarkers rather than tumour type, meaning they are spread across multiple cancer types; the target biomarkers can be common in certain tumours and rare in others (Figure 2).[3] This results in separate and diverse patient populations, many of which are relatively small. The standard of care, history of treatment and outcomes will all vary across tumour types.[5]

As noted by a recent European Society for Medical Oncology (ESMO) position paper, RCTs can present substantial challenges from a methodological and statistical perspective and there are situations where it may not be feasible or ethical to conduct them in a tumour-agnostic context.[1]

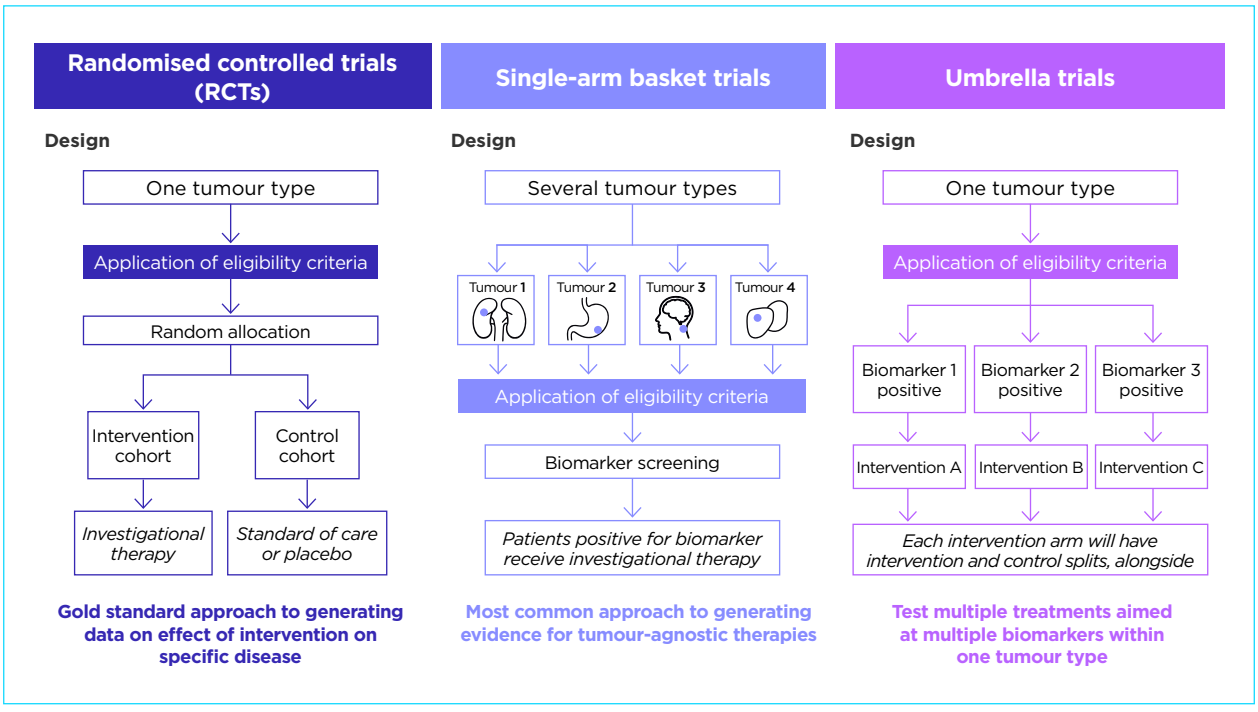
There are several practical considerations. If an RCT is solely used to generate evidence for a tumour-agnostic therapy, multiple trials or trial arms are necessary, each tailored to a specific tumour type. Each tumour type would require separate, matched groups of patients in the intervention and control arms.[5] With patients split between intervention and control arms, more patients would need to be recruited for the study to have the same statistical power.[1] For some tumours where patient recruitment will be a significant challenge, the need for even more patients could increase trial times to the extent that the trial's feasibility is impacted.[31] Even if technically feasible, longer timelines increase the chance that the standard of care will evolve during the trial, further complicating the value of the trial for regulators and HTA bodies.

The use of RCTs in tumour-agnostic therapy research also raises important ethical considerations. Many patients covered by potential trials may lack effective treatment options due to advanced disease or rare tumour type and biomarker combinations.[32–34] There is growing evidence, in general, that targeted therapies can be effective for those patients with actionable biomarkers.[35] Particularly when such an individual therapy's efficacy has already been demonstrated in earlier trials against the same biomarker, it may be unethical to run randomised trials that assign patients to control arms, knowingly withholding a treatment that is more likely to be effective.[32,36] This highlights the importance of embedding patient perspectives directly into trial design through advisory roles, ensuring solutions to such issues reflect patient needs and priorities. There are some situations in which it may be more feasible and ethical to run an RCT, such as in a tumour where a large number of patients have the relevant biomarker or when trialling a therapy in an early setting where established effective therapies already exist. Nonetheless, only relying on RCTs would hamper the development of tumour-agnostic therapies and deny patients with cancer timely access to potentially effective treatments.

Alternative approaches can broaden how we generate evidence for innovative therapies.

The scientific community has long explored alternative trial designs to RCTs to support evidence generation in settings where traditional RCTs are less feasible, including for those diseases with small patient populations, such as rarer cancers.[37] These include non-randomised single-arm basket trials. In tumour-agnostic therapies, these trials enrol patients with different types of cancer who share a molecular alteration and assess response to a single therapy, without a control arm (Figure 2).[28] Umbrella trials have also been used to generate evidence for tumour-agnostic therapies. They work by evaluating multiple targeted therapies across subgroups within a single cancer type, based on distinct biomarkers (Figure 2).[28] Approaches that depart from traditional RCTs, such as single-arm basket trials, can challenge conventional expectations around evidence generation from regulators and HTA bodies. However, similar approaches have already been used in other disease areas to support regulatory approval and access for innovative therapies, where RCTs have also been less feasible.[38]

Figure 2: Overview of trial designs: RCTs, single-arm basket trials and umbrella trials.[28,39]



These diagrams are illustrative, not definitive. Individual trials within each category may very.

Single-arm basket trials have become central to generating evidence for tumour-agnostic therapies.[3,4] These trials allow a potential treatment to be studied across different cancer types that share the same molecular alteration, enabling multiple tumour types to be assessed simultaneously rather than through separate studies.[28] Their design enables the enrolment of a larger number of trial participants, which is a key advantage when working with small, biomarker-defined populations, improving the statistical robustness of the findings.[40] As a result, these trials accelerate the generation of evidence for tumour-agnostic therapies and help patients gain earlier access to new treatment options.[5] Additional benefits include all participants receiving the potential therapy rather than a placebo or standard of care, and the opportunity to assess safety across different patient populations.[2,28] HTA bodies have been sceptical of trials without a comparator arm, arguing this is needed to assess relative clinical benefit and demonstrate added value.[5] However, given RCTs have limited feasibility due to the factors outlined above, alternative methods of generating evidence are needed.

There are several approaches that can strengthen the evidence generated from alternative trial designs, such as single-arm basket trials. These include real-world evidence (RWE) and synthetic control arms (Table 1).[41,42] Each offers a way to address some of the limitations of non-randomised clinical trial designs using real-world datasets, especially in the context of small, biomarker-defined populations. However, they are not without weaknesses, as these datasets often include uncontrolled external factors that can distort the observed relationship between treatment and outcome.[42] The most appropriate combination of trial design and supporting evidence for the therapy under investigation will vary for each therapy and depend on factors such as the biomarker being targeted and the size and distribution of the patient population (Case study 1).[1] As such, evidence generation strategies must incorporate patients' perspectives to ensure they address real needs, with involvement extending beyond clinical trial design to the collection and use of RWE.

Table 1: Overview of approaches to strengthen evidence from alternative trial designs

Supporting evidence generation approach	Explanation
Real-world evidence (RWE)	RWE is derived from real-world data (RWD) collected outside traditional clinical trials, such as electronic health records, registries or observational studies and is collected post-conditional regulatory approval.[42] It can provide insights into how therapies perform in routine clinical practice.
Synthetic control arms	Synthetic control arms use real-world historical or observational data to construct a comparator group for single-arm trials, applying statistical methods such as propensity score matching to align patient characteristics.[41]

CASE STUDY 1

ESMO Tumour-Agnostic Classifier and Screener (ETAC-S)[1]

The ETAC-S is a decision-support tool designed by the ESMO Precision Medicine Group to assess the tumour-agnostic potential of molecularly targeted therapies. It provides a framework to guide evidence generation and support drug development for tumour-agnostic therapies, offering standardised criteria for evaluating potential therapies. It notes that a drug should move to pan-tumour RCT if it demonstrates 'robust tumour-agnostic performance' in early phase trials. The framework argues that confirmatory evidence should ideally be generated using RCTs where possible, using the latest available standard of care as the comparison. If randomisation is not feasible or ethical, expanded basket trial cohorts supported by synthetic control arms (or other innovative designs) can be used.

The framework also highlights that previous tumour-agnostic approvals have involved evidence from one or more 'anchor tumours' where a higher prevalence of a biomarker makes it possible to have a larger sample and, in some cases, conduct a tumour-specific RCT alongside a basket trial covering other tumours.

THE TOOL:

1. Complements ESMO's Scale for Clinical Actionability of molecular Targets (ESCAT) scale by focusing on acceptable evidence generation strategies for therapies targeting rare molecular alterations across multiple cancer types[6]
2. Provides an early-stage reference for pharmaceutical developers when considering whether to pursue a tumour-agnostic indication, helping to promote innovation by reducing uncertainty

Reassessing HTA frameworks: Unlocking access

In Europe, regulators such as the European Medicines Agency (EMA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) assess therapies for safety and efficacy, while national HTA bodies determine clinical and cost effectiveness to inform reimbursement and access decisions.[43] These distinct roles often translate into different evidence requirements.[43] The acceptance of alternative trial designs, such as single-arm basket trials, by both groups varies, but the role of HTA bodies means they typically place a greater emphasis on comparative evidence.[5] This is a particular challenge for potential treatments where RCTs are infeasible and primarily evaluated through single-arm basket trials, including tumour-agnostic therapies.[5]

The EMA has accepted the use of alternative trial designs such as single-arm basket trials and umbrella trials for therapies targeting rare molecular alterations or small patient populations, including tumour-agnostic therapies.[44] In these cases, the EMA accepts that non-randomised trials may be appropriate provided the trial is well designed, the treatment effect is large and consistent, and the biomarker has a strong biological rationale.[44]

As regulators adopt more complementary approaches to tumour-agnostic therapies, HTA bodies continue to require comparative data and are generally less likely to accept single-arm evidence.[45] In simple terms, this is because HTA bodies require comparative data to establish the additional benefit of new therapies compared to those already in use.[46] As a result, potential therapies that show high response rates in single-arm basket trials may not gain appropriate reimbursement because of the need for a direct comparator. This creates a fundamental mismatch between how evidence can be generated for tumour-agnostic therapies and how it is assessed, delaying or denying access for patients with potentially few or no alternative treatment options.[46] A partial step toward addressing HTA bodies' comparative data requirements is the collection of high-quality real-world datasets to develop accurate synthetic control arms, though such resources remain scarce and may still not be accepted.[5,47] Independent research initiatives such as PRIME-ROSE (Case study 2) demonstrate progress in establishing acceptable methods to generate synthetic control arms as well as expanding alternative trial design.[48,49] For those tumour-agnostic therapies that have been given a positive decision, it is often granted conditionally to allow for more evidence to be collected through additional trials and RWE.[5,50]

CASE STUDY 2

PRIME-ROSE

A learning pilot for alternative evidence generation[48,49]

PRIME-ROSE is a project funded by Horizon Europe (the European Union's key funding programme for research and innovation) exploring treatment options in patients with advanced cancer who have exhausted treatment options. It uses basket and umbrella trials with few inclusion and exclusion criteria. It also aims to generate multiple synthetic control arms through established methods, enabling more accurate assessment of clinical efficacy and cost effectiveness. Under PRIME-ROSE, patient cohorts expand dynamically if early signs of benefit are seen.

It aims to develop an economic evaluation model covering the budget impact and cost-effectiveness of precision cancer medicines from diagnostic to treatment. Insights into local reimbursement criteria guide the analyses, comparing how system differences affect access, timing and affordability. The project builds on a series of bottom-up, clinician-initiated precision medicine trials. The pilot is currently active in 19 countries and will run from 2023 to 2028.

The variation between Europe's HTA bodies in the assessment of tumour-agnostic therapies is significant.

HTA bodies differ in both the processes and types of evidence required to assess the value of tumour-agnostic therapies.[51] This has resulted in a fragmented and inconsistent approach to evidence evaluation for tumour-agnostic therapies across Europe, creating uncertainty for developers and contributing to unequal patient access. There are several examples that illustrate the variation across national HTA bodies in Europe:

- **Limited acceptance of single-arm basket trials**
  Only a few European HTA bodies have reimbursed tumour-agnostic therapies.[3] In most cases, however, single-arm basket trial evidence is considered insufficient due to the absence of a comparator, limited survival data or concerns about its applicability to real-world practice (Table 2). Synthetic control arms are often submitted to address concerns over a lack of a comparator but are frequently rejected on methodological grounds.[52]

Table 2: Examples of guidance on basket trials published by European HTA bodies.

HTA body	Country	Approach to assessment of evidence from single-arm basket trials
National Institute for Health and Care Excellence (NICE)	United Kingdom	NICE published its HTA manual in July 2025, which highlights the acceptance of evidence from basket trials that meet several criteria.[53] Trials should involve relevant comparators, random allocation of treatment, appropriate endpoints and enrolment of all relevant patient groups.
Haute Autorité de Santé (HAS)	France	A position paper noted that basket trials in oncology offer advantages in evaluating a treatment across multiple cancers, including in those for which treatment development would not otherwise be possible.[54] It calls for comparative design with randomisation based on tumour location. If this is not possible within a trial, then an external control group, designated before the trial starts, is required. More recently, HAS published guidance covering all innovative trial designs, which affirmed the importance of RCTs but noted that adaptation is possible, with the right external comparators.[55]
Zorginstituut Nederland (ZIN)	Netherlands	Specific guidance was published in 2023 on how tumour-agnostic therapies using single-arm trials would be assessed.[56] This noted how effect sizes, evidence type and contextual factors, such as unmet need and study feasibility would be balanced in assessing treatments.

- **Inconsistent evaluation of RWE**
  Several European HTA bodies have required the submission of RWE following the conditional reimbursement of a tumour-agnostic therapy.[23] However, approaches to assessing RWE differ across HTA bodies, and concerns are often raised about data quality and external factors that may influence results, leading to frequent rejections or undervaluation.[7] This highlights the importance of establishing clear parameters for how RWE should be used in conjunction with clinical trial evidence.
- **Tumour-specific assessment frameworks**
  HTA bodies continue to evaluate efficacy on a strictly tumour-by-tumour basis, even when therapies are designed to target a common biomarker regardless of tumour type.[23] For example, some HTA bodies accept pooled cost-effectiveness models, which combine data across tumour types with a shared molecular alteration, while others view them as unreliable.[5,52] As a result, patients with the same biomarker but a different tumour site may be excluded from reimbursement due to perceived weaknesses in tumour-specific evidence.

There is a need to strengthen the pathway from conditional to full access.

In countries where tumour-agnostic therapies are available, European HTA bodies have commonly relied on conditional reimbursement pathways to initially provide access.[3] These often take the form of managed entry agreements, such as the England's Cancer Drugs Fund and the Netherlands' DRUG-Access Protocol (DAP), which allow therapies to be made available while additional evidence is collected and evaluated.[57,58] However, not all countries have such mechanisms in place, and where they do exist, their design and implementation vary significantly.[50] For patients, this means that the opportunity to benefit from new therapies can depend on where they live within Europe. Additionally, patients are impacted by how such conditional reimbursement schemes operate in practice; given the fact that conditional approvals are common in tumour-agnostic therapies, patients must be able to input into this decision-making process.

The collection of RWD plays a critical role in strengthening the evidence base for tumour-agnostic therapies.[59] However, limited dialogue between industry and HTA bodies often results in missed opportunities to align on evidence expectations.[5] As a result, valuable RWE may not be generated in a way that meets HTA bodies' requirements, reducing its acceptability and inclusion in final reimbursement decisions. Patients should be involved in shaping how RWD is collected, helping to ensure that data collected reflect the outcomes that matter to them and their lived experience, such as quality of life, alongside traditional clinical data. Given the lack of coordinated approaches to RWE generation and evaluation, the path from conditional reimbursement to full access will likely remain slow and uneven, risking patients losing access to tumour-agnostic therapies and prolonging uncertainty for developers.[60]

Combining testing and treatment costs distorts value assessment and reimbursement decisions.

A barrier to recognising the full value of tumour-agnostic therapies is the practice of including the cost of biomarker testing within the overall cost of treatment.[61] Diagnostic tools such as immunohistochemistry, next-generation sequencing and other diagnostic tools are often not treated as a separate component of care.[61] This approach can obscure the cost-effectiveness of a biomarker-targeted treatment, such as tumour-agnostic therapies, which could negatively impact decisions to include it in national reimbursement. For multi-biomarker tests, this also overlooks the broader role of the test in guiding multiple treatment decisions.[62] Diagnostics and treatment are distinct steps and should be viewed separately when making value assessments.

Reshaping clinical practice: Integrating tumour-agnostic therapies

Globally, cancer care remains appropriately centred around the tumour site of origin, reflecting established clinical guidelines and treatment pathways.[63] This structure has supported the delivery of high-quality specialist care, but it can challenge the integration of emerging tumour-agnostic therapies, which rely on biomarker identification rather than tumour location. However, as more treatments are developed, approved and reimbursed, clinical practice, such as treatment and testing guidelines, must adapt to ensure patients who could benefit receive them.

Biomarker testing infrastructure and capacity are necessary to identify patients eligible for biomarker-driven treatment.

As for other biomarker-driven treatments, the clinical uptake of tumour-agnostic therapies depends critically on access to high-quality and timely biomarker testing.[64] However, testing infrastructure remains highly variable across Europe, with significant gaps both within and between countries;[65,66] major academic hospitals and specialist cancer centres tend to have more advanced infrastructure and specialist expertise.[9] In contrast, community and regional hospitals often face challenges related to limited access to biomarker testing, including frequent operational bottlenecks that prevent comprehensive biomarker testing from being offered routinely.[9]

These operational issues are confounded by missing reimbursement, funding models and financial flows for biomarker testing, creating barriers to integrated and timely access to tumour-agnostic therapies.[67] Even where public funding exists, it often comes from a fragmented mix of laboratory, hospital and academic budgets, creating variability in access across test types and regions.[67,68] In the absence of coordinated public funding, industry support can help introduce and scale testing, but this is not

always permitted by national regulation. The Netherlands is one example of efforts to address these challenges, where a multi-stakeholder committee conducts a monthly review of biomarker tests to update guidance and inform funding decisions.[69]

The lack of clear guidelines and clinical support is limiting the adoption of tumour-agnostic therapies.

As more tumour-agnostic therapies gain approval and reimbursement, clear clinical guidelines are needed to support their appropriate adoption. Without them, it can be difficult for clinicians to determine when these therapies should be used over existing options, especially in the absence of comparator data. Limited exposure to biomarker-driven approaches can also contribute to low clinical awareness and confidence.[31] When clinicians lack confidence in using biomarker testing and tumour-agnostic therapies, patients may not receive treatments with the greatest potential to improve their condition. Clinicians report limited support in interpreting genomic results and translating them into treatment decisions, particularly those outside of specialist centres.[31,37] This risks treatment options not being fully discussed with patients, removing the ability to make an informed choice.[70] Patients need clear information about what a biomarker result means for their treatment options. As precision medicine, including tumour-agnostic therapies, continues to advance, this need will only increase.

Support structures, like molecular tumour boards (MTBs), can help address this gap by facilitating the implementation of precision oncology, assisting with the interpretation of genomic results and guiding therapy decisions in experimental settings.[10,71] MTBs are multidisciplinary teams that meet to review patients with cancer's clinical and molecular data and recommend tailored treatments or clinical trials based on their profiles.[10] While MTBs are a key enabler of biomarker-driven care, their availability and integration into standard clinical workflows vary widely in Europe, often restricted to major cancer centres.[11,72] Virtual MTB models could help extend this expertise to smaller hospitals and regional settings, ensuring more equitable access to precision oncology and tumour-agnostic therapies for patients living in these areas.[73] Although MTBs should not replace clinical guidelines for biomarker testing and therapy selection, they should have a clearly defined role in supporting the implementation of tumour-agnostic therapies across care settings.

Realising the potential of tumour-agnostic therapies

Successful integration of tumour-agnostic therapies in the fight against cancer requires coordinated change to ensure we evolve the systems that regulate, assess and deliver cancer care. It is crucial to adapt regulatory and HTA processes, as well as clinical pathways, to ensure that patients can benefit from tumour-agnostic therapies. Patient involvement must be seen as structured and essential across all these stages. If, on the contrary, we maintain the status quo, we risk delaying innovation, deepening unequal patient access and missing opportunities to reduce the cancer burden in Europe, leaving individual patients without the targeted treatments they may urgently need. We propose the following recommendations to support the timely, equitable and effective integration of tumour-agnostic therapies across Europe.

1. **Regulators and HTA bodies should publish guidance outlining requirements for the acceptance of alternative trial designs and RWE in the assessment of tumour-agnostic therapies.**

There is a need for decision-makers to accept the role of clinical trials beyond RCTs in generating evidence for innovative therapies. This must be accompanied by guidance from regulators and HTA bodies on the specific requirements for such evidence to be positively assessed. This guidance could build on the ESMO Tumour-Agnostic Classifier and Screener framework, which presents tools for aligning tumour-agnostic therapy development with regulatory and HTA expectations.[1] Existing frameworks or protocols in certain European countries may also offer a practical starting point for countries where such structures are not yet in place. Furthermore, HTA bodies must formally recognise the value of RWE in reimbursement decisions, including the development of clear pathways for its evaluation, as has begun in some European countries.[74]

2. **Structured engagement is needed on evidence requirements, conditional reimbursement and RWD collection to enable timely access to tumour-agnostic therapies, involving patients, regulators, HTA bodies, healthcare professionals and developers.**

Early, structured engagement between key stakeholders is essential to enable timely patient access to tumour-agnostic therapies. Creating new or utilising existing platforms for dialogue between regulators, HTA bodies, clinicians, patients and industry can help define and meet evidence requirements from the outset and reduce delays caused by unclear or conflicting standards. Crucially, due to the practical and ethical questions raised by traditional trial design, and the caution regulators and HTA bodies have shown regarding alternative evidence, patients directly affected must have a central role in all dialogue. Conditional reimbursement can offer a pragmatic solution for therapies that do not yet meet the evidence thresholds for full funding, enabling patient access to therapies while evidence continues to be generated through RWD collection.[75] Robust and standardised RWD collection is essential for generating reliable RWE to support HTA decision-making. By clarifying clear roles and responsibilities, these forums can support more predictable evidence planning, improve transparency and ensure that access decisions reflect both clinical realities and patient needs. Initiatives like the EU's joint scientific consultations mark an encouraging shift towards coordinated alignment on evidence requirements.[76]

3. **Regulators and HTA bodies should be ready to evolve guidance, policy and practice in response to new insights from pilot programmes, regulatory sandboxes and real-world experience.**

Tumour-agnostic therapies will continue to challenge traditional assumptions and push towards a more adaptive, forward-looking mindset. As this is a new class of therapies, the appropriate assessment and adoption of tumour-agnostic therapies will depend on responsive, learning health systems that actively integrate patient perspectives. Pilot initiatives like PRIME-ROSE, which blends elements of basket trials and RWE, clearly align with that principle.[59] Regulatory sandboxes offer an avenue to anticipate the impact of wider changes.[77] The insights and experiences from such programmes, alongside clinical trials and the real-world experience of therapies, are essential to inform the future evolution of guidance, policy and practice.

4. **Healthcare decision-makers must ensure that clinical practice keeps pace with tumour-agnostic therapies through guidelines, workflows and testing infrastructure.**

As more tumour-agnostic therapies are reimbursed across Europe, implementing the clinical components needed to deliver them to patients with cancer becomes increasingly critical. Clinical workflows must be designed to integrate biomarker-driven decision-making across all cancer practices, not just in specialist centres. Clear testing and treatment guidelines should be developed, with patient involvement, at the country level to support shared and informed decision-making between clinicians and patients in selecting the most appropriate therapy, including tumour-agnostic options where relevant. This must be supported with sufficient biomarker testing infrastructure and capacity, along with testing policies that evolve in line with the science. Biomarker testing must be available to identify all eligible patients for each available targeted therapy, including tumour-agnostic therapies, which will ultimately help to improve outcomes.

An appropriate precision medicine workforce is also essential to deliver tumour-agnostic therapies. With clear clinical guidelines implemented and forward-thinking workforce planning, MTBs should be able to prioritise their time for patients with more complex needs. Integration between tumour-specific multidisciplinary teams and molecular experts is critical to ensure that tumour-agnostic therapies complement tumour-specific care. Empowered and educated healthcare professionals are key to ensure that patients are, in turn, equipped to make meaningful choices about their treatment options. European cancer and life sciences strategies that both strengthen system infrastructure and workforce capability are important drivers of the successful adoption of precision medicine, including tumour-agnostic therapies.

Speed matters: Closing the gap between science, health systems and patients' needs

Tumour-agnostic therapies have great potential to improve outcomes for patients with cancer but remain constrained by systems built around tumour sites. While tumour-specific approaches remain the foundation of care, the rise of biomarker-driven science offers a powerful opportunity to expand how we treat cancer more precisely and for more patients.

Scientific progress is moving faster than the systems designed to deliver it: a persistent challenge but one we can no longer afford to accept. In Europe, policymakers, regulators, HTA bodies, payers, patient groups, industry and healthcare professionals have a clear opportunity to work together to realise the potential of tumour-agnostic therapies. Specifically, patients must be recognised as active partners in this process, bringing lived experience that can shape how innovation is translated into care that truly meets people's needs. Building learning health systems that can keep pace with new forms of evidence, accelerate access decisions and adapt clinical delivery will be essential. The question is how quickly we can deliver this change together, not only for future generations, but also for those living with cancer today.

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