IMPROVING TIME TO PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE

EVERY DAY COUNTS

July 2020

Authored by Vintura:
Christel Jansen
Bas Amesz

In collaboration with:
ASC Academics
Hague Corporate Affairs

Colophon

Copyright © 2020 Vintura.

Authors: Christel Jansen and Bas Amesz, Vintura
Design and illustrations: Chantal van Wessel and Sandrine Lauret, Hague Corporate Affairs.
Citation: Vintura, 2020. Every day counts – Improving time to patient access to innovative oncology therapies in Europe.

The report can be downloaded here.

This report was commissioned by EFPIA.
About this report

This report presents the outcomes of the “Time to Patient Access” initiative. The ambition of this initiative is to bring together stakeholders across Europe and to establish a common understanding of causes of delays in patient access to new oncology treatments. It also intends to find the common ground regarding solutions with the potential to reduce time to patient access. The overall aim of the initiative is to make access quicker, for those therapies that are bringing added value to patients and society, without compromising on careful deliberations and evidence-based decision-making.

The project was initiated and financed by the Oncology Platform (EOP) of the European Federation of Pharmaceutical Industries and Associations (EFPIA). The EOP is a collaboration of eighteen companies from the research-based pharmaceutical industry in Europe, launched in 2016, to combine forces and improve cancer patient outcomes in Europe.

The initiative has been carried out with the support of a consortium led by Vintura and comprising ASC Academics and Hague Corporate Affairs. The consortium worked together with two of Europe's leading experts in health economics and HTAs: Prof. Lieven Annemans (Ghent University) and Prof. Maarten Postma (University of Groningen).

This publication is the result of a multi-stakeholder collaboration gathering views through sounding board meetings and interviews. It does not necessarily reflect the positions of the individual organisations or people involved.
Executive summary

Unequal access to innovation in oncology
The unprecedented speed of innovation in oncology provides an important opportunity for further improvement of outcomes for cancer patients. Yet, no value is derived from innovation if patients for whom a new therapy is intended cannot have access to it. In fact, tremendous differences exist in patient access to innovative oncology treatments across European countries. Access to new oncology therapies varies significantly from country to country on three dimensions of access:

• Out of all oncology therapies with a European marketing authorisation, the proportion of therapies that receive Market Access, i.e. are reimbursed through social health insurance schemes, ranges from as low as 7% to as high as 98%.
• After receipt of a European marketing authorisation, the time to Market Access ranges from as low as 86 to almost 1,000 days.
• After twelve months of formal reimbursement, the relative level of Patient Access* ranges from as low as 22% to as high as 81%.

These differences undermine the ambition to promote equal access to healthcare and indicate opportunities for improvement.

A multi-stakeholder approach
This report represents the collective thinking of a group of over 30 organisations, covering health technology assessment (HTA) bodies, healthcare professional associations, patient organisations, policy makers, former politicians, payers and pharmaceutical companies concerned about timely and equal access throughout Europe. The aim is to bring stakeholders across Europe together around opportunities to improve time to patient access in which joint action is needed.

For patients, every day counts
During reimbursement discussions, time to market access can become an abstract objective. Whereas for patients, every day counts. Two case studies on different oncology therapies are presented in the report to show the actual impact of reducing delays in reimbursement decision-making and hence the time it takes for patients to access new therapies. The analysis illustrates the number of patients that could have been treated and the improved quality of life they could have gained if access timelines were shortened. These two case studies serve as a reminder of our common objectives and the urgency of addressing delays where possible.
The ten key factors delaying patient access

These are related to process, reimbursement criteria and health system readiness.

**Process**

1. **Late start of application and submission.** The national access process may start late compared to the European Union (EU) marketing authorisation, due to country regulations on the start of the process and/or manufacturers submission timelines under the influence of external reference pricing.

2. **Lack of adherence to maximum timelines.** There is not always a clear set of rules around the timelines for decision-making on national pricing and reimbursement, or these rules are not complied with, despite the maximum of 180 days set by the EU Transparency Directive.

3. **Multiple layers of decision-making.** After a national decision or recommendation on reimbursement, subnational decision-makers may make their own decisions on reimbursement or budget allocation, leading to duplication, in-country disparities and delays.

**Reimbursement criteria**

4. **Different evidence requirements across Europe.** The extent to which evidence for the clinical assessment is considered robust or acceptable varies greatly across HTA bodies in Europe, thereby prolonging alignment and/or leading to country-specific data collection.

5. **Lack of clarity of national requirements.** Within countries, requirements for the clinical- and cost-effectiveness assessment are not always consistently applied, which allows for a tailor-made assessment but also leads to unpredictability and prolonged alignment.

6. **Evidence gaps.** Meeting HTA evidence requirements is getting more difficult given the characteristics of today’s oncology therapies, leading to evidence gaps, uncertainty about the value of the therapy and prolonged reimbursement discussions.

7. **Misalignment on value and price.** Uncertainty about the value of the therapy leads to misalignment and long negotiations on value and price between national decision-makers and pharmaceutical companies, especially in the absence of mechanisms to deal with uncertainty.

**Health system readiness**

8. **Insufficient budget to implement decisions.** There is not always enough budget to implement a positive reimbursement decision, causing implementation to be delayed or resulting in budget depletion at the end of the budgeting period, putting a negative pressure on prescription and use.

9. **Low frequency of clinical guideline updates.** Clinical guidelines do not always include the most recent therapeutic innovations, leading to delays in HTA decision-making and hampering prescription and use due to a lack of clarity on the positioning of the new therapy in the treatment pathway.

10. **Suboptimal healthcare infrastructure.** Suboptimal organisation of healthcare systems in general and oncology care pathways in particular may lead to problems in absorbing and using a new therapy in the most optimal way.
The six priority areas for reducing the time to patient access
To address these factors, multi-disciplinary and concerted actions are needed in six priority areas. All stakeholders are invited to engage in a dialogue and to find novel ways of working together in order to:

1. Align dossier submission timelines
Stakeholders ought to create a joint understanding of the pros and cons of external reference pricing and explore alternatives. Furthermore, pharmaceutical companies should build HTA capabilities to prevent these from becoming the key bottleneck in aligning dossier submission timelines across countries in Europe.

2. Shorten reimbursement timelines
Optimal alignment between parties prior to European marketing authorisation, allowing for dossier submission and assessment as soon as possible after marketing authorisation, taking steps in parallel rather than sequential, and keeping the layers of decision-making to a minimum can reduce time to patient access in countries. Involving patients and making timelines transparent helps in maintaining a sense of urgency at every step of the process.

3. Align evidence requirements
Much like the European Medicines Agency (EMA) has improved the efficiency for granting market authorisations, European HTA alignment on clinical assessment (after which appraisal takes place at national level) would improve the timelines to patient access. In addition, European cooperation and alignment would reduce duplication of efforts and allow for more efficient use of scarce human and financial resources.

4. Be adaptive to rapidly evolving innovation
Reimbursement criteria need to be clear to allow for predictability, while at the same they should be flexible to enable applicability to a variety of therapies and cases. Furthermore, a comprehensive system of horizon scanning, early collaboration, managed access schemes, and real-world data generation should be in place to proactively manage today’s challenges and avoid delays, e.g. using novel pricing and payment models.

5. Improve healthcare infrastructures
Pricing and reimbursement decisions should lead to an update of the guidelines and budget provisions. Furthermore, to improve screening and diagnosis, clear roles and responsibilities need to be assigned. When it comes to treatment, centres of excellence for (rare) cancers should be accessible to all patients, e.g. with the use of e-health solutions.

6. Strengthen collaboration between all stakeholders
As important as it is obvious: stakeholders must collaborate. In each of these priority areas, a concerted effort is needed, as none of today’s challenges can be addressed by a single stakeholder. Current early dialogues and scientific advice should evolve into early collaboration to enable a joint quest for solutions to potential access challenges. In addition, controversial topics that further constrain stakeholder relations need to be addressed proactively.

A call for further dialogue and joint problem-solving
This report provides a high-level overview in this complex domain. It is a starting point. It is a call for further dialogue, analysis and joint problem-solving by all relevant stakeholders in order to further explore the six priority areas. To reduce the immense inequalities in patient access between European countries we need to find a common understanding and a common perspective. This is needed because all stakeholders are part of the current system in which we operate and none of the stakeholders involved can solve today’s challenges single-handedly. We need a collaborative approach now. For patients, every day counts.
4.8 Insufficient budget to implement decisions

4.7 Misalignment on value and price

4.6 Evidence gaps

4.5 Lack of clarity of national requirements

4.4 Different evidence requirements across Europe

4.3 Multiple layers of decision-making

4.2 Lack of adherence to maximum timelines

4.1 Late start of application and submission

3.2 The case of midostaurin in acute myeloid leukemia

3.1 The case of pertuzumab in early breast cancer

2.4 The five phases of access pathways in European countries

2.3 Reimbursement criteria applied

2.2 Levels of decisionmaking involved

2.1 Economic context

6. Working together to improve access to innovative oncology therapies

5.6 Strengthen collaboration between all stakeholders

5.5 Improve healthcare infrastructures

5.4 Be adaptive to rapidly evolving innovation

5.3 Align evidence requirements

5.2 Shorten reimbursement timelines

5.1 Align dossier submission timelines

5. The six priority areas for reducing the time to patient access

4.10 Suboptimal healthcare infrastructure

4.9 Low frequency of clinical guideline updates

4.8 Insufficient budget to implement decisions

4.7 Misalignment on value and price

4.6 Evidence gaps

4.5 Lack of clarity of national requirements

4.4 Different evidence requirements across Europe

4.3 Multiple layers of decision-making

4.2 Lack of adherence to maximum timelines

4.1 Late start of application and submission

3.2 The case of midostaurin in acute myeloid leukemia

3.1 The case of pertuzumab in early breast cancer

2.4 The five phases of access pathways in European countries

2.3 Reimbursement criteria applied

2.2 Levels of decisionmaking involved

2.1 Economic context

6. Working together to improve access to innovative oncology therapies

5.6 Strengthen collaboration between all stakeholders

5.5 Improve healthcare infrastructures

5.4 Be adaptive to rapidly evolving innovation

5.3 Align evidence requirements

5.2 Shorten reimbursement timelines

5.1 Align dossier submission timelines

5. The six priority areas for reducing the time to patient access

4.10 Suboptimal healthcare infrastructure

4.9 Low frequency of clinical guideline updates
1. Introduction

1.1 The high speed of innovation in oncology

We live in times when speed of innovation for cancer patients is unprecedented. This is shown by an increasing number of European marketing authorization in oncology and the fact that nearly 40% of ‘drugs in development* are oncology therapies (Hofmarcher, et al., 2019) (Albrecht, B; Andersen, S; Chauhan, K; Graybosch, D, 2018).

The new wave of scientific innovation is generating an unprecedented level of choice and promise in cancer treatments. Increasingly, therapy selection in oncology is tailored to the individual patient and disease characteristics, to improve the likelihood of patients responding to treatment. The body’s own immune system can be activated to attack the tumor. And gene and cell-based therapies provide a potential cure.

These pharmaceutical innovations contribute to significant advances in cancer outcomes, together with advances in e.g. effective prevention, screening programmes, radiotherapy and surgical care.

Today, the number of lung cancer patients that is alive one year after diagnosis is more than ten times higher than in 1995, when only five out of 100 lung cancer patients were alive after one year (Schiller, 2018). This is just one example of how cancer survival rates have increased dramatically over the past 35 years (Cancer Research UK). As a result, the number of cancer deaths in Europe shows slower growth than the number of cancer diagnoses (Hofmarcher, et al., 2019). This is illustrated in Figure 1.

---

* Defined as Phase I – III clinical trials.

Source: Hofmarcher, et al., 2019
Nevertheless, cancer incidence is growing. The number of people diagnosed with cancer across Europe has risen by approximately 50% over the past two decades. Today, cancer is responsible for one in every four deaths in Europe, making it the second leading cause of death and disability after cardiovascular disease. The impact on individual patients, their families and society is tremendous (Hofmarcher, et al., 2019).

Still, improvements in services and treatments are leading to better outcomes. In lung cancer, for example, 13,296 more patients were alive for at least five years following a diagnosis in 2014, compared to those diagnosed in 2004 (Hofmarcher, et al., 2019). However, more efforts are needed to ensure every patient has access to the latest standard of care and treatment no matter in which European country they reside.

1.2 Three milestones in bringing innovative therapies to patients

Innovation has no value if patients for whom new therapies are intended cannot have access to them. Once a new treatment has gone through a process of ten years of research and development on average, three further milestones have to be reached before patients have access to it (see Figure 2):

1. European Marketing Authorization needs to be granted, confirming the quality, the safety and the efficacy of the therapy.
2. Authorities within countries have to decide on Market Access meaning reimbursement of the therapy under an insurance or reimbursement scheme, in order to make the intervention financially accessible to all patients*. 
3. Once reimbursed, Patient Access must be achieved, meaning that the patients they are intended for use the innovations after prescription by a specialist, in accordance with their marketing authorization, reimbursement guidelines and the latest scientific insights.

1.3 European reimbursement inequalities in reimbursement and use of innovations in oncology

Following advice from the European Medicines Agency (EMA), the European Commission (EC) grants a centralized marketing authorization covering all European Union (EU) Member States. This takes away the need for pharmaceutical companies to seek marketing authorization for new therapies from each Member State separately.

By contrast, reimbursement decisions are organized by national and sometimes even subnational (regional) authorities. These authorities use different processes and requirements, leading to different decisions and considerable inequalities in patient access throughout Europe. These inequalities can be found in all three dimensions of patient access:

- **Market Access**, which refers to the proportion of oncology therapies with a European marketing authorization that subsequently receive a positive reimbursement decision. This rate ranges from as low as 7% in Latvia to as high as 98% in Germany (IQVIA, 2020).
- **Time to Market Access**, which refers to the number of days between a European marketing authorisation and a formal positive reimbursement decision (this excludes early access schemes during which certain patients may receive reimbursement before the formal HTA process is finalized). The difference between the country where patients gain access reimbursement first (Denmark, 86 days on average) and the country where patients gain access reimbursement last (Latvia, 981 days on average) is close to 2.5 years. This means that patients in Latvia had to wait 2.5 years before being able to receive treatments that benefited the lives of patients in Denmark within less than three months following marketing authorization (IQVIA, 2020).
- **Patient Access**, having reimbursement in place does not necessarily mean that the medicine is prescribed, i.e. that patients are actually treated with the new therapy. There are remarkable differences between countries in the actual use of new oncology therapies in clinical practice, once

---

*A For the purpose of this report, reimbursement refers to a formal reimbursement decision thereby excluding early access schemes as these schemes often provide reimbursement on a restricted or case-by-case basis without completion of the formal HTA procedure.
reimbursement is in place. After twelve months of formal reimbursement, the relative cumulative use ranges from as low as 22% in the Netherlands to as high as 81% in France. A description of the methodology used to quantify country differences in this dimension of patient access is provided in Box 1.

This report focuses on:

- **Time to Market Access**, i.e. delays in reimbursement, and
- **Patient Access**, i.e. actual prescription, and use.

Figure 3 highlights the three access challenges that patients in European countries are facing in these two dimensions. It shows that none of the countries included in this analysis has optimal access in terms of both time to Market Access and Patient Access.

A country that comes very close to this optimal situation is Germany. German patients are guaranteed immediate reimbursement after a therapy receives a European marketing authorization, while the decision-making about permanent reimbursement starts in parallel. This explains why Germany is among the countries with the shortest time to Market Access in Europe. However, the number of patients that have access to the therapy after 12 months is relatively low. The fact that a therapy is very new when it becomes available in Germany, may explain why it takes longer before it is actually prescribed to patients: the body of evidence (scientific publications, clinical guidelines) is still developing and both prescribers and patients need to become familiar with the new therapy. Furthermore, physicians may be reluctant to prescribe the new therapy, until it has gone through the formal HTA process. Another explanation may be the high proportion of oncology therapies with a European marketing authorization that receives a positive reimbursement decision in Germany (98%). This may imply that the number of alternative therapies in Germany is higher than in other countries, leading to a lower clinical use per individual therapy.

The Netherlands is an example of a country with the first access challenge: a relatively short delay but low patient access. On average, innovative oncology therapies in the Netherlands are reimbursed 234 days after European marketing authorization. However, in the 12 months following this decision, and compared to the country with the highest patient access, only 20% of the patients receives the therapy (compared to the number of patients that received the therapy in the country with the highest real-world access). This may be explained by the fact that after the national reimbursement decision, contracts need to be negotiated with individual hospitals (operating in a context of budget constraints) before the therapy can be prescribed. Another explanation could be the fact that it takes a long time for new therapies to be included in clinical guidelines.

Poland is an example of a country with the second access challenge: long delays and low patient access. In Poland, it takes on average 891 days before an innovative oncology therapy is reimbursed. And in the first 12 months after reimbursement, only 24% of the patients have access to the therapy. This may be explained by the fact that requests for reimbursement are submitted later in Poland, that the decision-making process is long, and/or that positive reimbursement decisions are made for a subgroup of the overall patient population for which a European marketing authorization was granted (which may be driven by budget impact considerations in a context of a relatively low GDP).

An example of a country with the third access challenge is France. In France, on average 80% of patients have access to an innovative therapy after the first 12 months of formal reimbursement. Yet it takes a long time before this formal reimbursement is in place: 579 days on average. Both characteristics may be explained by the French ‘Temporary Authorization for Use’ program (ATU). This early access program does not equal formal reimbursement, as it is not preceded by a formal HTA process and is not available for all therapies or patients. Nonetheless, it allows some patients to have access prior to formal reimbursement. Once this formal reimbursement is in place, patients and prescribers are more likely to be already familiar with a therapy, because they gained experience with the therapy through the ATU. This may explain the high level of patient access in the first 12 months after formal reimbursement.

The four examples provide an overview of the different access challenges that European countries are facing. A few potential factors causing delays in time to patient access are provided, but more research is needed to assess the specific factors at play in a specific country.

The present report can help in this endeavor. It provides an overview of the 10 key factors delaying time to patient access across European countries. It also provides six solution areas for eliminating these delays. It can be used by stakeholders to make a detailed assessment of the factors at play in their country and the relevant solutions to deploy: an endeavor that requires an effort from all stakeholders in the healthcare system.

---

* Calculated as the cumulative use in the first 12 months after reimbursement, relative to that of the country with the highest use. This was done for thirteen individual oncology therapies, after which the average was used as an indicator.

** Within six months, a health technology assessment is conducted, after which the actual reimbursement price is negotiated. This price replaces the initial price (list prices set by pharmaceutical companies) one year after launch.
Whilst we know the rate of Market Access and time to Market Access for innovative oncology therapies quite well based on the annual EFPIA W.A.I.T. Indicator Study (IQVIA, 2020), no analysis was available of European differences in actual use after reimbursement (Patient Access). To address this information gap, a European benchmark analysis was made to compare post-reimbursement use between countries, for a set of innovative oncology therapies.

For this benchmark, ‘use’ was measured by analysing volume sold per month (or patients treated per month, based on volume sold), per capita, using routinely collected business information from pharmaceutical companies and data providers. ‘Post-reimbursement’ was defined as the phase that starts when the first patient is treated under a formal reimbursement scheme. Therefore, early access schemes are excluded, as these schemes often reimburse on a case-by-case or restricted basis without completion of the formal HTA process.

Ten countries were included: Czech Republic, England, France, Germany, Greece, Italy, Netherlands, Poland, Spain and Sweden. The thirteen oncology therapies included cover Leukaemia (n=4), Breast cancer (n=3), Lung cancer (n=3), Bladder cancer (n=1), Multiple myeloma (n=1), Melanoma (n=1), Non-melanoma skin cancer (n=1) and Ovarian cancer (n=1): alectinib, midostaurin, olaparib, osimertinib, pertuzumab, stem cell transplantation (in the case of haematology) also be a symptom of a suboptimal access situation, and finally, per country, the average relative use across all therapies was calculated to arrive at one single indicator of post-reimbursement use compared to other countries. This information was combined with the latest information on delays in reimbursement (IQVIA, 2020; see Figure 3).

Two important aspects should be considered when interpreting the findings of the analysis. First, the benchmark illustrates differences rather than best practices. High clinical use for a specific therapy does not equal optimal access. High clinical use can also be a symptom of a suboptimal access situation, e.g. when a more advanced treatment option such as stem cell transplantation (in the case of haematology) is not available or accessible. Countries with the highest clinical use per therapy were set as the benchmark country (100%) to enable comparison, not to set a standard or best practice. However, since the benchmark covers multiple therapies in multiple indications, it provides a good indication of health system factors posing a barrier to patient access.

Second, the outcomes serve as the start of further research and discussions on European inequalities regarding post-reimbursement clinical use. They give a quantitative overview of the differences, without explaining the reasons behind these variances.

A detailed description of the methodology can be found in Annex B.

1.4 A multi-stakeholder perspective on challenges and solutions: the methodology

In order to connect all relevant stakeholders, this report combines the different perspectives and provides a comprehensive and unbiased overview of challenges and areas in which joint action is needed. It is the result of a collaborative approach by health technology assessment (HTA) bodies, healthcare professional associations, patient organizations, policy makers, former politicians, payers and pharmaceutical companies. Different methodologies and sources of information were used to develop and validate the content of this report.

Country case studies on delaying factors and solutions

LITTLE is known about the reasons behind variances and delays in time to patient access. Therefore, case studies were conducted in six European countries which together represent the diverse access contexts in Europe. Together, the group of six countries should represent the diverse access contexts in Europe and a set of selection criteria was defined to guide the country selection. Countries selected were England, Italy, the Netherlands, Poland, Portugal and Sweden.

Document reviews and interviews with regulators, payers, former politicians, HTA bodies, healthcare professional associations, patient organizations, industry organizations and experts allowed for an in-depth understanding of delaying factors, best practices and potential solution areas in these countries. Content analysis of the country findings allowed for identification of a first set of delaying factors and solution areas, potentially applicable to a broader European context. Details about the methodology and summaries of the six country profiles can be found in Annex A.

Patient Access Indicator

An analysis of patient access was undertaken to identify European differences in the use of new oncology therapies twelve months after reimbursement. Outcomes are presented in Chapter 1, section 1.3 (Figure 3). The methodology is described in detail in Annex B.

Mapping of European differences in evidence requirements

One cause for delays in patient access is the differences in evidence requirements across Europe. A comparative analysis of evidence requirements was performed for EMA and HTA bodies in the six case study countries. A detailed account of the differences and the level of alignment and predictability across agencies is provided in sections 4.4 and 4.5 (Figures 9 and 10). The methodology is described in detail in Annex C.

Impact analysis of improved time to market access

To make the potential impact of reducing delays in reimbursement decision-making and hence the time it takes for patients to access new therapies more tangible, an impact analysis was performed. The findings are presented in sections 3.1 and 3.2. They serve as a reminder of our common objective and the urgency of addressing delays where we can. The methodology is described in detail in Annex D.

Multi-stakeholder Sounding Board

A European multi-stakeholder sounding board was established to discuss and validate the project set-up and findings, and to place the information generated from case study countries into the larger perspective of all European Member States. In addition, the sounding board allowed for capturing different perspectives to ensure balanced outcomes. Over the course of the initiative, over 25 organizations operating at the European and/or national level participated in one or more sounding board meetings. An overview of all stakeholders that contributed to the initiative, e.g. through participation in interviews or one or more sounding board meetings, can be found in the list of Contributors at the end of this report.
2. The diversity of European access systems

Contrary to the unified marketing authorization process for EU Member States, reimbursement decisions are made by authorized bodies within the Member States. This is because medical need, effectiveness compared to the current standard of care, cost-effectiveness and budget impact are often influenced by local characteristics and are in the remit of each Member State.

The national settings in which these reimbursement decisions are made vary, in terms of economic context, levels of decision-making involved and main criteria for reimbursement.

2.1 Economic context

The latest data from the Organization for Economic Cooperation and Development (OECD) from 2017 clearly shows the European differences in economic context:

- Absolute healthcare spending ranges from EUR 5,300 per capita in Germany to EUR 1,300 per inhabitant in Romania.
- Relative healthcare spending as a % of overall GDP, is more than 2 times higher in France (11.3%) than in Romania (5.2%).
- Absolute pharmaceutical spending ranges from EUR 286 per inhabitant in Denmark to EUR 740 per inhabitant in Germany.
- Relative pharmaceutical expenditures as a % of overall GDP, is 3.5 to over 5 times higher in Greece or Bulgaria (2.2% and 3.3% respectively) compared to Luxembourg (0.62%).

2.2 Levels of decision-making involved

The Treaty of the Functioning of the EU leaves the budget and the management of the health system in the remit of Member States (Art. 168), in contrast to other areas of policy such as the internal market. Therefore, the way in which Member States organize and finance their health systems differs considerably. Consequently, European countries have different ways of organizing their reimbursement decision-making. As shown in Figure 4, some countries such as Iceland and Croatia organize price negotiations, assessment, appraisal and budget allocation on a national level. Other countries organize these decisions partly at a national level and partly at a regional level. In most European countries price negotiations, assessment and appraisal take place on a national level but budgets are allocated by healthcare insurers (a single payer institution or different health insurers) or on a hospital level. (WHO, 2018).

2.3 Reimbursement criteria applied

Although HTA bodies generally ask similar questions to inform reimbursement decisions, the specific assessment criteria differ, as does allocation on a national level. Other countries organize these decisions partly at a national level and partly at a regional level. In most European countries price negotiations, assessment and appraisal take place on a national level but budgets are allocated by healthcare insurers (a single payer institution or different health insurers) or on a hospital level. (WHO, 2018).

![Fig 4](image_url)

The context in which patients access takes place differs significantly between European countries: levels of decision-making involved for in-patient therapies

<table>
<thead>
<tr>
<th>Decision-making level for in-patient therapies</th>
<th>National</th>
<th>National &amp; Regional</th>
<th>Regional &amp; National</th>
<th>National &amp; HCI Hospital</th>
<th>HCI/Hospitals &amp; National</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pricing</td>
<td>National</td>
<td>National</td>
<td>National</td>
<td>National</td>
<td>National</td>
</tr>
<tr>
<td>Assessment and appraisal</td>
<td>National</td>
<td>National</td>
<td>Regional</td>
<td>National</td>
<td>Insurer</td>
</tr>
<tr>
<td>Budget allocation</td>
<td>National</td>
<td>Regional</td>
<td>Regional</td>
<td>Insurer/Hospital</td>
<td>Insurer/Hospital</td>
</tr>
</tbody>
</table>

their relative weight in the final appraisal and decision-making. Figure 5 below illustrates the dissimilarities in main reimbursement criteria for European countries. It provides more detail for the six case study countries that focus on different elements such as clinical effectiveness (e.g. Portugal and Italy), cost effectiveness (e.g. England and Sweden), both (e.g. the Netherlands), or clinical effectiveness, cost-effectiveness and budget impact (e.g. Poland).

2.4 The five phases of access pathways in European countries
Despite different contexts, European countries generally follow an access pathway comprised of five phases. For governments and payers, these phases form the basis to make evidence-based decisions on public healthcare expenditures.

1. Preparation: Early in the clinical development phase (prior to Phase 3), the early dialogue is an opportunity for pharmaceutical companies to discuss and receive early advice on the development plan. Furthermore, national HTA bodies and payers can apply horizon scanning to identify therapies in the clinical development phase in order to appropriately plan for the potential future assessment, budget implications and use of the therapy.

2. Application & submission: An application from the pharmaceutical company and direction from the HTA body on the reimbursement route to follow kick off the national reimbursement process. The HTA dossier is submitted, in line with the country-specific procedures and Start of the national process compared to EU marketing authorization differs

3. Assessment & appraisal: Often one committee within an HTA agency is responsible for critically reviewing evidence submissions or synthesizing evidence. Subsequently, another committee considers the wider context and provides advice or a recommendation. Likewise, in the case of EUnetHTA assessments, EUnetHTA synthesizes the evidence on clinical effectiveness, but refrains from conclusions or recommendations as this is done at the national level.

4. Pricing & reimbursement: Based on the findings and the recommendation, price

Fig. 5
Main reimbursement criteria
The context in which reimbursement decisions are made differs significantly between European countries: main reimbursement criteria applied

Fig. 6
Despite different contexts, in general European countries follow an access pathway comprising Five phases to make evidence-based decisions on public healthcare expenditures

Milestones (A, B, C)

A. Authorisation
- Start of the national process compared to EU marketing authorization differs

B. Market Access
- • Horizon scanning
- • Early dialogue
- • Application submission
- • HTA dossier submission
- • Company application
- • Assessment & appraisal
- • Recommendation
- • Reimbursement decision
- • Pricing negotiations
- • Reimbursement
- • Prescription by specialists
- • Administration and funding in place

C. Patient Access

Phases 1 to 6

Sources: Angelis, Lange, & Kanavos, 2018, WHO, 2018
negotiations with the pharmaceutical company will start. The pricing negotiations take place with different parties, depending on each country. This could for example be with the government, an organization representing all insurers, or an appointed agency established solely for pricing negotiations.

5. Prescription & use: Once the decision on reimbursement has been made, additional steps are often required to implement the decision. These steps take various forms in countries from an official decree, signature, publication, or addition to reimbursement lists, to regional or hospital agreements to procure the drug. In theory, after completion of this process, eligible patients should finally have access to the newly approved medication. This reimbursed access can only materialize when the health system infrastructure and oncology care pathways are adequate, when oncologists have the latest knowledge and expertise, and patients are able to access this expertise.

Phase one can be used to reduce the time needed for phases two to five. Any form of delay in the first four phases therefore ultimately results in a delay in reimbursement. In the last phase of prescription and use, delays or barriers hamper effective access and clinical use (see Figure 6).
### The case of midostaurin in acute myeloid leukemia

**Impact of earlier time to reimbursement for patients with a rare disease - the case of midostaurin in acute myeloid leukemia**

#### Midostaurin

**Acute myeloid leukemia (AML):** rapid growth of abnormal blood cells that build up in the bone marrow and blood and interfere with normal blood cells. As an acute leukaemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated. Around 80% of patients diagnosed with AML pass away within five years.

#### Market Access: dates at which the therapy was reimbursed under a formal reimbursement scheme

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Sep 17</td>
<td>Jan ’18</td>
<td>Feb ’18</td>
</tr>
<tr>
<td><strong>EC Directive</strong></td>
<td>0 days</td>
<td>135 days</td>
<td>228 days</td>
</tr>
<tr>
<td><strong>What if (scenarios):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>### days between EC authorization and patient access:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td><strong>SE</strong></td>
<td><strong>NL</strong></td>
<td><strong>UK-ENG</strong></td>
</tr>
<tr>
<td><strong>Ambitious</strong> scenario A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Directly after EC authorization:</strong></td>
<td>71</td>
<td>34</td>
<td>1,423</td>
</tr>
<tr>
<td><strong>As fast as the fastest country:</strong> 135</td>
<td>3,466</td>
<td>1,692</td>
<td>69,867</td>
</tr>
<tr>
<td><strong>EC Directive 180</strong></td>
<td>n/a</td>
<td>n/a</td>
<td>300</td>
</tr>
<tr>
<td><strong>“Best practice” scenario B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>3,67</td>
<td>159</td>
<td>7,399</td>
</tr>
<tr>
<td><strong>EFS</strong></td>
<td>n/a</td>
<td>n/a</td>
<td>1,558</td>
</tr>
<tr>
<td><strong>Basic</strong> scenario C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### In a highly ambitious scenario, if midostaurin had been reimbursed in Sweden, the Netherlands, England and Italy directly after EC marketing approval:

- 1,689 more patients with AML could have been treated.
- They could have lived altogether an additional 82,920 months.
- This would have corresponded to 8,665 months without the disease getting worse.

#### In the ‘best practice’ scenario, if midostaurin had been reimbursed in the Netherlands, England and Italy after 135 days, like in Sweden:

- 673 more patients with AML could have been treated.
- They could have lived altogether an additional 33,033 months.
- This would have corresponded to 3,433 months without the disease getting worse.

#### In the ‘basic scenario’, if midostaurin had been reimbursed in England and Italy as fast as agreed in the EC Transparency Directive (a condition fulfilled by the Netherlands and Sweden):

- 369 more patients with AML could have been treated.
- They could have lived altogether an additional 18,107 months.
- This would have corresponded to 1,876 months without the disease getting worse.

---

*Midostaurin for AML is not reimbursed in Poland. In Portugal it was only reimbursed as of September 2019, resulting in too little uptake information for inclusion in the analysis.*
3.2 The case of pertuzumab in early breast cancer

Impact of earlier time to reimbursement for a therapy in the neo-adjuvant setting - the case of pertuzumab in early breast cancer *,**

**Pertuzumab (pre-surgery or ‘neoadjuvant’)**

**Early stage breast cancer:** the cancer is contained in the breast or it has only spread to the lymph nodes in the underarm area. In this stage, it is highly treatable, through a combination of surgery and treatment, and often radiation. Almost 90% of all patients diagnosed still live after five years.

**Market Access:** dates at which the therapy was reimbursed under a formal reimbursement scheme

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>0</td>
<td>126</td>
<td>219</td>
<td>478</td>
</tr>
<tr>
<td>2016</td>
<td>180</td>
<td>1496</td>
<td>126</td>
<td>6,418</td>
</tr>
<tr>
<td>2017</td>
<td>126</td>
<td>1,056</td>
<td>1,083</td>
<td>5,959</td>
</tr>
<tr>
<td>2018</td>
<td>7</td>
<td>546</td>
<td>546</td>
<td>4,310</td>
</tr>
<tr>
<td>2019</td>
<td>42</td>
<td>1,138</td>
<td>1,180</td>
<td>4,408</td>
</tr>
</tbody>
</table>

What if (scenarios):

- **Scenario A:** at the time of the EC marketing authorisation.
  - In this ‘highly ambitious’ scenario, time to market access as short as possible. In this scenario, market access is achieved at the time of the European Commission’s (EC) marketing authorisation.

- **Scenario B:** as fast as the fastest country.
  - In this ‘best practice’ scenario, the potential gains are assessed for a situation in which all countries ensure market access as fast as the fastest country.

- **Scenario C:** at 180 days after the EC marketing authorisation.
  - In this ‘basic’ scenario, dossiers are submitted directly after EC marketing authorisation and all stakeholders involved adhere to a timeline of max. 180 days to achieve market access, in conformity with the EC Transparency Directive (European Commission, 1988).

The scenarios were researched in all six case study countries. A health economic model was developed to calculate for each therapy and country the impact of the three scenarios on the number of patients that could have been treated, and the resulting health impact. This was done using three steps (more details are provided in Annex D):

1. Calculate the improvement in time to patient access: determine the difference in days between the optimised scenario and the actual scenario.
2. Calculate the additional number of patients that could have been treated if the uptake curve had started at this new date (the endpoint for both uptake curves was set at five years).
3. Calculate the health gains per month based on the information in the country-specific reimbursement dossiers: multiply the number of patients with the incremental health gains per month, expressed in terms of overall survival (OS, per month), event-free survival (EFS, per month), life-years gained (LYG, translated into life-months gained, LMG) and/or quality-adjusted life years (QALYs, translated into quality-adjusted life-months, QALMs) gained versus the comparator.

In a highly ambitious scenario, if pertuzumab had been reimbursed in the Netherlands, Sweden and England directly after EC marketing approval:
- 2,180 more patients with early breast cancer could have been treated.
- They could have lived altogether an additional 12,718 months.
- This would have corresponded to 8,842 months when adjusted for the quality of life.

In the ‘best practice’ scenario, if pertuzumab had been reimbursed in Sweden and England after 126 days, like in the Netherlands:
- 1,180 more patients with early breast cancer could have been treated.
- They could have lived altogether an additional 6,772 months.
- This would have corresponded to 4,798 months when adjusted for the quality of life.

In the ‘basic scenario’, if pertuzumab had been reimbursed in Sweden and England as fast as EC Transparency Directive (a condition fulfilled by the Netherlands):
- 1,083 more patients with early breast cancer could have been treated.
- They could have lived altogether an additional 6,181 months.
- This would have corresponded to 4,408 months when adjusted for the quality of life.

Box 2 Impact analysis of improved time to market access – summary of methodology

For the impact analysis, the number of new patients on the therapy (uptake) per month were retrieved from the routinely collected business information of the companies involved, as of the date of formal reimbursement. Subsequently, three hypothetical scenarios were applied. In these scenarios, the number of new patients per month remained equal. But time to reimbursement (start of uptake) changed.

- **Scenario A:** at the time of the EC marketing authorisation.
  - In this ‘highly ambitious’ scenario, time to market access as short as possible. In this scenario, market access is achieved at the time of the European Commission’s (EC) marketing authorisation.

- **Scenario B:** as fast as the fastest country.
  - In this ‘best practice’ scenario, the potential gains are assessed for a situation in which all countries ensure market access as fast as the fastest country.

- **Scenario C:** at 180 days after the EC marketing authorisation.
  - In this ‘basic’ scenario, dossiers are submitted directly after EC marketing authorisation and all stakeholders involved adhere to a timeline of max. 180 days to achieve market access, in conformity with the EC Transparency Directive (European Commission, 1988).
4. The ten key factors delaying patient access

TEN reasons explain why many patients in European countries tend to have longer waiting times than needed to access new cancer medicines. These reasons are the result of the current systems in which stakeholders operate and can be categorized as factors related to:

- **Process**, i.e. how stakeholders organize the series of steps to take
  Three key process-related factors delaying patient access are: late start of application and submission, lack of adherence to maximum timelines and a multitude of layers involved in the decision-making process.

- **Reimbursement criteria**, i.e. what information stakeholders use to define value
  In this category, delays take place due to different evidence requirements across Europe and a lack of clarity of national assessment requirements. These are followed by gaps between evidence submitted and evidence required, and subsequent misalignment of views on value and price.

- **Health system readiness**, i.e. to what extent stakeholders integrate the therapy in clinical practice
  Once a positive reimbursement decision has been made, integration in clinical practice may be hampered due to prescriber’s depleted budgets before the end of the fiscal period, a low frequency at which clinical guidelines are updated and the state of the healthcare infrastructure.

Each of these factors is described in detail in this chapter. Applying this comprehensive framework enables a constructive dialogue and the identification of joint solutions.

4.1 Late start of application and submission

The longer it takes to initiate the national access pathway for a new therapy, the later patients will actually have access to this new therapy.

Often, countries await a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP), or in some case the formal decision from the European Commission (EC)*.

Following a CHMP opinion the European Commission usually adopts a legally binding authorization, within 67 days.

* or the formal publication in the Official Journal of the EU before a dossier can be submitted or is assessed. In some cases, countries even await decisions from other countries (Yfantopoulos & Chantzaras, 2018).

Figure 7 shows how the moment of starting the process differs for the six case study countries.

Most European countries use External Reference Pricing (ERP) to manage and negotiate pharmaceutical prices. With ERP, medicine price(s) in one or more other countries serve as a benchmark or reference price for setting or negotiating the price in a country. Here, list prices are used rather than the net transaction prices, as the latter are generally confidential. The number of countries considered in the basket varies across countries, ranging from 3 to 30 countries. This is reflected in Figure 8. External Reference Pricing is used in Europe but European countries are also referenced by non-European countries (Holtorf, Gialama, Wijaya, & Kaló, 2019).

In some cases, higher-income countries reference lower-income countries. Consequently, establishing a reimbursement price in countries with a lower ability to pay and hence a lower price level first, before
Every day counts
IMPROVING TIME TO PATIENT ACCESS TO INNOVATIVE ONCOLOGY THERAPIES IN EUROPE

The lifecycle of a medicine
This infographic shows the last milestones of the process: Authorisation, Market Access and Patient Access

1. Preparation
   - Horizon scanning
   - Early dialogue

2. Application & submission
   - HTA dossier submission
   - Company application

3. Assessment & appraisal
   - Recommendation
   - Health Technology Assessment (HTA)

4. Pricing & reimbursement
   - Pricing negotiation
   - Reimbursement decision

5. Prescription & use
   - Prescription by specialists
   - Administration and funding in place

6. Patients receive treatment

The ten key factors delaying patient access

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>REIMBURSEMENT CRITERIA</th>
<th>HEALTH SYSTEM READINESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Late start</td>
<td>8  Budget restraints</td>
</tr>
<tr>
<td>2</td>
<td>Undefined timelines</td>
<td>9  Outdated clinical guidelines</td>
</tr>
<tr>
<td>3</td>
<td>Multiple layers</td>
<td>10 Suboptimal healthcare infrastructure</td>
</tr>
<tr>
<td>4</td>
<td>Different requirements</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Lack of clarity</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Evidence gaps</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Misalignment on value and price</td>
<td></td>
</tr>
</tbody>
</table>
are often inclined not to accept an application for reimbursement until authorization to enter the European market has been confirmed. Similarly, companies (especially smaller and mid-sized companies) do not have the capacity to submit all national dossiers in parallel throughout Europe, as every single country requires the development of a tailor-made dossier in local language and compliance with a country-specific trajectory.

**4.2 Lack of adherence to maximum timelines**

Most European countries do not follow a clear set of rules around the timelines for decision-making on national pricing and reimbursement. Even when countries have such rules in place, compliance can be challenging. This results in delays and unpredictability of timelines. In the case of the Netherlands for example, the average time between a European marketing authorization and a positive formal reimbursement decision is 234 days for oncology therapies. However, actual delays vary a lot between therapies and may take up to ~700 days in the case of the Netherlands (as shown in the WAIT indicator report), depending e.g. on whether or not the clock stop procedure is used.

Recent evidence shows how delays in reimbursement of oncology therapies vary within countries, making the process unpredictable (IQVIA, 2020). This reflects a suboptimal implementation of the EU Transparency Directive (European Commission, 1988). The purpose of this directive is to ensure the transparency of measures that regulate pricing and reimbursement of medicinal products. It sets the maximum duration for reaching a national pricing and reimbursement decision to a strict national timeline of max. 180 days. This timeline starts from the moment a dossier is submitted and excludes time needed by companies to provide additional information (‘clock stops’).

**4.3 Multiple layers of decision-making**

Figure 4 (section 2.2) summarizes how European countries have a different way of organizing their reimbursement decision-making process. The more levels of decision-making, the more duplication of efforts occurs and the higher the chances of prolonging the time before patients can access treatments.

- Delays related to duplication of reimbursement decisions take place in countries such as Italy and Sweden. Here, regions (or counties) can make their own reimbursement decision. In Italy, regions can conduct the assessment themselves.
- Delays related to duplication of budget decisions take place in countries such as the Netherlands and Portugal. After a positive reimbursement decision at national level, individual negotiations on net price and inclusion of therapies in the hospital formulary need to take place with the hospitals themselves.
- Delays related to implementing budget decisions are seen in Poland for example, where budget allocation to hospitals can be delayed by several months. In addition, decentralized decision-making also increases the risk of inequalities in access within a country.

Another important factor at play behind these dynamics is the scarcity of human resources within both HTA bodies and pharmaceutical companies. Significant advances in medical science and deeper understanding of diseases have led to an acceleration of drug development in all disease areas. With the number of EU marketing authorizations increasing, even more capacity will be required. HTA bodies struggle to compete with private sector salaries and to ensure they have the required expertise in a rapidly advancing field (O’Rourke, Werkö, Merlin, Huang, & Schuller, 2019). For that reason, they are often inclined not to accept an application for reimbursement until authorization to enter the European market has been confirmed. Similarly, companies (especially smaller and mid-sized companies) do not have the capacity to submit all national dossiers in parallel throughout Europe, as every single country requires the development of a tailor-made dossier in local language and compliance with a country-specific trajectory.

It is important to note that timelines presented in this publication capture three delays which are excluded from the 180 days prescribed by the EU Transparency Directive. First, the delay between marketing authorization and dossier submission, since the 180 days start from the moment of dossier submission. Second, delays during the assessment due to ‘clock stops’ as the 180 days exclude time needed by companies to provide additional information. And third, delays due to putting formalities in place, as the Transparency Directive stops at the moment of the decision.
4.4 Different evidence requirements across Europe

Throughout Europe, different evidence is required for a clinical assessment, depending on the assessment agencies. Evidence required by the EMA to demonstrate safety and clinical efficacy and inform a marketing authorization decision differs from the evidence required by national HTA bodies to demonstrate clinical effectiveness and inform reimbursement decisions. This makes sense, as both agencies have different objectives.

Yet, even among HTA bodies, who all aim to answer similar evaluation questions, evidence requirements vary. When evaluating clinical effectiveness, HTA bodies look at the strength of the evidence generated by the manufacturer in a clinical trial. They assess whether the evidence is robust enough to demonstrate the effectiveness compared to existing alternatives (e.g., the current standard of care). They look at the patient population that was studied, the comparator therapy that was used, the clinical endpoints (outcomes) that were measured, the way in which the trial was set-up, and the statistical analyses that were run.

However, the extent to which this evidence (coming from the same clinical trial) is considered robust or acceptable varies greatly across HTA bodies. This is demonstrated in Figure 9, which maps the self-reported level of acceptance of 19 trial characteristics for the HTA bodies in England, Italy, the Netherlands, Poland, Portugal and Sweden.

The level of alignment is highest for the use of biomarkers and real-world evidence (RWE) for example. These elements are “often accepted” by all HTA bodies. The level of alignment is lowest when HTA bodies are asked for acceptance of surrogate endpoints other than progression-free survival (PFS). Every agency looks at the use of surrogate endpoints other than OS or PFS in a different way: these are accepted in Poland and often accepted in Sweden; not accepted in the Netherlands and often not accepted in Portugal. England and Italy determine acceptance on a case-by-case basis.

These differences prolong discussions and alignment between pharmaceutical companies and HTA bodies at a national level, especially when no early discussions took place to align on evidence generation in advance. It may even lead to additional, country-specific data collection, thereby seriously extending patients’ waiting times.

4.5 Lack of clarity of national requirements

In addition to a lack of coherence on evidence requirements between HTA bodies, also within countries the evidence requirements for the clinical assessment and the cost-effectiveness assessment are often difficult to predict. Although case-dependency allows for a tailor-made assessment, it also results in an unpredictable evaluation. The absence of clearly defined criteria and requirements, or their inconsistent application, perpetuates national discussions and misalignment between pharmaceutical companies and HTA bodies, thereby delaying access for patients.

Unclear evidence requirements for clinical assessments, within countries

Figure 10 demonstrates the difficulty of predicting evidence requirements for the clinical assessment with national HTA bodies.

In Figure 9, the grey color code reflects acceptance on a case-by-case basis. The blue color code (“often not accepted”) and lighter orange color (“often accepted”) also reflect a certain level of unpredictability. To highlight the level of predictability more clearly, in Figure 10 the information from Figure 9 is translated into levels of predictability, using the general rules:

- ‘accepted’ and ‘not accepted’ are classified as ‘predictable’
- ‘often accepted’ and ‘often not accepted’ are classified as ‘not fully predictable’
- ‘case-dependent’ are classified as ‘highly unpredictable’.

Mapping the information in this way shows how the level of predictability of evidence requirements is particularly low for the accepted patient population, the selected comparator, the use of PFS as an endpoint, cross-over in trials, a short time period of a trial (e.g. because of promising results and early, conditional marketing authorization) and post-hoc subgroup analyses.

Unclear criteria for cost-effectiveness assessments, within countries

Similarly, criteria for the cost-effectiveness assessment are not always defined in a clear manner, nor is the definition used in a
They define different thresholds to allow applicability in different settings. In England, specific thresholds are set for end-of-life settings and very rare diseases, to indicate a higher willingness to pay in these instances. In the Netherlands, willingness to pay is higher when the burden of the disease for patients is higher. These differences demonstrate the difficulty of defining and consistently applying clear thresholds in specific situations. In most countries, thresholds have not changed for many years (in some cases they have never been adjusted).

In Sweden, the HTA body assesses the price per QALY at different price levels but does not use a standard maximum price to reflect what is considered a reasonable amount per QALY (Svensson, Nilsson, & Arnberg, 2015). Countries like Italy or Portugal also do not have a formal ICER threshold. In order to decide on an acceptable price, they compare the price of a new therapy to prices of similar therapies and/or prices in other countries (Iannazzo, et al., 2016). The differences are summarized Figure 11.

Other European countries do not define clear thresholds at all.

4.6 Evidence gaps

Increasingly, reimbursement dossiers for oncology therapies risk not meeting evidence requirements from HTA bodies, leading to evidence gaps and uncertainty about the real-world value of these therapies. This can be due to non-robust evidence generation, but also due to the fact that meeting traditional HTA evidence requirements is getting more difficult given the characteristics of today’s oncology therapies.
How oncology therapies inherently bring challenges in meeting evidence requirements for the clinical assessment, leading to gaps and uncertainty

<table>
<thead>
<tr>
<th>THERAPY CHARACTERISTIC</th>
<th>CLINICAL TRIAL CHARACTERISTIC</th>
<th>UNCERTAINTY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy-characteristic</td>
<td>• Selected comparator: The standard of care at the start of the trial has already been replaced at the time of evidence submission.</td>
<td>Uncertainty about effectiveness compared to country’s standard of care.</td>
</tr>
<tr>
<td>Targeting life-threatening or highly debilitating disease</td>
<td>• Single-arm trial: The absence of alternative treatment makes it unethical to use a control group of patients not receiving the potentially effective therapy.</td>
<td>Uncertainty about validity of findings.</td>
</tr>
<tr>
<td></td>
<td>• Cross-over in trial: The absence of alternative treatment makes it unethical to keep patients in the control arm when their disease progresses.</td>
<td>Uncertainty about the relation between the observed effect and mortality or morbidity.</td>
</tr>
<tr>
<td></td>
<td>• Short time period: The promising effect makes it unethical to await all phases of the clinical trial before applying for marketing authorisation and reimbursement, meaning that ‘hard’ data on overall survival may not be available at the time of reimbursement discussions.</td>
<td></td>
</tr>
<tr>
<td>Targeting rare cancers (orphan drugs, molecular targets, or genomic alterations (targeted therapies and tumor-agnostic therapies))</td>
<td>• Evidence from small populations: As the disease, targeted molecule, or genomic alteration is rare, there are too few patients for:</td>
<td>Uncertainty about statistical significance of findings.</td>
</tr>
<tr>
<td></td>
<td>• having information on natural course of disease as comparison</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• developing a validated questionnaire to measure the effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• measuring a statistically significant effect size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Post-hoc subgroup analysis: The targeted effect does not occur in all patients, but it is not known (yet) in which patients exactly, making it impossible to predict in advance, in what subgroup the targeted effect will take place.</td>
<td></td>
</tr>
<tr>
<td>Targeting cancers that progress slowly or have a long-term, curative effect</td>
<td>• Short time period; due to the slow progression of the disease, no ‘hard’ data on overall survival may be available within a reasonable timeframe, or no evidence on the actual duration of the (potential) curative effect may be available within a reasonable timeframe.</td>
<td>Uncertainty about the relation between the observed effect and mortality or morbidity.</td>
</tr>
<tr>
<td></td>
<td>Uncertainty about the long-term duration of the effect.</td>
<td></td>
</tr>
</tbody>
</table>

- generally developed in a context with a high speed of innovation
- often targeting life-threatening or highly debilitating disease
- frequently targeting rare cancers, molecular targets, or genomic alterations
- sometimes targeting cancers that progress slowly (especially when targeting the cancer at an early stage when there is more potential to significantly prolong life expectancy)
- sometimes able to cure.

Table 1 describes how these characteristics result in clinical trial designs not meeting national evidence requirements for the clinical assessment. Consequently, they bring evidence gaps and uncertainty about real-world value.

This is complicated further by the fact that these therapies also pose challenges to determining cost-effectiveness. In the case of some multi-indication therapies or tumor-agnostic therapies for example, the same therapy is used for different types of tumors. This poses the difficulty of applying different value assessments per indication and indication-specific prices (the latter is often hampered by the way in which information on prescription is collected at the hospital level). In the case of therapies with a curative intent, the uncertainty about the duration of the effect is of particular consequence due to the upfront payment that has to be made for this one-off therapy.

### 4.7 Misalignment on value and price

Decision-makers are faced with the enormous challenge of striking a balance between fast patient access, uncertainty about real-world value, and a reasonable price reflecting the (potential) value. They have to do this in the context of assessment criteria and evidence requirements that are not black-and-white and amid different views from pharmaceutical companies and the decision-makers on value and affordability.

As described in the previous sections, the evidence submitted may contain gaps compared to evidence requirements. This could be due to evidence requirements being different across Europe (section 4.4), being unpredictable within countries (section 4.5), being incompatible with the therapy characteristics, or because pharmaceutical companies underestimate the information need (section 4.6).

Whatever their cause, these evidence gaps are the source of a vicious circle:

**Misalignment on value and price:** pharmaceutical companies and decision-makers have difficulty in achieving a shared perspective on the value of the therapy: does it have a high added value, or does it have a highly uncertain effect? Misalignment on value hampers alignment on price: is the price reflective of an appropriate return for value and risk, or does it pose an unjustified budget risk in the absence of certainty about the real-world effect?

**Long negotiations and decreasing trust:** consequently, long negotiations take place that focus merely on price in the absence of mechanisms to deal with the uncertainty about value. In these price negotiations, the common ground is often simply lost. Pharmaceutical companies and decision-makers find themselves in opposing positions on price, without room for a constructive, comprehensive dialogue focused to find a shared solution.

This lack of trust is adding to the strain on the relationship between healthcare stakeholders and their growing disconnect, caused by:

- Increasing pressure on healthcare budgets, due to aging populations, higher incidence
of chronic diseases and the rapid evolution of therapeutic options, targeting smaller populations (implying higher list prices per patient).

- (Perceived) asymmetry of information due to lack of insights in costs involved in research and development of a therapy.
- Examples of bad decisions by individual companies and instances of negative media exposure and framing.

Subsequently, during new reimbursement trajectories, there is less trust when value and price are being discussed.

### 4.8 Insufficient budget to implement decisions

Once a reimbursement decision has been made, there are still factors that can delay the time to patient access. One of these factors includes ensuring enough budget is available to implement the decision in practice, and/or to fund the medicine for the remainder of the financial year. When an insufficient budget is in place, this delays access or hampers access by putting negative pressure on the prescription and use of the new medication.

In England for example, although the National Health Service (NHS) is required to fund reimbursement recommendations from the National Institute for Health and Care Excellence (NICE) nationally through NHS England and locally through Clinical Commissioning Groups (CCGs), in practice “postcode prescribing” (geographical variation in access) occurs because of local budget constraints (Edwards, Appleby, & Timmins, 2019).

In the Netherlands, the same “postcode prescribing” may occur when prescribers need to refer patients to other care centers because of “selective purchasing” (healthcare insurers reimburse certain medicines only when prescribed in specific hospitals), or because a reimbursement cap set by healthcare insurers is reached (NZa, 2019).

In Poland, new patient enrolment in the Drug Program may be delayed because of budget depletion for the ongoing budget period.

### 4.9 Low frequency of clinical guideline updates

As shown in Figure 12, clinical guidelines do not always include the most recent therapeutic innovations, even for Europe’s five main cancer types (WHO International Agency for Research on Cancer, 2020). The absence of clinical guidelines may cause prescribers to hold back from starting to use new therapies due to a lack of clarity on the positioning of the new therapy in the treatment pathway. Pharmaceutical companies have an important role to play in developing the required body of evidence and creating awareness to inform clinical guidelines.

#### Suboptimal healthcare infrastructure

The health infrastructure faces constraints in many European countries, leading to a suboptimal organization of oncology pathways. For that reason, even after reimbursement, healthcare systems may face difficulties absorbing and using a new therapy in the most optimal way. As basic conditions, patients need to have access to high quality health facilities, diagnostic centres and health personnel. More specifically, the oncology care pathway should facilitate the optimal use of innovative therapies through:

- **Screening:** focus on early detection and the use of the growing evidence on risk factors (e.g. inherited genetic mutations).
- **Diagnosis:** the availability of rapid diagnostic centers and reimbursement of appropriate (genetic/biomarker) testing methods.
- **Referral and treatment:** timely access to centers of excellence specialized in (rare) cancers, access to the latest information on accessibility of innovative oncology therapies, and absence of financial considerations with prescribers and patients when selecting a therapy.
- **Follow-up:** optimal adherence to (chronic and/or extramural) treatment regimens and monitoring of investments and (patient-relevant) outcomes to inform future prescriptions.

#### Year of publication of the most recent clinical guidelines for Europe’s main cancers

*Most recent new active substance approved by EMA (2013 - 2018)
Most recent label extension, in case of no new active substance approved by EMA (2013 - 2018)

Address all ten factors causing cancer patients in Europe to wait longer to get access to new cancer medicines.

5.1 Align dossier submission timelines

Almost all European countries apply external reference pricing, i.e. set maximum prices based on the prices of other countries. In some cases, higher-income countries reference lower-income countries, creating an incentive for companies to launch in high-income countries first (Kanavos, Fontrier, Gill, & Efthymiadou, 2020). As a result, external reference pricing leads to countries with a lower ability to pay waiting much longer for the introduction of new medications.

This is partly mitigated through highly confidential discounts which allow for differential pricing without impacting on list prices that are used for ERP. However, a negative side effect is that a lack of transparency on actual prices increases mistrust with stakeholders who were not involved in the national pricing and reimbursement discussions.

If countries could address external reference pricing and its unintended consequences, the need for later introduction in countries with a lower ability to pay and confidential discounts would be greatly reduced. This would facilitate earlier submission in these countries, whilst increasing transparency and trust in the system at the same time.

To realize this, stakeholders ought to evaluate current strategies and their impact on dossier submission timelines and explore improvements or alternatives. An alternative could e.g. be a European solidarity system, wherein prices are differentiated explicitly, based on a single reference price and objective and previously agreed parameters reflecting the economic situation of a country. This should be accompanied by efforts to reduce differences in healthcare expenditures by countries that currently spend less on healthcare compared to the European average, to avoid erosion of this solidarity system. An aspect to consider is the cross-border trade of oncology medicines that may follow from important price differences between countries. And finally, also HTA capacity within pharmaceutical companies should allow for parallel dossier submission across European countries once the bottleneck of ERP is addressed.

### Delaying factor(s) addressed

• (#1) Late start of application and submission, due to external reference pricing.

---

### 5. The six priority areas for reducing the time to patient access

There are six priority areas to address the ten factors causing delays in patient access. In each of these priority areas, a concerted effort is needed. It is not a matter of individual stakeholders taking responsibility within their respective areas of work. It requires stakeholders to break through comfort zones and to actively look for common ground with other stakeholders.

The six priority areas shown in Table 2 serve as a starting point for a further and constructive dialogues and joint problem-solving. Each of these areas are described in more detail below. After a short description, recommendations for tangible next steps are exemplified using best practices that already exist. Together, these priority areas for action would allow for parallel dossier submission in Europe.

<table>
<thead>
<tr>
<th>Category</th>
<th>#</th>
<th>Priority area</th>
<th>Stakeholders</th>
<th>Next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCESS</td>
<td>1</td>
<td>Align dossier submission timelines</td>
<td>National authorities &amp; Multi-stakeholder collaborations</td>
<td>Evaluate the advantages and disadvantages of current ERP strategies and explore improvements or alternatives.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Shorten reimbursement timelines</td>
<td>Academics and experts</td>
<td>Identify alternative solutions for ERP, e.g. based on explicit differential pricing (solidarity) and smaller differences in healthcare expenditures.</td>
</tr>
<tr>
<td>REIMBURSEMENT CRITERIA</td>
<td>3</td>
<td>Align evidence requirements</td>
<td>Pharmaceutical companies</td>
<td>Build HTA capabilities to allow for more dossier submissions in parallel across European countries once ERP as a bottleneck is addressed.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Be adaptive to rapidly evolving innovation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEALTH SYSTEM READINESS</td>
<td>5</td>
<td>Improve healthcare infrastructures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Strengthen collaboration between all stakeholders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Best practices
The United Kingdom, Denmark and Sweden do not apply external reference pricing to determine and negotiate prices (Panteli, et al., 2016).

Kanavos et al. evaluated the impact of ERP on key health policy objectives in different national contexts. They concluded ERP has not regulated prices efficiently and has unintended consequences that reduce benefits arising from it (Kanavos, Fontrier, Gill, & Efthymiadou, 2020).

Poland decided to increase healthcare spending as % of GDP with 25% by 2024, thereby reducing differences in healthcare expenditures between European countries, an important prerequisite in the case of a differential pricing system based on solidarity (Sowada, Sagan, & Kowalska-Bobko, 2019).

5.2 Shorten reimbursement timelines
In the preparation phase, early dialogues, horizon scanning and early collaboration allow for optimal preparation already prior to European marketing authorization. Pre-alignment in this stage provides a great opportunity for quicker alignment during the subsequent phases (e.g. on requirements, evidence gaps, value and price).

Dossier submission could start earlier than the moment a European marketing authorization is formally granted. It could also start much earlier by avoiding waiting for decisions from other countries. During the process, steps could be taken in parallel instead of sequentially and the layers of decision-making could be reduced to a minimum to reduce time to patient access. This requires enough HTA capacity within HTA bodies.

A key challenge of the medicine reimbursement process is that the traditional provider-consumer transaction is distorted. The patient as the consumer of the final product is represented by collective payer institutions. As a result, the patient perspective is easily replaced by an administrative and financial dialogue. The demand for urgency is not structurally included in the process. Informed patients should be engaged in every step of the decision-making process, as a continuous reminder to all stakeholders that for patients, every day counts. Last but not least, making timelines transparent helps in maintaining a sense of urgency at every step of the process.

There are many opportunities to improve reimbursement timelines and countries can learn a lot from other countries. In Germany for example, an access pathway is used whereby therapies are reimbursed directly after marketing authorization, prior to the HTA, based on list prices set by pharmaceutical companies. Within six months, an HTA is conducted, after which the actual reimbursement price is negotiated. This price replaces the initial price one year after launch. In England, dossiers can be submitted prior to a positive CHMP opinion, to allow for taking as many steps in the process in advance.

In particular by preparing well in advance of EU marketing authorization, delays due to the following factors can be addressed:

• (#4) Different evidence requirements across Europe
• (#5) Lack of clarity of national requirements
• (#6) Evidence gaps
• (#7) Misalignment on value and price

Delaying factor(s) addressed
• (#1) Late start of application and submission, due to national timelines
• (#2) Lack of adherence to maximum timelines
• (#3) Multiple layers of decision-making

In the Netherlands, a pilot is ongoing to evaluate a parallel instead of sequential procedure for authorization and reimbursement (Zorginstituut Nederland, 2019).

In Belgium, Denmark, and the Netherlands, multi-year, multi-indication agreements include light-touch or no assessments for new indications, and the price and impact on budget of new indications are discussed at the beginning of the agreement (Wilson, Voncina, Breen, & Roediger).

In England, NICE proactively invites manufacturers to submit their dossiers before a positive CHMP opinion is in place. Assessment timelines are published on the NICE website (NICE, 2018). All decisions are made at the central level and will also be recognized in Wales. For positive reimbursement decisions the NHS is obliged to ensure budget for local implementation (Edwards, Appleby, & Timmins, 2019). For cancer drugs that are recommended for use within the Cancer Drugs Fund (CDF), the NICE appraisal process starts much earlier with the aim of publishing draft guidance prior to a drug receiving its marketing authorization and then final guidance within 90 days of marketing authorization (NHS England, 2016).

Italy’s fund for innovative oncology drugs enables faster patient access by removing budgetary barriers at the regional level (Flume, et al., 2018).

The European Patients’ Academy (EUPATI) has launched a training course for academia and industry professionals on the principles of good patient engagement and helps participants plan for including the right patients at the right time for the right purpose. In this way, EUPATI supports engagement of informed patients and strengthens a sense of urgency at every step of the access pathway (EUPATI, 2020).

Shorten reimbursement timelines - recommended next steps

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>National authorities</td>
<td>Evaluate the access pathway from a process-optimisation perspective and identify opportunities to shorten timelines.</td>
</tr>
<tr>
<td>Build HTA capabilities</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical companies</td>
<td>Have the dossier ready in time and submit as soon as possible</td>
</tr>
<tr>
<td>Patient organisations</td>
<td>Educate and support authorities regarding the engagement of informed patients at every step of the access pathway.</td>
</tr>
</tbody>
</table>
5.3 Align evidence requirements

Much like the EMA has improved the efficiency for granting market authorizations, European HTA alignment on clinical assessment (after which appraisal takes place at the national level) would improve the timelines to patient access. In addition, European cooperation and alignment would reduce duplication of efforts and allow for more efficient use of scarce human and financial resources (Huic, 2016). The European Network for Health Technology Assessment (EUnetHTA) started in 2009 following a call from the European Commission. It has become the network for HTA collaboration across Europe and joint clinical assessments (JCA)s. It has been put in place until 2021 and currently works on establishing a permanent HTA working structure for Europe, with a focus on the clinical assessment. In follow-up to EUnetHTA, in 2018 the European Commission published a Proposal for a Regulation on Health Technology Assessment, to formalize European collaboration further and introduce Joint Clinical Assessments (European Commission, 2018). The Proposal has since been extensively discussed but divergent positions remain (Vella Bonanno, et al., 2019).

However, given the serious delays caused by differences in evidence requirements in the various European jurisdictions, all stakeholders should contribute to approval of a fit-for-purpose EC Regulation on HTA. At the very least, countries should exchange their views on requirements and assessment methodologies, particularly for new generations of medicines.

**Delaying factor(s) addressed**
- (4) Different evidence requirements across Europe
- (5) Lack of clarity of national requirements (clinical assessment)

**Best practices**
Since 1995, single European marketing authorizations are granted based on an opinion from EMA and a legally binding decision from the European Commission (EMA, 2020). EUnetHTA facilitates HTA collaboration across Europe and joint clinical assessments (EUnetHTA, 2020).

The European Commission Proposal for a Regulation on Health Technology Assessment aims to formalize European collaboration further and introduce JCA-s after the expiry of EUnetHTA’s mandate (European Commission, 2018).

To help generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies, EMA and EUnetHTA offer joint scientific advice on development programmes (Tafuri, et al., 2016).

Since its start, pharmaceutical companies have submitted seven oncology therapies through EUnetHTA (Joint Action 1, 2 and 3), thereby contributing to the strengthening of joint clinical assessments in Europe: pazopanib, sorafenib, ramucirumab, midostaurin, regorafenib, alectinib and the combination of polatuzumab vedotin, bendamustine and rituximab (EUnetHTA, 2020).

5.4 Be adaptive to rapidly evolving innovation
All countries struggle with the same questions: how to define and assess value? How to manage uncertainty about the real-world value of therapies with high prices and/or high budget impact? How to assess cost-effectiveness of tumor-agnostic therapies and combination therapies? And how to manage the budget impact of one-off, curative therapies? These questions need to be answered in advance, to prevent delays when a new generation of therapies is brought forward for reimbursement.

Table 3: Example of reimbursement criteria in France

<table>
<thead>
<tr>
<th>Category</th>
<th>Level of actual benefit</th>
<th>Price level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMR V</td>
<td>No improvement</td>
<td>Lower price/overall cost than comparators.</td>
</tr>
<tr>
<td>ASMR IV</td>
<td>Minor improvement</td>
<td>Parity price (for same population) or higher (for more restricted population).</td>
</tr>
<tr>
<td>ASMR III</td>
<td>Moderate improvement</td>
<td>Faster access (price notification instead of negotiation) and price consistency with rest of Europe.</td>
</tr>
<tr>
<td>ASMR II</td>
<td>Important improvement</td>
<td></td>
</tr>
<tr>
<td>ASMR I</td>
<td>Major improvement</td>
<td></td>
</tr>
</tbody>
</table>

Clear criteria reflecting society's definition of value
Reimbursement criteria need to be clear to allow for predictability, while at the same they should be flexible to enable applicability to a variety of therapies and cases.

The ‘value-informed and affordable’ pricing model provides an example of clear, yet flexible set of reimbursement criteria. It makes explicit which criteria influence decision-making and how. In this case, the theoretical model departs from the concept of ‘value-based’ pricing (as opposed to ‘cost-based’ pricing) and the aspects of disease severity and affordability are added. Cost-effectiveness thresholds are applied based on these dimensions: what does the payer consider good value for money for this disease severity, and given the size of the patient population (budget impact)? By allowing for cost-effectiveness thresholds that differ depending on disease severity and budget impact, the model makes explicit a higher societal willingness to pay in the case of a higher disease burden to patients and/or a small patient population and lower overall budget impact (Annemans, 2019).

The assessment framework used in France provides another example of clear reimbursement criteria. The framework also departs from ‘value-based’ pricing, with value being defined as the actual benefit compared to the standard of care (‘amélioration de service médical rendu, ASMR’).
This is measured based on:
- Severity of the disease and its impact on morbidity and mortality
- Clinical efficacy/effectiveness and safety of the therapy
- Aim of the therapy: preventive, symptomatic or curative
- Therapeutic alternatives
- Impact on public health

Assessment against these criteria allows for determining the level of actual benefit, and thereby the appropriate price level (see Table 3).

A comprehensive system to manage uncertainties

Once reimbursement and assessment criteria are clear, the next challenge is to deal with uncertainty about the real-world value of therapies, due to evidence gaps that are increasingly inherent to today’s oncology therapies.

A comprehensive system of horizon scanning, early collaboration, managed access schemes, and RWD generation should be in place to proactively manage today’s challenges and avoid delays arising from them (see Figure 13).

Although European countries currently have different levels of implementing the four elements above, no comprehensive systems exist yet, in which:

1. Horizon scanning is used to identify and prepare for challenges related to assessment, reimbursement, and use after reimbursement.

2. Early collaboration supersedes today’s early dialogue, symbolizing a move from early scientific advice towards broader discussions between stakeholders prior to EU marketing authorization, with the aim of aligning on challenges and jointly finding solutions (e.g. managed access scheme, novel payment models).

3. Managed access schemes allow for addressing access barriers and finding an optimal balance between uncertainty, price and fast access (e.g. fast track, conditional approval, novel payment models).

4. Real-world data is collected in a harmonized way, to develop evidence of real-world value (and costs) in a structured and comprehensive way to allow for closing of evidence gaps and novel payment models such as outcome-based agreements.

Fig. 13

Comprehensive system to manage uncertainty

Be adaptive to rapidly evolving innovation - recommended next steps
Best practices
In Sweden, a working group specifies the HTA methodology for e.g. CAR-T therapies. Another initiative aims to harmonize and expand patient registries to collect patient outcome data.

In Poland, an ongoing initiative aims to differentiate HTA/Reimbursement criteria for orphan from other innovative drugs, allowing for more flexible ICER and more transparency of decision-making criteria.

Since 2016, NHS England’s Cancer Drugs Fund (CDF) allows for reimbursement of oncology therapies for which clinical uncertainties exist at the time of reimbursement discussions. This allows for evidence gaps to be closed during interim funding from CDF, until permanent reimbursement can be granted (NHS England, 2016).

In the Netherlands, the Drug Rediscovery Protocol (DRUP) provides an alternative data generation and reimbursement pathway for oncology precision drugs targeting small populations. In small cohorts, evidence is gathered to identify activity for off-label therapies. When activity has been demonstrated, outcome-based reimbursement is put in place (Van der Velden, et al., 2019).

The Belgian payer INAMI/RIZIV initiated the “Tool for Reducing Uncertainties in the evidence generation for Specialized Treatments for Rare Diseases” (TRUST-4RD) concept on the potential of RWE to close evidentiary gaps for HTA/payer decisions. Key in this concept is an early dialogue and collaboration to determine together the (real-world) evidence needed before and after reimbursement (TRUST-4RD, 2018).

The International Consortium for Health Outcome Measurement (ICHOM) develops standard sets of outcomes that matter most to patients. These sets cover five main cancer types, thereby providing a basis for harmonized and aligned real-world data collection (ICHOM, 2020).

The Innovative Medicines Initiative supports projects such as the European Health Data and Evidence Network (EHDEN), GetReal and Big Data for Better Outcomes (BD4BO) that support the transition towards more outcomes-focused and sustainable healthcare systems in Europe, making optimal use of real-world data (IMI, 2020).

5.5 Improve healthcare infrastructures
Even after reimbursement, patient access is not a given. Outdated guidelines prevent the adoption of innovations into practice, as do budgets when not aligned with reimbursement decisions.

Pricing and reimbursement decisions should lead to an update of the guidelines. A direct and continuous update of guidelines would be ideal, but an annual update should be considered a minimum. Given the high speed of innovation in oncology, these guidelines are an important tool to inform oncologists of new developments, especially in peripheral settings.

Similarly, pricing and reimbursement decisions should be reflected in (updated) budget provisions to ensure budget for immediate implementation and until the end of the financial year. Much of the information on delays in patient access due to budget scarcity or preliminary budget depletion is anecdotal, suggesting that these potential barriers and their impact on patient access should be monitored more closely.

To improve screening and diagnosis, clear roles and responsibilities need to be assigned. Whilst this sounds obvious, in practice limited accountability limits optimal screening and diagnosis. Furthermore, patients (especially with rare diseases) often do not have access to centres with the required specific expertise. Assigning clear centres of excellence for (rare) cancers and ensuring their accessibility (e.g. using e-health solutions) is key.

Delaying factor(s) addressed
• (#8) Low frequency of clinical guideline updates
• (#9) Insufficient budget to implement decisions
• (#10) Suboptimal healthcare infrastructure

Best practices
In the United States, the National Comprehensive Cancer Network (NCCN) allows companies to submit a request for review of data for a specific indication, either before or after approval from the Food and Drug Administration (FDA).

In England, NICE developed interactive flowcharts comprising the content of both the latest clinical guidelines as well as additional treatment information based on recent technology appraisals.

In Italy, clinical guidelines are updated on an annual basis. Likewise, in Sweden, a Regional Cancer Centre developed guidelines for close to 40 cancer diseases/conditions that are updated on an annual basis.

The International Horizon Scanning Initiative (IHSI) is a collaboration of Belgium, Denmark, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland that started in October 2019. The joint horizon scan should provide insight into which new innovations and products are reaching the market, thereby enabling decision-makers to effectively manage budgetary resources ahead of time (International Horizon Scanning Initiative, 2020).

In the Netherlands, the Dutch Healthcare Authority (NZa) monitors impact of budget on...
delays on access to hospital therapies on an annual basis through hospital surveys (NZa, 2019).

Spain created a dedicated department to coordinate treatment with cell and gene therapies at all stages of treatment, from diagnosis, through rapid confirmation of reimbursement, to ensure delivery of care within 28 days.

In Germany, the concept of the tumor conference was established to facilitate access to the center of expertise at the Charité campus of the University Hospital of Berlin. The interdisciplinary online tumor board meetings bring together cancer specialists and practitioners. Following a systematic approach, patient data, relevant external clinical evidence and therapy preference are presented to the participants. An individual therapy recommendation for each patient is reached by consensus discussion (Schroeder, et al., 2011).

5.6 Strengthen collaboration between all stakeholders
As important as it is obvious: stakeholders must collaborate. In each of these priority areas, a concerted effort is needed.

Early collaboration is a crucial instrument to address today’s challenges. Current early dialogues and scientific advice should evolve into early collaboration to enable a joint quest for solutions to potential access challenges.

In addition, controversial topics that further constrain stakeholder relations need to be addressed proactively. These comprise questions such as: What do we consider ‘true’ innovation or value? What are relevant endpoints to measure ‘true’ innovation? What is a ‘fair’ price? Where could we increase transparency, and thereby trust, in our current operating system?

Delaying factor(s) addressed
• (#1-10) All delaying factors require stakeholder collaboration
• (#7) Misalignment on value and price: this delaying factor in particular needs to be addressed by stronger collaboration and alignment

Best practices
In England, “safe harbour” discussions are used for early engagements between NICE (Early Scientific Advice and Office of Market Access), NHS England and pharmaceutical companies (NICE, 2020).

The World Health Organization (WHO) convenes a series of Fair Pricing Forums to enable stakeholders to discuss options for a fairer pricing system for pharmaceuticals (WHO, 2020).

Strengthen collaboration between all stakeholders - recommended next steps

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-stakeholder collaborations</td>
<td>Define requirements and platforms for high quality early collaborations focused on problem-solving.</td>
</tr>
<tr>
<td></td>
<td>Define the aspects (what), objectives (why), pros and cons (how) of transparency.</td>
</tr>
<tr>
<td></td>
<td>Align on what constitutes ‘real’ innovation or value and a ‘fair’ price.</td>
</tr>
</tbody>
</table>

6. Working together to improve access to innovative oncology therapies

To reduce the immense inequalities in patient access between European countries we need to find a common understanding and a common perspective. This is needed because all stakeholders are part of the current system in which we operate and none of the stakeholders involved can solve today’s challenges single-handedly.

As described in Chapter 5, all stakeholders have a role to play in realizing the objectives of the six solution areas. They cannot do this in isolation, as actions from one stakeholder are needed for actions by other stakeholders to be successful. In each of the six priority areas, a concerted effort is needed to design and further strengthen effective solutions.

The efforts are summarized per stakeholder and per solution area in Table 4. This overview serves as a starting point. It is a call for further dialogue, analysis and joint problem-solving by all relevant stakeholders in order to further explore the six priority areas. We need a collaborative approach now. Because for patients, every day counts.
Table 4  None of the priority areas can be realized by one stakeholder in isolation

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy makers</td>
<td>Together with all relevant stakeholders, evaluate the advantages and disadvantages of current ERP strategies and explore improvements or alternatives.</td>
<td>Evaluate the access pathway from a process-optimisation perspective and identify opportunities to shorten timelines.</td>
<td>Politically support joint clinical assessments and approval of a fit-for-purpose EC Regulation on HTAs.</td>
<td>Collaborate to define clear joint reimbursement criteria.</td>
<td>Appoint an authority for improving screening and diagnosis.</td>
<td>Work with national authorities to evaluate the advantages and disadvantages of current ERP strategies and explore improvements or alternatives.</td>
</tr>
<tr>
<td>Regulators and HTA bodies</td>
<td></td>
<td>Internationally exchange and create consensus on requirements and assessment methodologies.</td>
<td></td>
<td>Develop a comprehensive system of horizon scanning, early collaboration, managed access schemes, and RWD generation to be ready for novel therapies.</td>
<td>Identify centres of excellence and ensure optimal accessibility of expertise.</td>
<td>Harmonise and align the collection of RWD.</td>
</tr>
<tr>
<td>Payers</td>
<td>Involve informed patients to maintain a sense of urgency at every step of the access pathway.</td>
<td>Build HTA capabilities.</td>
<td></td>
<td></td>
<td></td>
<td>Define requirements and platforms for high quality early collaborations focused on problem-solving.</td>
</tr>
<tr>
<td>Pharmaceutical companies</td>
<td>Build HTA capabilities to allow for more dossier submissions in parallel across European countries once ERP as a bottleneck is addressed.</td>
<td>Have the dossier ready in time and submit as soon as national timelines permit.</td>
<td>Submit pharmacotherapeutic dossiers through EUnetHTA or a future European HTA coordination mechanism.</td>
<td>Prepare strong evidence-generation plans for effective early collaborations.</td>
<td>Ensure robust clinical data to enable decisions on inclusion in the guidelines.</td>
<td>Define the aspects (what), objectives (why), pros and cons (how) of transparency.</td>
</tr>
<tr>
<td>Healthcare professionals/Scientific associations</td>
<td>Design trials which fit the joint requirements.</td>
<td></td>
<td>Prepare well-substantiated pricing and financing proposals that address payer concerns.</td>
<td>Take payer concerns into account when developing price proposals.</td>
<td></td>
<td>Align on what constitutes ‘real’ innovation or value and a ‘fair’ price.</td>
</tr>
<tr>
<td>Patient organisations</td>
<td>Educate and support authorities regarding the engagement of informed patients at every step of the access pathway.</td>
<td></td>
<td></td>
<td>Monitor the impact of budget scarcity/depletion on patient access.</td>
<td></td>
<td>Involve patient organisations and representatives in all parts of decision-making and create clarity on what is required when from patient representatives in terms of knowledge, role, and commitment.</td>
</tr>
<tr>
<td>Academics and experts</td>
<td>Identify alternative solutions for ERP.</td>
<td></td>
<td></td>
<td>Support the development of clear reimbursement criteria.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Organisation First name Last name
1. Association Internationale de la Mutualité (AIM) Thomas Kanga-Tona
2. European Commission (EC) - DGSANTE Fabio D’Atri
3. European Regional and Local Health Authorities (EUREGHA) Valentina Polykas
4. National Institute for Health and Disability Insurance (RIZIV INAMI) Francis Arikk
5. National Institute for Health and Disability Insurance (RIZIV INAMI) Vinciane Knappenborg
6. Agence fédérale des médicaments et des produits de santé (AFMPS) Olga Kholmanskikh
7. Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC) Magdalena Władysiuk
8. Centre Fédéral d’Expertise des Soins de Santé (KCE) Frank Hulstaert
9. National Health Care Institute (ZIN), the Netherlands Ly Tran
10. EUnetHTA Anne Willemsen
11. Norwegian Medicines Agency (Statens legemiddelverket) Karen Marie Ulshagen
12. Belgian Society of Medical Oncologists (BSMO) Joelle Collignon
13. European Association of Nuclear Medicine (EANM) Wolfgang Wadsak
14. European CanCer Organization (ECO) Ian Banks
15. European Hematology Association (EHA) Robin Doeswijk
16. European Oncology Nursing Society (EONS) Eleonora Varntoumian
17. European Public Health Alliance (EPHA) Yannis Natsis
18. European Public Health Alliance (EPHA) Fiona Godfrey
19. European Union of Private Hospitals (UEHP) Ilaria Giannico
20. Italian Association of Medical Oncology (AIOM) Roberto Bordonaro
22. Acute Leukemia Advocates Network (ALAN) Zack Pemberton-Whitely
23. Association of European Cancer Leagues (ECL) Ward Rommel
24. Dutch Cancer Society (KWF) Anna Prokupkova
25. Digestive Cancers Europe (DICE) Guy Muller
26. European Cancer Patient Coalition (ECPC) Stefan Gijssels
27. European Cancer Patient Coalition (ECPC) Robert Greene
28. European Hematology Association (EHA) Kathi Apostolidis
29. European Hematology Association (EHA) Tamara Hussong
30. Lymphoma Coalition Europe (LICE) Natacha Bolaños
31. Lymphoma Coalition Europe (LCE), Hodgkin and Non-Hodgkin VZW Frederik Vernimmen
32. Portuguese Leukaemia and Lymphoma Association (APLL) Isabel Leal Barbosa
33. WECAN Susanna Leto di Prilo
34. Youth Cancer Europe (YCE) Šarūnas Narbutas
35. Comité de Transparence (CT) / Mediualité Ladiaia Wolff
36. Ex-member of parliament, Netherlands Arno Rutte
37. Ex-Ministry of Health, Poland Krzysztof Landa

Sounding Board participants

<table>
<thead>
<tr>
<th>#</th>
<th>Organisation</th>
<th>First name</th>
<th>Last name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vintura</td>
<td>Bas Amesz</td>
<td>Partner</td>
</tr>
<tr>
<td>2</td>
<td>Vintura</td>
<td>Christel Jansen</td>
<td>Manager</td>
</tr>
<tr>
<td>3</td>
<td>Vintura</td>
<td>Silvia Rohr</td>
<td>Senior Consultant</td>
</tr>
<tr>
<td>4</td>
<td>Vintura</td>
<td>Lisette van Eijck</td>
<td>Consultant</td>
</tr>
<tr>
<td>5</td>
<td>ASC Academics</td>
<td>Evgeni Dvortsin</td>
<td>CEO</td>
</tr>
<tr>
<td>6</td>
<td>ASC Academics</td>
<td>Sharon Wolters</td>
<td>HEOR Consultant</td>
</tr>
<tr>
<td>7</td>
<td>Hague Corporate Affairs</td>
<td>Sandrine Lauret</td>
<td>Account Director European Affairs</td>
</tr>
<tr>
<td>8</td>
<td>Hague Corporate Affairs</td>
<td>Chantal van Wessel</td>
<td>Graphic Designer</td>
</tr>
<tr>
<td>9</td>
<td>University of Groningen</td>
<td>Prof. Maarten Postma</td>
<td>Academic Advisor</td>
</tr>
<tr>
<td>10</td>
<td>Ghent University</td>
<td>Prof. Lieven Annemans</td>
<td>Academic Advisor</td>
</tr>
</tbody>
</table>

Disclaimer: this publication is the result of a multi-stakeholder collaboration but does not necessarily reflect the views of individual organisations or persons involved through sounding board meetings.

Contributors

Consortium members and academic advisors

<table>
<thead>
<tr>
<th>#</th>
<th>Organisation</th>
<th>Name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vintura</td>
<td>Bas Amesz</td>
<td>Partner</td>
</tr>
<tr>
<td>2</td>
<td>Vintura</td>
<td>Christel Jansen</td>
<td>Manager</td>
</tr>
<tr>
<td>3</td>
<td>Vintura</td>
<td>Silvia Rohr</td>
<td>Senior Consultant</td>
</tr>
<tr>
<td>4</td>
<td>Vintura</td>
<td>Lisette van Eijck</td>
<td>Consultant</td>
</tr>
<tr>
<td>5</td>
<td>ASC Academics</td>
<td>Evgeni Dvortsin</td>
<td>CEO</td>
</tr>
<tr>
<td>6</td>
<td>ASC Academics</td>
<td>Sharon Wolters</td>
<td>HEOR Consultant</td>
</tr>
<tr>
<td>7</td>
<td>Hague Corporate Affairs</td>
<td>Sandrine Lauret</td>
<td>Account Director European Affairs</td>
</tr>
<tr>
<td>8</td>
<td>Hague Corporate Affairs</td>
<td>Chantal van Wessel</td>
<td>Graphic Designer</td>
</tr>
<tr>
<td>9</td>
<td>University of Groningen</td>
<td>Prof. Maarten Postma</td>
<td>Academic Advisor</td>
</tr>
<tr>
<td>10</td>
<td>Ghent University</td>
<td>Prof. Lieven Annemans</td>
<td>Academic Advisor</td>
</tr>
</tbody>
</table>
## EFPIA members

<table>
<thead>
<tr>
<th>#</th>
<th>Organisation</th>
<th>First name</th>
<th>Last name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>European Federation of Pharmaceutical Industries and Associations (EFPIA)</td>
<td>Mihai</td>
<td>Rotaru</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thomas</td>
<td>Alvin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edith</td>
<td>Frénory</td>
</tr>
<tr>
<td>2</td>
<td>Association of the British Pharmaceutical Industry (ABPI)</td>
<td>Andrew</td>
<td>Minuks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paul</td>
<td>Catchpole</td>
</tr>
<tr>
<td>3</td>
<td>Apifarma Portugal</td>
<td>Heitor</td>
<td>Costa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paula</td>
<td>Costa</td>
</tr>
<tr>
<td>4</td>
<td>Farmindustria Italy</td>
<td>Antonella</td>
<td>Moroni</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carlo</td>
<td>Riccini</td>
</tr>
<tr>
<td>5</td>
<td>Inffarma Poland</td>
<td>Ewa</td>
<td>Kiersztyn</td>
</tr>
<tr>
<td>6</td>
<td>Pharmaceutical Industry Association Service Sweden (LIF)</td>
<td>Dineke</td>
<td>Amsing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wim</td>
<td>de Haart</td>
</tr>
<tr>
<td>7</td>
<td>Association for Innovative Medicines Netherlands (VIG)</td>
<td>Minxian</td>
<td>Congé</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Philip</td>
<td>Schwab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marie-Charlotte</td>
<td>Le Goff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tatiana</td>
<td>Arzul</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ines</td>
<td>Bartalim</td>
</tr>
<tr>
<td>8</td>
<td>Abbvie</td>
<td>Marie-Helene</td>
<td>Fandel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tessa</td>
<td>Scharringhausen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marie-Sharmila</td>
<td>Blandino</td>
</tr>
<tr>
<td>9</td>
<td>Amgen</td>
<td>Barbara</td>
<td>McLaughlan</td>
</tr>
<tr>
<td>10</td>
<td>Astellas</td>
<td>Sarah</td>
<td>Mee</td>
</tr>
<tr>
<td>11</td>
<td>AstraZeneca</td>
<td>Paul</td>
<td>Naish</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suzanne</td>
<td>Håkansson</td>
</tr>
<tr>
<td>12</td>
<td>Bayer</td>
<td>Tobias</td>
<td>Helmstorf</td>
</tr>
<tr>
<td>13</td>
<td>Boehringer Ingelheim</td>
<td>Simone</td>
<td>Lenhard</td>
</tr>
<tr>
<td>14</td>
<td>Eli Lilly</td>
<td>Sonia</td>
<td>Ujapan</td>
</tr>
<tr>
<td>15</td>
<td>GSK</td>
<td>Aikaterini</td>
<td>Farmel</td>
</tr>
<tr>
<td>16</td>
<td>Ipsen</td>
<td>Olivier</td>
<td>Ponet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jan</td>
<td>Swiderski</td>
</tr>
<tr>
<td>17</td>
<td>Johnson &amp; Johnson</td>
<td>Aleksandra</td>
<td>Krygel-Nael</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agnieszka</td>
<td>Krukowska</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stefan</td>
<td>Mees</td>
</tr>
<tr>
<td>18</td>
<td>Merck</td>
<td>Hugh</td>
<td>Pullen</td>
</tr>
<tr>
<td>19</td>
<td>MSD</td>
<td>Alexander</td>
<td>Roediger</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Christian</td>
<td>Sellaars</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Matthijs</td>
<td>Van Meerveld</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ilana</td>
<td>White</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raphael</td>
<td>Normand</td>
</tr>
<tr>
<td>20</td>
<td>Novartis</td>
<td>Ivana</td>
<td>Cattaneo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kalitsa</td>
<td>Filoussi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamis</td>
<td>Chahoud</td>
</tr>
<tr>
<td>21</td>
<td>Pfizer</td>
<td>Franjo</td>
<td>Caic</td>
</tr>
<tr>
<td>22</td>
<td>Roche</td>
<td>Rickard</td>
<td>Sandin</td>
</tr>
</tbody>
</table>

## Interview respondents

<table>
<thead>
<tr>
<th>#</th>
<th>Country</th>
<th>Organisation</th>
<th>First name</th>
<th>Last name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EU</td>
<td>One of the EMA Human Medicines Committees</td>
<td>Anonymous</td>
<td>Anonymous</td>
</tr>
<tr>
<td>2</td>
<td>England</td>
<td>Acute Leukemia Advocates Network (ALAN)</td>
<td>Zack</td>
<td>Pemberton-Whiteley</td>
</tr>
<tr>
<td>3</td>
<td>England</td>
<td>NHS Eastern Cheshire Clinical Commissioning (CCE)</td>
<td>Graham</td>
<td>Duce</td>
</tr>
<tr>
<td>4</td>
<td>England</td>
<td>Salus Alba HTA Consultancy</td>
<td>Andrew</td>
<td>Walker</td>
</tr>
<tr>
<td>5</td>
<td>England</td>
<td>Association for Cancer Surgery (BASO)</td>
<td>Zaed</td>
<td>Hamady</td>
</tr>
<tr>
<td>6</td>
<td>England</td>
<td>ABPI</td>
<td>Paul</td>
<td>Catchpole</td>
</tr>
<tr>
<td>7</td>
<td>England</td>
<td>National Institute for Health and Care (NICE)</td>
<td>Zoe</td>
<td>Garrett</td>
</tr>
<tr>
<td>8</td>
<td>Italy</td>
<td>L’Agenzia Italiana del Farmaco (AIFA)</td>
<td>Armando</td>
<td>Genazanni</td>
</tr>
<tr>
<td>9</td>
<td>Italy</td>
<td>Associazione Contro il Melanoma (AICO)</td>
<td>Antonella</td>
<td>Romani</td>
</tr>
<tr>
<td>10</td>
<td>Italy</td>
<td>Italian Association of Medical Oncologists (AIOIM)</td>
<td>Roberto</td>
<td>Bordonaro</td>
</tr>
<tr>
<td>11</td>
<td>Italy</td>
<td>University of Rome and University of Ferrara (UNIF)</td>
<td>Fabrizio</td>
<td>Gianfrate</td>
</tr>
<tr>
<td>12</td>
<td>Italy</td>
<td>Farmindustria</td>
<td>Antonella</td>
<td>Moroni</td>
</tr>
<tr>
<td>13</td>
<td>The Netherlands</td>
<td>National Health Care Institute (ZIN)</td>
<td>Jolanda</td>
<td>De Boer</td>
</tr>
<tr>
<td>14</td>
<td>The Netherlands</td>
<td>National Health Care Institute (ZIN)</td>
<td>Pauline</td>
<td>Pasman</td>
</tr>
<tr>
<td>15</td>
<td>The Netherlands</td>
<td>Medicines Evaluation Board (CBG)</td>
<td>Kevin</td>
<td>Liebrand</td>
</tr>
<tr>
<td>16</td>
<td>The Netherlands</td>
<td>Medicines Evaluation Board (CBG)</td>
<td>Paula B.</td>
<td>van Hannik</td>
</tr>
<tr>
<td>17</td>
<td>The Netherlands</td>
<td>Dutch Society of Medical Oncology (NVMO)</td>
<td>Haiko</td>
<td>Bloemendal</td>
</tr>
<tr>
<td>18</td>
<td>The Netherlands</td>
<td>Royal Dutch Pharmacists Association</td>
<td>Laurens</td>
<td>Rook</td>
</tr>
<tr>
<td>19</td>
<td>The Netherlands</td>
<td>Royal Dutch Pharmacists Association</td>
<td>Aad</td>
<td>Noordermeer</td>
</tr>
<tr>
<td>20</td>
<td>The Netherlands</td>
<td>Netherlands Association of Cancer Patients (NFP)</td>
<td>Pauline</td>
<td>Evers</td>
</tr>
<tr>
<td>21</td>
<td>The Netherlands</td>
<td>Agenda</td>
<td>Caroline</td>
<td>van der Meiijen</td>
</tr>
<tr>
<td>22</td>
<td>The Netherlands</td>
<td>Association for Innovative Medicine (VIG)</td>
<td>Caroline</td>
<td>Wim</td>
</tr>
<tr>
<td>23</td>
<td>Poland</td>
<td>Ailvia - Oncology Foundation</td>
<td>Wojciech</td>
<td>Wisniewski</td>
</tr>
<tr>
<td>24</td>
<td>Poland</td>
<td>Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC)</td>
<td>Magdalena</td>
<td>Wladysik</td>
</tr>
<tr>
<td>25</td>
<td>Poland</td>
<td>Meritum L.A. Ltd</td>
<td>Magdalena</td>
<td>Wladysik</td>
</tr>
<tr>
<td>26</td>
<td>Poland</td>
<td>Warsaw Institute of Mother and Child</td>
<td>Krysztof</td>
<td>Landa</td>
</tr>
<tr>
<td>27</td>
<td>Poland</td>
<td>INFARMA</td>
<td>Marcin</td>
<td>Czech</td>
</tr>
<tr>
<td>28</td>
<td>Portugal</td>
<td>Assembly of the Republic, Portugal</td>
<td>Ricardo</td>
<td>Baptista Leite</td>
</tr>
<tr>
<td>29</td>
<td>Portugal</td>
<td>EUPATI</td>
<td>Natacha</td>
<td>Vaz Liti</td>
</tr>
<tr>
<td>30</td>
<td>Portugal</td>
<td>EVITA - Hereditary Cancer</td>
<td>Tamara</td>
<td>Hussong Milagre</td>
</tr>
<tr>
<td>31</td>
<td>Portugal</td>
<td>Infarmed</td>
<td>Rita</td>
<td>Bastos</td>
</tr>
<tr>
<td>32</td>
<td>Portugal</td>
<td>Infarmed</td>
<td>Claudia</td>
<td>Furtado</td>
</tr>
<tr>
<td>33</td>
<td>Portugal</td>
<td>Portuguese Association of Hospital</td>
<td>Alexandre</td>
<td>Lourencio</td>
</tr>
<tr>
<td>34</td>
<td>Portugal</td>
<td>Administrators (APAH)</td>
<td>Alexandre</td>
<td>Lourencio</td>
</tr>
<tr>
<td>35</td>
<td>Sweden</td>
<td>Dental and Pharmaceutical Benefits</td>
<td>Niklas</td>
<td>Hedberg</td>
</tr>
<tr>
<td>36</td>
<td>Sweden</td>
<td>Agency (TLV)</td>
<td>Niklas</td>
<td>Hedberg</td>
</tr>
<tr>
<td>37</td>
<td>Sweden</td>
<td>New Therapies Council (NT Council)</td>
<td>Gerd</td>
<td>Larfars</td>
</tr>
<tr>
<td>38</td>
<td>Sweden</td>
<td>Swedish Council for Health Technology Assessment (SBU)</td>
<td>Jan</td>
<td>Liliemark</td>
</tr>
<tr>
<td>39</td>
<td>Sweden</td>
<td>LIF</td>
<td>Johan</td>
<td>Brun</td>
</tr>
</tbody>
</table>
Agnostic therapy

See ‘Tumor-agnostic therapy’.

Biomarker

A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body or a patient responds to a treatment for a disease or condition. An example is the prostate-specific antigen (PSA), which is measured to screen for prostate cancer, as high PSA levels could be a sign of prostate cancer. The key issue at hand is determining the relationship between any given measurable biomarker and relevant clinical endpoints.

Budget impact

The impacts of the new therapy on the health budget.

CAR-T

CAR T-cell therapy is a cancer treatment that uses a patient’s own immune system cells (T cells), after these cells have been modified to better recognise and kill the patient’s cancer. The T cells are engineered in the laboratory and then expanded to large numbers and infused back into the patient. CAR stands for chimeric antigen receptor, which represents the genetically engineered portion of the T cell. Once in the body, the CAR T cells can further grow to large numbers, persist for long periods of time, and provide ongoing tumour control and possible protection against recurrence.

Clinical endpoint

An endpoint is the primary outcome that is being measured by a clinical trial. Overall survival (OS) is often considered the most common and most meaningful clinical endpoint in cancer.

Clinical efficacy

Clinical efficacy describes how a medication performs in an idealized or controlled setting: a clinical trial.

Clinical effectiveness

Clinical effectiveness describes how a medication performs in a real-world setting where patient populations and other variables cannot be controlled.

Clinical guideline

Recommendations on how to diagnose and treat a medical condition, often written by and for doctors but also used by other health care professionals. Guidelines summarize the current medical knowledge, weigh the benefits and harms of diagnostic procedures and treatments, and give specific recommendations based on this information, supported by scientific evidence. Because of the evolving medical knowledge and scientific evidence, clinical practice guidelines must be updated regularly. Guidelines aren’t legally binding, but deviations from guidelines must be justified.

Clinical trial

Clinical trials are studies to test new treatments and evaluate their effects on human health outcomes. They need to be approved before they can start, and people (called subjects) volunteer to take part. There are 4 phases of biomedical clinical trials:

- Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects.
- Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects.
- Phase III studies are conducted on larger populations and in different regions and countries, often the last step right before a new treatment is approved.
- Phase IV studies take place when, after approval, there is a need for further testing in a wide population over a longer timeframe. The Randomised Controlled Trial (RCT) is considered the most powerful form of a clinical trial (see: ‘Randomised Controlled Trial’).

Clock stop

A period of time during which the evaluation of a medicine is officially stopped, while the manufacturer prepares responses to questions from the agency. The counting of the number of days resumes when the applicant has sent its responses.

Companion diagnostics

A companion diagnostic is a diagnostic test, used in combination with a therapeutic drug, to prospectively help predict likely response or severe toxicity or to monitor patients’ responses for the purpose of adjusting treatment. Companion diagnostics assist in making optimal treatment decisions.

Cost-based pricing

An approach for determining prices for pharmaceutical products, based on costs incurred for research and development. In
doing so, costs incurred for research and development are rewarded rather than the added value for patients (see: ‘value-based pricing’). The starting point for price negotiations should be an agreement among all parties about how much it costs to develop a new medicine. Another challenge is that the approach may lead to the wrong incentives: the higher the R&D costs (e.g. based on medicines that failed to make it to patients), the higher the price that theoretically could be justified.

Cost-effectiveness
Cost-Effectiveness Analysis (CEA) quantifies the gains, or regressions, in population health as a result of an innovative therapy against the cost of this therapy. The gains are typically measured in quality-adjusted life years (QALYs). Subsequently, the net costs of the therapy per QALY are quantified. It provides a method for prioritizing the allocation of resources to therapies, by identifying therapies that have the potential to yield the greatest improvement in health for the least resources.

Cross-over
In oncology randomised controlled trials (RCTs) offering patients the opportunity to cross over to treatment from the other arm at disease progression is a routine practice to address ethical issues. In this situation, it is common to justify that the intervention has a PFS benefit but not an overall survival (OS) benefit due to the crossover. However, some argue that “real” innovations could impact in OS despite crossover, and that minor gain in PFS should not be considered relevant.

Dossier
A reimbursement or value dossier presents a summary of the clinical, economic, and societal value and supporting evidence (studies) for a new therapy, as well as background information on that disease (i.e., burden of illness, epidemiology, etc.) in line with the agency requirements.

Drug Rediscovery Protocol (DRUP)
In 2016, the Drug Rediscovery Protocol was launched in the Netherlands. This is an innovative pan-cancer clinical trial that seeks to expand the use of EMA and/or FDA-approved targeted therapies beyond their approved indications. In the DRUP, patients with metastasized cancer, with a specific tumour and mutational profile, and without any further treatment options, are given a medicine that was registered for another cancer type. The aim is to identify and provide access to potentially effective therapies. Patients are enrolled in parallel groups (cohorts) defined by study drug, tumour type and tumour profile. A cohort starts with eight patients and is doubled in size when efficacy targets are met. If the larger cohort also meets efficacy targets, the study continues. Manufacturers finance the first studies in eight and sixteen patients. When the study continues, the therapy is reimbursed for patients benefiting from it.

Early Access Schemes
In many European countries, patients can gain access to oncology medicines through early access schemes before the medicine/indication is covered or sometimes before it is approved. Such schemes may be limited to medicines treating severe diseases, for which no effective treatments are available. Oncology products often meet these criteria, making them eligible for early access mechanisms. The programs are called “early access scheme”, “compassionate use program”, “temporary authorisations for use”, or “named patient programs”. The various programs can be differentiated based on their breadth (available to a large cohort of patients vs. for individual patients only) and source of funding (donation from pharmaceutical companies vs. financed by the authorities). These programs are no substitute for general coverage, since prior authorisation is required for individual patients thereby limiting the breadth of access and making access significantly more complex for prescribers and patients (e.g. in named patient programs) and/or because the financing is based on donation from pharmaceutical companies.

Early collaboration
An updated form of today’s early dialogue, symbolizing a move from scientific advice on clinical development plans towards broader discussions between stakeholders prior to EU marketing authorisation, with the aim of aligning on challenges and jointly finding solutions (e.g. managed access scheme, novel payment models). Ideally, early dialogues are used to (i) arrive at an equal level of understanding of the therapy, (ii) jointly identify potential access barriers and solutions, and (iii) identify implications for the assessment and set-up of the clinical trial and phase IV evidence generation plans.

Early dialogue (or Scientific Advice)
Early dialogues (or scientific advice procedures) are a fee-based service offered by regulators and HTA agencies to manufacturers. During early dialogues, a non-binding scientific advice is provided before the start of a pivotal clinical trial, in order to improve the quality and appropriateness of the data produced by the manufacturer in view of future HTA assessment.

Evidence gap
Gaps between the evidence presented in a reimbursement dossier and the evidence requirements from an HTA agency. Evidence gaps may lead to a negative reimbursement decision, a delayed decision due to additional data collection, or a positive decision on the condition that a Phase IV study takes place for further evidence generation and to close the evidence gap.

Evidence requirements
Evidence requested by HTA agencies in order to inform a (positive) reimbursement decision.

External Reference Pricing
The use of medicine price(s) in one or more other countries to serve as a benchmark or reference price for setting or negotiating the price of the product in a given country. List prices are used rather than the net transaction prices. The number of countries considered in the basket varies across countries (ranging from 3 to 30 countries), as does the frequency of price revisions. External Reference Pricing is used in Europe, but European countries are also referenced by non-European countries.

This regional authorisation takes away the requirement to seek marketing authorisation for new medicines from each Member State separately.
Also referred to as International Reference Pricing.

Health Technology Assessment
A multidisciplinary process that assesses and appraises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. It informs the final reimbursement decision.

Horizon scanning
The process of identifying new medicines or new uses of existing medicines that are expected to receive marketing authorisation in the near future and gathering preliminary information about their clinical properties, costs, expected benefits, and broader health system impact. Horizon scanning is often used to systematically assess the potential impact of new technologies, to identify which technologies will be subject to a national HTA process and to strategically plan for HTA and health system resources and capabilities.

Incremental Cost-Effectiveness Ratio (ICER)
The incremental cost-effectiveness ratio (ICER) is a statistic used in cost-effectiveness analysis to summarise the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. Costs are usually described in monetary units, while effects can be measured in terms of health status or another outcome of interest. A common application of the ICER is in cost-utility analysis, in which case the ICER is synonymous with the cost per quality-adjusted life year (QALY) gained.

Indication
Specific setting in which a medicine is used. One medicine can receive multiple EMA authorisations for different tumour locations, types or stages (indications).

Joint Advice (or Parallel Advice)
Scientific advice from a range of agencies at the same time.

Life-Years Gained (LYG)
Life Years gained (LYG) is a mortality measure where remaining life expectancy is considered. This method accrues more weight to a younger patient. It expresses the additional number of years of life that a person lives as a result of receiving a treatment. It is used in economic evaluation to assess the value of medical interventions.

List price
The formal price a drug manufacturer initially sets and that is publicly available. The list price of a drug greatly differs from the net price, which incorporates discounts and rebates. These discounts and rebates can be mandated by governments during reimbursement discussions, negotiated with insurers and hospitals, and/or voluntarily offered to patients. The discounts and rebates are confidential, to avoid any negative impact on prices in other countries based on external reference pricing, which is most often based on publicly available list prices.

Managed access schemes
Alternative, prospectively planned, iterative approaches to medicines development and data generation for a specific set of medicines to which the criteria for a managed access scheme apply. The aim is to achieve an optimal balance between timely access for patients who are likely to benefit most from the medicine and the need to provide adequate evolving information on the benefits and risks of the medicine itself. It often refers to the generation of evidence after marketing authorisation for therapies for which clinical uncertainties exist at the time of reimbursement discussions, e.g. with the use of patient registries or performance-based agreements. So far, most of the agreements are financial in nature and aim to mitigate risks on budget impact (e.g. volume-price agreements) (OECD, 2020).

Medical need (unmet medical need)
Chronically or seriously debilitating diseases or diseases considered to be life threatening and that cannot be treated satisfactorily by an existing (approved and reimbursed) pharmaceutical product are considered and area of high (unmet) medical need.

Morbidity
Morbidity refers to the degree of adverse health. It is not directly related to mortality but may over time increase the risk of death.

Mortality
Mortality refers to the risk of death.

Net price
The price that is received by a drug manufacturer, after deduction of discounts and rebates. These confidential discounts and rebates can be mandated by governments during reimbursement discussions, negotiated with insurers and hospitals, and/or voluntarily offered to patients. The discounts and rebates are confidential, to avoid any negative impact on prices in other countries based on external reference pricing.

Network Meta-Analysis (NMA)
A network meta-analysis (NMA) combines numerical data from multiple separate studies, to compare three or more treatments. It uses direct comparisons within randomized controlled trials (RCTs) and indirect comparisons across trials based on a common comparator.

Orphan designation
A status assigned by the EMA to a medicine intended for use for a rare condition, typically based on prevalence criteria as per the EU Orphan Regulation No 141/2000. This regulation was introduced to incentivize research for rare diseases, through e.g. protocol assistance, fee waivers and 10 years market exclusivity.

Overall survival (OS)
The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed are still alive. In a clinical trial, measuring the overall survival (OS) is one way to see how well a new treatment works. It is often considered the most common and most meaningful clinical endpoint in cancer.

Parallel Advice
See “Joint Advice”.

Post-hoc subgroup analysis
The analysis of subgroups in clinical trials is essential to assess differences in treatment effects for distinct patient groups. It is done to demonstrate consistent results over e.g. male and female, young and elderly patients; i) to identify patient subsets with a particular treatment effect, either positive or negative; or iii) to identify patient subsets with a significant treatment effect when this treatment effect is not present in the overall patient population. Especially with targeted therapies, manufacturers do not always know upfront which subgroup responds best to the treatment. However, these subgroup analyses specified after trial completion are met with concerns, as the number of patients may be too small to arrive at generalisable conclusions (limited statistical power), or because it may be chosen to best fit a
hypothesis whilst in fact being a result of statistical play of chance.

Progression Free Survival (PFS)
The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring Progression Free Survival (PFS) is one way to see how well a new treatment works.

Quality-Adjusted Life Year (QALY)
The quality-adjusted life year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions. One QALY equates to one year in perfect health. QALY scores range from 1 (perfect health) to 0 (dead).

Randomised Controlled Trial (RCT)
A study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. The control may be the standard of care, a placebo ("sugar pill"), or no intervention at all. RCTs seek to measure and compare the outcomes after the participants receive the interventions.

Relative clinical effectiveness
The extent to which an intervention does more good than harm compared with one or more alternative interventions under the usual circumstances of healthcare practice.

Real-World Data (RWD)
Data obtained outside the context of randomized controlled trials (RCTs) and generated during routine clinical practice.

Real-World Evidence (RWE)
Evidence obtained from real world data (RWD).

Reimbursement
European countries need to make evidence-based decisions on public healthcare expenditures. To inform reimbursement decisions for innovative oncology therapies, typical questions that need to be answered by national HTA bodies are:

i) Medical need: Does this therapy address a health need?
ii) Relative clinical effectiveness: Is it more effective than current therapies?
iii) Cost-effectiveness: Is the price a good reflection of the added value?
iv) Budget impact: Could we afford the overall costs of this therapy?
This is done separately by each country. How countries make these decisions varies, leading to significant disparities in patient access throughout Europe.

Reimbursement criteria
Health Technology Assessment (HTA) should be an unbiased and transparent exercise. Therefore, predefined decision-making criteria are formulated to allow for rational, consistent and transparent reimbursement decisions based on e.g. (unmet) medical need, relative clinical effectiveness, cost-effectiveness, budget impact, societal value and ethical considerations.

Scientific Advice
See: “Early Dialogue”.

Standard of care
A treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance according to the latest standards. It is the level at which the average, prudent provider in a given community would practice. Or how similarly qualified practitioners would have managed the patient’s care under the same or similar circumstances.

Statistical significance
Statistical significance is the likelihood that a relationship between two or more variables (e.g. the effect of a therapy) is not likely to occur randomly or by chance but is instead likely to be attributable to a specific cause.

Surrogate endpoint
A surrogate endpoint is a substitute for a clinical endpoint used in trials where the use of a clinical endpoint might not be possible or practical. Surrogate endpoints do not represent direct clinical endpoints such as overall survival (OS), but instead predict them. For example, tumor shrinkage could be used as a surrogate endpoint for OS. Some surrogates are said to be “established” or “validated,” meaning they have been proven to predict clinical benefit. Other surrogates have not been validated but are “reasonably likely” to predict clinical benefit.

Time to Patient Access
Time to Patient Access refers to the time needed for patients to have access to the right therapies. For the purpose of this report, it is measured by:

• Time to Market Access: the number of days elapsing from the date of EU marketing authorisation to the day of completion of administrative processes related to a positive reimbursement decision.
• Patient Access: the actual use in the first twelve months after the first patient is treated under a reimbursement scheme. Reimbursement refers to a formal reimbursement scheme, thereby excluding early access schemes as these schemes often provide reimbursement on a case-by-case or restricted basis without completion of the formal HTA procedure.

Tumor-agnostic therapy
A cancer treatment based on the cancer’s genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker, regardless of the tissue or location in which the tumor is located.

Transparency Directive
The EU ‘Transparency Directive’ (Directive 89/105/EEC) aims to ensure the transparency of measures regulating the pricing and reimbursement of medicinal products. It describes the obligation of Member States to adhere to a strict national timeline of max. 180 days between the moment a dossier is submitted and the final decision on pricing and reimbursement. The 180 days exclude time that passes between EU marketing authorisation and dossier submission, as well as time needed by companies to provide additional information (‘clock stops’).
Abbreviations

AIFA | Italian Medicines Agency (Italy)
AML | Acute Myeloid Leukaemia
AOTMiT | Agency for Health Technology Assessment and Tariffs (Poland)
ASM | Advanced Systemic Mastocytosis
ASMR | Actual Benefit (L’Amélioration de Service Médical Rendu)
ATU | Temporary Authorisations for Use (Autorisation Temporaire d’Utilisation)
CBG | Medicines Evaluation Board (Netherlands)
CDF | Cancer Drugs Fund
CEA | Cost-Effectiveness Analysis
CHMP | Committee for Medicinal Products for Human Use
CTS | Technical Scientific Committee (Italy)
CUP | Compassionate Use Program
DRUP | Drug Rediscovery Protocol (Netherlands)
EAS | Early Access Scheme
EC | European Commission
EFPIA | European Federation of Pharmaceutical Industries and Associations
EFS | Event-Free Survival
EMA | European Medicines Agency
EOP | EFPIA Oncology Platform
EQ-5D | EuroQol Five Dimensions Health Questionnaire
ERP | External Reference Pricing
EU | European Union
EUnetHTA | European Network for Health Technology Assessment
EUPATI | European Patients’ Academy
FDA | Food and Drug Administration (United States of America)
G-BA | Federal Joint Committee (Germany)
GDP | Gross Domestic Product
HTA | Health Technology Assessment
ICER | Incremental Cost-Effectiveness Ratio
ICHOM | International Consortium for Health Outcome Measurement
INAMI/RIZIV | National Institute for Health and Disability Insurance (Belgium)
JCA | Joint Clinical Assessment
LMG | Life-Months Gained
LYG | Life-Years Gained
NCCN | National Comprehensive Cancer Network (United States of America)
NHS | National Health Service (United Kingdom)
NICE | National Institute for Health and Care Excellence (England)
NMA | Network meta-analysis
NPP | Named Patient Program
NT | New Therapies (Sweden)
NZa | Dutch Healthcare Authority (Netherlands)
OECD | Organization for Economic Co-operation and Development
OS | Overall Survival
pCR | Pathological Complete Response
PFS | Progression Free Survival
PRIME | PRIority MEDicines scheme under EMA
PSA | Prostate-Specific Antigen
QALM | Quality-Adjusted Life Months
QALY | Quality-Adjusted Life Years
QoL | Quality of life
RCT | Randomised Controlled Trial
RWD | Real-world data
RWE | Real-world evidence
SEED | Shaping European Early Dialogue
TLV | Dental and Pharmaceutical benefits board (Sweden)
ZIN | National Health Care Institute (Netherlands)
Country codes

AT Austria
BE Belgium
BG Bulgaria
CH Switzerland
CY Cyprus
CZ Czech Republic
DE Germany
DK Denmark
EE Estonia
ES Spain
FI Finland
FR France
GE Georgia
GR Greece
HR Croatia
HU Hungary
IE Ireland
IS Iceland
IT Italy
LT Lithuania
LU Luxembourg
LV Latvia
MT Malta
NL Netherlands
NO Norway
PL Poland
PT Portugal
RO Romania
SE Sweden
SI Slovenia
SK Slovakia
UK United Kingdom
UK-ENG England
UK-SCT Scotland

References


Four analyses were carried out to inform the findings presented in this report. The methodologies are described in the following annexes:

**A. Country case studies on delaying factors and potential solutions**  
Authors: Silvia Rohr (Vintura), Christel Jansen (Vintura)

**B. Patient Access Indicator**  
Authors: Christel Jansen (Vintura), Bas Arnesz (Vintura)

**C. Mapping of differences in evidence requirements in various European jurisdictions**  
Authors: Sharon Wolters (ASC Academics), Christel Jansen (Vintura), Prof. Maarten Postma (University of Groningen)

**D. Impact analysis of improved time to market access**  
Authors: Sharon Wolters (ASC Academics), Evgeni Dvortsin (ASC Academics), Christel Jansen (Vintura), Bas Arnesz (Vintura), Prof. Maarten Postma (University of Groningen)
THE unprecedented speed of innovation in oncology provides an important opportunity for further improvement of outcomes for cancer patients. Yet, no value is derived from innovation if patients for whom a new therapy is intended cannot have access to it. In fact, tremendous differences exist in patient access to innovative oncology treatments with in Europe.

This report brings stakeholders across Europe together around opportunities to improve time to patient access for innovative, value-adding oncology therapies. It focusses on reducing European inequalities in terms of delays in ensuring reimbursement and delays in ensuring actual access once reimbursement is in place.

The report is the result of a collaborative approach by health technology assessment (HTA) bodies, healthcare professional associations, patient organisations, policy makers, former politicians, payers and pharmaceutical companies. Its purpose is to provide a comprehensive and unbiased overview of challenges and solutions, thereby moving away from polarised debates which often occur nowadays.

It describes the ten factors delaying time to patient access and six priority areas to address these delays. In each of these priority areas, a concerted effort is needed. It is not a matter of individual stakeholders taking responsibility within their respective areas of work. It requires stakeholders to break through comfort zones and to actively look for common ground with other stakeholders.

To reduce the important inequalities in patient access between European countries we need to find this common ground and a common perspective. Because all stakeholders are part of the current system and none of the stakeholders involved can solve today’s challenges single-handedly. We need a collaborative approach now. Because for patients, every day counts.

The publication is endorsed by the following organisations:

- Association of Medical Oncologists (AIOM), Italy
- Association of Oncology Nurses (AEOP), Portugal
- Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC)
- Digestive Cancers Europe (DICE)
- European Association of Nuclear Medicine (EANM)
- European Cancer Patient Coalition (ECPC)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- European Patients’ Academy (EUPATI), Portugal
- European Union of Private Hospitals (EUHP)
- EVITA - Hereditary Cancer, Portugal
- Hodgkin and Non-Hodgkin VZW, Belgium
- Lymphoma Coalition Europe (LCE)
- Youth Cancer Europe (YCE)