Comparator Report on Cancer in Europe 2025 - Disease Burden, Costs and Access to Medicines and Molecular Diagnostics

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Foreword - 20 years of Comparator Reports

We published the first Comparator Report in 2005 against the backdrop of the approval of the very first targeted cancer medicines such as rituximab, trastuzumab, and imatinib at the turn of the millennium. Combining our expertise in health economics and medical oncology, the report examined the disease and economic burden of cancer, advances in medicines and diagnostics, and policies shaping cancer research and management. It was the first pan-European comparison – of old and new EU member states – of access to new cancer medicines and revealed great disparities across countries. It concluded that new treatment options improve outcomes but pose challenges for healthcare systems in optimizing their use for patient benefit.

The first Comparator Report covered the preceding decade, while this edition allows us to review three decades of progress in cancer research and management. It also gives us an opportunity to reflect on whether the necessary data is available to inform policy decisions for better outcomes.

Cancer's growing impact on health and healthcare in Europe is evident. Between 1995 and 2022, new cancer cases increased by 58%, reaching 3.2 million. This is the number of people that the healthcare system has to take care of and provide the best possible care for to improve outcomes. In 2022, almost two thirds of cases were in those aged 65 and older, with most of the increase occurring in this age group. Among those under 65, cancer was the leading cause of death, surpassing cardiovascular diseases. However, cancer mortality in this group has significantly declined over the last three decades, reducing the number of productive years lost by a third. This led to a decline in indirect costs. While further reductions are expected, they will be smaller relative to the rising direct costs. In 1995, indirect costs were 50% higher than direct costs; by 2023, they were 50% lower.

Perhaps surprisingly, cancer's share of total healthcare expenditure has remained relatively stable at around 6-7% over the last decades, despite overtaking cardiovascular diseases in disease burden in many European countries. However, the composition of the direct costs has changed. Cancer medicines have accounted for a growing share, though the exact figures remain uncertain due to confidential prices. Sales of cancer medicines at list prices have increased from under 10% to over 40% during the period 1995-2023. However, rebates on list prices have increased over time, which reduces the costs for the healthcare systems. These rising medicine costs have been offset by fewer hospital admissions and shorter stays. In Sweden, between 1998 and 2023, hospital admissions for cancer fell by a third, inpatient days halved, but outpatient visits to specialist care doubled. Since hospital stays cost four times more than outpatient visits, the net effect has been a reduction in this part of the direct costs for cancer by about one third.

The shift in the composition of the direct costs of cancer raises two key policy questions: Can cancer's share of healthcare spending remain stable, or will cuts elsewhere be needed to accommodate rising cancer costs? And how can spending on new cancer medicines, diagnostics, and follow-up be optimized for cost-effectiveness? Since 1995, the EMA has approved 194 new cancer medicines, with approvals increasing from one per year in 1995–2000 to 14 per year in 2021–2024, alongside 318 new indications for existing medicines. Wealthier Western European countries reimburse more medicines and do so more quickly than countries in Central and Eastern Europe, where financial constraints limit access. The main drivers of these disparities are income per capita and healthcare spending per capita. If medicine prices remain uniform,

reducing inequalities across countries will require faster economic growth in lower-income countries and better prioritization of cost-effective treatments.

To be able to make informed choices, patients, oncologists, and policymakers need reliable data on potential outcomes of different interventions. Yet an increasing number of new cancer medicines lack clinical trials with relevant comparators, endpoints, and outcomes. We also see fewer trials being conducted within European healthcare systems, leaving reimbursement agencies with uncertainty about relative effectiveness and cost-effectiveness in their healthcare settings. This data gap could lead to inefficiencies, as better clinical effectiveness data could reduce costs, improve outcomes for patients, and guide future research.

Beyond clinical trial data, we lack information on how cancer medicines are used in clinical practice and to what extent eligible patients have access. This report and all previous Comparator Reports use aggregate sales data – in value and volume – to approximate patient access but lack information on which indications the medicines are used for. Despite investments in clinical cancer registries and healthcare statistics, there is still insufficient data to evaluate resource allocation, outcomes, and efficiency of spending across countries. Healthcare systems, responsible for both patient care and cost-effective spending, must ensure this information is available and used for cancer care as well. This report shows that healthcare systems invested around €146 billion in cancer care in 2023. Only a fraction of this amount would probably be enough to create more relevant data. A stronger evidence base for cancer medicines built on treatment optimization studies is crucial, requiring increased public funding alongside stricter EMA requirements for companies to provide relevant data for pricing and reimbursement decisions. The Europe's Beating Cancer Plan with its €4 billion of funding for the years 2021–2027 would have been opportunity to trigger action in this area, but it has not yet delivered in this regard.

The introduction of new cancer medicines has significantly improved patient outcomes, but isolating their precise contribution is difficult. Advances in surgery, radiation therapy, palliative care, and overall healthcare improvements have also played a role. While progress will continue, today's advances pose new challenges. Pharmaceutical industry investments in cancer research have outpaced public funding, leaving a gap in publicly available data on research expenditures and priorities. Without transparency on the magnitude and direction of both public and private spending on cancer research, there is little possibility for a meaningful dialogue between the different actors, leading to inefficiencies in research output and fewer breakthrough treatments being introduced.

The rapid growth in new cancer medicines underscores the need for research into their optimal use for the best patient outcomes. When we wrote the first Comparator Report, we recognized the importance of molecular diagnostics for targeted therapies and the necessity of outcome studies and economic evaluations. While the number of targeted medicines being introduced has far exceeded our expectations, evidence on their best use remains insufficient. In 1977, political scientist Aaron Wildavsky wrote an article on health policy titled "Doing Better and Feeling Worse." His argument applies here: we are spending more on cancer care and improving outcomes, yet we know what is needed to do even better – but are we willing to do it?

Stockholm, March 2025
Bengt Jönsson & Nils Wilking

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The Comparator Report series was created by Prof. Bengt Jönsson (Stockholm School of Economics) and Prof. Nils Wilking (Karolinska Institutet) in 2005. The following reports have been published previously:

- 2005: A pan-European comparison regarding patient access to cancer drugs
- 2007: A global comparison regarding patient access to cancer drugs
- 2009: Comparator Report on Patient Access to Cancer Drugs in Europe
- 2016: Comparator Report on Patient Access to Cancer Medicines in Europe Revisited
- 2019: Comparator Report on Cancer in Europe 2019 – Disease Burden, Costs and Access to Medicines

Summary

Cancer is set to become the leading cause of death in Europe, although recent data indicate a stabilization in mortality trends.

Cancer is the second leading cause of death in Europe[1], accounting for 23% of all deaths. However, it is already the leading cause of death in several Northwestern European countries and was previously projected to be the top cause of death in the EU by 2035. Among those under 65, cancer is the leading cause of death, responsible for 32% of all deaths in 2022. This emphasizes the urgent need for continued efforts in prevention, early detection, diagnosis, and treatment. Encouragingly, 12 countries experienced a decline in cancer deaths per 100,000 inhabitants between 1995 and 2022, signaling a turning point in the fight against cancer. Overall, cancer deaths in Europe have stabilized at around 1.3-1.4 million annually since 2008.

The number of newly diagnosed cancer cases has increased by nearly 60% since 1995.

Cancer incidence in Europe rose from 2.1 million new cases in 1995 to 3.2 million in 2022, largely driven by population aging. Projections indicate the annual number could reach 4.1 million by 2050 if no further improvements in prevention occur. While demographic factors contribute to this predicted rise, changes in exposure to risk factors - smoking, obesity, alcohol consumption, unhealthy diet, UV radiation from the sun, HPV infection, etc. – will also play a role. Around 30-50% of new cancer cases are linked to these risk factors and are therefore theoretically avoidable. Almost every second man and more than every third woman in the EU are expected to be diagnosed with cancer at some point during their lives before turning 85.

Cancer survival has improved across Europe, yet there are disparities between countries and differences between cancer types.

Despite rising cancer incidence, cancer mortality has not increased at the same pace in Europe. This is because advances in cancer care have improved the survival rates of most cancer types since the 1990s. Part of these improvements were achieved through the introduction of new, more effective cancer medicines, although their exact contribution is difficult to ascertain and also differs by cancer type. The greatest survival improvements were observed for hematologic cancers, which also have seen a great number of new medicine launches. However, some solid tumor types (bladder, brain, gynecological, laryngeal cancer) recorded little or no improvement. Several cancer types have now a five-year survival rate exceeding 90% in the best-performing countries, including breast, prostate, testicular, and thyroid cancer, melanoma skin cancer, and Hodgkin lymphoma. Almost 200,000 cancer deaths could be avoided every year if all 15 countries with available survival data matched the survival rates of Sweden, the best-performing country in Europe.

Health spending on cancer care has increased considerably and varies nearly three-fold across countries.

Between 1995 and 2023, health spending on cancer care (direct costs) more than doubled from €62 billion to €146 billion in Europe (in 2023 prices and exchange rates). This increase has generally paralleled overall health expenditure growth, with cancer accounting for 4–8% of total health expenditure in all countries. Cancer is a disease where the health spending share (7%)

[1] Europe is in this report defined as the EU-27 countries, Iceland, Norway, Switzerland, and the UK.

remains below the share of the disease burden that it causes (23% of deaths, 17% of DALYs) in Europe. Estimated per-capita health spending on cancer varied widely across countries in 2023, ranging from below €150 in Bulgaria, Croatia, Hungary, Latvia, and Romania to over €400 in Germany and Switzerland (PPP-adjusted). Nevertheless, some degree of convergence in spending levels was observed between 1995 and 2023.

Higher cancer care spending is associated with higher survival rates, but efficient spending matters.

Countries with higher per-capita spending on cancer care tend to achieve higher survival rates, highlighting the importance of adequate investment in cancer. However, the relationship is non-linear – while increased spending improves survival, the benefits per additional euro spent seem to diminish beyond a certain level. Significant inefficiencies exist, as some countries achieve similar survival rates despite vastly different spending levels. For example, Sweden and Switzerland have comparable survival rates, yet Switzerland's per-capita spending is more than double that of Sweden.

The total economic burden of cancer has grown, while the burden per patient has not increased.

While direct costs of cancer have risen, better patient outcomes have reduced indirect costs, particularly from lost productivity due to premature mortality. Between 1995 and 2023, indirect costs in Europe declined from €97 billion to €82 billion (in 2023 prices and exchange rates). However, the sum of direct and indirect costs still increased by 43% from €159 billion to €228 billion in 1995-2023. When these costs are contrasted with the underlying growth in the number of cancer patients, a different picture emerges. The economic burden per new cancer patient was rather constant at around €70,000-78,000 between 1995 and 2023.

Research in cancer biology has spurred the development of new medicine classes over the past decades, with new breakthroughs on the horizon.

Cancer treatment has shifted dramatically with the introduction of targeted therapies at the turn of the millennium and the Nobel Prize-winning immunotherapies in the 2010s. While targeted therapies focus on molecular targets crucial for cancer cell survival, immunotherapies enhance the immune system's ability to combat cancer. Antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), and CAR T-cell therapies have recently expanded the therapeutic arsenal. The development of new medicines and medicine classes in oncology continues to accelerate. Oncology trials represented 29% of the initiated trials across all therapeutic areas in 2023 globally (up from 27% in 2018). New types of cell-based therapies might soon achieve a breakthrough together with novel medicine classes such as therapeutic cancer vaccines (based on mRNA technology), proteolysis-targeting chimeras (PROTACs), gene editing/therapy, oncolytic virotherapy, and RNA interference.

Molecular diagnostics has become indispensable in modern oncology to realize the potential of precision medicine, yet its availability varies.

In the last two decades, biomarker testing has become a cornerstone of cancer care, guiding therapeutic decisions to determine whether a certain treatment works for a patient. Almost half of the new cancer medicines approved by the EMA for solid tumors in 2015-2020 were associated with a predictive biomarker. In many clinical settings, single and sequential biomarker testing has been replaced by complex assays such as next-generation sequencing (NGS) that enable assessing multiple genes at the same time. Yet while single-gene tests are widely available across Europe, access to NGS is limited in many countries, especially in Central

and Eastern European countries. A major strand of current biomarker research is focusing on developing tests that can assess relevant markers of cancer in the blood. Liquid biopsies offer a non-invasive alternative to tissue biopsies, enabling testing in difficult to biopsy patients, monitoring of minimal residual disease, and facilitating early cancer detection.

The EMA has approved almost 200 new cancer medicines since 1995, but stark country inequalities in reimbursement exist.

From 1995 to 2024, the European Medicines Agency (EMA) approved 194 new cancer medicines. The number of approvals has increased significantly from on average one new medicine per year in 1995-2000 to around 14 medicines per year in 2021-2024. In addition, there were 318 approvals of new indications of previously approved medicines. Far from all cancer patients in Europe have access to these medicines. Western European countries tend to reimburse more cancer medicines and reimburse them faster than countries in Central and Eastern Europe and smaller countries. For example, Germany reimbursed nearly all cancer medicines with EMA approval in 2019-2022 within 100 days, whereas countries such as Malta, Estonia, Slovakia, and Romania reimbursed fewer than 20% of new medicines and the average time to reimbursement was close to 900 days in Latvia and Lithuania, leading to stark inequalities in patient access to new treatments.

The uptake of new cancer medicines has converged across countries, although access is still worse in Central and Eastern Europe.

The real size of cancer medicine expenditure is unknown, but - based on list prices – wealthier countries in Western Europe spend significantly more on cancer medicines per capita than countries in Central and Eastern Europe. Despite some convergence between 2014 and 2023, per-capita spending varied six-fold across countries in 2023, from €31 in Latvia to €195 in Austria (based on list prices). The uptake of new cancer medicines (defined as the use in milligrams per cancer case) has converged somewhat across Europe. The gap between the two highest- and lowest-uptake countries shrank from a 5.3-fold difference in 2018 to a 3.3-fold difference in 2023, narrowing the access gap for patients. However, persistent disparities still exist. Austria, Switzerland, and France lead in adopting newer cancer medicines in clinical practice, while many Central and Eastern European countries, in particular Latvia, Poland, Estonia, and Slovakia, have the lowest uptake levels. Notable exceptions to this geographic pattern are the Netherlands and Portugal with below EU-average uptake. Cancer types with a clear regional divide and lower uptake in Central and Eastern European countries are gynecological cancers and lung cancer, where limited biomarker testing acts as a bottleneck.

Structural barriers hinder equitable access to cancer medicines.

Beyond regulatory approval by the EMA, disparities in national pricing and reimbursement timelines, criteria in health technology assessment (HTA), and budgetary constraints affect patient access to new cancer medicines across European countries. The lack of reimbursement of companion diagnostics despite reimbursement of medicines, limited infrastructure for performing molecular diagnostics, infrequent updates to clinical guidelines, and insufficient continuing medical education contribute to slower adoption of new treatments in some countries. Delayed adoption of new, effective medicines results in opportunity costs of a potential loss of life years for patients and society.

The rising expenditure for cancer medicines calls for consistent use of HTA and recognizing societal benefits beyond direct healthcare outcomes.

While new medicines contribute to reducing the disease burden, the rising expenditure on cancer medicines also poses affordability challenges. More stringent and consistent application of HTA plays a crucial role in evaluating cost-effectiveness and budget impact, ensuring that investments provide meaningful patient benefits while maintaining financial sustainability. In addition, a more holistic approach is needed in HTA. New cancer medicines not only improve survival but also contribute to societal and economic benefits, such as increased possibility to return to work for patients and reduced caregiver burden. Frameworks like the ISPOR Value Flower emphasize the broader impact of treatments, highlighting the need for HTA to adopt a societal perspective.

Prioritizing the value of new cancer medicines and optimizing the use of reimbursed medicines can improve the allocation of resources.

Greater use of (performance-based) managed entry agreements (MEAs) and multi-speed HTA processes could help prioritize access to medicines with proven clinical benefit while ensuring follow-up for those with uncertain value. In addition, optimizing cancer medicine usage can improve efficient use of resources without compromising patient outcomes. Approaches such as biomarker-driven patient stratification, optimizing treatment sequencing, minimizing overtreatment at end-of-life, reducing medicine spillage, and promoting adoption of generics and biosimilars can significantly reduce expenditure. This creates financial headroom for new medicines without limiting patient access to existing treatments.

The lack of real-world data on treatment patterns and survival statistics hampers evidence-based policymaking.

The lack of systematic real-world data on treatment patterns and survival statistics from cancer registries hampers evidence-based policymaking. Currently only 15 out of 31 European countries publish five-year survival rates for all cancers combined and by type, 3 countries publish them by type only, and 13 countries provide no data on national websites/reports. Additionally, most countries lack comprehensive real-world data on how patients are treated across hospitals and regions on a national level. Improving data collection is critical for assessing treatment effectiveness, demonstrating value of new technologies, and guiding policy decisions.

Sustaining Europe's momentum in the fight against cancer is crucial, with ongoing policy efforts promising to mitigate access disparities.

The EU has played a pivotal role in cancer control for over 40 years, culminating in the launch of the Europe's Beating Cancer Plan (EBCP) in 2021. Together with the EU Cancer Mission, it has driven research, policy action, and funding. However, with most EBCP actions concluding by 2025 and shifting EU priorities inside and outside healthcare, sustaining momentum is crucial. The new HTA Regulation (HTAR) and the proposed revision of the EU pharmaceutical legislation aim to accelerate reimbursement decisions and incentivize companies to market medicines in all EU countries. However, successful implementation of the HTAR depends on national acceptance of joint clinical assessments. In addition, the commitment by EFPIA member companies from 2022 to file for pricing and reimbursement in all EU countries within two years of EMA approval could further reduce disparities. Lastly, with Europe's share of global oncology clinical trials falling from 41% in 2008 to 21% in 2023, strategic EU initiatives, including the "Draghi Report" and the Competitiveness Compass, recognize the importance of research and innovation in maintaining Europe's leadership in cancer care in the years to come.

List of abbreviations

ADC	Antibody-drug conjugate
AI	Artificial intelligence
ALCL	Anaplastic large-cell lymphoma
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BiTE	Bispecific T-cell engager
BRCA	Breast cancer gene
BsAbs	Bispecific antibodies
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CDK4/6	Cyclin-dependent kinase 4 and 6
CHMP	Committee for Medicinal Products for Human Use
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
ctDNA	Circulating tumor DNA
DALY	Disability-adjusted life years
DDD	Defined daily dose
DLBCL	Diffuse large B-cell lymphoma
EBCP	Europe's Beating Cancer Plan
ECIR	European Cancer Inequalities Registry
ECIS	European Cancer Information System
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFS	Event-free survival
EMA	European Medicines Agency
EOL	End of life
ER	Estrogen receptor
ESCAT	ESMO Scale for Clinical Actionability of Molecular Targets
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FGFR2	Fibroblast growth factor receptor 2
FISH	Fluorescence in situ hybridization
FIT	Fecal immunochemical test
FL	Follicular lymphoma
FOBT	Fecal occult blood test
GDP	Gross domestic product
GDPR	General Data Protection Regulation
GIST	Gastrointestinal stromal tumor
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor 2
HGBCL	High-grade B-cell lymphoma
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRQoL	Health-related quality of life
HST	Highly specialized technology
HTA	Health technology assessment
HTAR	Health Technology Assessment Regulation
HUC	Highest-uptake country
IARC	International Agency for Research on Cancer
ICD-10	10th revision of the International Classification of Diseases
IHC	Immunohistochemistry
ISPOR	The Professional Society for Health Economics and Outcomes Research
IV	Intravenous
IVD	In vitro diagnostics
IVDD	In Vitro Diagnostic Directive
IVDR	In Vitro Diagnostic Medical Devices Regulation
JCA	Joint clinical assessments
LBCL	Large B-cell lymphoma
LDTs	Laboratory-developed tests
MCBS	Magnitude of Clinical Benefit Scale
MCL	Mantle cell lymphoma
mCRPC	Metastatic castration-resistant prostate cancer
MEA	Managed entry agreement
mHSPC	Metastatic hormone-sensitive prostate cancer
MIR	Mortality-to-incidence ratio
MMR	Mismatch repair
MPR	Major pathologic response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI-H	Microsatellite instability high
MZL	Marginal zone lymphoma
NGS	Next-generation sequencing
nmCRPC	Non-metastatic castration-resistant prostate cancer
nmHSPC	Non-metastatic hormone-sensitive prostate cancer
NSCLC	Non-small cell lung cancer
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
pCR	Pathologic complete response
PCR	Polymerase chain reaction
PDC	Peptide drug conjugate
PD-L1	Programmed death-ligand 1

PET	Positron emission tomography
PFS	Progression free survival
PMBCL	Primary mediastinal large B-cell lymphoma
pp	Percentage points
PPP	Power purchasing parity
PR	Progesterone receptor
PREM	Patient-reported experience measure
PROM	Patient-reported outcome measure
PROTACs	Proteolysis-targeting chimeras
PSA	Prostate specific antigen
PYWLL	Potential years of working life lost
QALY	Quality-adjusted life years
R&D	Research and development
RCC	Renal cell carcinoma
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RWD	Real-world data
SCLC	Small cell lung cancer
SWD	Standard weekly dose
TA	Technology appraisal
TCR	T cell receptor
TDCC	T cell-dependent cellular cytotoxicity
THE	Total health expenditure
TIL	Tumor-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TMB	Tumor mutational burden
USPSTF	US Preventive Services Task Force
UV	Ultraviolet
WES	Whole exome sequencing
WGS	Whole genome sequencing
WHO	World Health Organization
WM	Waldenström macroglobulinemia

Country abbreviations

AT	Austria
BE	Belgium
Big Five	France, Germany, Italy, Spain, UK
BG	Bulgaria
CH	Switzerland
CEE	Central and Eastern Europe
CY	Cyprus
CZ	Czechia
DE	Germany
DK	Denmark
EE	Estonia
EL	Greece
ES	Spain
EU	European Union
EU-27	EU member states
FI	Finland
FR	France
HR	Croatia
HU	Hungary
IE	Ireland
IS	Iceland
IT	Italy
LT	Lithuania
LU	Luxembourg
LV	Latvia
MT	Malta
NL	Netherlands
NO	Norway
NW	Northern and Western Europe
PL	Poland
PT	Portugal
RO	Romania
SE	Sweden
SI	Slovenia
SK	Slovakia
UK	United Kingdom
US	United States

1. Introduction

Cancer is one of the biggest and persistent health challenges of our time. Population aging and unhealthy lifestyles continue to increase the number of new cancer cases worldwide (1). In many high-income countries around the world, cancer has become the number one disease burden. By 2035, cancer might become the leading cause of death in the European Union (EU) (2). Estimates from the International Agency for Research on Cancer (IARC) show that the number of new cancer cases in Europe has been rising for a long time; see Figure 1. In 1995, around 2.1 million new cancer cases (incidence) were diagnosed, and this number grew by 58% to 3.2 million until 2022. During the same period, the number of cancer deaths grew by 24% from 1.2 to 1.5 million. Notably, the number of deaths increased at a lower rate than the number of new cases. The widening gap between incidence and mortality of cancer is a sign of progress. It also results in an increasing number of cancer survivors, a number estimated to be around 22 million in the EU in 2020 (3).

Looking ahead, Figure 1 also shows projections of cancer incidence and mortality between 2022 and 2050 by IARC. These projections take into account the forecasted demographic development (overall population growth and population aging), while assuming no further improvements in cancer care or prevention. If the status quo remains (with base year 2022), the anticipated demographic changes will considerably increase incidence and mortality in the EU, reaching 4.1 million new cancer cases and 2.1 million deaths in 2050. These projections underscore the importance of further improvements and investment in all areas of cancer care – prevention, early detection, diagnostics & treatment, survivorship – to meet the demographic challenge and to achieve a lasting turnaround in cancer incidence and mortality.

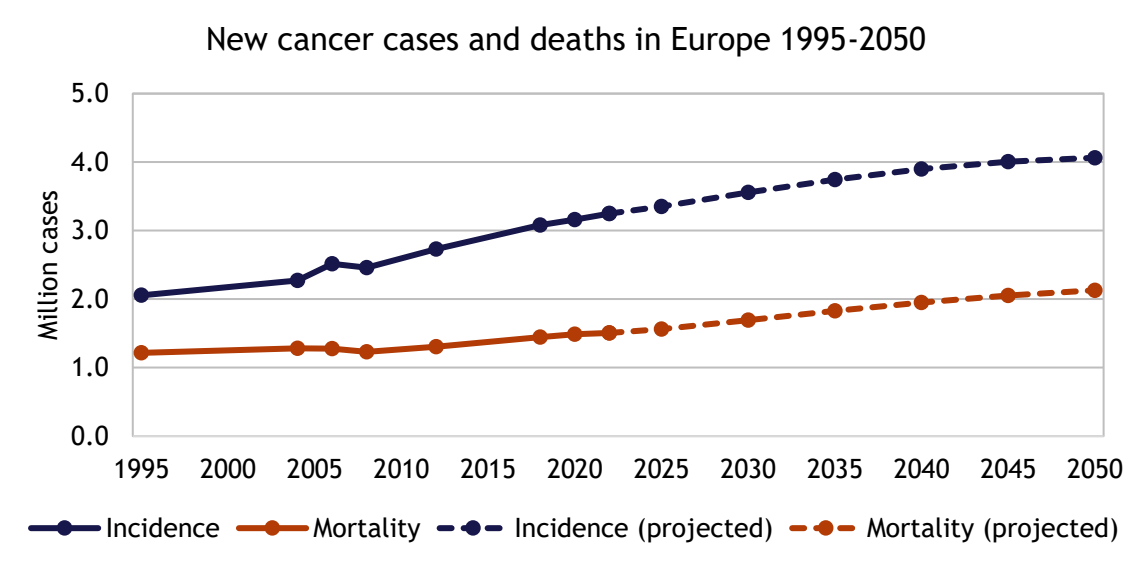


Figure 1: Estimated cancer incidence and mortality (in million cases) in Europe, 1995-2022 and projection of status quo 2022-2050.

Notes: Europe includes the EU-27, IS, NO, CH, and UK. Cancer is defined as ICD-10 C00-C97/C44. All numbers are estimates from IARC and do not take into account the impact of the COVID-19 pandemic. Source: (4-10).

While the trends of incidence and mortality on the population level seem daunting, the burden of cancer on the individual level has never looked better. In fact, we have seen solid progress in outcomes of cancer patients over the past decades. For instance, the five-year survival rate of prostate cancer increased from around 50% in the 1970s to over 90% in 2015-2019 in the Nordic countries, and for kidney cancer it increased from around 35% to 80% during the same

period (11). Great progress has also been achieved in many hematologic cancers, such as multiple myeloma, where the five-year survival rate in Ireland soared from 27% in 1994–1998 to 64% in 2014–2018 (12). This progress is the result of joint improvements in several areas of cancer care – early detection, diagnostics, and treatment (13, 14).

The epidemiological development of cancer also has implications for its economic burden. The latest estimate for Europe for 2018 showed that around half of the total economic burden of €199 billion consisted of healthcare expenditure related to cancer care, while the other half comprised costs outside the healthcare system including productivity losses (from sick leave, early retirement, premature mortality) and the value of informal care (15). Over time, healthcare expenditure on cancer has increased, partly fueled by the increasing number of cancer cases, whereas productivity loss from premature mortality has declined owing to increasing survival rates. Although the costs for cancer treatment (diagnostic and therapeutic interventions) are covered by public payers in Europe, patients (as well as their caregivers) may still incur considerable out-of-pocket payments (e.g., for co-payments on services, over-the-counter medicines, costs of travel to and from appointments and parking, specialist dressings, wigs) and a drop in earnings from employment (16).

Since the publication of the latest Comparator Report in December 2019, there have been several major developments that shaped cancer care in Europe and beyond. This includes the following:

- The COVID-19 pandemic caused major disruptions in healthcare services that also affected cancer care services (17, 18).[2]
- Artificial intelligence (AI) has quickly gone from an abstract concept to be incorporated in routine care of radiology (analyzing medical images), pathology (characterization of histological features), treatment planning, monitoring of patient health (wearable technology), and medicine discovery and development (26, 27).
- Precision medicine in oncology has started to come of age with the first recommendation by the European Society for Medical Oncology (ESMO) on the routine use of next-generation sequencing (NGS) in the diagnosis of several cancer types in 2020 (28).
- The launch of new cancer medicines has accelerated, with payers across European countries indicating that they find it increasingly difficult to cover them (29).

Cancer policy has also witnessed an unprecedented development. At the EU level, the launch of the Europe's Beating Cancer Plan (EBCP) in February 2021 by the European Commission as well as the EU Cancer Mission as part of the Horizon Europe research and innovation program for the years 2021–2027 marked major milestones (2, 30). The aim of the EBCP is to tackle the entire cancer disease pathway. It is structured around the four pillars of prevention, early detection, diagnosis and treatment, and quality of life of cancer patients and survivors; see Figure 2. It contains 10 flagship initiatives and multiple supportive actions. Following the launch of the EBCP, many EU countries have updated their national cancer plans or created their very first one (as in Romania in 2022) and incorporated the holistic structure of the EBCP as well as its priority areas and targets values.

[2] Effects on the overall detection of new cancer cases turned out to be relatively modest with registered decreases in absolute incidence from 2019 to 2020 of, e.g., 1% in Austria (19), 8% in Czechia (20), 4% in Germany (21), 5% in the Netherlands (22), 3% in the Nordic countries (23), 15% in Poland (24), and 6% in Slovenia (25). By contrast, effects on treatment outcomes are still to be determined.

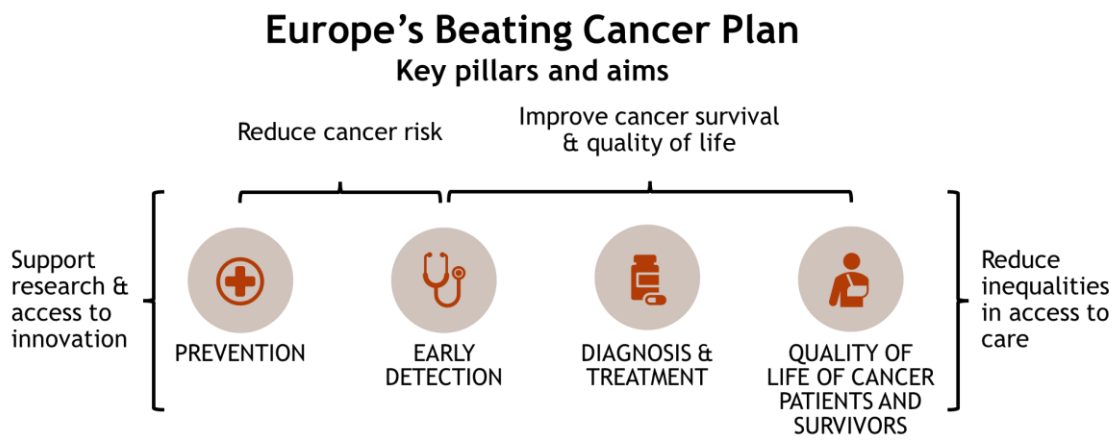


Figure 2: Key pillars and aims of the Europe's Beating Cancer Plan.

Source: European Commission (2).

Many initiatives have already grown out of the EBCP (31). The European Cancer Inequalities Registry (ECIR) was launched in February 2022 (32), which complements the existing European Cancer Information System (ECIS) (33), and has the ambition to measure and support the reduction of inequalities in cancer care both between and within member states. The Council of the EU adopted recommendations on screening programs (updating breast, cervical, and colorectal cancer and adding lung, prostate, and gastric cancer) in December 2022 and vaccine-preventable cancers (focusing on human papillomaviruses (HPV) and hepatitis B virus (HBV)) in June 2024 (34, 35). The Organisation for Economic Co-operation and Development (OECD) has on behalf of the European Commission published Country Cancer Profiles for all EU countries in 2023 and 2025 (36), as well as two major reports on cancer care 2024 (37, 38). The European Cancer Pulse, co-developed by the European Cancer Organisation, the EFPIA Oncology Platform, and IHE, was launched in November 2022 to provide a comprehensive overview of country inequalities in all areas of cancer care (39). Lastly, a Lancet Oncology Commission "European Groundshot" was launched in November 2022 as a call to action to achieve the ambitious 70:35 target: 70% average 10-year survival for all European cancer patients by 2035 (40).

Outside of Europe, the Cancer Moonshot was reignited by the Biden Administration in the United States (US) in 2022, after previously having been launched by the Obama II Administration in 2016 (41). The 70th World Health Assembly in Geneva in 2017 adopted a cancer resolution that represented a global call for action (42). Following this, the World Health Organization (WHO) launched the Cervical Cancer Elimination Initiative in 2020 (which was later incorporated in the EBCP) and the Global Breast Cancer Initiative in 2021 (43, 44).

1.1 Purpose and outline of the report

This report follows in the 20-year long footsteps of the very first Comparator Report by Prof. Nils Wilking and Prof. Bengt Jönsson, published in 2005 (45). Triggered by the arrival of new types of cancer medicines (targeted therapies) at the turn of the millennium, this report was the first to offer a comparative perspective on access to and utilization of cancer medicines across European countries. Later editions of this series published in 2007, 2009, 2016, and 2019 continued to shed light on the disparities between European countries in cancer epidemiology, the economic burden of cancer, and access to cancer medicines (46-49).

The purpose of this report is to provide decision makers with a clear picture of cancer in Europe in order to support efforts to plan and take action to reduce the burden of cancer. The provision of up-to-date statistics is important to measure progress and define realistic aims for future policy goals. For instance, the ECIR of the European Commission has become a valuable source of information for policymakers in Europe (32). It already includes some statistics on the cancer burden from the 2019-Comparator Report. However, the indicators in the area of diagnosis and treatment in the ECIR are rather few and do not cover aspects related to molecular diagnostics and cancer medicines (apart from essential medicines for childhood cancers).

The outline and scope of this report primarily follows the 2019-Comparator Report. The report consists of four main chapters. Chapter 2 analyzes the evolution of the disease burden and the economic burden of cancer since 1995. Chapter 3 describes advances and future directions in the medical field, with a focus on cancer medicines and molecular diagnostics. Chapter 4 analyzes access to and uptake of cancer medicines and molecular diagnostics. Chapter 5 discusses policy issues related to the provision of high-quality cancer care and access to cancer medicines.

The scope of this report does not cover all aspects of cancer care. Apart from contextual factors (disease and economic burden), the main focus here is on cancer medicines and molecular diagnostics. Compared to the 2019-Comparator Report, the stronger focus on molecular diagnostics reflects the ongoing transition to precision medicine in oncology. In relation to the four pillars of the EBCP, the scope of this report only covers some key elements within the third pillar of diagnosis and treatment. Other diagnostic modalities (histopathology and radiology) and treatment modalities (surgery, radiation therapy, stem cell and bone marrow transplants) are not extensively covered here. The EBCP's first two pillars of prevention and early detection of cancer are already well covered in a 2024 report of the OECD that studies 29 countries in Europe (37).

The geographic scope of this report are 31 countries in Europe, consisting of the 27 member states of the EU (EU-27), Iceland, Norway, Switzerland, and the United Kingdom (UK). They are collectively referred to as "Europe" in this report. For reasons of comparison and clarity, the population-weighted average of the EU-27 member states is included in statistics throughout the report. The country selection aligns with previous Comparator Reports. The inclusion of additional European countries in Eastern Europe and on the Balkan is hampered by the lack of data availability.

1.2 Methodology

This report brings together existing and new evidence. In chapter 2, the analysis of the disease burden relies mainly on data published by IARC as well as selected data from national cancer registries. The analysis of the economic burden follows the methodology of the previous Comparator Reports and is described in a forthcoming manuscript. Chapter 3 provides a review of medical literature, with an extensive focus on molecular diagnostics and medicines. Chapter 4 builds on an analysis of data sourced from the European Medicines Agency (EMA), data from EFPIA and ESMO, as well as medicine sales data from IQVIA MIDAS for most countries together with data from Signum Life Science for Denmark, Ravimiamet for Estonia, Frumtök for Iceland, and Farminform for the Netherlands. A more detailed description of the methodology applied in chapter 4 can be found in Appendix C. Chapter 5 brings together different policy-relevant topics that follow from the analysis in the previous chapters.

2. Disease burden and economic burden of cancer

Key messages of this chapter

Cancer is set to become the leading cause of death in Europe, although recent data indicate a stabilization in mortality trends.

Cancer was the second leading cause of death behind cardiovascular diseases in Europe in 2022, accounting for almost a fourth (23%) of all deaths. Yet in several countries in Northwestern Europe cancer is already the leading cause. The European Commission predicts that cancer will become the leading cause of death by 2035 in the EU. Already now, cancer is the leading cause of death in people under 65, representing 32% of deaths in 2022. Cancer also accounted for the joint largest disease burden (measured as disability-adjusted life years, DALYs) together with cardiovascular diseases in 2021 (each accounting for 17% of the total DALYs). Encouragingly, 12 countries experienced a decline in cancer deaths per 100,000 inhabitants between 1995 and 2022, signaling a turning point in the fight against cancer.

The number of newly diagnosed cancer cases has increased by nearly 60% since 1995.

Cancer incidence in Europe grew by almost 60% from around 2.1 million new cases in 1995 to 3.2 million cases in 2022. This development was mostly driven by demographic factors – especially population aging, as cancer is foremost an aging-associated disease. Even in the absence of these unfavorable demographic changes, cancer incidence would have increased in nearly all countries, as increased exposure to risk factors in the past (e.g., smoking, obesity, alcohol, unhealthy diet, sun exposure, HPV infection) leads to the development of more cases now. In 2022, almost every second man and more than every third woman in the EU were expected to be diagnosed with cancer at some point during their lives before turning 85.

Continued improvements in cancer care are needed to avert at least some of the anticipated rise in cancer incidence and mortality.

Projections by IARC indicate that the expected demographic developments will lead to a rise in cancer incidence from 3.2 million cases in 2022 to 4.1 million cases in 2050. In addition, cancer mortality is predicted to increase from 1.5 million deaths in 2022 to 2.1 million deaths in 2050. A stronger focus on primary prevention (vaccination programs for vaccine-preventable cancers and measures to facilitate the adoption of healthier lifestyles) is needed to slow the growth in cancer incidence, and continued innovation in the care process is needed to halt the increase in cancer mortality. Improvements in cancer care have already led to a decoupling of the trend in mortality from the trend in incidence. Estimations show that 5.4 million cancer deaths have been avoided in the EU over the period from 1988 to 2022 due to falls in age-standardized mortality rates.

Cancer survival has improved across Europe, yet there are disparities between countries and differences between cancer types.

The 5-year survival rates of most cancer types have improved since the 1990s in all countries. The greatest improvements were observed for hematologic cancers, while some solid tumors (bladder, brain, gynecological, laryngeal cancer) saw little or no improvement. Several cancer types have now a survival rate exceeding 90% in the best-performing countries, including breast, prostate, testicular, and thyroid cancer, melanoma skin cancer, and Hodgkin lymphoma. Almost 200,000 cancer deaths could be avoided every year if all 15 countries with available survival data matched the survival rates of Sweden, the best-performing country in Europe.

Health spending on cancer care has increased considerably in absolute numbers but grew mostly in line with overall healthcare spending.

Health spending on cancer care (direct costs of cancer) more than doubled from €62 billion to €146 billion in Europe between 1995 and 2023 (in 2023 prices and exchange rates). The increase in cancer care spending generally paralleled the overall rise in health expenditure, as the available evidence from most countries shows that cancer care spending did not significantly exceed the growth in total health spending. In addition, between 4% and 8% of the total health expenditure is spent on cancer in all countries, without a clear correlation between national wealth (GDP per capita) or cancer incidence and the share spent on cancer. Cancer is a disease where the health spending share (7%) remains below the share of the disease burden that it causes (23% of deaths, 17% of DALYs) in Europe.

Health spending on cancer care per capita differs three-fold between countries.
Per-capita health spending on cancer varied widely across countries in 2023. It ranged from below €150 in some Central and Eastern European countries (Bulgaria, Croatia, Hungary, Latvia, and Romania) to more than €400 in Germany and Switzerland (PPP-adjusted). On average, 6.6% of the health expenditure in European countries is related to cancer, translating to per-capita costs of €260 in 2023. A certain degree of convergence was observable between 1995 and 2023, as per-capita health spending on cancer increased more rapidly in the less affluent Central and Eastern European countries than in other regions. When comparing expenditure between countries, it should be remembered that these costs only represent a single number of the monetary value of all resources used. For the monetary input to yield the highest benefits to patients, an effective allocation and organization of resources is pivotal.

The indirect costs of cancer have been decreasing due to better patient outcomes.
The indirect costs of cancer equal the productivity loss from premature death and from morbidity (sick leave and early retirement) of patients in working age. Between 1995 and 2023, the indirect costs decreased by 16% from €97 billion to €82 billion (in 2023 prices and exchange rates). This decline is a direct result of the reduction in cancer deaths in working-age people. All countries recorded a decline in the potential years of working life lost from premature cancer death. The decrease in the indirect costs indicates that the economic benefits of increased health spending on cancer care have largely been realized outside the healthcare system itself. The fact that indirect costs are sizeable even compared to the health expenditure on cancer underlines the importance of applying a societal perspective in the design of policy measures to tackle cancer.

The total economic burden of cancer has grown, while the burden per patient has not increased.
The rising direct costs of cancer in Europe have to some extent been offset by a decrease in the indirect costs between 1995 and 2023. However, the sum of direct and indirect costs still increased by 43% from €159 billion to €228 billion in 1995-2023 (in 2023 prices and exchange rates). When these costs are contrasted with the underlying growth in the number of cancer patients, a different picture emerges. The economic burden per cancer patient (defined as incident case) was rather constant at around €78,000 between 1995 and 2010, before experiencing a slight drop until 2015 and then again plateauing at around €70,000-72,000 until 2023. Nevertheless, the future economic burden is closely tied to the growing number of cancer patients and the success in improving patient outcomes.

Higher cancer care spending is linked to higher survival rates, but efficiency matters.
Countries with higher per-capita spending on cancer care tend to achieve higher survival rates, highlighting the importance of adequate investment in cancer. However, the relationship is non-linear – while increased spending improves survival, the benefits per additional euro spent seem to diminish beyond a certain level. Significant inefficiencies exist, as some countries achieve similar survival rates despite vastly different spending levels. For example, Sweden and Switzerland have comparable survival rates, yet Switzerland's per-capita spending is more than double that of Sweden. To maximize patient outcomes, health systems should ensure cost-effective allocation of resources, prioritize high-value interventions, and identify and address inefficiencies along the entire patient pathway.

2.1 Who gets cancer and why?

Cancer is foremost an aging-associated disease (50). The risk of getting cancer increases dramatically with age, yet it affects people of all ages. During childhood and adolescence (0-19 years), cancer is rarely diagnosed (51); see Figure 3. There were around 15 new cancer cases diagnosed per 100,000 children and adolescents in Europe in 2022, corresponding to 0.5% of all new cases (52). The risk of getting cancer remains low up to the age of 40. Above the age of 40, a cancer diagnosis becomes increasingly more likely. According to the latest estimates from IARC for Europe for the year 2022, most new cancer cases – in absolute numbers – were diagnosed between the ages of 65 to 79, with around half a million cases in each five-year age group (52). Almost two thirds (65%) of all cases were diagnosed in people aged 65 or older. In

relative numbers, which take into account that there are fewer people alive at older ages, the incidence rate was highest among people over 80 years (in men: 3000 new cases per 100,000 men; in women 1750 new cases per 100,000 women) in Europe. Among the "oldest old" (≥85 years), data from Finland show that age-specific incidence rates peak at age 85–89 in men and age 85–94 in women and declined thereafter in both sexes (53).

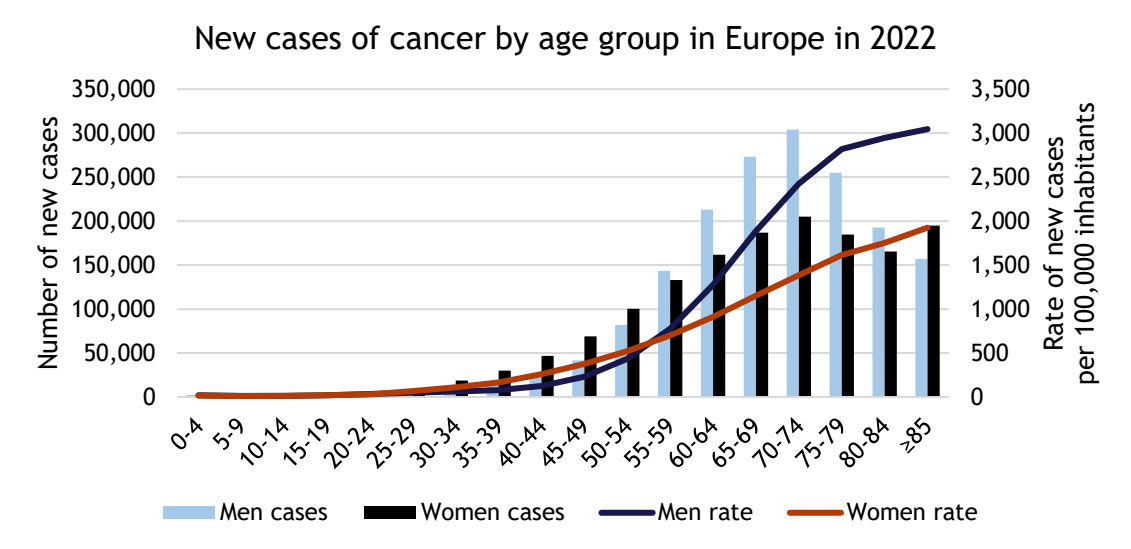


Figure 3: Cancer incidence and age-specific rates by age group and sex in Europe in 2022.

Notes: Cancer refers to all cancer sites but non-melanoma skin cancer. Source: Estimates by IARC (52) and own calculations of age-specific rates based on population data from Eurostat and OECD (54, 55).

Cancer affects men more than women, as 53% of new cases occurred in men in the EU-27 in 2022. Men had on average a 48% risk of being diagnosed with cancer[3] before the age of 85, while women had a 36% risk (52). This means that almost every second man and more than every third woman are expected to be diagnosed with cancer at some point during their lives before turning 85. Appendix A presents the risk of developing cancer by country, revealing that Norway leads among men with a 54% risk to be diagnosed before 85, while Denmark leads for women with a 46% risk. Bulgaria recorded the lowest risk for both men (39%) and women (28%).

Info box 1. Age and sex patterns in cancer diagnosis

Different age patterns in cancer diagnosis between men and women are visible in Figure 3. More cases are diagnosed in women between the ages of 15 to 54, whereas more cases are diagnosed in men between the ages of 55 to 84. The reason for this is that common cancer types in women, such as breast cancer and cervical cancer, occur at comparatively younger ages than prostate cancer, which is the most common cancer type in men. The reason for the higher absolute number of cancer cases in women in the ≥85 years age group despite a lower relative rate to get cancer at that age stems from the higher number of women still alive at that age.

Cancer is the collective name of a group of over 100 disease subtypes that are characterized by uncontrolled growth and division of cells (56). Cancer starts with changes (mutations) in one cell or a small group of cells in the body (a process called "carcinogenesis" or "oncogenesis"). The mutations make cells start to grow and multiply too much. Mutations might happen for several reasons. In general, cancer is much more likely to arise in older people because the cellular repair mechanisms that are supposed to detect and destroy mutated cells become less

[3] All cancers excluding non-melanoma skin cancer.

effective as a person grows older. Aging is therefore the biggest risk factor for cancer in general (57-59). As unwanted mutations and aging cannot be prevented, people will always run a risk of getting cancer. Since the number of people reaching older ages is increasing rapidly in Europe (60), the number of new cancer cases will also continue to increase.

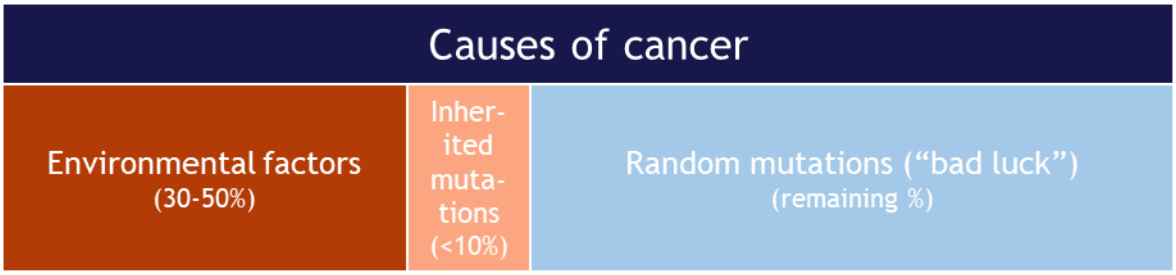


Figure 4: Causes of cancer.

Exactly why a certain person gets cancer at a specific point in time is usually not known. In 2015, a publication by Tomasetti & Vogelstein in Science triggered a debate around what came to be known as the "*bad luck hypothesis*" (61). They showed that "only" one third of the variation in cancer risk is attributable to environmental factors or inherited predispositions, whereas the majority is due to random mutations which was termed as "bad luck"; see Figure 4. Despite the controversial debate around the phrasing of the findings, it roughly aligned with previous estimates by the WHO and other international bodies:

- **Environmental factors:** According to the WHO, around 30–50% of cancer cases are linked to modifiable risk factors (56). These environmental factors include tobacco use, alcohol use, overweight and obesity, unhealthy diet, physical inactivity, infection with carcinogenic viruses (e.g., HPV and HBV) and bacteria (e.g., Helicobacter pylori), exposure to air pollution, and ionizing and UV radiation. As exposure to these risks increases with age, so does the cancer risk.
- **Inherited predispositions:** Certain genetic variants are passed down from parents to children and increase the cancer risk. Up to 10% of cancers are due to inherited genetic changes (62). Notable examples include Lynch syndrome, which raises, e.g., the risk to get colorectal and endometrial cancer, and BRCA1/2 gene mutations, which increase the risk of, e.g., breast, ovarian, pancreatic, and prostate cancer (62, 63).

2.2 Burden of disease

In most cases, cancer is a lethal disease if left untreated. In 2022, an estimated 1.5 million people died from cancer in Europe (52). This makes cancer one of the leading causes of death (64). In fact, cancer has been the second leading cause of death behind cardiovascular diseases in Europe for many decades, yet the gap has narrowed over time; see Figure 5. In 2000, cancer was responsible for 24% of all deaths. By 2022, the share of deaths attributed to cancer had slightly decreased to 23%, yet it remained the second most common cause of death behind cardiovascular diseases which themselves saw a greater reduction (from 44% to 32%). The EBCP notes that unless decisive action is taken, cancer is set to become the leading cause of death in the EU by 2035 (2).

In several countries, including Denmark, France, Ireland, the Netherlands, Norway, and the United Kingdom, cancer overtook cardiovascular diseases between 2000 and 2022 to become the leading cause of death (64). By contrast, in all Central and Eastern European (CEE) countries, cardiovascular diseases still dominate the overall death pattern, e.g., they

accounted for 61% of deaths in Bulgaria (cancer only 14%) and for 53% in Lithuania (cancer 18%) in 2022. The diverse mortality patterns have been attributed to higher rates of risk factors (including smoking, hypertension, hypercholesteremia, diabetes) for cardiovascular diseases in CEE countries along with lower quality of medical services, cost (out-of-pocket payments), access to preventative prescription medicines (such as statins, ß-blockers, and antithrombotic agents), and non-adherence with treatment (65-67). People who die from cardiovascular diseases (such as heart attacks and strokes) at a younger age will not live long enough to get cancer.[4] Indeed, the overall life expectancy in Europe is lowest in the CEE region, with, e.g., Bulgaria having had a life expectancy at birth of 74 years compared to the EU-27 average of 81 years in 2022 (68).

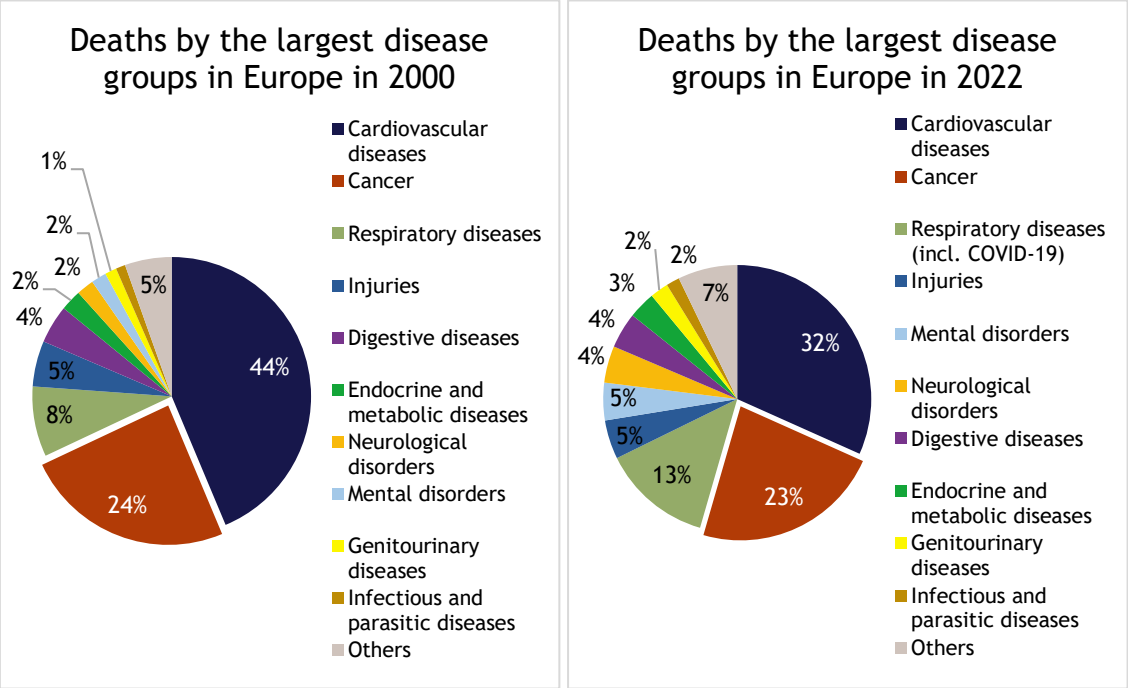


Figure 5: Top 10 causes of death in Europe, 2000-2022.

Notes: ICD-10 main disease groups were considered. Examples of specific diseases within these groups are the following. Cardiovascular diseases (I00-I99) include heart attacks and strokes. Cancer (C00-C97). Respiratory diseases (J00-J99) include asthma, pneumonia, chronic obstructive pulmonary disease, and in 2022 also COVID-19. Injuries (V01-Y89) include accidents, falls, and suicides. Digestive diseases (K00-K93) include appendicitis and Crohn disease. Endocrine and metabolic diseases (E00-E90) include diabetes and cystic fibrosis. Neurological disorders (G00-H95) include Alzheimer's disease and multiple sclerosis but also sensory conditions such as glaucoma. Mental disorders (F00-F99) include depression and schizophrenia. Diseases of the genitourinary system (N00-N99) include kidney failure and endometriosis. Infectious and parasitic diseases (A00-B99) include tuberculosis and viral hepatitis. The 2000 figures use data from Metropolitan France and data from 1999 for BE and from 2004 for CY. Source: Eurostat and ONS (64, 69, 70).

The total number of deaths and the number of cancer deaths across age groups in Europe in 2022 is illustrated in Figure 6. The total numbers of cancer deaths and deaths from other causes increase throughout most age ranges. Cancer deaths reach their highest numbers in the 70-74, 75-79, 80-84 age groups, with over 200,000 deaths in each group. The peak in deaths from any cause occurs later in the 85-89 age group, with over one million deaths. When looking at the share of cancer deaths relative to all deaths (line in Figure 6), there are two notable peaks. The first peak occurs during childhood (ages 5 to 9), where cancer accounts for 24% of deaths.

[4] The same logic also applies to cancer and age-related neurological diseases (such as Alzheimer's disease and Parkinson's disease). As more people survive cancer, they live long enough to develop other diseases that are associated with old age. This trend is visible in Figure 5, characterized by a growing share of deaths from neurological diseases.

The second peak occurs at the end of working age at 60-64 years, where almost 40% of all deaths are due to cancer. In general, cancer was the leading cause of death for people under 65 representing 32% of deaths in 2022, whereas the second leading cause of death were cardiovascular diseases with 20%.

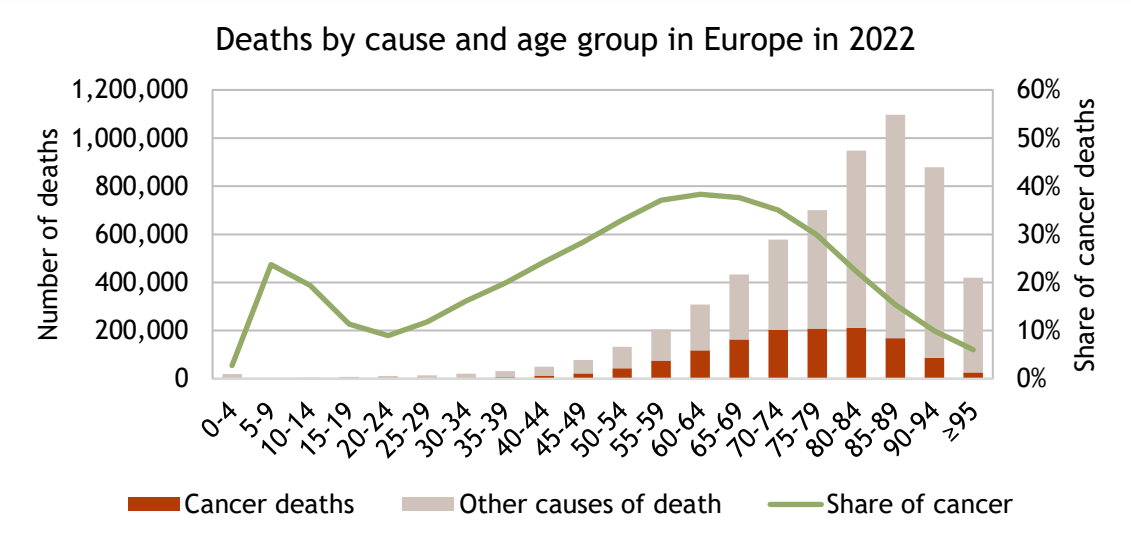


Figure 6: Number of deaths by cause (left scale) and cancer deaths as share of total deaths (right scale) by age group in Europe, 2022.

Notes: Cancer is defined as ICD-10 C00-C97 and other causes as all causes of death (A00-Y89) excluding S00-T98 and C00-C97. Deaths refer to all deaths reported in a country. Source: (64, 70).

Focusing only on the cause of death overlooks key aspects of the burden of other diseases. Factors such as the age at death (e.g., at age 30 or 80) and the quality of life while living with a debilitating but non-fatal disease/condition (e.g., psoriasis, depression, chronic back pain) also significantly affect the overall burden on society and health systems. Disability-adjusted life years (DALYs), provide a comprehensive measure of the disease burden (71). DALYs capture both morbidity (the impact of a disease on quality of life) and premature mortality (premature death due to the disease, defined as dying before the age of 92).

Figure 7 illustrates that in 2000, cancer accounted for 18% of the DALYs in Europe, ranking second after cardiovascular diseases. By 2021, the proportion of DALYs attributable to cancer remained relatively stable at 17%, positioning it as a joint leading cause alongside cardio-vascular diseases, which saw its share decline from 24% to 17% over the same period. Notably, the share of DALYs of respiratory diseases rose significantly from 6% to 12% between 2000 and 2021, driven by the impact of COVID-19 infections in 2021.

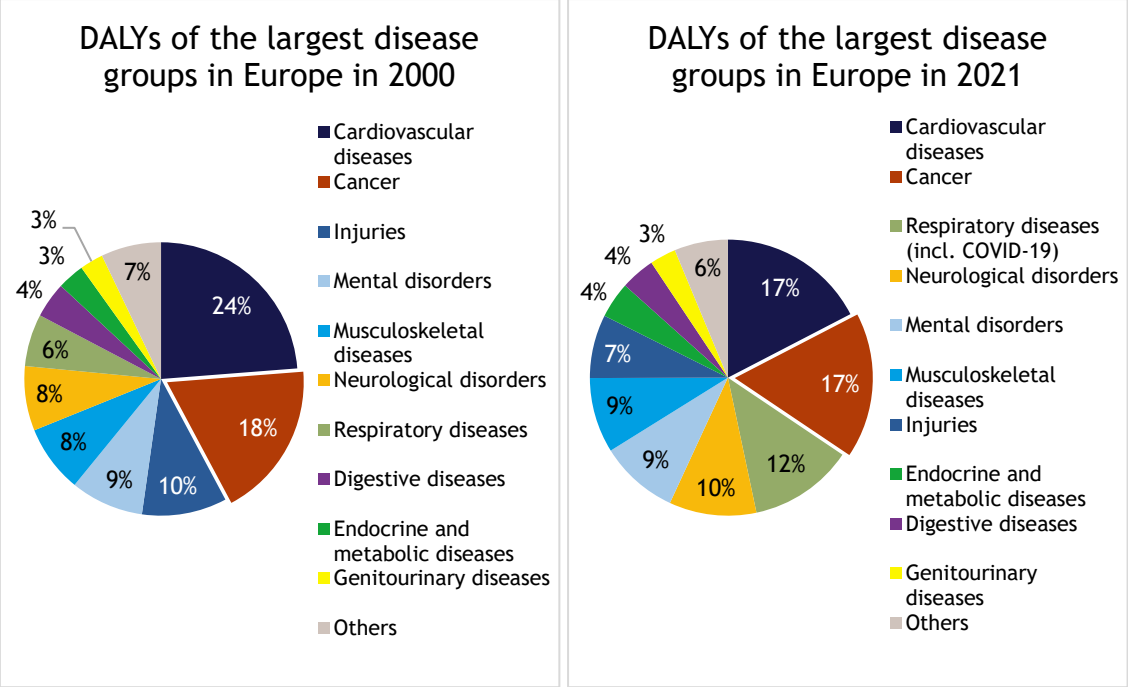


Figure 7: Top 10 causes of DALYs in Europe, 2000-2021.

Notes: see the note for Figure 5. In addition, musculoskeletal diseases (M00-M99) include rheumatoid arthritis and osteoporosis. Source: (72).

Info box 2. Future development of the disease burden

The future disease burden of cancer, in terms of the proportion of total deaths or total DALYs, depends on several factors. The increasing number of new cancer patients contributes to a higher disease burden, while the growing number of cancer survivors helps to reduce it. The development in other diseases, particularly cardiovascular diseases, will also impact the relative burden of cancer. Decreasing mortality rates for major cardiovascular diseases, such as heart attacks and strokes, allow more people to live longer lives. However, this also means there are more individuals who may develop and potentially die from cancer, as it is an age-associated disease with the highest risk occurring after 80 years (see Figure 3).

The management of diseases by healthcare services requires resources (see also section 2.5). Figure 8 details the cost distribution across the top ten disease groups in Germany and Sweden, revealing some significant discrepancies between resource allocations and disease burden. Some 9% of healthcare spending in Germany[5] in 2020 and 5% in Sweden in 2017 were caused by cancer, making it the 6th and 8th most costly disease, respectively (73, 74). Spending on cancer as a proportion of total healthcare spending (5-9%) is low compared to the proportion of DALYs (17%) and deaths (22%) from cancer in Europe in 2021/2022. Cardiovascular diseases share the pattern of low health spending (13% in both Germany and Sweden) compared to their disease burden (17% of DALYs and 33% of deaths in 2021/22 in Europe). By contrast, health spending is relatively high for digestive diseases (6-11% in Germany and Sweden) compared to their disease burden (4% of DALYs and deaths in 2021/22 Europe).

[5] The numbers from Germany for all disease groups are inflated in 2020 as they do not include costs related to COVID-19, because COVID-19 was only classified as a secondary diagnosis in the official statistics.

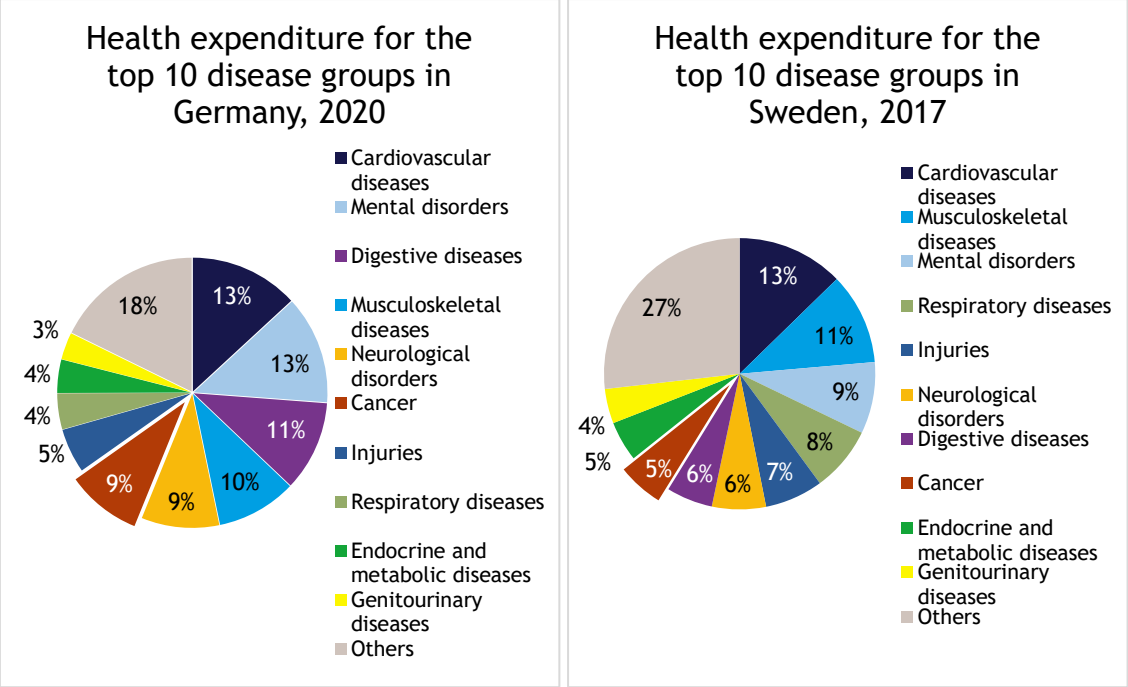


Figure 8: Distribution of health expenditure across the top 10 disease groups in Germany and Sweden.

Notes: Total health expenditure in Germany was EUR 432 billion in 2020 and SEK 323 billion in Sweden in 2017. In Sweden, cancer includes also benign neoplasms. Source: (73, 74).

2.3 Incidence and mortality

Two key epidemiological metrics to assess the burden of cancer are incidence, which refers to the annual number of newly diagnosed cancer cases, and mortality, which denotes the annual number of cancer deaths. These measures are essential for understanding the scope and impact of cancer within a population.

2.3.1 Incidence

Cancer incidence refers to the number of new cancer cases diagnosed within a certain year in a specific geographical area. In 1995, the estimated cancer incidence[6] was 2.05 million in Europe[7]; 0.94 million women and 1.11 million men (5). Until 2022, the corresponding number had increased by 58% to 3.24 million; 1.51 million women and 1.73 million men (52). As summarized in Table 1, several factors explain this increase, with demographic changes being the main drivers. Cancer incidence and its development over time are important indicators for policymakers to plan the need for cancer care services and to assess the success of prevention measures.

[6] All cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). Non-melanoma skin cancer is commonly excluded from incidence data, as its registration is often incomplete and inaccurate, as it is usually non-fatal and treated in primary care.

[7] The number for 1995 for Europe as defined in this report was estimated based on sex-specific growth rates in cancer incidence between 1995 (5) and 2018 (7) in a greater sample of Europe, including EU-27 (except CY), IS, NO, CH, UK, the remaining Balkan countries, Belarus, Moldova, Russia, and Ukraine.

Table 1: Explanations for the increase in incidence between 1995 and 2022

	**Population growth** The population of Europe increased from 495 to 531 million, a growth of over 7% (64, 75). Assuming a constant risk of developing cancer, a growing population leads to more cancer cases in absolute terms. However, cancer incidence rose also in per-capita terms; see Figure 9.
	**Population aging** As the risk of developing cancer increases with age, an aging population contributes to a rising number of cancer cases. The population aged 65 and older increased from 71.9 to 98.4 million in Europe, expanding its share among the total population from 15% to 21% (64). Appendix A presents age-standardized incidence rates, which account for the impact of an aging population. While this explains a large part of the increase in cancer cases, there remains a significant rise in incidence that is not accounted for.
	**Risk factors** The prevalence of some but not all cancer-causing lifestyle factors has increased in recent decades. This includes obesity (linked to colorectal cancer), alcohol consumption (linked to liver cancer), and exposure to UV radiation from sunbathing (linked to skin cancer). In contrast, smoking (linked to lung cancer), which is the biggest risk factor, has declined among men and women in Europe (60, 76). However, declining smoking rates do not immediately lead to a decrease in cancer incidence, as there are significant time lags – usually several decades – between exposure to risk factors and the development of cancer.
	**Epidemiological development in other diseases (competing risks of death)** Due to advancements in healthcare and medicine, people are now surviving diseases that were previously fatal, particularly cardiovascular diseases. As a result, more people are reaching advanced ages, thereby increasing the number of individuals at risk of developing cancer.
	**Screening** Nationwide population-based screening programs for breast cancer, cervical cancer, and, since the early 2010s, colorectal cancer have been implemented in many European countries. Additionally, opportunistic PSA testing for prostate cancer has been common in Europe since the 1990s, resulting in the detection of latent cases that might never have become symptomatic or led to death (77). These detections artificially inflate cancer incidence statistics (77).
	**Cancer registration** Cancer registration has been expanding in Europe since the early 1990s and has become a crucial part of the EU's strategy against cancer (78). Almost 200 population-based cancer registries are currently operating in Europe, covering around 60% of the population, with an upward trend. More complete registration of cases (and any resulting changes for the estimates from IARC) might inflate incidence numbers.

Besides the absolute incidence numbers, the number of newly diagnosed cases per 100,000 inhabitants (called crude rates) are mostly used to track the burden over time. Figure 9 shows incidence crude rates for all cancers combined for both sexes. All countries with available data saw increases in incidence between 1995 and 2022, with the EU average rising by 44% from 426 to 614 cases per 100,000 inhabitants. Among the countries for which data are available for 1995, Italy had the highest incidence rates with around 570 cases per 100,000 inhabitants, while Bulgaria and Lithuania had the lowest rates with 300 cases or less per 100,000 inhabitants. From 1995 to 2022, most countries recorded increases in the crude incidence rates of around 50%, with the highest increases in Lithuania (+92%) and Bulgaria (+82%) and the lowest ones in Iceland (+14%) and Austria (+18%). In 2022, Denmark and Croatia topped the list with more than 700 cases per 100,000 inhabitants, while Iceland, Bulgaria, and Luxembourg had the lowest crude rates with around 450 cases per 100,000 inhabitants.

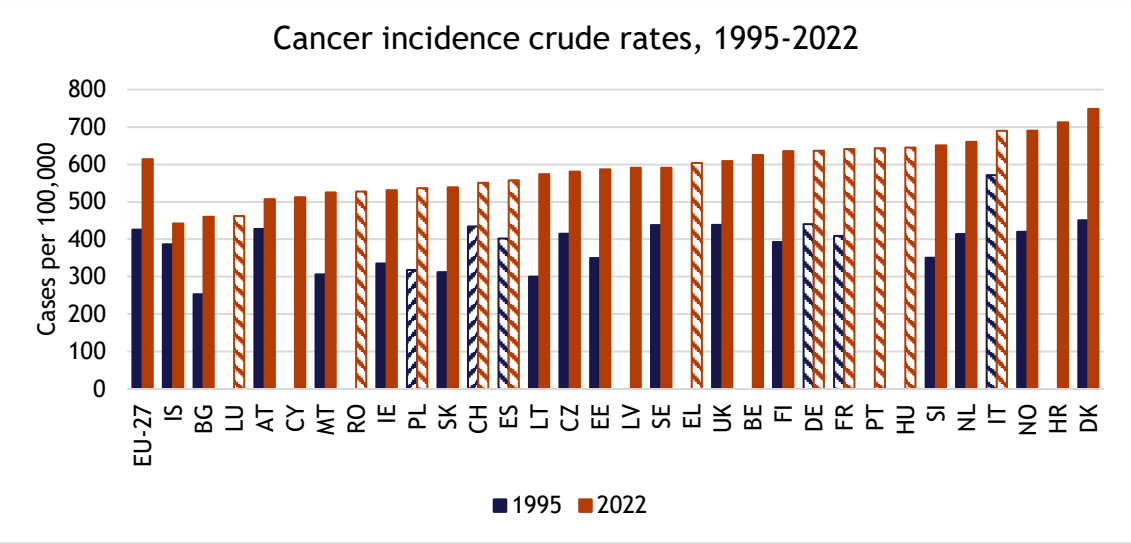


Figure 9: Estimated number of cancer incidence cases per 100,000 inhabitants (crude rates for both sexes), 1995-2022.

Notes: EU-27 shows the weighted average in EU member states with available data. Hatched bars indicate that national estimates are based on regional data (FR, DE, IT, PL, PT, RO, ES, CH) or neighboring countries (EL, HU, LU). Cancer refers to all cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44). BE, HR, CY, EL, HU, LV, LU, PT, RO are missing in 1995 due to lack of data. Incidence cases in 1995 were based on regional data in Germany (North Rhine-Westphalia, Saarland), France (Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Manche, Somme, Tarn), Italy (Ferrara, FVG, Latina, Liguria, Macerata, Modena, Parma, Ragusa, Romagna, Sassari, South Tyrol, Trento, Tuscany, Umbria, Varese), Spain (Balearic Islands, Basque Country, Girona, Granada, La Rioja, Navarra, Tarragona), and the UK (England, Northern Ireland, Scotland, Wales). Source: (47, 79-82).

Appendix A presents estimated age-standardized incidence rates separately for men and women (5, 80). In men, incidence rates increased in all but seven countries between 1995 and 2022. Similarly, incidence rates among women increased in all countries except in Iceland. Larger increases in women than men (+27% vs. +9% in the EU-27, respectively) narrowed the gender gap over time, yet incidence rates among women in the EU-27 were still 22% lower than among men in 2022.

Incidence by cancer type and age

While the number of new cancer cases has increased during the past decades, the development has not been consistent across all cancer types. As a result, the share of different cancer types has shifted markedly since 1995; see Figure 10 and Figure 11. The eight most common cancer types accounted for about 70% of all cases in men and women in 1995 and 2022.

In 1995, lung cancer was the most common cancer type in men, accounting for 22% of all new diagnoses, as shown in Figure 10. By 2022, its share had decreased to 14%. Meanwhile, prostate cancer emerged as the leading type, comprising 22% of cases in 2022, doubling its share since 1995. It remains uncertain, however, to what extent this significant increase in prostate cancer cases is due to the detection of latent disease, amplified by more widespread opportunistic PSA testing (77). The notable reduction in lung cancer cases from 1995 to 2022 among men is likely linked to the declining smoking rates observed since the 1980s and 1990s (60). Stomach cancer disappeared from the list of most common cancers, which has been attributed to progress in eradication of Helicobacter pylori bacteria and better food preservation practices linked to refrigeration during the transport and storage of food (83).

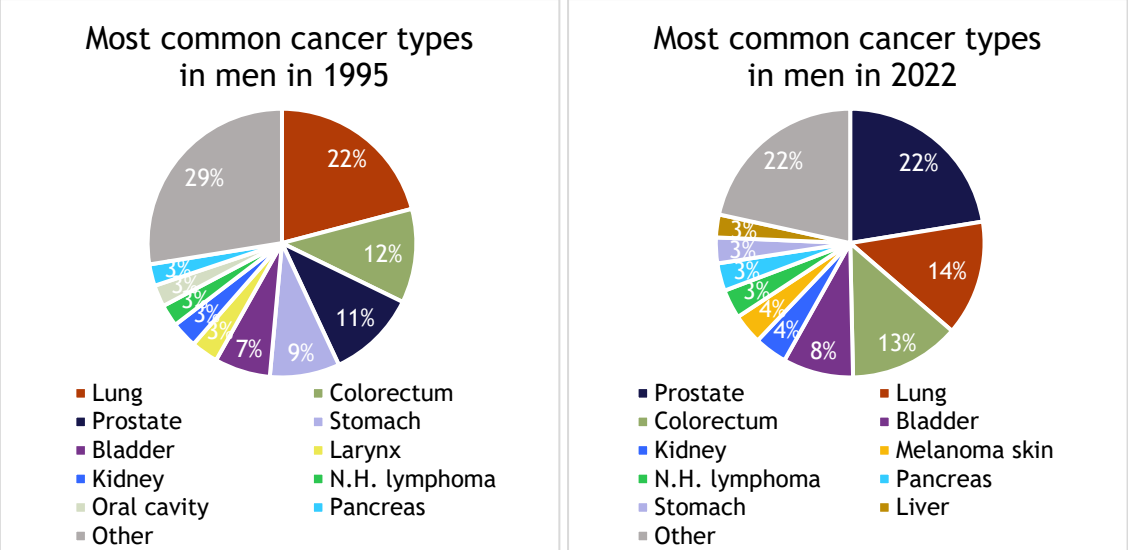


Figure 10: Most common cancer types diagnosed in men in 1995 and 2022, Europe.

Notes: For 1995, 'Europe' encompasses the EU-27, IS, NO, CH, UK, and the remaining Balkan countries, Belarus, Moldova, Russia, and Ukraine. For 2022, Europe refers to the definition used in this report. N.H. = non-Hodgkin. Source: (5, 80).

Among women, breast cancer remained the most common type between 1995 and 2022, accounting for almost 30% of all new diagnoses, as shown in Figure 11. In contrast to trends observed in men, the incidence of lung cancer in women rose from 5% to 9%. In many high-income countries, women's smoking rates peaked later than men's, and the effects of higher smoking prevalence in past decades are now becoming evident, even though smoking rates among women have been declining since the 1990s (76). Additionally, the incidence rates for stomach and cervical cancers have each decreased from 6% to 2%, attributable to improvements in diet and widespread cervical cancer screenings[8], respectively (83, 84).

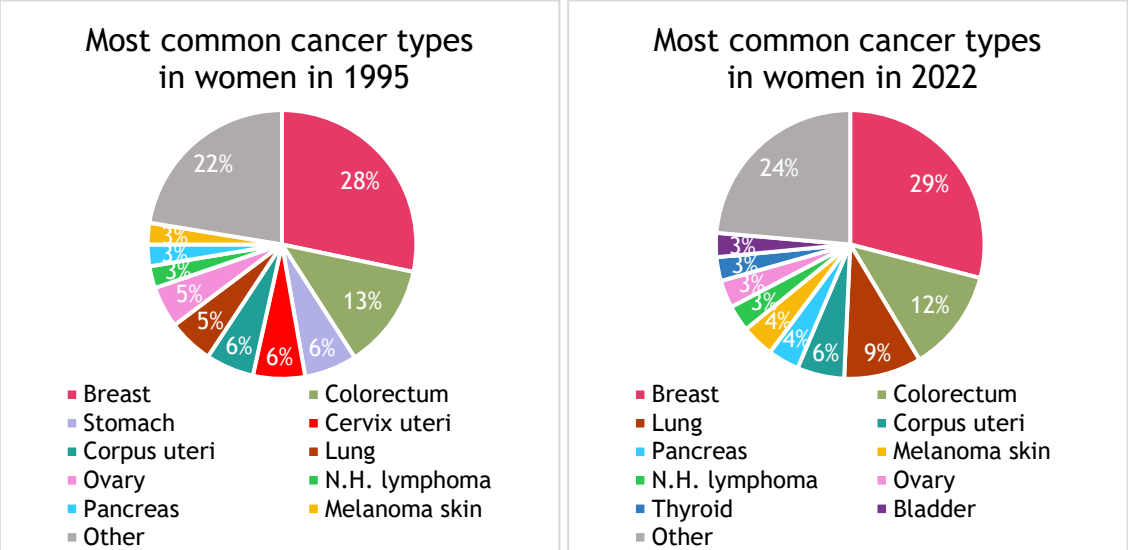


Figure 11: Most common cancer types diagnosed in women in 1995 and 2022, Europe.

Notes: See notes and sources for Figure 10. N.H. = non-Hodgkin.

[8] Pap smears are effective at identifying abnormal cervical cells before they progress to invasive cancer. By detecting these changes early, healthcare providers can intervene with treatments that remove precancerous lesions, thereby preventing the development of cancer.

Absolute cancer incidence has not increased uniformly across all age groups in recent decades. Figure 12 illustrates the trend of newly diagnosed cases in the Nordic countries from 1995 to 2022 and in Slovenia from 1995 and 2021. Similar data for Europe as a whole are unavailable due to the lack of nationwide cancer registries in the past. Overall, the Nordic countries experienced a gradual increase by 69% in newly diagnosed cases between 1995 and 2022, while Slovenia saw an 85% increase between 1995 and 2021, reflecting the broader estimated trends in Europe mentioned earlier. However, considerable differences between age groups are noticeable. In the Nordic Countries, the cancer incidence in children (0 to 14 years) remained relatively stable during the entire period, and in Slovenia it remained stable after 1997. In young adults (15 to 39 years), the incidence remained stable in Slovenia whereas it increased by 32% in the Nordic countries. Prime age adults (40-64 years) saw rather similar increases of around 50% until 2010 before plateauing in both geographies. In contrast, cancer incidence in individuals aged 65 and older has continuously risen and exhibits the highest growth of all age groups since 1995, with notably higher growth (+138%) in Slovenia than in the Nordic countries (+80%).[9] Given the aging population, this older age group is expected to continue being the primary driver of the overall increase in cancer incidence in the future.

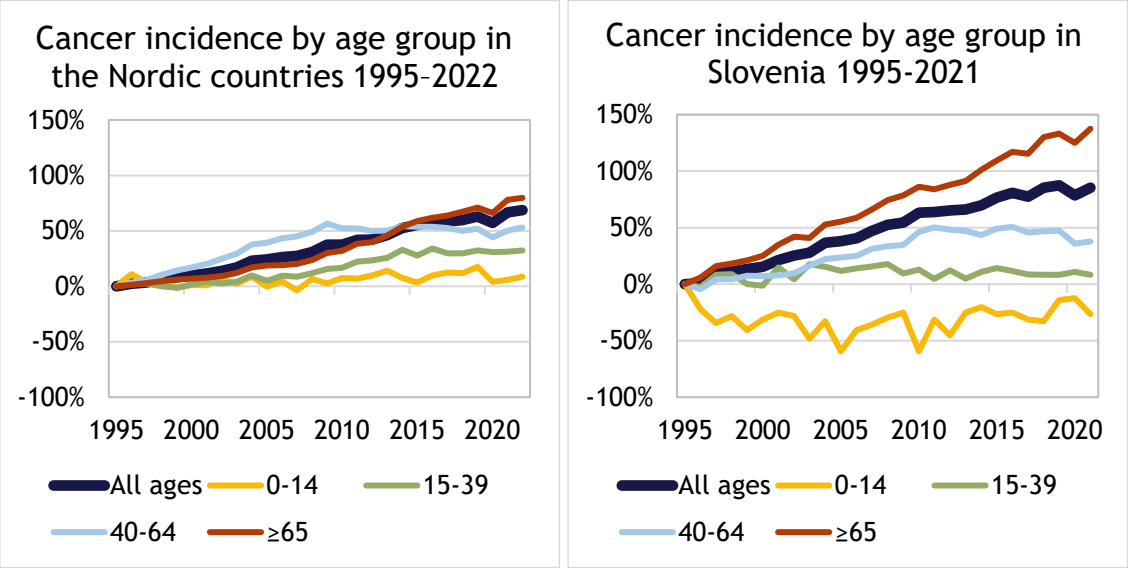


Figure 12: Cancer incidence by age group in the Nordic countries 1995-2022 and in Slovenia 1995-2021 (1995=base year).

Notes: Nordic countries = DK, FI, IS, NO, SE. Cancer is defined as all sites but non-melanoma skin cancer. The development is based on the total number of cancer cases. Source: (82, 86).

2.3.2 Mortality

Cancer mortality refers to the number of deaths caused by cancer in a certain year in a specific geographical area. In 1995, the estimated cancer mortality[10] was 1.21 million in Europe[11]; 0.53

[9] To put these numbers into perspective, the total number of cancer diagnoses in the US increased by 60% between 1995 and 2021 (85). The largest relative rise was observed in the 50-64 age group, while the smallest increase occurred among individuals under 50, with a 25% rise.
[10] All cancer sites but non-melanoma skin cancer (ICD-10 C00-C97/C44).
[11] The number for 1995 for Europe as defined in this report was estimated based on sex-specific growth rates in cancer mortality between 1995 (5) and 2018 (7) in a greater sample of Europe, including EU-27 (except CY), IS, NO, CH, UK, the remaining Balkan countries, Belarus, Moldova, Russia, and Ukraine.

million women and 0.68 million men (5). Until 2022, the corresponding number had increased by 24% to 1.51 million; 0.67 million women and 0.83 million men (52).

Info box 3. What explains the rise in cancer mortality in 1995-2022 and why did it increase less than incidence?

Factors linked to incidence: As described in section 2.3.1, there was an estimated 58% increase in newly diagnosed cancer cases during this period. Therefore, all factors linked to trends in cancer incidence (demographic developments, changes in lifestyle factors, etc.) also indirectly influence trends in cancer mortality. More diagnoses will inevitably lead to more deaths, unless compensated for by improvements in survival.

Early detection and treatment: As cancer mortality increased by only 24% compared to the simultaneous increase in incidence of 58%, factors occurring after diagnosis must have changed. The slower increase in mortality suggests that the survival prospects for patients improved. There are two potential reasons for this. Firstly, earlier detection of cancer cases (e.g., due to screening programs that countries implemented) improved survival, as there is typically a much higher chance of survival if the cancer is detected early. For instance, the stage distribution in newly diagnosed breast cancer in European countries shifted towards earlier stages between 2000-2003 and 2014-2017 (87). Secondly, advances in treatment (better surgical techniques, more precise radiation therapy, more effective cancer medicines) improve survival chances. For instance, much of the decline in age-adjusted mortality from breast cancer in the US has been attributed to improvements in treatment of both early-stage and metastatic breast cancer (88).

Figure 13 shows crude rates for cancer mortality for all cancers combined for both sexes. In the EU-27, mortality rates increased by 9% from 238 to 259 deaths per 100,000 inhabitants between 1995 and 2022. However, 12 countries saw decreases in mortality between 1995 and 2022. In 1995, Hungary and Denmark had the highest mortality rates with more than 300 cases per 100,000 inhabitants, while Cyprus, Iceland, and Romania had the lowest rates with fewer than 180 cases per 100,00 inhabitants. In 2022, Hungary was still among the top two countries with the highest mortality rate of just over 300 cases per 100,000 inhabitants along with Croatia. The lowest rates were recorded in Luxembourg, Cyprus, and Iceland with fewer than 180 cases per 100,000 inhabitants.

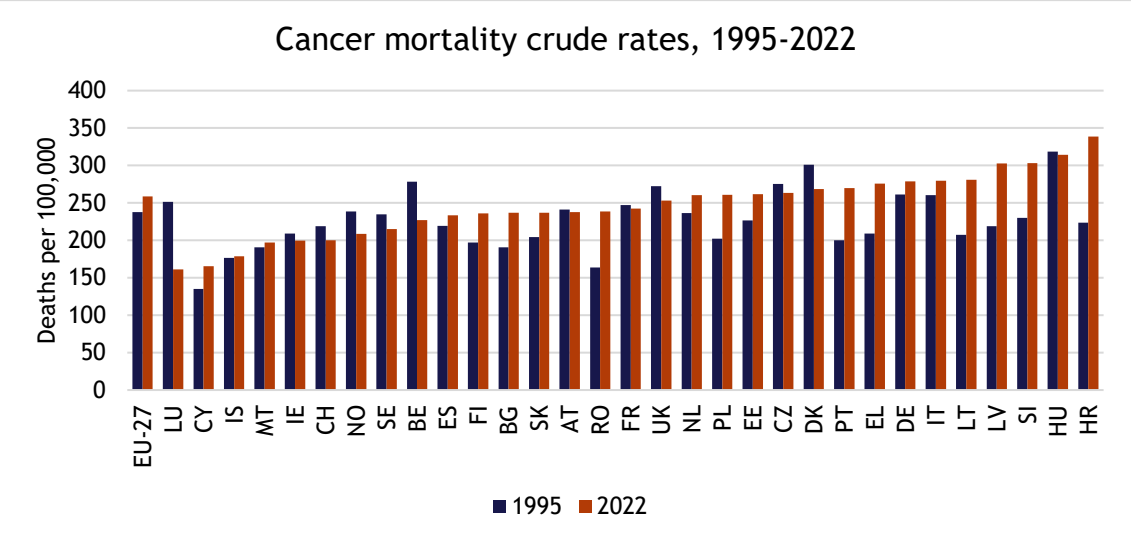


Figure 13: Number of cancer mortality cases per 100,000 inhabitants (crude rates for both sexes), 1995-2022.

Notes: Cancer is defined as all cancer sites and HIV disease resulting in malignant neoplasms (ICD-10 C00-C97, B21) in 1995 and all cancer sites in 2022 (ICD-10 C00-C97). Data for CY for 1995 is from 2004. Source: (64, 69, 89).

The magnitude and the trend in mortality crude rates should not be interpreted in isolation. A low or high mortality rate of a country does not necessarily indicate something about that country's effectiveness in managing cancer. In fact, countries with the world's lowest mortality rate are located in Sub-Saharan Africa and the Middle East (52). Higher mortality rates in Europe than elsewhere are primarily a result of higher incidence rates. For instance, Croatia had the second-highest incidence rate and the highest mortality rate in Europe in 2022, while Iceland had the lowest incidence rate and the third-lowest mortality rate.

Appendix A presents estimated age-standardized mortality rates separately for men and women (5, 80). In men, mortality rates decreased in all countries between 1995 and 2022, except in Bulgaria and Romania. Similarly, mortality rates among women decreased in all countries except in Poland, Bulgaria, and Romania. The decline in men was stronger than in women (-24% in men and -12% in women in the EU-27), mirroring the development in incidence rates and narrowing the gender gap over time; however, mortality rates among women in the EU-27 were still 38% lower than those among men in 2022.

Mortality by cancer type and age

While the absolute number of deaths from cancer has increased during the past decades, the development has not been consistent across all cancer types. As a result, the share of different cancer types has shifted markedly since 1995; see Figure 14 and Figure 15. The eight most common cancer types accounted for around 70% of all cancer deaths in men and women in 1995 and 2022.

Among men, lung cancer remained the deadliest cancer type, although its proportion of all cancer deaths declined from 29% in 1995 to 23% in 2022; see Figure 14. This is partly a reflection of its decreasing proportion among incident cases of cancer. Colorectal cancer was the second most fatal type, with its share increasing from 10% to 12%. The proportion of deaths from prostate cancer also rose slightly, overtaking stomach cancer, which has declined over time, mirroring again the pattern observed for incidence. The slight increase in prostate cancer deaths suggests that the surge in newly diagnosed cases, was not solely attributable to the detection of latent cases through PSA testing.

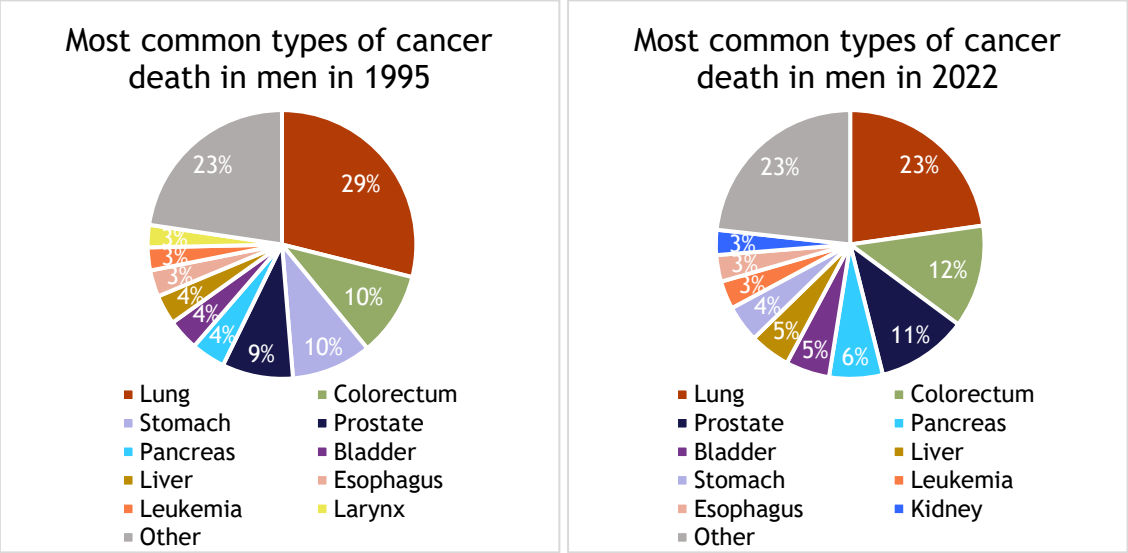


Figure 14: Most common types of cancer death in men in 1995 and 2022, Europe.

Notes: See notes and sources for Figure 10.

Among women, breast cancer was the most common cause of cancer-related death, although its proportion decreased from 19% in 1995 to 17% in 2022, as shown in Figure 15. The share of deaths from colorectal cancer decreased slightly from 13% in 1995 to 12% in 2022. Meanwhile, lung cancer became more prevalent, increasing from 10% to 15% of all cancer deaths, making it the second most common fatal cancer type in 2022. Additionally, the share of deaths attributed to stomach cancer declined over time, while the share of pancreatic cancer increased over time.

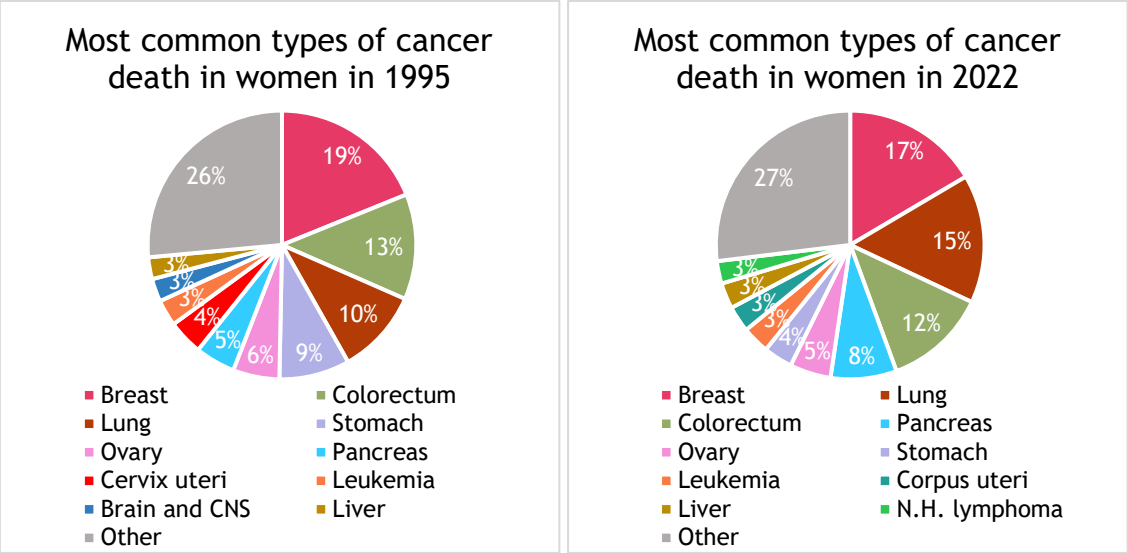


Figure 15: Most common types of cancer death in women in 1995 and 2022, Europe.

Notes: See notes and sources for Figure 10. CNS = central nervous system. N.H. = non-Hodgkin.

Cancer mortality has not increased uniformly across all age groups in recent decades. Figure 16 shows the development of recorded (rather than estimated) cancer deaths in Europe between 1995 and 2022. Overall, there was a gradual increase of 13% between 1995 and 2022. However, all age groups below 65 years recorded decreases in mortality. Cancer mortality in children (0 to 14 years) decreased by more than 50%, in young adults (15 to 39 years) by almost 50%, and in people aged 40 to 64 years by more than 20%. In contrast, cancer mortality in individuals aged 65 and older increased by 30%. This diverging trend between younger and older age groups partly mirrors the patterns observed for incidence, and it is partly influenced by varying magnitudes of improvement in survival for different age groups; see section 2.4.2. Population aging and the resulting increase in cancer incidence make it challenging to reverse the increasing mortality trend in the oldest age group.

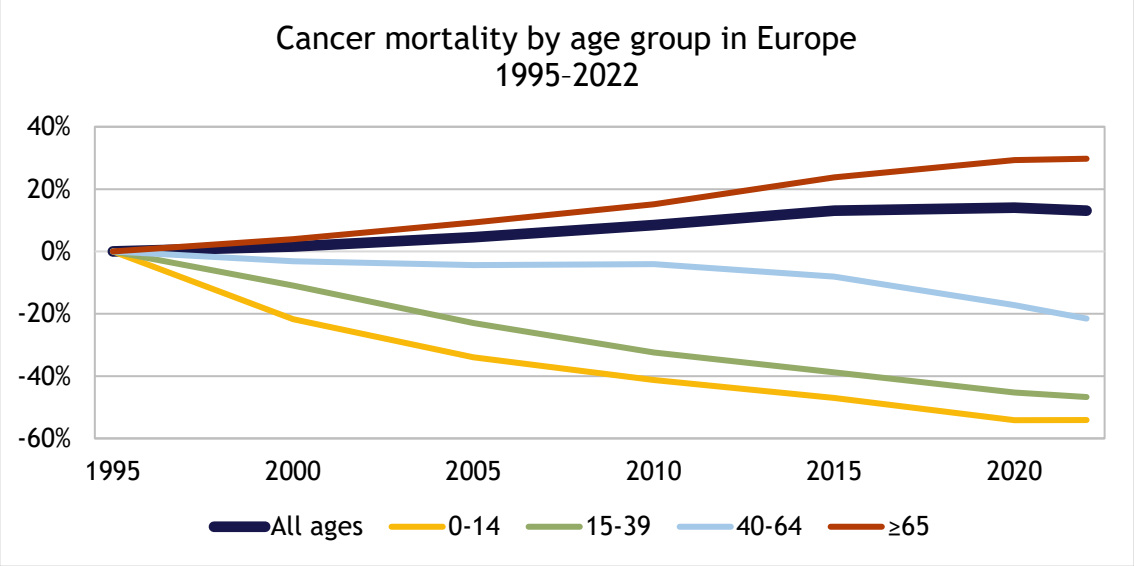


Figure 16: Cancer mortality by age group in Europe (1995=base year), 1995–2022.

Notes: Cancer is defined as C00-97,B21 in 1995–2010 and as C00-97 in 2015–2022. The development is based on the total number of cancer deaths. Data for 1995 and 2000 include figures for 2004 for CY. Source: (64, 69, 89).

2.3.3 Incidence and mortality trends

In order to compare the development of cancer incidence and mortality over time both within and across countries, rates of incidence and mortality are commonly used. The definition of these rates may lead to confusion about how to interpret trends over time. This is because there are two definitions of these "rates". Firstly, the "crude rate" shows the annual number of new cases or deaths per 100,000 inhabitants; see Figure 9 and Figure 13. Secondly, the "age-standardized rate" shows the annual number of cases per 100,000 inhabitants with fixed population weights applied to five-year age-specific rates, thereby assuming a hypothetical constant age structure of the population which removes the effect of population aging (see Appendix A). Therefore, a study that finds an increase in mortality rates in Europe could be correct, but another study that finds a decrease could also be correct.

Crude and age-standardized rates of cancer in 19 European countries are presented in Figure 17. The development of crude incidence rates shows a continuous increase for both men and women between 2003 and 2016. Crude mortality rates have risen more slowly compared to incidence rates in men and women. Age-standardized incidence rates in men have remained relatively stable, while age-standardized incidence rates in women increased. Age-standardized mortality rates, on the other hand, have decreased, with a stronger decline among men than among women.

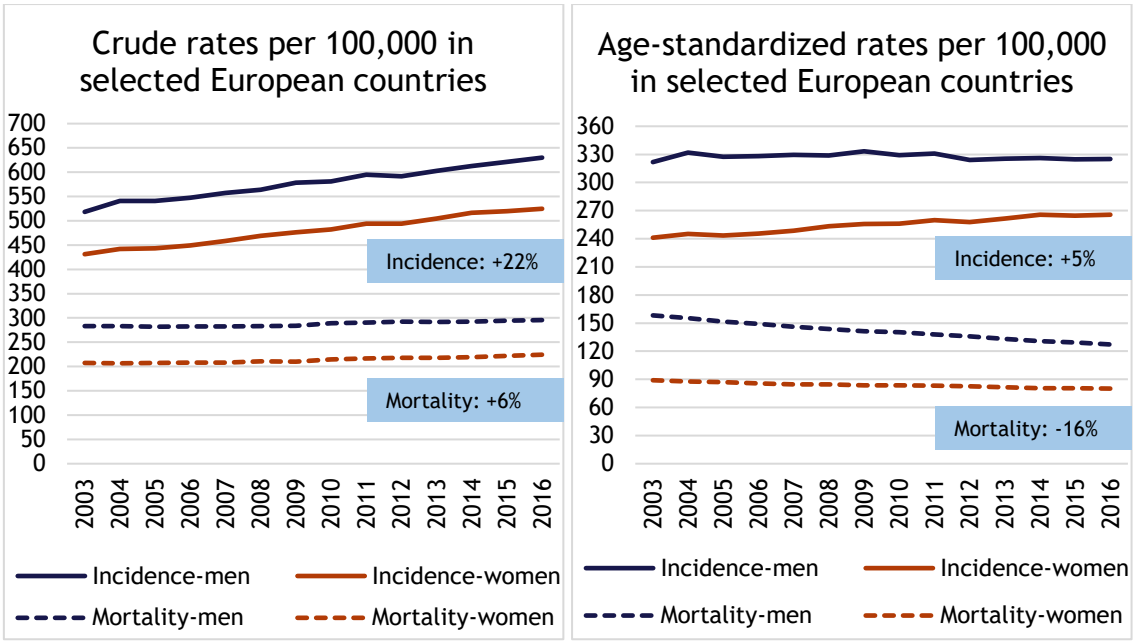


Figure 17: Crude rates and age-standardized rates (world) of cancer incidence and mortality in selected European countries, 2003-2016.

Notes: Cancer refers to all types except non-melanoma skin cancer. The countries included are AT, HR, CZ, DK, EE, FI, FR (metropolitan), DE, IE, IT, LV, LT, NL, NO, PL, SI, ES, SE, and CH. For age-standardized rates, the "world standard population" was used. Source: (10, 90).

Opposing trends in risk factors, such as declining smoking rates and rising obesity levels, contribute to the divergent patterns observed in cancer incidence and mortality rates, both overall and between sexes. For instance, between 2011 and 2021, lung cancer mortality rates in Europe decreased by 24% among men but increased by 9% among women (60). This contrast reflects the later rise in smoking rates among more recent generations of women, compared to men, whose smoking rates peaked and declined earlier. On the other hand, the increase in obesity, a known risk factor for several cancers such as colorectal, breast (postmenopausal), and endometrial cancer, contributes to rising incidence rates (91). The percentage of cancer cases attributed to obesity is higher for women than for men. This is due to obesity's stronger impact on hormone-sensitive cancers, such as breast and endometrial cancers, which are almost exclusively occurring in women. In the US, approximately 10% of cancer cases in women and 5% in men are attributed to obesity (92).

What are the health implications of the observed decrease in age-standardized mortality rates?

Studies regularly estimate the number of "hypothetically averted deaths" from cancer in Europe. In the EU, age-standardized mortality rates were highest in 1988 (93). If these rates had remained unchanged from 1988 to 2022, an additional 5.4 million people would have died from cancer over the period, including 369,000 cancer deaths in 2022 alone (93). The number of averted cancer deaths is larger for men than for women because the mortality rate in men peaked higher and declined faster, owing to developments in smoking and lung cancer.

2.4 Survival

Survival is an epidemiological measure of cancer at the individual level, whereas cancer incidence and mortality (described in section 2.3) are measures at the population level. Survival is the link between incidence and mortality. It measures the share of people that have been diagnosed with cancer in a certain year and that are still alive after a certain period of time. Survival is commonly measured as 5-year survival rates, indicating the share of people diagnosed with cancer in year t that is still alive in year t+5.[12,13]

International comparisons of cancer survival based on cancer registry data from European countries are available through the EUROCARE program (hosted by the Italian National Institute of Health, ISS) and the CONCORD program (a global surveillance program led by the London School of Hygiene & Tropical Medicine). The EUROCARE-3 project published data for 1990-1994 (98), followed by the EUROCARE-4 project for 1995-1999 (99), and the EUROCARE-5 project for 1999-2007 (13). The CONCORD-2 program estimated survival for ten cancer types diagnosed during 1995–2009 and followed up to December 31, 2009 (97). The CONCORD-3 program extended the analysis to 18 cancer types diagnosed during 2000–2014 and followed up to December 31, 2014 (100). Newer comparable survival data across European countries were not available (as of March 2025).

In anticipation of updated survival data from EUROCARE or CONCORD, Figure 18 presents a collection of the latest available survival rates from European countries where national or regional cancer registries provide such data in the public domain. The development between around the year 2000 and the latest available year of around 2020 is shown. It is very important to stress that these data are not fully comparable, because of different years in the comparison, different methodologies to estimate the survival rates, and different inclusion/exclusion criteria for cancer cases. Overall, all countries experienced increases in survival rates. This demonstrates the positive impact of advances in early detection, diagnostics, treatment, and follow-up care. Despite the incomplete data picture, there is a pattern of wealthier countries tending to record higher survival rates than poorer countries, in line with findings in the previous Comparator Reports. These country differences in cancer survival can also be translated into lives lost. If all 15 countries with known survival data in Figure 18 achieved the same survival rate as the best-performing country (Sweden), almost two hundred thousand (185,551) cancer deaths could be avoided every year.[14]

[12] This means that data on the 5-year survival rate of cancer patients diagnosed in 2024 can only be definitely evaluated after 2029 with a method called “cohort analysis”. However, alternative methods (“period analysis” and “mixed analysis”) can provide a good estimation of the likely result already earlier (94, 95).

[13] Two adjustments are routinely made to 5-year survival rates to ensure comparable rates across time and countries. Firstly, relative (also called “net”) survival rates rather than absolute (“gross” or “overall”) survival rates are measured. The relative survival rate is the ratio of two survival rates: the absolute survival rate of cancer patients divided by the expected survival rate of people in the general population with similar age and sex in the same country and calendar year (96). This adjusts survival rates for the effect of competing causes of death (background mortality) that would otherwise bias comparisons across time and countries. Thus, relative survival rates indicate the hypothetical situation in which cancer is the only cause of death (94). Secondly, the age structure of cancer patients is standardized across time and countries. As relative survival rates for most cancer types vary by age (typically they decrease with age; see section 2.4.2), they are adjusted for age at diagnosis, typically using the International Cancer Survival Standards (ICSS) (97).

[14] This back-of-the-envelope estimation combines estimated incidence numbers for all cancers excluding non-melanoma skin cancer from IARC for the year 2022 with the survival rates of the latest data period in each country with available data shown in Figure 18.

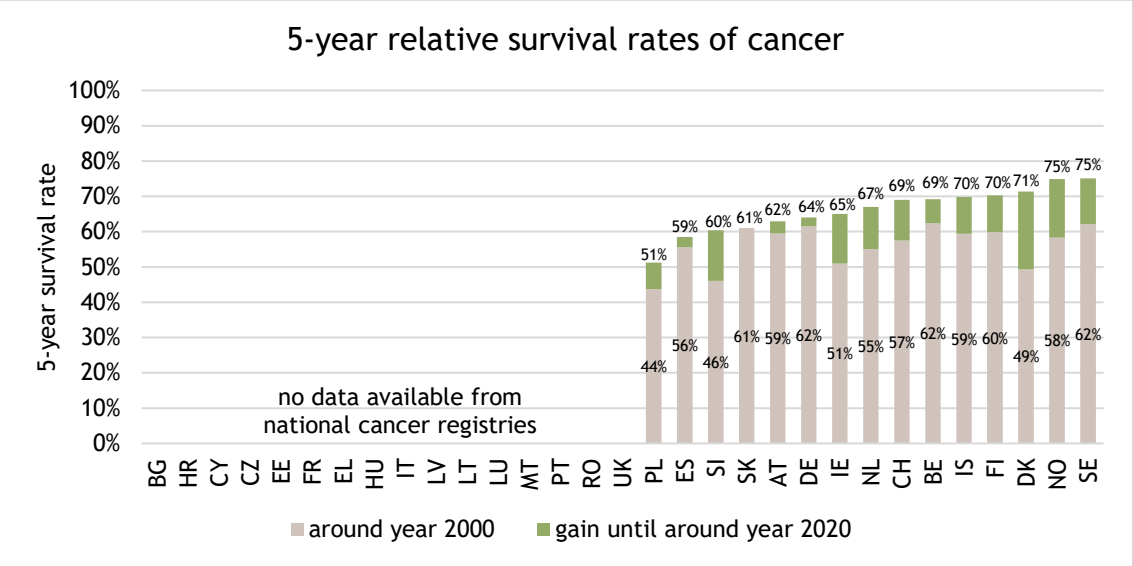


Figure 18: Five-year relative survival rates of cancer.

Notes: Cancer is defined as all sites but non-melanoma skin cancer (except in Poland) in all countries, although with varying inclusion/exclusion criteria. Survival rates are age-standardized in some but not all countries, with potentially different methods used for standardization. The period around year 2000 is 2000-2004 in AT and NL, 2004-2008 in BE, 1998-2002 in DK, FI, IS, NO, SE, 2007-2008 in DE, 1999-2003 in IE, 2000-2005 in PL, 1997-2001 in SI, 2002-2007 in ES, 1996-2000 in CH, while the latest period with available data was 2015-2019 in AT and NL, 2013-2022 in BE, 2018-2022 in DK, FI, IS, NO, SE, 2019-2020 in DE, 2014-2018 in IE, 2010-2015 in PL, 2017-2021 in SI and CH, 2008-2013 in ES while the data for SK only refer to 2017. The data for the latest period was either based on a cohort analysis or period analysis. Source: (82, 101-112).

2.4.1 Survival by cancer type and sex

There is a general upward trend in survival across most cancer types for both men and women over time, likely reflecting advancements in early detection, diagnostics and treatment, and overall healthcare quality. Figure 19 and Figure 20 show how 5-year survival rates in Austria and Sweden have evolved since the 1990s. There are several common observations:[15]

- **Survival rates have improved most for hematologic cancers**: Multiple myeloma has enjoyed improvements of around 24 percentage points[16] (pp) in Austria and around 30 pp in Sweden. Leukemia and non-Hodgkin lymphoma have also improved by more than 10 pp in Austria and more than 20 pp in Sweden.
- **Many solid tumors have seen improvements of around 10 pp**: This includes breast, head & neck, kidney, lung, prostate, and thyroid cancer as well as many gastrointestinal cancers (colorectal, esophageal, liver, pancreatic, stomach cancer).
- **Some solid tumors have seen no or little improvement**: This includes bladder cancer (in Austria but not in Sweden), brain cancer, and laryngeal cancer, gynecological cancers (cervical, uterine, ovarian cancer in Austria but not in Sweden), and testicular cancer (which is already close to 100%).
- **Several cancer types have now a survival rate exceeding 90%**: This includes breast cancer (not in Austria), Hodgkin lymphoma (not in Austria), melanoma skin cancer (not in Austria), prostate, testicular, and thyroid cancer.
- **Some cancer types still have a survival rate of 30% or less**: This includes three gastrointestinal cancers (esophageal, liver, pancreatic cancer), lung cancer (yet at the brink of breaking through 30%), and brain cancer.
- **Women have higher survival rates than men for most cancer types**:[17] The only cancer types where men have higher survival rates than women in both Austria and Sweden are bladder and kidney cancer.
- **The overall survival rate has improved more for men than women:** This is driven by the changing composition of common cancer types (see section 2.3.1). Lung cancer with its low survival rate has become relatively less common in men and hence raised their overall survival rate, while lung cancer in women has become more common and therefore suppressed their overall survival rate.

[15] There are some differences in the definition of the cancer types in Austria in Sweden, in particular for colorectal cancer (includes anal cancer in AT), ovarian cancer (includes tubes in SE), bladder cancer (includes urinary tract in SE) (82, 103). In addition, the Swedish Cancer Registry does not search for and perform follow-back in other registers for cancer cases identified from death certificates, which overestimates survival for cancers especially with high lethality (82).

[16] A percentage point is the absolute difference between two percentages. It is used to describe changes in percentages without confusing them with relative percentage changes. For example, if the survival rate improves from 20% to 30%, the increase is 10 percentage points whereas the relative change is 50%.

[17] Although women in Sweden have higher survival rates than men for almost every cancer type that occurs in both sexes, the survival rate for all cancers is higher for men. This is driven by the large proportion of prostate cancers in men, which have a high survival rate and therefore raise the overall survival rate.

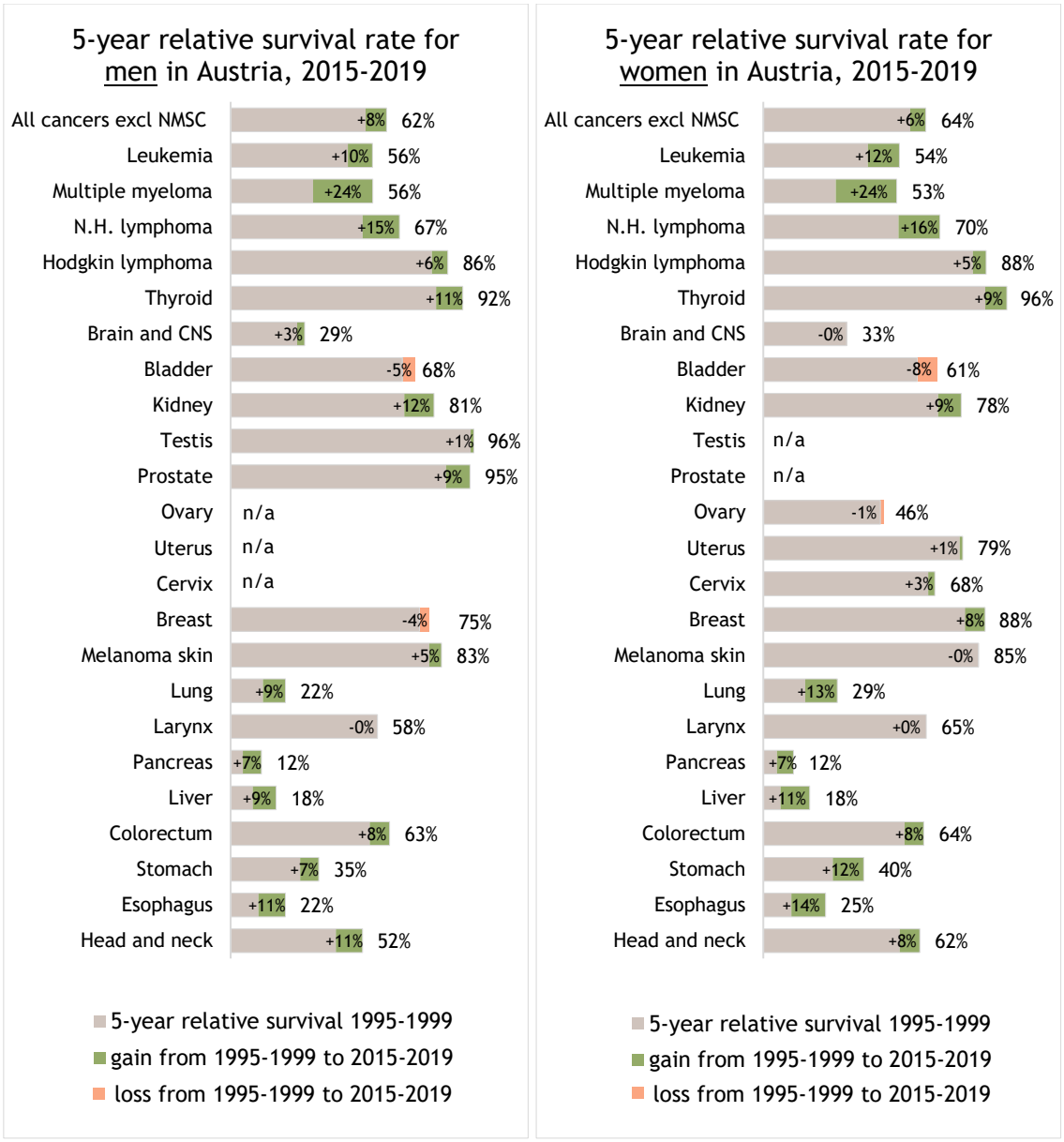


Figure 19: 5-year relative cancer survival rates for men and women in Austria, 2015-2019.

Notes: NMSC = non-melanoma skin cancer, N.H. = non-Hodgkin. CNS = central nervous system. The survival rates are followed up until Dec 31, 2024. Source: (103).

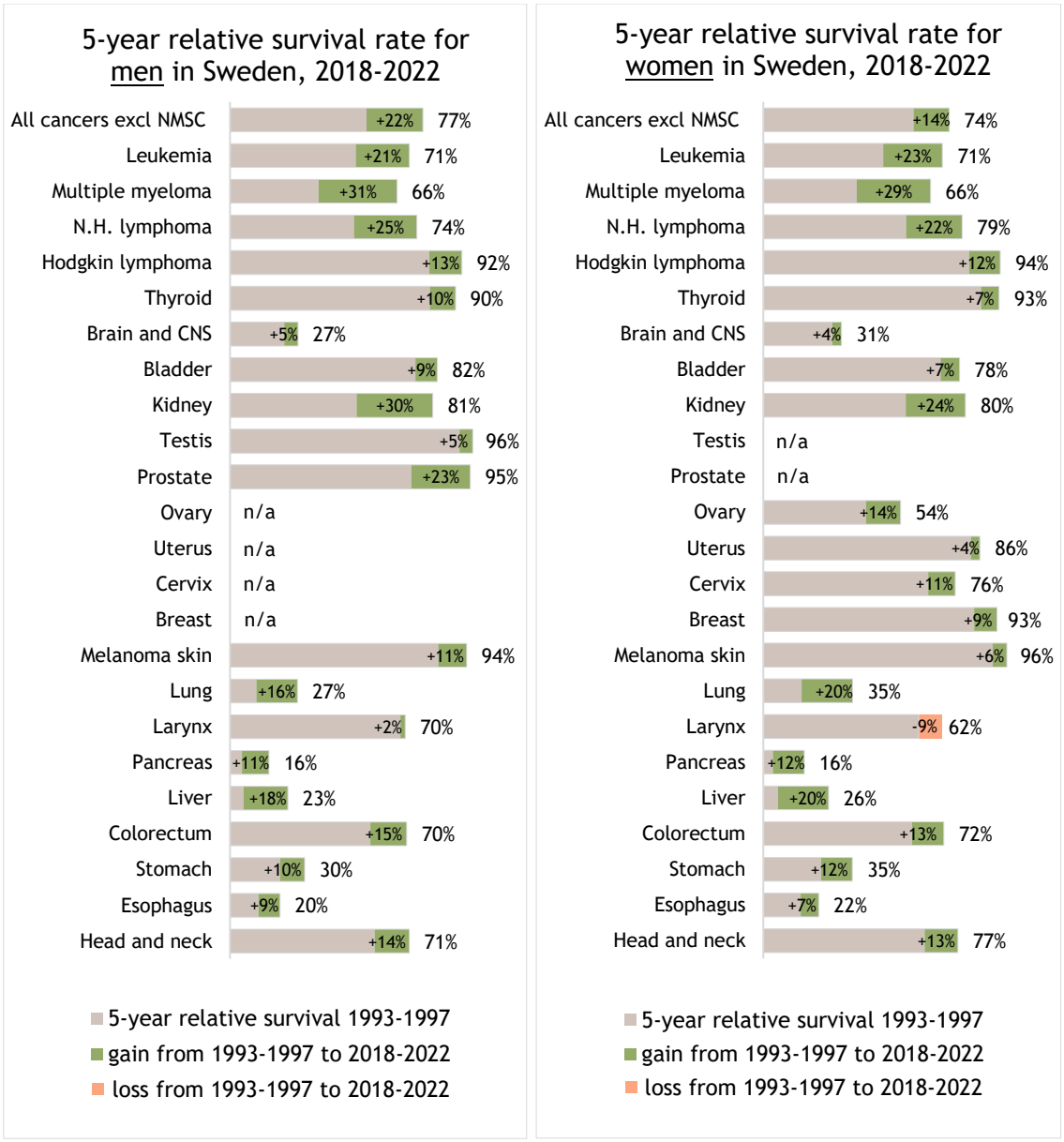


Figure 20: 5-year relative cancer survival rates for men and women in Sweden, 2018-2022.

Notes: NMSC = non-melanoma skin cancer, N.H. = non-Hodgkin. CNS = central nervous system. The survival rates are age-standardized with the International Cancer Survival Standards. For brain and pancreatic cancer in men, the 5-year survival rate from the closest available data point (1998-2002) was used instead of 1993-1997. Source: (82).

2.4.2 Survival by stage at diagnosis and age

Survival rates vary greatly by stage at diagnosis. Patients with tumors detected in stage IV when they have already metastasized (i.e., spread across the body from the original tumor site) have the lowest survival rates, while patients with tumors detected early in stage I when they are still small and confined to the original tumor site have the highest survival rates. Improvements in survival across all stages of cancer have been recorded in the past decades; see the example of the Netherlands in Figure 21. The magnitude of improvement varies by stage. Survival rates for early-stage cancers (stages I and II) were already comparatively high in 1995-1999 and increased by 8 pp and 6 pp, respectively, until 2015-2019, yet there was little or no progress from 2005-2009 to 2015-2019. Stage III cancers witnessed the largest gains with a 22-pp increase over the period, suggesting advancements in treatment for regionally advanced cancers. Stage IV cancers have the poorest outcomes, yet the 8-pp improvement reflects meaningful progress in treatment, with greater progress observed from 2005-2009 to 2015-2019.

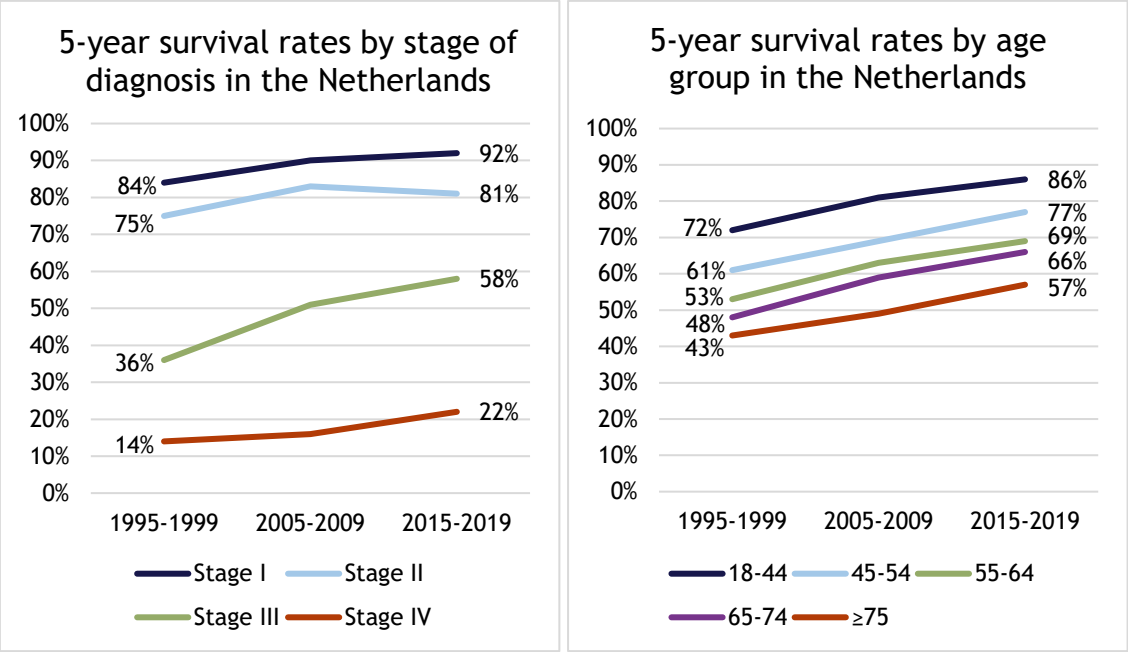


Figure 21: 5-year relative survival rates by stage of diagnosis and by age group in the Netherlands, 1995-1999 to 2015-2019.

Notes: Data were age-standardized according to International Cancer Survival Standard classification and survival rates aggregated for all cancers. The overall 5-year relative survival rate improved from 51% in 1995-1999 to 67% in 2015-2019. Source: (113).

Figure 21 shows how 5-year survival rates differ by age at diagnosis in the Netherlands. Younger patients have the highest survival rates and older patients have the lowest survival rates. Nevertheless, survival rates improved for all age groups between 1995–1999 and 2015–2019. The greatest improvement was observed in the 65–74 age group with an 18-pp increase, followed by prime age adults (45–64 years) with a 16-pp improvement in both subgroups. The youngest and oldest age groups both experienced a 14-pp increase in survival rates. While younger patients already had comparatively high survival rates in 1995-1999 (72%), the older group (≥75 years) still lagged behind in 2015-2019 (57%), reflecting ongoing challenges in treating elderly patients with comorbidities or frailty as well as in early detection after the end of eligibility for screening programs.

2.5 Economic burden

Cancer imposes an economic burden on society in addition to the costs arising for patients and their families. The economic burden is here defined more broadly than in an everyday meaning. Generally, three types of costs can be distinguished as shown in Table 2 (46).

Table 2: Components of the economic burden of cancer

Component	Description
Direct costs (medical and non-medical expenditure) 	These costs encompass both public and private expenditures for services within the healthcare system (including and treatments as well as preventive measures such as HPV vaccination program and public health campaigns focusing on risk factors, screening programs, diagnostic procedures, treatments, rehabilitation services, psychosocial care) and any formal support services outside the healthcare system. Non-medical expenditures cover transportation expenses for patients traveling to healthcare facilities.
Indirect costs (productivity loss) 	These are costs corresponding to patients' productivity loss arising from the inability to work due to the disease. They consist of the temporary inability (sick leave) or permanent inability (early retirement) to work in the formal labor market (called morbidity-related productivity loss) and from premature death (called mortality-related productivity loss) of working-age patients.
Informal care costs 	These costs represent the value of the time spent by family members and friends providing unpaid care. This includes the time spent on transporting a patient to a healthcare facility and assistance with household chores.

The purpose of this section is to assess the economic impact of cancer in Europe and to explore how it has evolved from 1995 to 2023. The methodology for estimating direct and indirect costs follows that in previous Comparator Reports and is described in a forthcoming manuscript. All costs are calculated in euros (€) to facilitate a comparison between countries. As the estimates cover the period from 1995 to 2023, the effects of a general increase in prices (inflation) and of fluctuating exchange rates must be taken into account. The main results are therefore presented in 2023 price levels and exchange rates. To take into account different price levels between countries, costs are adjusted for differences in purchasing power parity (PPP) in some comparisons.

2.5.1 Direct costs

The direct costs of cancer encompass mostly expenditure within the healthcare system for care services. In order to contextualize the health expenditure specifically for cancer, Table 3 shows first the development of total health expenditure (for all diseases and illnesses) across Europe over time. In 1995, total health expenditure amounted to €620 billion and more than tripled to €2,216 billion by 2023. When adjusted for inflation and exchange rates to 2023 values, the total health expenditure in 1995 would be equivalent to €1,056 billion, which is around half the size of the spending level in 2023. Similarly, expenditure per capita more than tripled in unadjusted figures (from €1,252 to €4,169) and doubled in adjusted figures (from €2,133 to €4,169) in 1995-2023. Health spending also increased in relative terms, with the share of health expenditure of gross domestic product (GDP) rising from 8% in 1995 to 10% in 2023.

Table 3: Total health expenditure in Europe, 1995-2023

	1995	2000	2005	2010	2015	2020	2023	Change 1995-2023
Current prices (in billion €)	620	835	1,093	1,343	1,591	1,875	2,216	+257%
2023 prices (in billion €)	1,056	1,301	1,566	1,792	1,911	2,218	2,216	+110%
Current prices per capita (in €)	1,252	1,672	2,155	2,601	3,045	3,547	4,169	+233%
2023 prices per capita (in €)	2,133	2,606	3,088	3,469	3,657	4,194	4,169	+95%
Share of GDP	8%	8%	9%	10%	10%	11%	10%	

Notes: Total health expenditure for CY and MT in 2023 was calculated based on GDP data from 2023 and the share of total health expenditure from 2022. The adjustment for inflation was carried out with country-specific inflation rates. The 1995 estimates are only adjusted for inflation between 1996 and 2023. Missing annual inflation rates for BG (1996; 3%), HR (1996–1997; 3%), and CH (1996–2004; 1%) were imputed. Source: (114-118).

In line with the previous Comparator Reports, the direct costs of cancer were estimated in a top-down manner, where the share of total health expenditure that is spent on cancer care is the key component. Ideally, we would require estimates of cancer-specific health expenditure for every country and every year between 1995 and 2023. However, national estimates could only be identified for 22 out of the 31 countries (2 more than in the 2019-Comparator Report); see section 5.3.1 for a list of countries. For 10 of these countries, information on the cancer-specific health expenditure was available for more than one year and was provided by the same source; see Figure 22. In these countries, the shares of cancer-specific health expenditure remained mostly stable (Estonia, Finland, Norway, Slovenia, UK), increased slightly (Czechia, France, Germany, Poland), or increased more significantly (the Netherlands) from the 2000s until the last available data point.

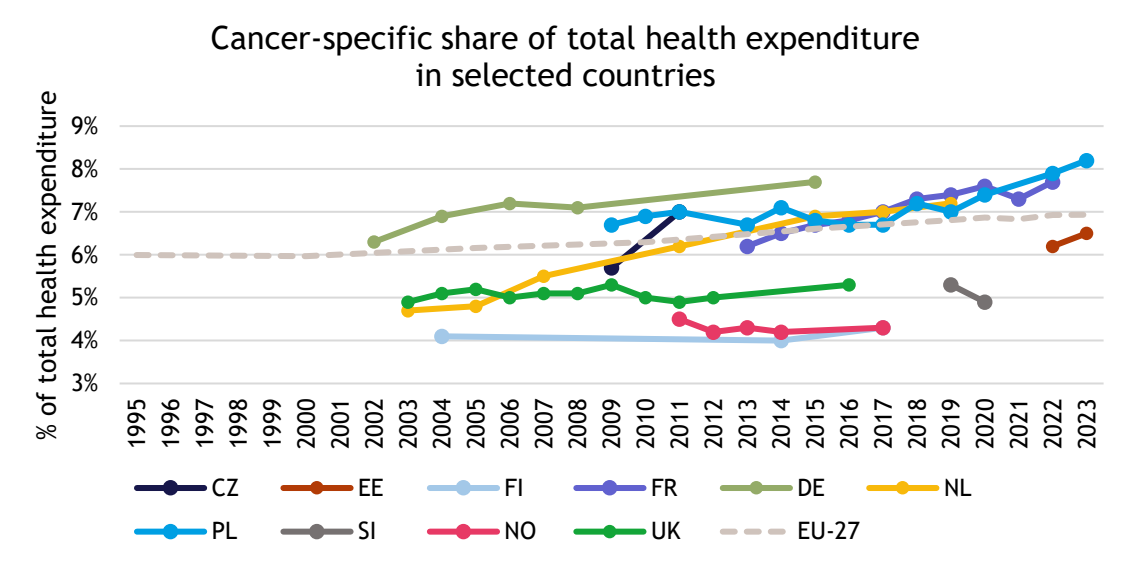


Figure 22: Cancer-specific share of total health expenditure in selected countries.

Notes: See previous Comparator reports and a forthcoming manuscript for sources and estimations of the shares.

Info box 4. Why has the share of healthcare resources devoted to cancer remained relatively stable?

The comparatively stable share suggests that the growth in absolute expenditure on cancer care has not outpaced the overall growth of total healthcare expenditure. This might be explained by the following developments:

- **Shift of the treatment setting from inpatient care to outpatient care:** Cancer care has become more effective as new and improved treatment modalities have been introduced. In many cases, these improvements enable shorter hospital stays, entail fewer side effects, and result in quicker recovery and potentially fewer recurrences/relapses of the disease (119). For example, the introduction of antiemetic medicines in the early 1990s meant that patients treated with chemotherapy no longer had to suffer from vomiting and nausea, which are common side effects of chemotherapy. This enabled more patients to be shifted from expensive inpatient care to cheaper outpatient care.

  Example: Sweden

  The shift in treatment settings is reflected in the composition of direct cancer costs in Sweden between 2013 and 2022 (120, 121). In 2013, inpatient care accounted for 42% of direct costs (SEK 6.5 billion), but this share decreased to 30% in 2022 (9.4 billion SEK). Conversely, outpatient care increased from 25% in 2013 (SEK 4.1 billion) to 38% of total direct costs in 2022 (SEK 12.1 billion). Medicines increased its share from 18% (SEK 2.7 billion) to 26% (SEK 8.1 billion). This development is a continuation of the trends shown in the previous Comparator Report based on the example from Finland in the period 2004-2014 (46, 122).

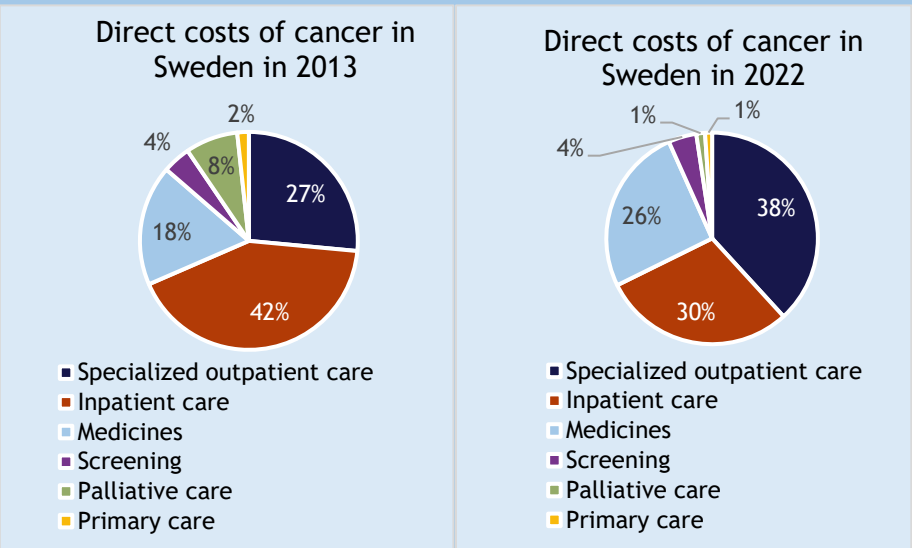


Figure 23: Direct cost of cancer in Sweden, 2013 & 2022.

Source: (120, 121).

- **More efficient use of radiation therapy**: Hypofractionation is a method to deliver high doses of radiation at fewer treatment sessions. It was introduced during the last ten years, offering the benefits of shortening treatment time without impeding health outcomes. Recent estimates indicate that, e.g., the cost of breast cancer treatment with hypofractionation is around 30% lower than with conventional radiation therapy (123). Hypofractionation also reduces non-medical costs for patients and their families, such as travel costs and the time spent by informal caregivers going back and forth to the hospital every day.
- **Changing method of administration of medicines:** There has been a shift from chemotherapy to targeted therapies (see section 4). Some of these targeted therapies come in the form of tablets rather than intravenous infusion. Additionally, some targeted therapies and recently also immunotherapies can be administered as a subcutaneous injection, which reduces the administration time and might be more convenient for patients (124). As more patients can receive treatment at home (with oral tablets) or quicker at a clinic (with subcutaneous injection), the demand for both inpatient and outpatient care decreased.

A stable pattern in the cancer-specific share of total health expenditure has also been observed in the US over a much longer period. Between 1963 and 1995, this share remained close to 5% (125). In 2010, cancer-related costs amounted to $125 billion, while total health expenditure reached $2,438 billion, corresponding to a share of 5.1% (118, 126). The cancer-related costs increased further to $171 billion[18] in 2015, corresponding to a share of 5.7% (118, 127). While the cancer-specific share of health expenditure remained relatively stable, total health expenditure as a share of GDP increased in the US. As a result, more resources were allocated to healthcare overall, but the proportion spent on cancer did not change markedly. This situation mirrors the one in Europe. The European and US numbers are also similar to estimates from China, where cancer accounted for around 5.8% of total health expenditure in 2017 (128).

An overview of the health expenditure and the results of the estimation of the direct costs of cancer by country in 2023 is shown in Table 4. The proportion of total health expenditure devoted to cancer care ranged from around 4% in Finland and Iceland to around 8% in France, Germany, and Poland. There was no clear link between the share spent on cancer and national wealth (GDP per capita) or cancer incidence (see Appendix B). On average, 6.6% of the health expenditure in European countries is related to cancer, translating to per-capita costs of €260. Per-capita spending on cancer varied widely, ranging from below €150 in some Central and Eastern European countries to more than €400 in Germany and Switzerland. When comparing the direct costs of cancer between countries, it should be remembered that these costs only represent a single number of the monetary value of all resources used. For the monetary input to yield the highest benefits to patients, an effective allocation and organization of resources is pivotal (129).

Table 4: Total health expenditure and direct costs of cancer (adjusted for PPP), 2023

	Total health expenditure (THE)			Direct costs of cancer		
	% of GDP	total (million €, PPP)	per capita (€, PPP)	% of THE	total (million €, PPP)	per capita (€, PPP)
Austria	11.0%	45,766	5,012	6.9%*	3,135	343
Belgium	10.9%	58,008	4,928	6.4%	3,713	315
Bulgaria	7.7%	12,095	1,876	7.7%*	925	144
Croatia	7.6%	8,539	2,166	6.0%*	512	130
Cyprus	9.1%	3,182	3,432	6.3%	200	216
Czechia	8.5%	32,431	2,981	7.0%	2,270	209
Denmark	9.4%	27,129	4,561	4.4%	1,194	201
Estonia	7.6%	3,208	2,348	6.5%	208	153
Finland	10.1%	22,620	4,056	4.3%	973	174
France	11.6%	304,423	4,458	7.7%	23,441	343
Germany	11.8%	439,144	5,196	7.7%	33,814	400
Greece	8.4%	22,858	2,167	7.3%	1,669	158
Hungary	6.4%	17,557	1,830	7.1%	1,247	130
Iceland	9.0%	1,734	4,570	3.8%	66	174
Ireland	6.6%	27,874	5,263	5.3%*	1,477	279
Italy	8.4%	186,172	3,156	6.7%	12,474	211
Latvia	7.8%	3,768	2,002	7.1%*	266	141
Lithuania	7.3%	6,975	2,429	7.6%	530	185

[18] The original source states cost of $183 billion measured in 2019 prices (127), which correspond to $171 billion in 2015 prices (own calculations).

	Total health expenditure (THE)			Direct costs of cancer		
Luxembourg	5.8%	3,467	5,192	7.5%*	261	391
Malta	9.8%	2,248	4,061	6.8%*	152	275
Netherlands	10.1%	91,513	5,119	7.2%	6,589	369
Norway	9.3%	33,383	6,024	4.3%	1,435	259
Poland	7.0%	79,131	2,103	8.2%	6,489	172
Portugal	10.0%	32,343	3,058	5.4%	1,747	165
Romania	5.9%	33,392	1,752	7.7%*	2,554	134
Slovakia	8.6%	13,099	2,400	7.1%*	923	169
Slovenia	9.4%	6,956	3,280	4.9%	341	161
Spain	9.6%	157,497	3,255	4.9%	7,717	160
Sweden	10.9%	49,799	4,698	5.1%	2,540	240
Switzerland	12.0%	62,485	7,088	6.0%	3,749	425
United Kingdom	10.9%	262,020	4,132	5.3%	13,887	219
Europe	10.2%	2,050,818	3,951	6.6%	136,498	260
EU-27	10.1%	1,691,195	3,860	6.9%	117,361	268

Notes: GDP = gross domestic product, PPP = purchasing power parity, THE = total health expenditure. * The estimated share is based on data from similar countries; see a forthcoming manuscript for the methodology. Source for THE: see Table 3. Source for direct costs of cancer: own estimates based on national sources; see forthcoming manuscript. Population data for per capita costs was gathered from Eurostat and ONS (54, 75).

Differences between countries in per-capita health spending on cancer in 2023 are also visualized in Figure 24. The three Benelux countries, the three German-speaking countries, and France topped the chart, spending between €315 and €425 per capita on cancer (PPP-adjusted). In contrast, three Nordic countries (Denmark, Norway, Sweden), the UK, Ireland, Italy, Czechia, Malta, and Cyprus fell into a mid-range of €200 to €280 per capita. Many Central and Eastern European countries spent the least, with Hungary, Croatia, Romania, Latvia, and Bulgaria spending less than €150 per capita. The spending gap between countries widens when price differences are not considered. In this case, Switzerland's unadjusted spending reaches a staggering €666, eight times higher than Romania's €76. This vast difference does not stem from cancer receiving a smaller spending proportion in Romania, because this proportion (estimated at 7.7% of total health expenditure) actually exceeds the proportion in Switzerland (6.0%). Instead, Romania invests only half as much of its GDP into health care as Switzerland (5.9% of GDP in Romania vs. 12.0% in Switzerland). A comparatively low expenditure on health care in general is a systematic pattern observed across most Central and Eastern European countries. The remaining differences are explained by the higher wealth of countries in Western Europe.

Although the direct costs of cancer varied significantly across countries in 2023, the disparities were even more pronounced in 1995. At that time, Romania, Bulgaria, Poland, and the Baltic countries spent less than €10 per capita on cancer in non-PPP adjusted terms, while Switzerland's expenditure was almost €200. All aforementioned countries were still below the Swiss spending level observed 28 years ago in 2023. Nevertheless, a certain degree of convergence was observable between 1995 and 2023, as per-capita health spending on cancer increased more rapidly in the less affluent Central and Eastern European countries than in other regions.

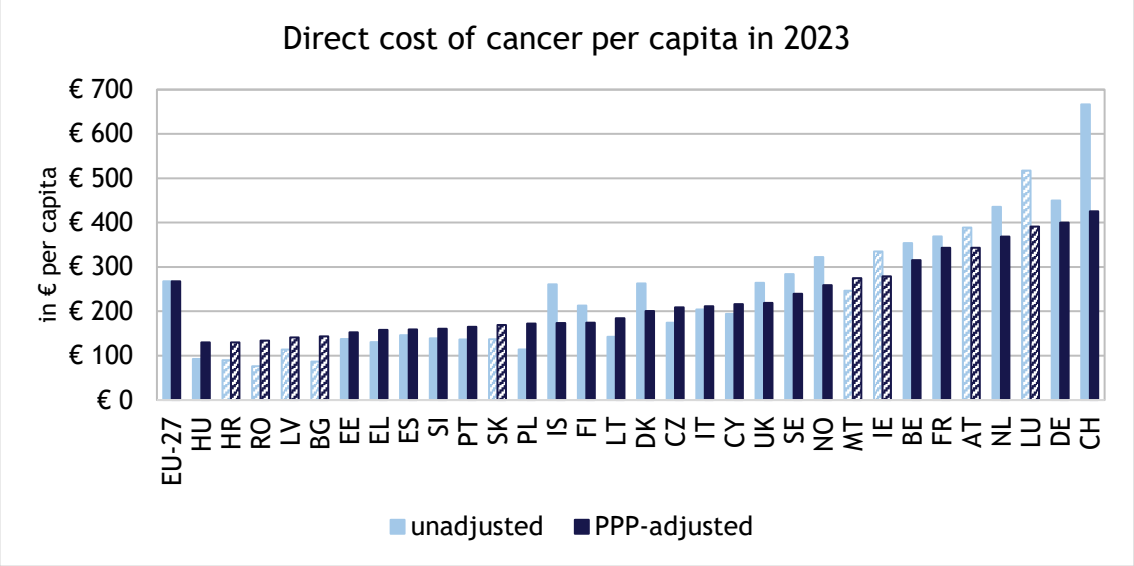


Figure 24: Direct costs of cancer per capita (in €), 2023.

Notes: Hatched bars indicate that the direct costs are estimated based on data from similar countries. PPP = purchasing power parity. Source: own estimates based on national sources; see forthcoming manuscript.

The development of the direct costs of cancer in Europe as a whole between 1995 and 2023 is shown in Figure 25 (per-capita figures are shown in Appendix B). Measured in current prices and exchange rates, total health expenditure spent on cancer amounted to €36 billion in 1995 and quadrupled (301% increase) to €146 billion in 2023. Adjusting for inflation and applying constant exchange rates, the direct costs amounted to €62 billion in 1995 and then more than doubled (135% increase) until 2023.

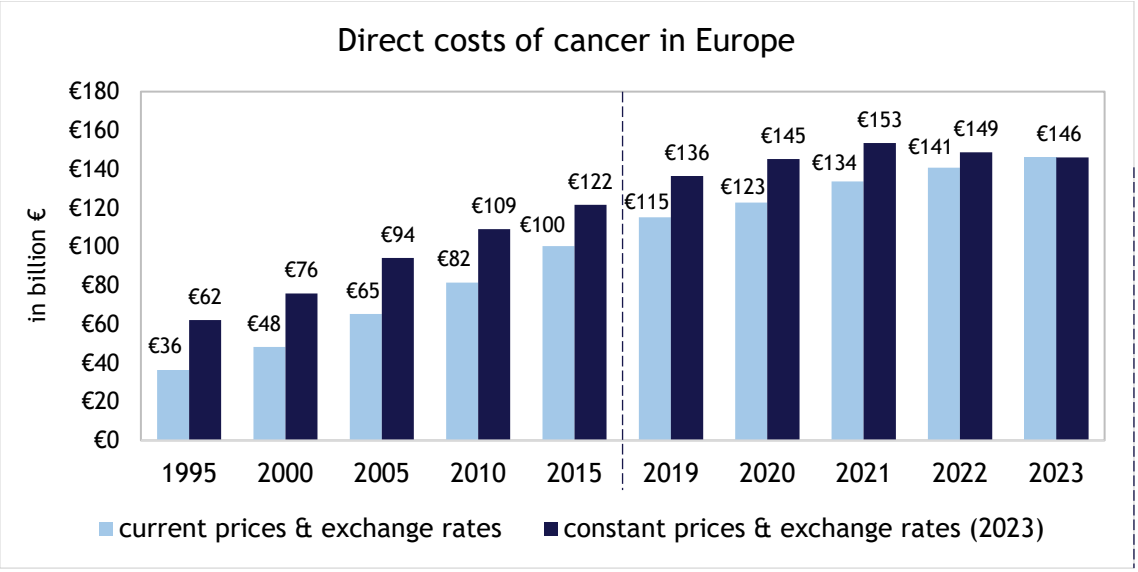


Figure 25: Direct costs of cancer in Europe in billion €, 1995-2023.

Notes: Inflation adjustments were made using country-specific inflation rates. Due to data limitations, the 1995 estimates were adjusted for inflation only for the years 1996 to 2023. Source: (115, 130) and own estimates based on national sources.

2.5.2 Indirect costs

The indirect costs of cancer are costs corresponding to patients' productivity loss arising from the inability to work due to the disease. They consist of the temporary inability (sick leave) or permanent inability (early retirement) to work in the formal labor market (called morbidity-related productivity loss) and from premature death (called mortality-related productivity loss) of working-age patients. In line with the previous Comparator Reports, the productivity loss is estimated based on the human-capital method. This method views costs from the patient's perspective and considers every hour not worked due to illness or death as a loss of productivity for the economy; see a forthcoming manuscript for a detailed explanation of the methodology.

The key component for the estimation of the mortality-related productivity loss are the potential years of working life lost (PYWLL). These are the number of working years that a person of working age (uniformly defined as 15-64 years) loses due to death before retirement age (uniformly defined as 65 years). Figure 26 shows the development of the PYWLL in Europe between 1995 and 2023, which reflects the trends already shown for cancer mortality in Figure 16 in section 2.3.2. There was a continuous reduction from 2.91 million PYWLL for both men and women in 1995 to 1.96 million PYWLL in 2023, corresponding to a 33% decrease. This decline occurred despite the overall population in the 15–64 age range growing by 3% from 331 to 340 million over the same period (131). The reduction in PYWLL is attributed to a reduction and shift of cancer deaths to older ages, reflecting also improved survival rates as shown in section 2.4. Figure 26 also highlights that PYWLL have consistently been higher among men than women throughout the period, yet with a steeper decline for men (-38%) than for women (-26%) between 1995 and 2023 which has almost eroded the entire gender gap. This mirrors the greater overall rise in survival rates among men than among women, as shown in section 2.4.1.

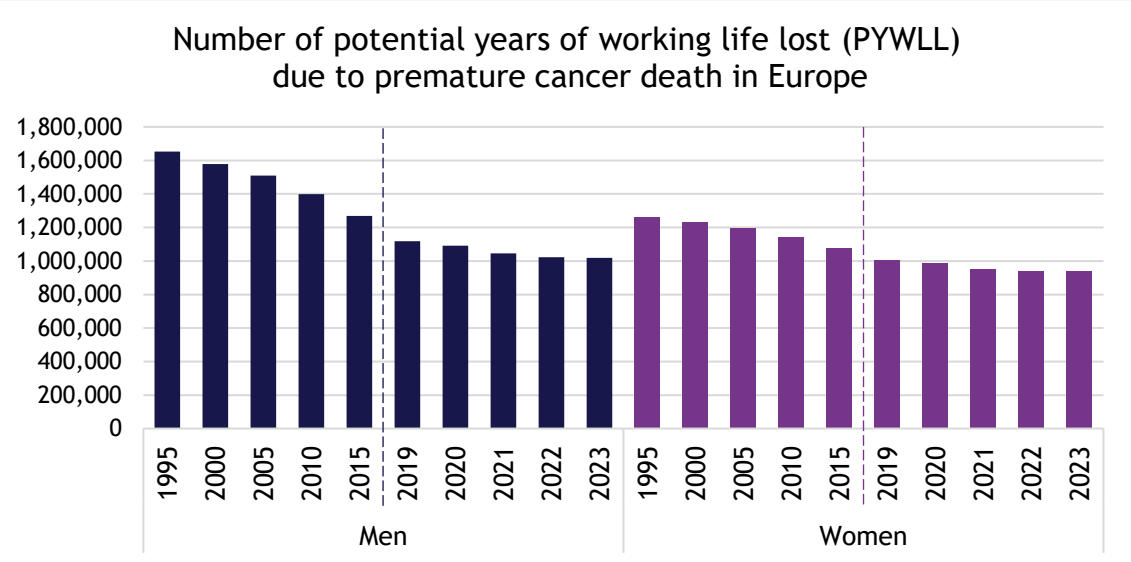


Figure 26: Number of PYWLL due to premature cancer death in Europe, 1995-2023.

Notes: PYWLL = potential years of working life lost. Cancer is defined as C00-D48. Working age stretches from 15 to 64 years inclusive. Sources: (64, 70, 89, 131).

The development in the number of PYWLL on the country level is shown in Figure 27. In 1995, Hungary had the highest PYWLL rate with around 1,500 years lost per 100,000 inhabitants aged 15-64, whereas Cyprus had the lowest rate with around 500 years lost per 100,000. Until 2023, all countries recorded a decline in the PYWLL rates, ranging from less than 15% in Portugal and Greece to over 50% in Czechia, Denmark, and Luxembourg. In 2023, Sweden, Luxembourg, and

Iceland reported the lowest rates at some 350 years lost per 100,000 inhabitants aged 15-64, which was less than half of the rates of Hungary, Bulgaria, Lithuania, Latvia, and Romania.

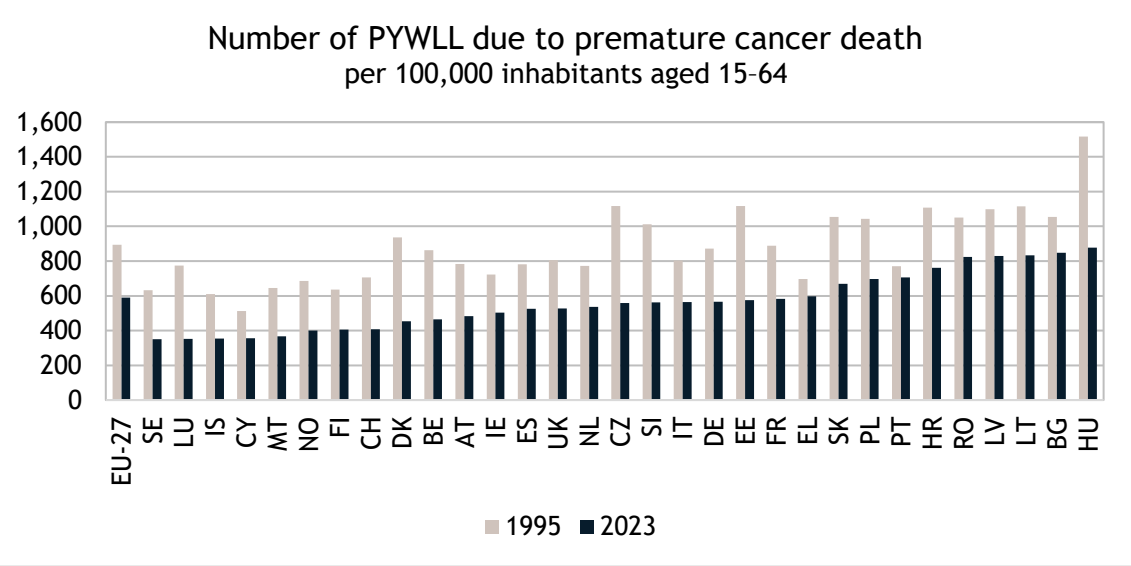


Figure 27: Number of PYWLL due to premature cancer death per 100,000 inhabitants aged 15-64, 1995 & 2023.

Notes: PYWLL = potential years of working life lost. Cancer is defined as C00-D48. Sources: (64, 70, 89, 131).

Key components for the estimation of the morbidity-related productivity loss are (i) sick leave that working cancer patients need to take after the diagnosis or start of treatment as well as (ii) early retirement if the repercussions of treatment permanently inhibit the ability to return to work. The extent of sick leave and early retirement from cancer across European countries is not well documented. In Sweden, the number of starts of sick leave from cancer (lasting longer than 14 days in a row) has been relatively stable at around 17,000 starts per year between 2006 and 2023; see Figure 28.[19] The number of approved applications for early retirement has also been quite stable with around 500 annual approvals between 2009 and 2023. This development closely aligns with the relatively steady number of newly diagnosed cancer patients (not all of whom are working) of around 19,000 cases per year in the age group 15-64 years since 2006.

[19] An aspect not captured by the public data in Sweden is the length of a sick leave. Changes in early detection, surgical techniques (e.g., greater use of organ-preserving surgery, minimally invasive surgery), the administration of radiation therapy (e.g., switch from conventional therapy to hypofractionated therapy), the route of administration of medicines (e.g., oral or subcutaneous instead of intravenous administration), and the side effects profile of newer medicines are examples of potential factors that could have an impact on the length of sick leaves.

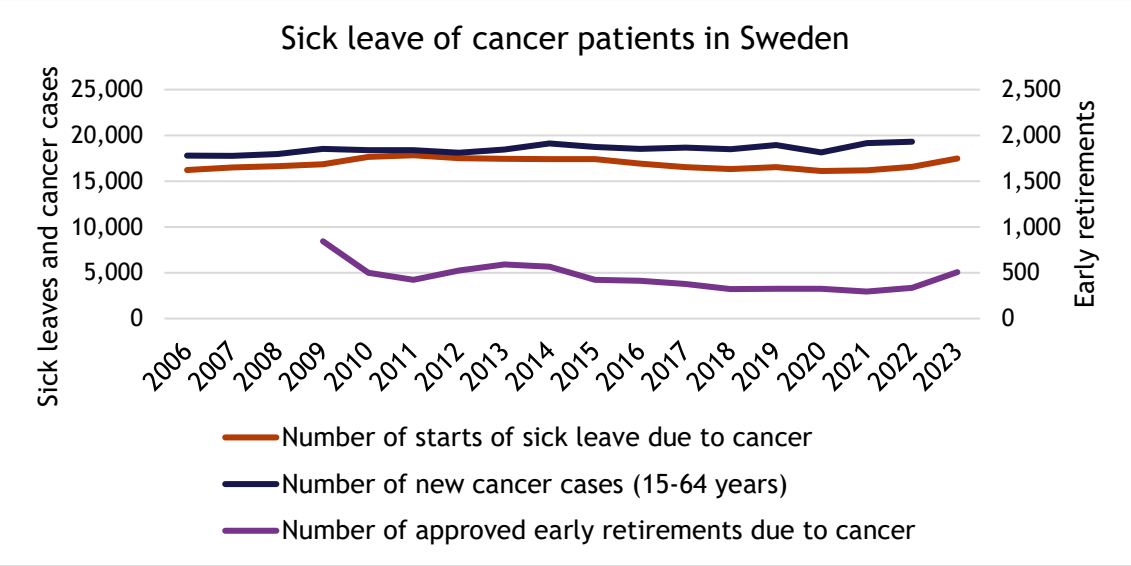


Figure 28: Sick leave of cancer patients in Sweden, 2006-2023.

Notes: Only starts of sick leave lasting longer than 14 days in a row are shown. A patient might have repeated sick leaves within a single year. Early retirement covers people aged 19-65 years. For sick leave and early retirement, cancer is defined as "neoplasms", ICD-10 C00-D48. For new cancer cases, cancer is defined as ICD-10 C00-97, D09.0-D09.1, D30.1-D30.9 D32-D33, D35.2-D35.4, D41.1-D41.9, D42-D43, D44.3-D44.5, D45-D47. Source: (82, 132, 133).

The development of the indirect costs of cancer between 1995 and 2023 in Europe as a whole is shown in Figure 29 (per-capita figures are shown in Appendix B). Over the entire period, the indirect costs fell by 16% from €97 billion to €82 billion (in 2023 prices and exchange rates). This decline is a direct result of the reduction in productivity loss from premature mortality, which witnessed a gradual 23% reduction that aligns with the fall in the PYWLL shown above in Figure 26. The productivity losses from morbidity remained steady at €24-25 billion throughout the period, following methodological assumptions made in the estimations and also reflecting the Swedish data shown in see Figure 28. The results indicate that the productivity loss from premature mortality – despite its decline – still outweighs the loss from morbidity. This is in line with many studies on the indirect costs of cancer, which have been summarized in a previous Comparator Report (47).

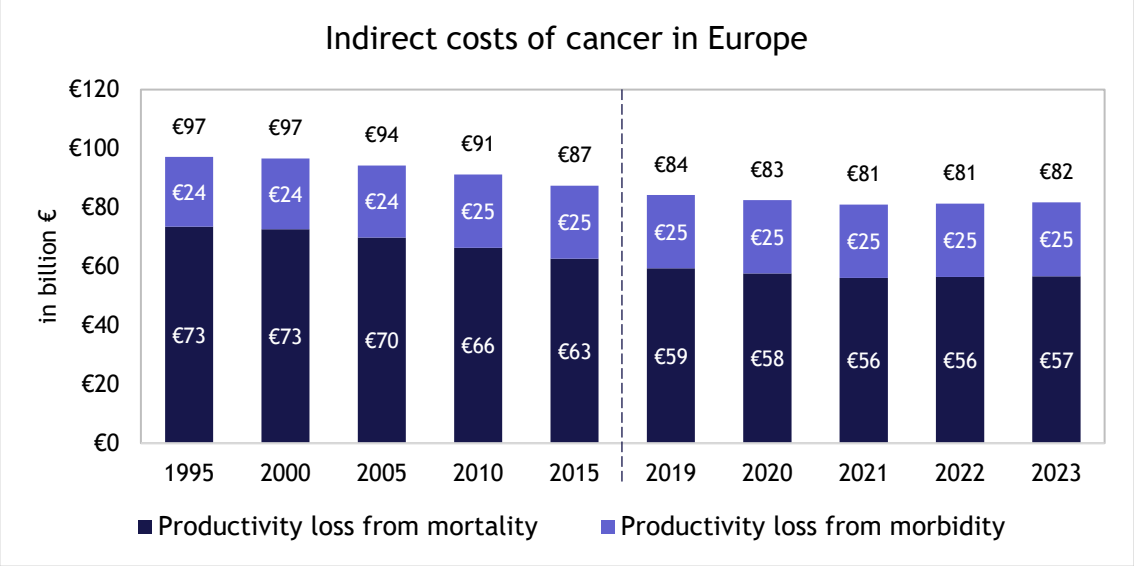


Figure 29: Indirect costs of cancer in Europe in billion € (2023 prices & exchange rates), 1995-2023.

Source: own calculations.

The indirect costs of cancer per capita amounted to €148 in 2023. Differences between countries are illustrated in Figure 30. Croatia, Denmark, Switzerland, Belgium, the Netherlands, and Norway had the highest costs of more than €200 per capita (PPP-adjusted), while Cyprus and Malta the lowest costs of around €75 per capita. In unadjusted terms for PPP differences, Switzerland, Denmark, and Iceland had the highest per-capita costs, which were around five times higher than in Bulgaria with the lowest per-capita costs.

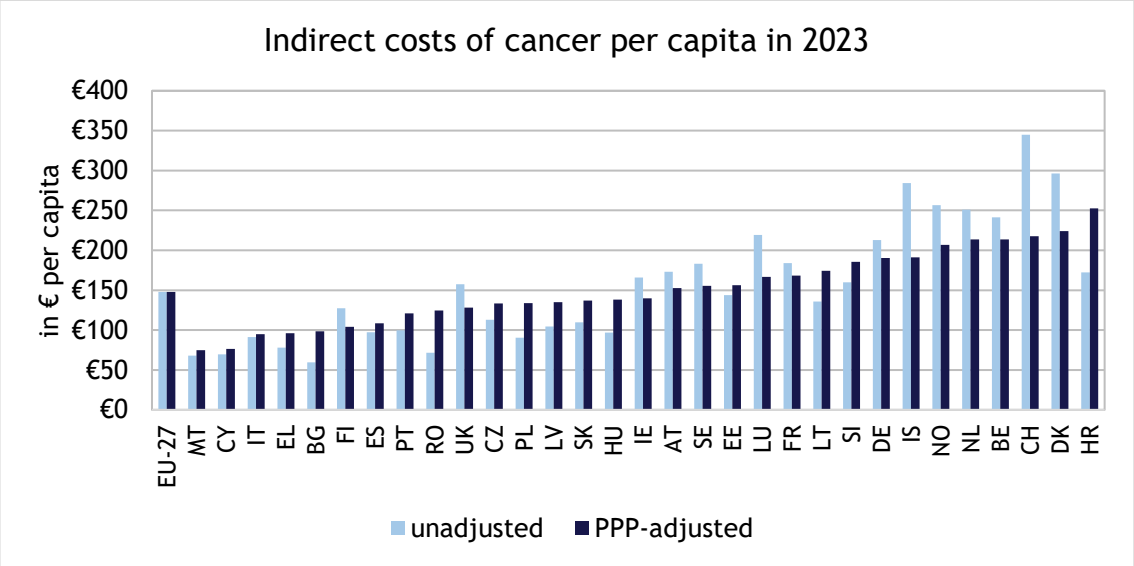


Figure 30: Indirect costs of cancer per capita in 2023.

Notes: PPP = purchasing power parity. Source: own calculations.

2.5.3 Total costs

The economic burden of cancer in Europe is summarized in Figure 31 (per-capita figures are shown in Appendix B). Between 1995 and 2023, direct costs and indirect costs developed in opposite directions. In 1995, the direct costs (not including informal care costs) amounted to €62 billion (€125 per capita) and were exceeded by the indirect costs with €97 billion (€188 per capita) (in 2023 prices and exchange rates). While direct costs grew continuously and amounted to €146 billion (€275 per capita) in 2023, indirect costs decreased to €82 billion (€148 per capita). The sum of direct and indirect costs increased by 43% from €159 billion to €228 billion in 1995-2023, and the total per-capita costs increased by 35% from €313 to €423. This increase in the economic burden can also be viewed in relation to the underlying epidemiological development. As shown in section 2.3, the total number of new cancer cases has been increasing steadily in Europe since 1995. In fact, the estimated cancer incidence grew slightly faster than the economic burden. As a result, Figure 32 shows that the economic burden of cancer per patient was rather constant at around €78,000 between 1995 and 2010 (in 2023 prices & exchange rates), before experiencing a slight drop until 2015 and then again plateauing at around €70,000-72,000 until 2023.

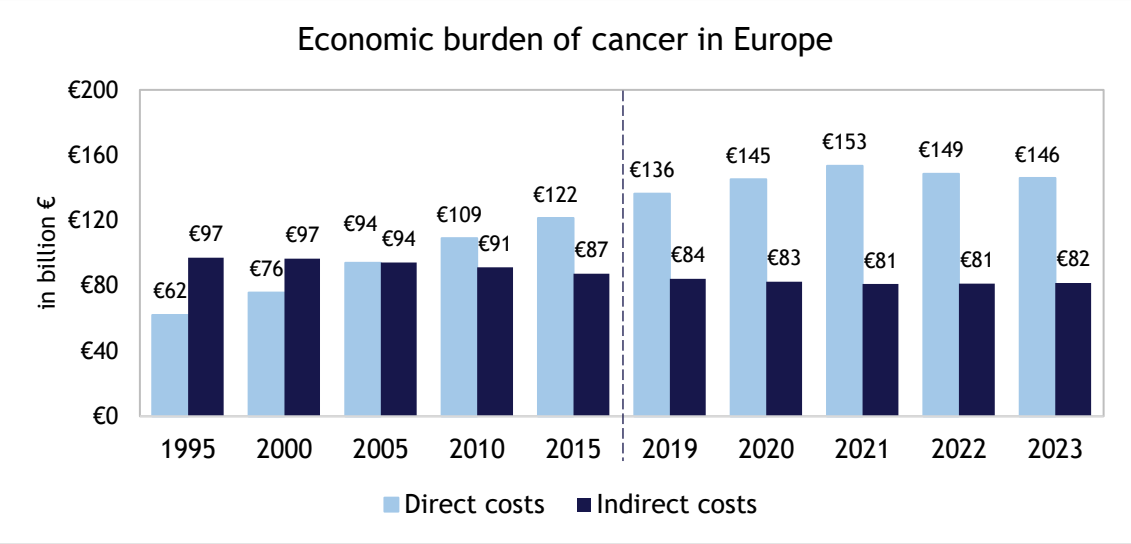


Figure 31: Economic burden of cancer in Europe in billion € (2023 prices & exchange rates), 1995-2023.

Notes: Cancer is defined as neoplasms (C00-D48). See Figure 25 and Figure 29 for further details on the calculations.

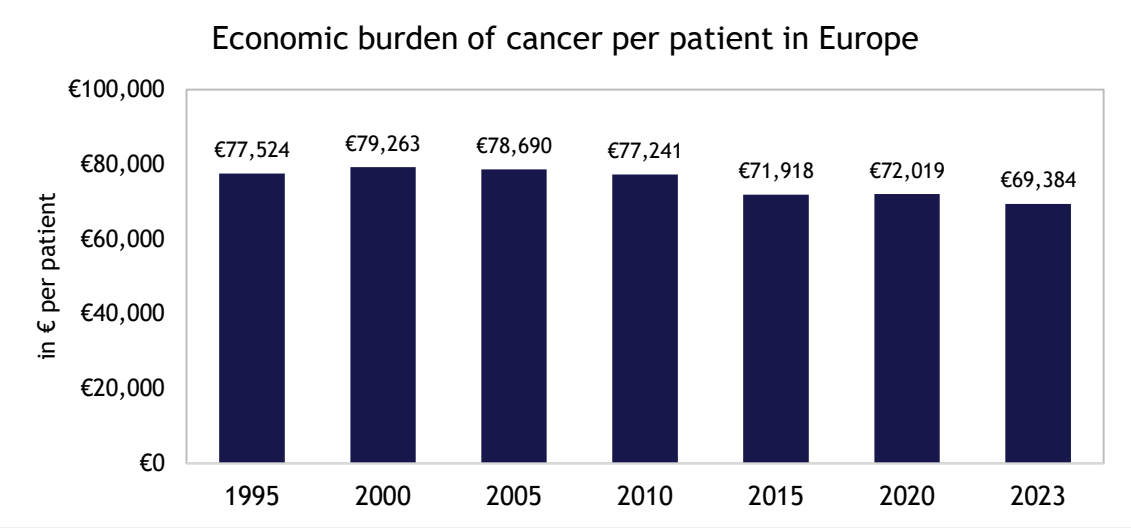


Figure 32: Economic burden of cancer per patient in Europe in € (2023 prices & exchange rates), 1995–2023.

Notes: "Patient" is defined as incidence case, using estimated data from IARC shown in Figure 1 and linear interpolations for missing years. The economic burden is the sum of direct and indirect costs. Cancer is defined as neoplasms (C00-D48). See Figure 31 for further details.

Figure 33 summarizes the development of the economic burden of cancer by country. It is evident that most countries experienced a similar pattern between 1995 and 2023, consisting of an increase in direct costs (typically by 100–200% in wealthier countries, and more than 300% in less affluent countries) and a decrease in indirect costs (typically by 20–30% in wealthier countries, and 5–30% in poorer countries). Exceptions to this pattern are Bulgaria, Croatia, Ireland, and Portugal which only recorded small decreases in indirect costs over the period, mainly related to significantly improved labor market attachment which increased the value of potentially lost working hours of working-age patients.

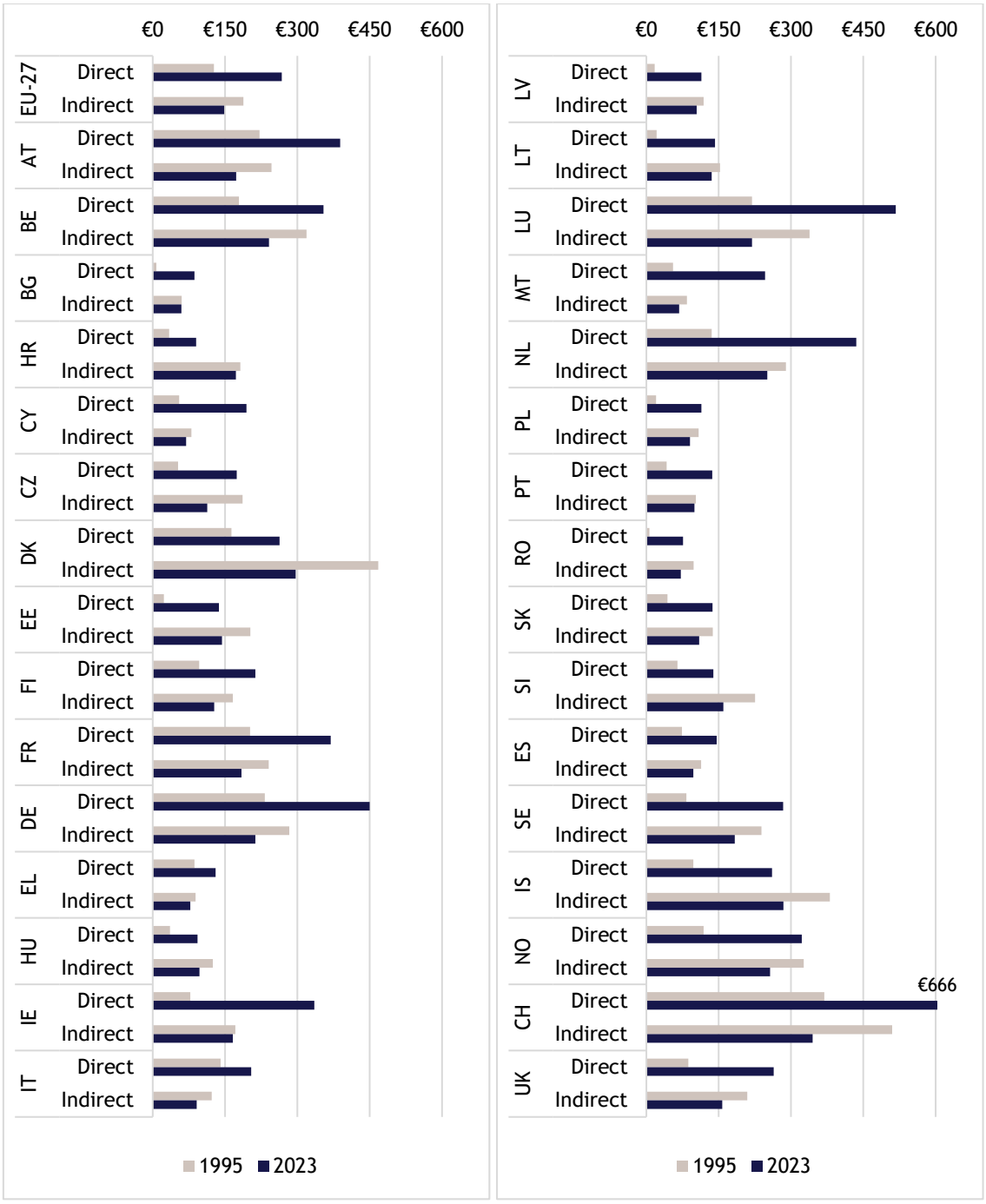


Figure 33: Economic burden of cancer per capita (in €; 2023 prices & exchange rates), 1995 & 2023.

Notes: see Figure 31. Numbers are not adjusted for PPP. The bar for direct costs in CH is truncated (true size is €666).

Future development of the economic burden

The past and future development of the economic burden of cancer over time is closely tied to epidemiological development (see sections 2.3 and 2.4). The predicted increase in the number of new cancer cases due to population aging poses a major challenge for all healthcare systems. The increasing number of cancer survivors also means that there is a growing demand for regular monitoring after treatment completion as well as rehabilitation services and psycho-oncology

services to address physical and mental needs. It will require further investment in all areas of cancer care – prevention, early detection, diagnosis and treatment, rehabilitation – as well as an effective and efficient organization to meet this challenge of increasing numbers of patients and survivors. This will very likely increase the direct costs of cancer.

Innovations in cancer care delivery will also affect the economic burden. In the foreseeable future, the introduction of additional organized screening programs, such as for lung cancer and prostate cancer, more extensive molecular testing in newly diagnosed patients, as well as the introduction of new cancer medicines at a faster rate than older ones go off patent (see section 4) will further increase the direct costs of cancer. While the introduction of innovations increases the direct costs in the short and medium term, they can in some instances be expected to decrease the costs in the long run, e.g., through earlier detection, avoidance of disease recurrences, avoidance of administering medicines to patients that will not respond, or reduced need to treat side effects. The start of HPV vaccination programs in the second half of the 2000s and the 2010s across most European countries are also expected to start yielding sizable economic benefits in the coming decade. The perhaps two biggest innovative leaps that would drastically reduce the direct costs are through early detection – either through AI-aided data mining of medical records to detect early symptoms or through screening with liquid biopsies (blood tests) for multiple cancer types simultaneously.

Although the share of cancer-specific health expenditure has remained comparatively stable in the last decades in Europe (around 6-7%), this may change in the future. Until now, increasing costs from the introduction of new cancer medicines seem to have been largely offset by reductions in the costs for inpatient care. The process of transforming cancer care from an inpatient to an outpatient setting has progressed far and might produce less savings in the future. As the possibility for further offsets through this route becomes exhausted, it might become increasingly difficult to finance further investments in new cancer medicines without an increase in the share of health expenditure devoted to cancer care. Yet other emerging routes, such as the use of AI-aided early detection, new prognostic tools to guide a more rational use of medicines, further improvements in surgical techniques, and greater precision of radiation therapy, could help to offset costs in the future.

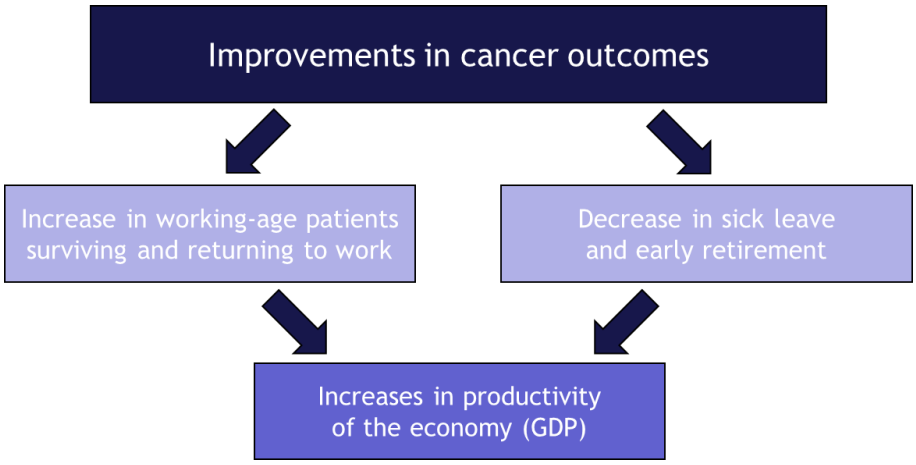


Figure 34: Indirect economic benefits of improved cancer outcomes.

The economic benefits of past improvements in cancer outcomes are reflected in the development of the indirect costs. The past decline in the indirect costs shows that the economic benefits from increased health spending on cancer care have accrued outside the healthcare system. As long as cancer care keeps improving outcomes, thereby leading to the

avoidance of deaths in working-age people as well as a reduction of sick leave and early retirement, the indirect costs of cancer will keep decreasing. This will continue to benefit the economy; see Figure 34. The same is true for informal caregivers of working age who might need to help patients less if treatments outcomes improve, which means they need less time off from work for care responsibilities.

Info box 5. Impact of COVID-19 on the disease and economic burden of cancer

(1) Disease burden

The impact of the COVID-19 pandemic on cancer care services in Europe was severe, especially during the initial months of the pandemic in 2020. The European Cancer Organisation estimated that at the height of the pandemic in Europe more than 100 million screening tests were not performed, and an estimated 1 million cancer cases went undiagnosed (134, 135). The European Commission's Joint Research Centre also conducted a survey among European cancer registries to understand how the first wave of the COVID-19 pandemic affected cancer screening, diagnoses, and care from March to May 2020 (136). This survey indicated that in most countries there were interruptions or slowdowns of organized population-based screening for breast, cervical and colorectal cancers. Cancer registries reported a significant decrease in the number cancer diagnoses. Disruptions also happened in treatment, with surgery being the most affected followed by treatment with medicines and radiation therapy. As a result, the Joint Research Centre predicted that all these disruptions lead to:

- a lower number of reported cancer incident cases in 2020;
- increases in the stage at diagnosis;
- an unquestionably negative impact on survival.

The numbers presented in this report on the disease burden of cancer show that some of these adverse consequences were perhaps less severe than anticipated. In year-to-year comparisons, the number of reported cancer incident cases in 2019 vs. 2020 was lower, but the extent ranged from -1% in Austria to -15% in Poland (19, 24); see section 1 and footnote 1. The stage distribution of cancer in the Netherlands in 2020 compared to 2019 was slightly worse (stage I cases accounted for 28% of all diagnoses in 2019, 27% in 2020, and 29% in 2021, while stage IV cases accounted for 20% of all diagnoses in 2019, 21% in 2020, and 20% in 2021) (137). The 3-year survival rate of all cancer cases diagnosed in the Netherlands in 2020-2022 was 73%, which is slightly higher than the 72% of cases diagnosed in 2015-2019 (113). In addition, the number of cancer deaths in Europe (see Figure 16) also showed no noticeable uptick in 2020 compared to previous or later years. Although a more systematic overview would be needed to carefully follow up on the predicted consequences of COVID-19 on the disease burden of cancer, the data presented here provide evidence of the remarkable resilience of cancer care systems in Europe.

(2) Economic burden

The disruptions caused by COVID-19 are also expected to impact the economic burden of cancer in several ways. Fewer diagnoses, canceled screenings, and postponed physician visits and treatments may have reduced spending on cancer care in the very short term. However, this would lead to higher spending later on as late-stage cancers, which are more expensive to treat, are diagnosed more frequently. A higher number of late-stage cancers in working-age patients would also result in higher indirect costs from premature mortality and sick leave and early retirement.

The cases of France and Poland show that a major impact on the direct costs, viewed as the cancer-specific share of total health expenditure, is unnoticeable. In France, this share was 7.4% in 2019, 7.6% in 2020, 7.3% in 2021, and 7.7% in 2022 (138, 139), while in Poland it was 7.0% in 2019, 7.4% in 2020, (no data for 2021), 7.9% in 2022, and 8.2% in 2023 (140).

Indirect costs also do not seem to have been impacted greatly. Data from Sweden on the starts of sick leave and approved early retirements due to cancer have been entirely unaffected as shown in Figure 28. The situation is a bit different in Austria, where the starts of sick leave due to cancer decreased by 14% from 2019 to 2020, but rebounded already in 2021 and remained stable until 2023 (141). The number of early retirements in Austria due to cancer increased by 6% from 2019 to 2020, but decreased by 11% from 2020 and 2021 and remained stable until 2023 (142).

2.6 Health spending and survival

The results from section 2.4 beg the question of why some countries achieve higher survival rates than others. From a health-economic perspective, survival is considered an "outcome" of the healthcare process. Differences in outcomes might stem from differences in inputs and the process of how inputs are used to produce outcomes. Therefore, a crude way to explore the reasons for varying survival rates is to look at how health expenditure on cancer care ("inputs") relates to survival ("outcomes"). Cancer-related health expenditure is arguably a simple measure of inputs, but it constitutes the very basis for all services that the healthcare system uses to produce health.

The country-level association between cancer-specific health expenditure per capita (see section 2.5) and survival (see section 2.4) is shown in Figure 35. Note that cancer-specific health expenditure refers to the year 2015 and survival (approximated by the complement of the mortality-to-incidence ratio; 1-MIR) to the year 2022. The following three important observations can be made:

- Adequate spending on cancer care seems to be a prerequisite for achieving high survival rates.[20] The upward sloping trend line indicates that countries with higher spending tend to record higher survival rates and countries with lower spending tend to record lower survival rates.
- The association between spending on cancer and survival rates might be non-linear. The positive association is most visible for countries spending between €50 and €200 per capita, whereas countries spending more than €200 do not seem to achieve higher survival rates. This indicates that each additional euro spent on cancer care improves survival rates, but the improvements for every additional euro spent might become smaller the more euros that have already been spent.
- There seem to be considerable inefficiencies in cancer care. This is indicated by the great variation in spending on cancer care between countries that achieve similar survival rates. For instance, Sweden and Switzerland both recorded a survival rate (1-MIR) of 60%, but per-capita spending on cancer in Switzerland (€313) was twice as high as in Sweden (€142). Although this is a rather crude way of inferring inefficiencies, this observation might motivate a reconsideration of the current allocation of cancer care expenditure into areas with evidence-based added clinical benefits. For countries below the trend line, there might be room to improve patient outcomes with existing resources and thereby increase the added value for each additional euro spent.

A positive association between healthcare spending or cancer care spending and cancer patient outcomes has also been documented in previous Comparator Reports (46, 47), as well as in other parts of the world. The latter includes analyses of OECD countries, studying the relationship between total health spending per capita and 5-year cancer survival rate (14), and the relationship between a measure of the quality of health systems and the cancer mortality-to-incidence ratio (a crude proxy of survival) (143). For countries in the Asia-Pacific region, a strong positive association between total health spending per capita and the complement of the cancer mortality-to-incidence ratio was found (144).

[20] Note that the associations in Figure 35 does not to be fully causal. The positive relationship could potentially also be driven by some third factor (e.g., the level of health literacy in a country) that is related to both the amount of cancer-specific health expenditure and survival.

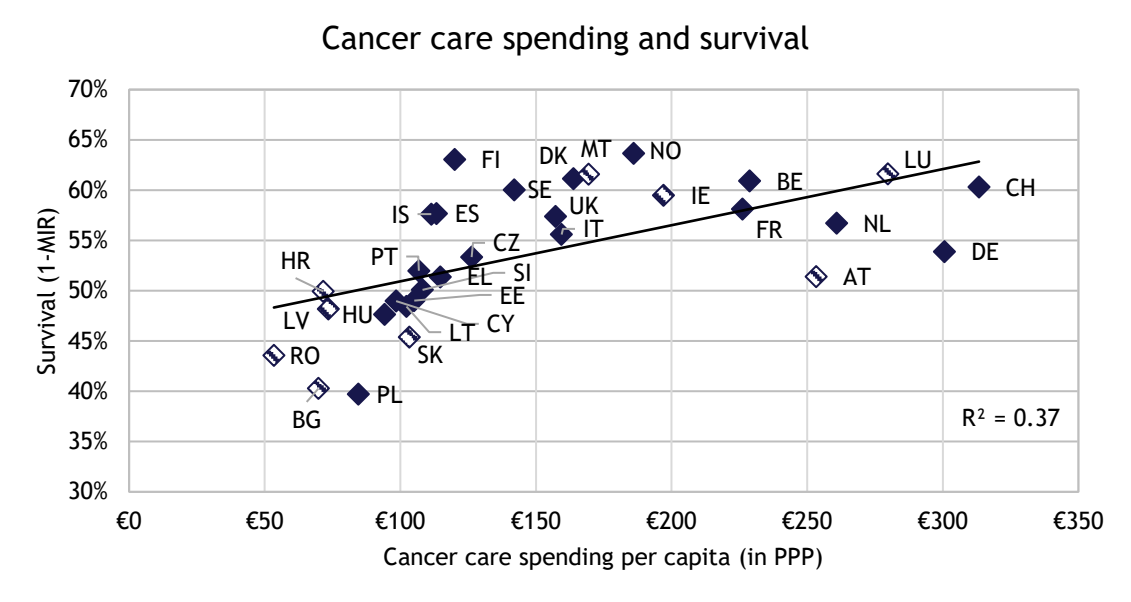


Figure 35: Cancer expenditure (in € per capita, PPP-adjusted) in 2015 and survival (1-MIR) in 2022 in European countries.

Notes: Hatched dots indicate that the national estimate for cancer expenditure is based on data from similar countries. Survival is approximated by the complement of the mortality-to-incidence ratio (1-MIR), using age-standardized rates of all cancers excluding non-melanoma skin cancer. Source: own calculations for 1-MIR based on ECIS (see section 2.3), and own estimations for cancer care expenditure (see section 2.5).

The positive association between health spending and patient outcomes in Figure 35 does not need to be causal, but it indicates that health spending might be a stronger driver of patient outcomes. Health policymakers should weigh the costs from investing in cancer care against the potential improvements in patient outcomes. This ensures that constrained resources are used in a cost-effective way and provide value-for-money for patients and taxpayers. It should also be noted that such a balanced view on "cost effectiveness" is different from other sole views on "effectiveness" and "cost containment", as the former is only concerned about outcomes and the latter is only concerned about inputs.

Going forward, continued improvements in survival will depend on future advances in early detection and screening, diagnostics, and treatment. The implementation of these advances in clinical practice will likely require additional health spending – both in absolute terms (€) and in relative terms (% of total health expenditure). This is because new technologies either (i) constitute something entirely new without an existing alternative, or (ii) replace or are added to existing technologies but come at a higher price, e.g., on-patent immunotherapy replacing or being added to off-patent chemotherapy. The important task for health systems is to make sure that the limited resources are used in a cost-effective way. Considerations of cost-effectiveness should influence decisions to adopt new technologies in all areas of care, and not just for cancer medicines. Policymakers should also review the current organization and use of resources along the entire patient pathway to identify and remedy existing inefficiencies. Access to better and relevant data – on resource use, patient outcomes, and costs – are vital to identify current inefficiencies and shortcomings in the care process along the entire patient pathway.

3. Advances in cancer medicines and molecular diagnostics

Key messages of this chapter

Around 30-50% of new cancer cases are theoretically preventable, with smoking being by far the most critical modifiable risk factor.

With most of the preventable burden of cancer relating to lifestyle factors (such as smoking) and environmental factors (such as UV radiation), the use of medicines for cancer prevention is currently limited to specific settings. One setting includes medicines to treat diseases that can cause cancer such as treatments for hepatitis C, HIV, Helicobacter pylori, and obesity. Another setting includes vaccines and medicines that are administered to healthy people to directly prevent cancer, such as HPV vaccines, Hepatitis B vaccines, and hormone therapies. A better biological understanding of the carcinogenic process may identify new targets for cancer prevention.

Early detection through screening can increase survival rates and reduce treatment costs, with innovations such as AI-assisted imaging and liquid biopsies offering new opportunities.

For most cancer types, survival rates decrease with late diagnosis while treatment costs increase, underscoring the importance of early detection. For example, breast cancer survival rates drop from almost 100% in stage I to less than 30% in stage IV, with treatment costs being at least twice as high in stage IV as in stage I. Screening programs for breast, cervical, colorectal, lung, prostate, and stomach cancer are recommended by the Council of the EU since 2022, but challenges with implementation and participation remain. Future avenues to detect asymptomatic cancers in a less invasive and more convenient way include liquid biopsies (blood tests) and AI-based diagnostic prediction tools using medical records, which may improve accessibility and acceptability in the target population.

Biomarker testing has become indispensable in modern oncology to realize the potential of precision medicine.

In the last two decades, biomarker testing has become a cornerstone of cancer care, guiding therapeutic decisions to determine whether a patient is likely to respond to a certain treatment. Almost half of the new cancer medicines approved by the EMA for solid tumors in 2015-2020 were associated with a predictive biomarker to tailor treatments. In many clinical settings, single and sequential biomarker testing has been replaced by complex assays such as next-generation sequencing (NGS) that enable assessing multiple genes at the same time. NGS has revolutionized oncology by enabling comprehensive tumor genome analysis. Costs for whole-genome sequencing have dropped immensely – from USD 3 billion during the Human Genome Project to approximately USD 600 today, with predictions suggesting a USD 100 price tag in the near future, which would enable widespread use of precision medicine and preventive genomics.

Liquid biopsies are about to redefine cancer care by enabling non-invasive monitoring of minimal residual disease and early cancer detection.

A major strand of current biomarker research is focusing on developing tests that can assess relevant markers of cancer in the blood. Liquid biopsies offer a non-invasive alternative to “traditional” tissue biopsies, enabling testing in difficult to biopsy patients, monitoring of minimal residual disease (MRD), and facilitating early cancer detection. MRD monitoring enables early detection of recurrence, often months before clinical progression is seen on imaging or can be detected by other methods. Improving the sensitivity of liquid biopsy testing across various cancer types is the key to increasing its utility in more clinical settings.

Research in cancer biology has spurred the development of new medicine classes over the past decades.

Cancer treatment has shifted dramatically with the introduction of targeted therapies at the turn of the millennium and the Nobel Prize-winning immunotherapies in the 2010s. While targeted therapies focus on molecular targets crucial for cancer cell survival, immunotherapies enhance the immune system's ability to combat cancer. The development of new medicines and medicine classes in oncology continues to accelerate. Oncology trials represented 29% of the initiated trials across all therapeutic areas in 2023 globally (up from 27% in 2018). Some 44% of the new industry-sponsored oncology trials

were phase I trials in 2023, which indicates a high number of new agents and combinations in development.

Breakthrough therapies, including antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), cell-based therapies, and radioligand therapy, offer new hope for tackling cancer.

Recent years have witnessed a surge in different directions of therapy development. There were advancements in more "mature" types of therapies such as small molecular kinase inhibitors and immune checkpoint inhibitors, which are continuing to expand in neo/adjuvant treatment settings of early-stage cancer and in combination with other agents. We have just seen the tip of the iceberg with the arrival of the first ADCs and BsAbs, with several hundred agents in clinical development. Cell-based therapies are starting to expand beyond CAR T-cell therapies to tumor-infiltrating lymphocyte (TIL) therapies and TCR-T cell therapies. More radioligand therapies are also expected. Novel medicine classes that might soon achieve a breakthrough include therapeutic cancer vaccines (based on mRNA technology), proteolysis-targeting chimeras (PROTACs), gene editing/ therapy, oncolytic virotherapy, and RNA interference.

AI is reshaping cancer diagnostics, enhancing the precision of genomic analysis, early detection, and precision medicine.

AI is already used in clinical care for imaging analysis and in medicine development. In addition, AI is increasingly integrated into cancer diagnostics, enhancing accuracy in molecular data analysis. AI tools improve early cancer detection through liquid biopsies and better integration of genomic, proteomic, and imaging data. These advancements also aid in identifying patients who are most likely to respond to specific treatments, fostering precision medicine. As a result, AI can improve quality of care and reduce stress for physicians by assisting in treatment decisions. However, rigorous validation of AI in different datasets to prove performance together with viable solutions to ensure patient integrity and confidentiality are needed to guarantee safe and effective use in clinical practice.

Countless genetic changes occur in the cells of our body every day, but they are in most cases stopped by the cell's own protection systems. The requirement for a normal cell to change into a cancer cell is a combination of many events happening at the same time (145). Over the past decades, research has tremendously increased our knowledge about the human cell and its molecular mechanisms. Progress in molecular medicine increased our understanding of cancer evolution, cancer cells characterization, and defects in DNA repair mechanisms.

The research progress enabled medical oncology to enter a new phase in the 21st century with novel medicines targeting different molecular targets (46). The era of "personalized/precision medicine" started with the introduction of targeted therapies toward the end of the 1990s; see Figure 36. These medicines act on specific molecules that are involved in the growth and survival of cancer cells. They have now become one of the main treatment options for some tumors. During the 2010s, immunotherapies, such as immune checkpoint inhibitors and more recently CAR T-cell therapies, which help the body's immune system to recognize and attack cancer cells, have been added to the therapeutic arsenal. At the same time, older backbones in the medical treatment – chemotherapy and hormone therapy – are still essential in the treatment of many cancer types. What we are seeing now is an increased use of combinations of all major medicine classes or newer medicines that combine the features of several medicine classes to achieve additive effects (146).

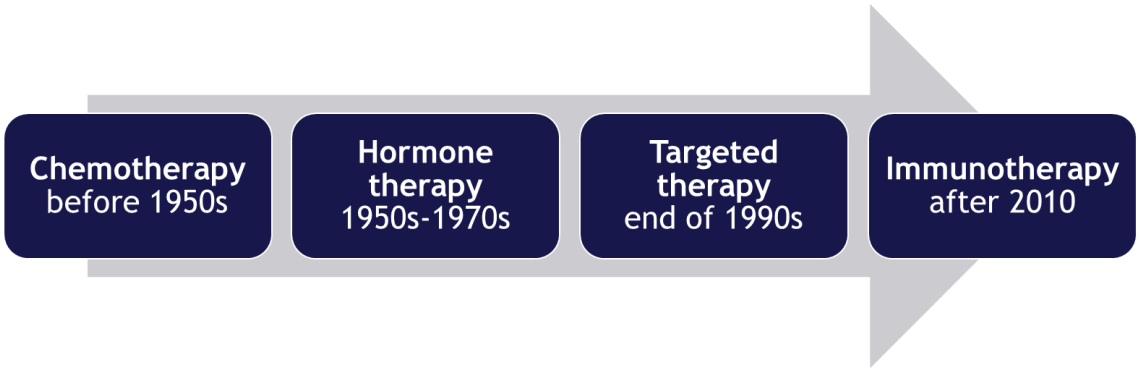


Figure 36: Timeline of introduction of new, major medicine classes in oncology.
Source: (147).

The following sub-sections focus on present and future trends in prevention (section 3.1) and screening (section 3.2). Advances in molecular diagnostics and biomarkers for prognostic and predictive testing to guide the most promising, personalized therapeutic approach are described in section 3.3. The latest developments in existing and potentially new medicine classes are discussed in section 3.4. The increasing role of artificial intelligence (AI) in oncology (section 3.5), surrogate endpoints in clinical studies (section 3.6), and clinical effectiveness and real-world data (section 3.7) are also briefly covered.

3.1 Prevention

According to the WHO, between 30–50% of all cancer cases are theoretically preventable because they are believed to be caused by modifiable risk factors (148).[21] In Denmark, 32% of cancer cases are estimated to be preventable, whereas this number is 28% in Sweden, 38% in the UK, and 40% in the US; see Table 5.

Table 5: Preventable proportion of new cancer cases

Country	Preventable proportion	Top 3 biggest preventable factors	Source
Denmark	32% in 2018	Cigarette smoking (15%) Sun exposure, UV (6%) Obesity/overweight (3%)	(150)
Sweden	28% in 2018	Cigarette smoking (11%) Sun exposure, UV (7%) Unhealthy diet (3%)	(151)
UK	38% in 2015	Cigarette smoking (15%) Obesity/overweight (6%) Sun exposure, UV (4%)	(152)
US	40% in 2019	Cigarette smoking (19%) Obesity/overweight (8%) Alcohol (5%)	(153)

Notes: All studies excluded cases of non-melanoma skin cancer.

[21] The 2020 World Cancer Report of the WHO lists tobacco consumption, infectious agents (e.g., Helicobacter pylori, HPV, hepatitis B and C viruses), alcohol consumption, sunlight and UV radiation, ionizing radiation (from both natural sources and artificial sources such exposure to medical radiation), diet and nutrition (high intake of processed meat and red meat and low intake of fruits and vegetables), physical inactivity, obesity, dietary carcinogens (e.g., aflatoxin and aristolochic acid), contamination of air (airborne particulate matter originating from, e.g., fuel combustion for transportation and domestic heating and cooking), water, soil, and food (e.g., through arsenic), occupational carcinogens (e.g., asbestos, polycyclic aromatic hydrocarbons, heavy metals), and pharmaceuticals (e.g., hormonal contraceptives) (149).

Modifiable risk factors can be grouped into three classes:

- **Lifestyle and behavioral risk factors** (e.g., smoking, obesity, alcohol, unhealthy diet)
- **Infectious agents** (e.g., HPV, hepatitis B and C, human immunodeficiency virus (HIV), Epstein-Barr virus, Helicobacter pylori)
- **Environmental and occupational risk factors** (e.g., UV radiation, air pollution, occupational carcinogens such as asbestos)

Most of the preventable cancer cases are related to a few lifestyle and behavioral factors. The single most important risk factor is cigarette smoking. In Denmark, almost half (45%) of all preventable cancer cases are related to cigarette smoking. Even in a country such as Sweden, which has one of the lowest cigarette smoking rates in the world (6% daily smokers compared to the EU average of 18%) (154), almost 40% of all preventable cases relate to cigarette smoking.

Infections with viruses and bacteria are linked to around 2-4% of new cancer cases in Denmark, Sweden, and the US (150, 151, 153). The single most important infection is with HPV. In Europe, HPV causes around 2.5% of all cancers in women and men (155).

The European Environment Agency estimates that exposure to air pollution, carcinogenic chemicals, radon, UV radiation and second-hand smoke together may cause over 10% of new cancer cases in Europe (156).

The proportion of preventable cases differs largely between cancer types. Among the four major cancer types in the US, close to 88% of lung cancer cases are estimated to be preventable (mostly linked to cigarette smoking), followed by 54% of cases of colorectal cancer (linked among others to obesity/overweight, physical inactivity, diet, alcohol), 31% of cases of breast cancer (linked among others to obesity/overweight, physical inactivity, alcohol), but no cases of prostate cancer (153).

3.1.1 Past and current policy efforts

Prevention measures aim to decrease exposure to modifiable risk factors of cancer. At the individual level, these measures will influence a person's risk of getting cancer. At the country level, these measures will affect the level of cancer incidence. Cancer prevention has a long history of slow progress and lack of implementation. This is probably related to the fact that most preventable cases are linked to common unhealthy lifestyles.

Prevention requires most often a combination of efforts to improve awareness and health literacy (i.e., the skill to make informed decisions for one's own health) and public-led efforts. In 1987, the first edition of the European Code Against Cancer was published by the European Commission. The fourth and latest edition was published in 2015 (157). It contains 12 ways of how individuals can reduce their risk of getting cancer. Even though these 12 ways are directed towards individuals and their behavior/lifestyle; successful implementation of these requires public efforts as well. Such public efforts include:

- Campaigns to raise awareness / build health literacy around major risk factors of cancer
- Excise taxes on unhealthy products (e.g., tobacco, alcohol, sugar-sweetened beverages, etc.)
- Smoking bans in workplaces, restaurants, and public spaces
- Bans or limits of cancer-causing substances at workplaces (e.g., asbestos, chemicals)
- Efforts to combat air pollution (install filters, switch from fossil fuel-based vehicles and factories to renewable sources)
- Vaccination programs against HPV and hepatitis B

An update of the European Code Against Cancer was foreseen in Europe's Beating Cancer Plan (2). This work is currently underway as part of the EU-funded ECAC5 project, with the aim of publishing the fifth edition in 2025 (158).

3.1.2 Medicines for cancer prevention

The use of medicines for cancer prevention is currently limited to specific scenarios. This includes two groups. The first group are medicines that treat a disease that can cause cancer, thereby indirectly preventing the occurrence of cancer. This includes the following:

- **Hepatitis C**: Direct-acting antiviral medicines have a cure rate of greater than 95% for chronic hepatitis C. Successful treatment greatly reduces the risk of developing liver cancer (159).
- **HIV**: Antiretroviral therapy medicines stop the virus from replicating in the body. This prevents the development of Kaposi sarcoma and other HIV-related cancers (160).
- **Helicobacter pylori**: Treating the infection with this bacterium can prevent the development of stomach cancer (161).
- **Diabetes and obesity**:
  - Metformin: Originally used for diabetes, metformin is being studied for its potential to reduce the risk of several cancers, including breast, colorectal, and prostate cancers. Its effects may be related to lowering insulin levels, which could reduce cancer cell growth. Still, the current conclusion is that metformin does not have a major influence on cancer incidence (162).
  - Anti-obesity medicines: As obesity is a known risk factor for several cancers, medicines that help in weight management, such as the recently introduced GLP-1 agonists (e.g., semaglutide) and GIP/GLP-1 agonists (e.g., tirzepatide), have a potential role in cancer prevention. In a recent study, these medicines have been shown to reduce a number of obesity-related cancers (163). These results are still preliminary and the potential of these medicines for cancer prevention on a broad scale is still unclear given the present price levels.

The second group are vaccines and medicines that are (or used to be) given to healthy people to directly prevent cancer (164). This includes the following:

- **HPV vaccines**: They prevent infection with HPV types that are responsible for nearly all cases of cervical cancer and a majority of cases of anal cancer, penile cancer, vaginal cancer, vulvar cancer, and cancers in the oral cavity and pharynx (165, 166).
- **Hepatitis B vaccines**: Globally, almost 300 million people are affected by hepatitis B virus, and it is estimated that almost 200 000 deaths yearly are linked to liver cancer due to the infection (167). Although most of the burden is concentrated in East Asia and Sub-Saharan Africa (160), our global way of living make it also highly relevant in Europe.
- **Certain types of hormone therapy (Selective estrogen receptor modulators (SERMs) and aromatase inhibitors):** In 2006, results of the Study of Tamoxifen and Raloxifene (STAR) showed that postmenopausal women at increased risk of breast cancer can reduce their risk of developing the disease if they take the antiestrogen medicine raloxifene (147). Raloxifene, a common osteoporosis medicine, prevented breast cancer to the same extent (but with fewer serious side effects) than tamoxifen and is approved by the US Food and Drug Administration (FDA) in this setting. Similar preventive effects have also been shown in studies of aromatase inhibitors (157). The problem with breast cancer prevention based on antiestrogens and aromatase inhibitors

has been the limited acceptance from patients due to cumbersome side effects. In a meta-analysis it was found that only 16% of eligible women continued the medication (168). Molecular profiling may identify subgroups of women for whom the risk-harm ratio is in favor of medical prevention (169, 170).

- **Aspirin**: Aspirin is an example of a repurposed preventive compound with consistent 20–30% reductions in colorectal adenoma incidence and colorectal cancer risk and mortality in a large array of observational and experimental studies. In 2016, the USPSTF (US Preventive Services Task Force) recommended low-dose aspirin in individuals aged 50–59 and a 10% ten-year risk for cardiovascular events, noting additional benefits of reductions in colorectal cancer with long-term use (171). The balance of benefits and harms may change substantially with age, because the risk of major bleeding increases with age. For that reason, the USPSTF rated the evidence "Insufficient (I)" for people aged 70 or older. In 2022, the USPSTF revised its recommendations regarding aspirin for primary prevention of cardiovascular diseases and withdrew its recommendation regarding colorectal cancer, deeming the evidence supporting aspirin's reduction of colorectal cancer risk as "inadequate" (172-174). Still, aspirin has been shown to reduce both colorectal cancer as well as other gastrointestinal cancers (175).
- **PARP inhibitors**: These medicines have shown promise in preventing cancers in people with certain genetic predispositions, such as BRCA1/2 mutations, which are associated with higher risks of breast, ovarian, and prostate cancer (176, 177).

3.2 Screening

Early detection of cancer increases the chances for survival (178). Screening for cancer aims to detect abnormal cells among healthy people without any symptoms as early as possible and being able to initiate treatment at early stages of the disease (179). The potential for screening is greatest for cancers that have a natural history allowing the detection and treatment of precursor lesions (such as in cervical cancer and colorectal cancer) even before the development of invasive cancer.

The effectiveness of a population-level screening program is measured based on the reduction in disease-specific mortality accomplished with an acceptable balance of benefit to harm (180). Key requirements for broad use of a screening method are accuracy (high sensitivity and specificity to prevent overdiagnosis and underdiagnosis) and acceptable method (e.g., a mammography might be painful, and women might experience discomfort/embarrassment from undressing in front of healthcare personnel; people might feel disgust associated with the handling of a stool sample for colorectal screening). The successful implementation of population-based screening programs requires an appropriate definition of risk groups and measures to achieve high participation rates.

3.2.1 Past and current policy efforts

Population-level screening programs are an integral tool to tackle the growing disease burden of cancer. Screening programs for breast cancer and cervical cancer have existed for several decades in some high-income countries and programs for colorectal cancer have been introduced during the last two decades. These three programs have also been recommended by the Council of the EU in 2003; see Table 6. In 2022, this recommendation was updated and introduced some changes to the target groups and screening methods of the three existing

programs as well as called for the introduction of screening programs for three additional cancer types – lung, prostate, and stomach cancer.

Table 6: Recommended screening programs in the EU

Cancer type	Target group	Method
Council of the EU recommendation from 2003		
Breast cancer	Women aged 50–69	Mammography every 2 years
Cervical cancer	Women aged 20/30–60	Pap smear test (cytology testing) every 3–5 years
Colorectal cancer	Men and women aged 50–74	Stool test (initially FOBT, since 2010 FIT)
Council of the EU recommendation from 2022		
Breast cancer	Women aged 45–74	Mammography 2–3 years for women aged 45–49, 2 years for women aged 50–69, and 3 years for women aged 70–74
Cervical cancer	Women aged 30–65	HPV testing every 5 years
Colorectal cancer	Men and women aged 50–74	Stool test (FIT) at least every 3 years
Lung cancer	Current heavy and ex-smokers aged 50–75	Low-dose computed tomography (CT)
Prostate cancer	Men up to age 70	PSA testing, and MRI scanning as follow-up
Stomach cancer	Men and women in places with high gastric cancer incidence and death rates	Screening for Helicobacter pylori

Notes: fecal occult blood test (FOBT), fecal immunochemical test (FIT), prostate-specific antigen (PSA), magnetic resonance imaging (MRI). Sources: (34, 181).

Despite the implementation of screening programs in most EU countries and beyond, participation remains low in many locations. For example, participation in breast cancer screening programs in the EU in 2022 was highest in the Nordic countries and Slovenia with around 80% of women in the age group 50-69 participating, whereas only around 30% of women in Latvia, Hungary, Cyprus, and Slovakia participated (182). Similar geographical patterns are observable for other screening programs. Participation in cervical cancer screening programs among women aged 20-69 was over 70% in Sweden, Czechia, Ireland, Finland, and Slovenia but less than 30% in Hungary, Malta, Poland, and Romania in 2022 (182). Participation in colorectal cancer screening programs among men and women aged 50-74 was over 60% in Finland, Netherlands, Sweden, and Denmark but less than 20% in Latvia, Germany, and Hungary in 2022 (182). High-educated people are generally more likely to attend screening than low-educated people (37), pointing to gaps in health literacy between socioeconomic groups.

Some of the disparities in participation rates between countries might stem from differences in the organization of screening programs. This includes the coverage (national or only regional), the type of organization (organized or opportunistic), the target age group, screening interval, and test method (aligned with the Council recommendations or not), and the invitation strategy, and the availability of self-sampling (183). There is also a continuous need for development and implementation of workforce planning strategies and investment in workforce training to ensure there is sufficient capacity and capabilities to diagnose and treat more patients early.

Info box 6. Benefits of early detection of breast cancer

The chances of surviving breast cancer vary by stage at diagnosis. Survival chances are far greater when the tumor is detected early and is still small in size and not spread. At a late stage, when the tumor has started to spread to other parts of the body, survival chances are smaller. The 5-year survival rate for breast cancer ranges from 98% in stage I down to 25% in stage IV in the UK; see Figure 37.

Early detection through screening has also economic implications. The implementation and running of screening programs costs money and requires resources for testing and administration. However, the additional costs for screening might be partially offset by reduced costs for treatment. Treatment costs of breast cancer patients diagnosed with stage I are lowest, whereas treatment costs of patients diagnosed with stage IV are highest and at least more than twice as high (>100%) as in stage I. Screening thus can increase the proportion of "cheaper patients" and decrease the proportion of "more expensive patients".

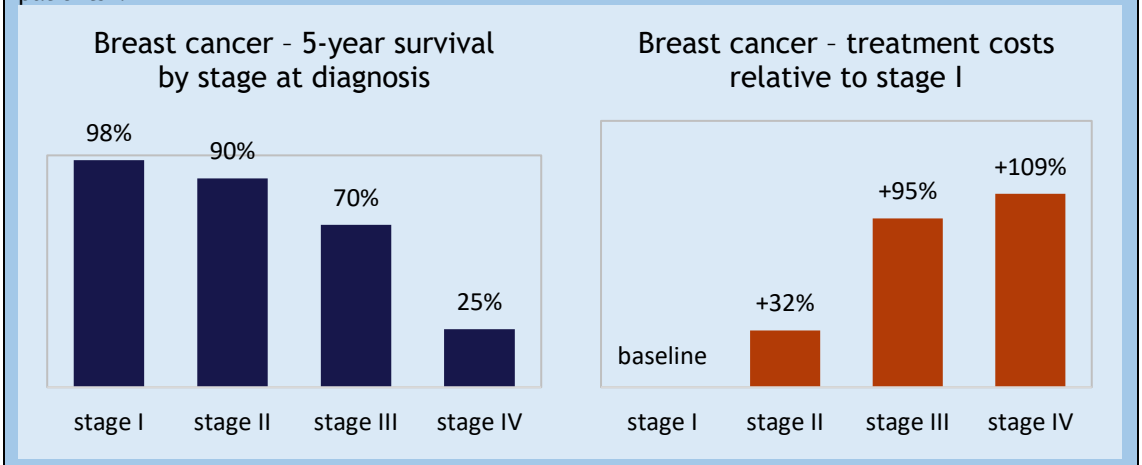


Figure 37: 5-year net survival rates for breast cancer of adult patients diagnosed in England in 2013-2017 (left graph) and treatment costs of breast cancer (right graph) by stage at diagnosis.

Source: Survival rates from ONS and treatment costs from a systemic review of 20 international studies of breast cancer by Sun et al. (2018) (184, 185).

3.2.2 Future directions

Early detection of cancer can both improve health outcomes and reduce treatment costs. Different avenues exist for advancing early detection in the future, many of which contain elements of AI.

Table 7: Future avenues for early detection of cancer

Breast cancer	AI-assisted mammography has already been incorporated in the screening process in several countries. AI-supported mammography screening resulted in a similar or higher cancer detection rate compared with standard double reading, without increasing false positives and leading to a substantially lower screen-reading workload (around -44%), indicating that the use of AI in mammography screening is safe and effective (186, 187). AI-assisted mammography with support of ultrasound may further improve detection rates (188).
Cervical cancer	The impact of HPV vaccination on cervical cancer will in the future likely influence screening for the disease. Women who had received the full vaccination at a young age might no longer be invited to regular screenings (189).
Colorectal cancer	The collection of stool samples may be associated with disgust and colonoscopy as a tool for proper diagnosis upon positive findings in a stool test is afflicted with access and acceptance problems. New technologies for non-invasive diagnosis (including for precursor lesions) using molecular diagnosis of fecal genetic alterations are being explored. A test developed by Geneoscopy to stabilize and extract eukaryotic RNA biomarkers from stool samples may allow for improved diagnosis and management of

	gastrointestinal diseases such as colorectal cancer and already received a Breakthrough Designation by the US FDA in January 2020 (190). Other AI-assisted technologies for identifying premalignant adenomas are presently being developed and could in combination with robot-assisted surgery improve the screening process (191, 192).
Lung cancer	AI tools, such as a tool called Sybil, may accurately predict the risk of lung cancer for individuals with or without a significant smoking history using data from a single low-dose chest CT scan (193). Other AI-assisted technologies also show promising results in lung cancer screening (194, 195). However, geographic barriers and capacity constraints might limit uptake and create access disparities between urban and rural areas, although the introduction of AI in the radiology process could address some of the constraints (196).
Skin cancer	Skin cancer is another area where AI-assisted examinations are being explored. In this area examination in primary care combined with AI-supported clinical experience may play a significant role for early detection in the future (197-199).
Liquid biopsies (blood tests)	A long-term vision is to use a single drop of blood to assess the presence of asymptomatic cancers, possibly by screening people of a certain age (e.g., 50 to 70 years) once a year or every two years. People could take the test at home and then send the blood sample to a laboratory. The use of liquid biopsies using blood samples for cancer detection and monitoring holds the potential to profoundly change cancer care (200-202). They would detect circulating tumor DNA (ctDNA) in patients with early-stage cancer, either in the form of single-cancer detection (SCD) or multi-cancer detection (MCD) tests (203). Improving the sensitivity of liquid biopsies to detect low levels of tumor DNA is still a major challenge even in cases where research only focuses on detecting a single cancer type (e.g., pancreatic cancer) rather than multiple cancer types. In addition, it is challenging to detect those cases which really need treatment, thus avoiding overdiagnosis of benign cancers (204-206).
AI-based diagnostic prediction tools using medical records	Electronic medical records may contain a wealth of data from routine visits and laboratory tests. There is a major interest in training AI algorithms on the basis of routine clinical and laboratory data to predict a future diagnosis of cancer (207-210). This is based on symptom patterns that would usually go unnoticed by healthcare professionals (especially in primary care) but that are found to be predictive of developing cancer (211). The detection of such patterns in a person's medical records would automatically trigger a warning to the healthcare system and lead to a follow-up visit for diagnostic confirmation. A potentially limiting factor for the application of AI algorithms in clinical care is to respect patient integrity and confidentiality in line with privacy regulations such as GDPR.
Portable apps	At present there is limited support for the use of personal portable apps in cancer screening, but several projects are ongoing (212).

3.3 Diagnostics and biomarkers

Molecular profiling (also called predictive biomarker testing, molecular diagnostics, tumor testing, tumor profiling, or tumor genetic testing) in pathology has grown tremendously in importance over the last two to three decades with the introduction of targeted therapies and immunotherapies (213). Medical treatments are increasingly becoming individualized moving away from a one-size-fits all approach based on the tissue where the tumor originated. Molecular profiling is a cornerstone of personalized/precision medicine as it detects the presence of a target in tumors thus identifying which patients may benefit from targeted therapies. A diagnostic test that is used to identify suitable patients for a specific medicine is called a "companion diagnostic". An analysis of all EMA approvals of new indications for solid tumors found that almost half (47%) of all approvals between 2015 and 2020 were associated with a biomarker (214).

3.3.1 Advances in biomarker testing technologies

An early test method was immunohistochemistry (IHC), a method allowing the visualization of a specific antigen within the tissue. IHC is still used in many indications, for instance to detect estrogen, progesterone, and HER2 expression in breast cancer to guide treatment decisions on hormone therapies and HER2 targeted therapies, and for the detection of CD20 in lymphoma where it is used to determine treatment with CD20 targeted agents. In the last two decades, the sensitivity and specificity of IHC have improved significantly due to advances in antibody development and the automation of staining processes. Automated platforms have allowed for improved reproducibility and consistency, which is important clinically. IHC will remain an important biomarker, especially for therapies targeting surface-expressed proteins, such as antibody-drug conjugates (ADCs). For biomarkers indicating a genomic alteration, IHC may still serve as a screening or surrogate marker in low-income settings.

The technologies used to perform biomarker testing have undergone changes in the last 15 years, moving away from analysis of single biomarkers at a time to parallel sequencing of biomarkers with next-generation sequencing (NGS) technology (215, 216). The traditional approach for predictive biomarker testing was to test tumor tissue for a single genomic marker followed by using tumor-marker specific therapy, e.g., testing for HER2 status to guide administration of trastuzumab. Since the 2010s, predictive biomarker testing has started to move beyond single biomarker testing (typically by polymerase chain reaction, PCR) to large NGS panels and in some cases even whole-genome sequencing. PCR testing will however likely continue to be used in indications where there are only a few actionable genetic alterations, and broad PCR panels – covering alterations across multiple genes (217) - may provide a useful alternative in patients who are not eligible for clinical trials and in countries/indications where the cost of NGS testing is prohibitive and rapid turnaround time is required.

NGS is an advanced DNA/RNA sequencing technology that allows rapid sequencing of large amounts of DNA/RNA. NGS panels can include different genes and can include analysis of different numbers of genes ranging from a few dozen to thousands of genes. It has an important role in emerging, more complex biomarkers, such as tumor mutational burden (TMB), microsatellite instability (MSI), and homology-directed repair (HDR) that are based on mutation signatures and require a large gene panel design. The performance and the reporting from different NGS platforms are not identical as they use different technologies, different bioinformatics, and annotation. However, comparisons of NGS platforms currently reveal that overall, the results are fairly similar (218).

Multi-gene testing with NGS in cancer treatment

Multi-gene testing with NGS has grown in importance over the last decade in certain cancer types. The prime example is advanced-stage non-small cell lung cancer (NSCLC), where an increasing number of medicines have received regulatory approval that target various mutations (more specifically, EGFR, ALK, ROS1, BRAF, NTRK1-3, MET, RET, KRAS G12C, HER2), and where single biomarker testing for all of these mutations one at a time is no longer feasible as sample material tends to be very limited and sequential testing leads to depletion of samples. In 2020, ESMO issued its first recommendation of routine use of NGS on tumor samples in advanced non-squamous NSCLC, prostate cancer, ovarian cancer, and cholangiocarcinoma as well as consideration of use in colon cancer (28), which was extended to breast cancer, gastrointestinal stromal tumors (GIST), sarcoma, thyroid cancer, and cancer of unknown primary in 2024 (219). Multi-gene testing has also been developed for assessment of alterations in genes that increase the risk of developing cancer such as BRCA1, BRCA2, HRD genes, APC,

VHL and others which are becoming of increasing relevance and interest (220). BRCA and HRD analysis has in recent years also become standard assessments in some patients with breast cancer and ovarian cancer, as having mutations in those genes has therapeutic implications (PARP inhibitors).

Predictive biomarkers

The introduction of immunotherapy has led to extensive research in predictive biomarkers. PD-L1 (221) and microsatellite instability high (MSI-H) / mismatch repair (MMR) deficiency (222-225) have been approved by regulatory authorities in multiple indications. Tumor mutational burden (TMB) (226-228) has been approved by the FDA based on data from a large number of indications but approval has not yet been granted by the EMA. With increasing understanding of tumor biology, a model for hallmarks in immune escape has recently been presented that highlights key elements such as antigen camouflage, immune cell reprogramming and metabolic control (229). Many markers relating to these hallmarks, such as IFN-γ signature (226), tumor microenvironment (230-233), TGF-β (234, 235), $CD8^+$ exhaustion (236), mutations in genes encoding MHC molecules or beta-2 microglobulin (237), inactivation of antigen presentation (238, 239), HLA allele-specific loss (240, 241), mutations in JAK1/JAK2, gene expression algorithms (242), assessment of expression changes in patients tumors through transcriptomic analysis (243), and gut microbiome (244), are being assessed to identify potential predictive markers. Further understanding of driver mutations/oncogenic pathways and potential immune escape mechanisms associated with such alterations is warranted as they may enable improved selection of patients and potentially allow the mechanisms of resistance become therapeutically targetable.

Liquid biopsies

Liquid biopsy assessment of actionable genomic alterations has been available for a few years, dominated by NGS-based and PCR-based technologies. PCR is currently a frequently used method in clinical routine for liquid biopsy, e.g., for EGFR (lung cancer) and ESR1 (breast cancer)-mutation and BCR-ABL fusion (CML) monitoring (245-247). Decreasing costs of NGS and improved bioinformatics capabilities have also enabled the development of large mutation panels for use in liquid biopsies. This approach is increasingly incorporated into clinical trials and used in selecting patients for clinical care when it is challenging to obtain tissue biopsies. The highest clinical utility for liquid biopsy assessment is currently in cases where it is difficult to collect sufficient tissue samples for analysis (248), and where there is a need to understand resistance mechanisms associated with acquired mutations, particularly in NSCLC, which is challenging to re-biopsy. The sensitivity of liquid biopsy testing limits its utility in patients with metastatic disease, where sensitivity is still in the 75–90% range, with high sensitivity for SNVs and deletions but lower sensitivity for fusions (249).

Liquid biopsies have also emerged as a tool for the assessment of minimal residual disease (MRD) and early detection. MRD monitoring through liquid biopsy enables early detection of recurrence, often months before clinical progression is seen on imaging or can be detected by other methods. In hematology, MRD is used in diseases like acute myeloid leukemia (250), acute lymphoblastic leukemia (251), chronic lymphocytic leukemia (252), and multiple myeloma (253), where molecular relapse precedes clinical relapse. In multiple myeloma, MRD has been accepted as a valid regulatory endpoint in medicine development by the FDA based on a meta-analysis of a large number of MRD trials in the disease (254). This represents a milestone for MRD as a concept and we will likely see MRD used in medicine development and medicine approvals going forward. This has been demonstrated in solid malignancies like for instance

colorectal cancer (255) and lung cancer (256), where the detection of ctDNA post-surgery correlates with disease recurrence. In the MRD setting, exquisite sensitivity is required as very little tumor will be present. Multiple approaches are used to increase sensitivity: sequencing depth improves sensitivity, allowing for the detection of very low-frequency ctDNA variants but this comes at the cost of higher assay complexity and expense. Methylation patterns and other epigenetic modifications can also be leveraged to improve sensitivity. Lastly, patient-specific assays are being developed. These assays require analysis of the surgical specimen where mutations present are selected and a liquid biopsy panel comprising 10-50 of such selected mutations is developed to assess each patient over time. This approach is currently the most sensitive but is also very expensive, which will limit its clinical use.

Early detection is another promising application. By analyzing ctDNA, circulating tumor cells (CTCs), or exosomes, it is possible to detect cancer at an early stage, potentially before clinical symptoms arise. Early detection is particularly of high value in cancers where symptoms often present late (e.g., pancreatic or ovarian cancer) resulting in poor outcomes. Detecting early-stage disease requires very high sensitivity and in order to increase sensitivity, assays tend to include different approaches ranging from detecting common variants in the disease to cancer-specific DNA methylation patterns and fragmentomics. Tumor-derived DNA tends to have distinct fragmentation profiles compared to normal circulating free DNA, and incorporating fragment size distribution into the analysis can enhance detection accuracy, particularly in early cancers where ctDNA abundance is low. Novel methods such as targeted sequencing of phased variants have also proved to offer increased sensitivity for identifying ctDNA (257). Some assays are available for commercial use with regulatory approvals by the FDA. For instance, GALLERI is a pan cancer assay that can detect >50 cancer types from a single blood draw with an overall sensitivity of 51.5% (all stages) (258), CancerSEEK has demonstrated sensitivity of about 70% in 8 selected indications (259), Shield, is another example of an assay based on analysis of blood that can detect colorectal cancer with a sensitivity of 83% for invasive cancer and 13% for precancerous lesions (260).

Apart from blood-based assays, assays are also being developed using urine, saliva, and stool samples. There are, for instance, FDA-approved assays based on non-invasive (stools) screening tools in colorectal cancer (261), where the assay with the highest reported performance has a 95% sensitivity for invasive colorectal cancer and 43% for advanced precancerous lesions, outperforming fecal immunochemical test (262). Although these assays do not replace the need for colonoscopies, they may increase compliance with screening programs. There is also extensive research in developing assays based on other analytes such as proteomics (263, 264), glycosaminoglycans (265), and metabolomics (266).

Table 8: Testing technologies for molecular diagnostics

Description of tests	In clinical use since…	Pros and cons
Immunohistochemistry (IHC) staining Allows for the assessment of proteins on pathology slides in a semi-quantitative fashion.	1970s (application in oncology)	• Pros: Specific, inexpensive, short turnaround time. • Cons: Historical issues with reproducibility and standardization, but automation platforms have improved this recently. Challenging to assess multiple targets. Cannot detect specific genomic variants.
FISH (fluorescence in situ hybridization) test Allows for assessment of copy number alteration and fusions.	1980s	• Pros: Inexpensive, specific. Good at detecting fusions. • Cons: Issues in reproducibility and standardization.

Description of tests	In clinical use since…	Pros and cons
Polymerase chain reaction (PCR) test Allows for assessing gene expression and actionable variants. Not feasible when wanting to look at mutations in large genes or large number of genes at the same time.	1980s	• Pros: Inexpensive, sensitive, specific, fast with short turnaround time. • Cons: Difficult to assess many mutations/genomic regions at the same time.
Next-generation sequencing (NGS) testing Allows for the sequencing of a large portion of the tumor's genome. NGS can be targeted (focusing on specific areas known to have mutations) or more comprehensive (WES, whole-exome sequencing; WGS, whole-genome sequencing).	2005	• Pros: Sensitive and specific. Can assess many genes simultaneously from a very limited sample material. • Cons: Although costs are decreasing, the total expense for a complex, large panel (including the cost of goods, machines, bioinformatics updates, and clinical reporting) remains high.
Liquid biopsies Currently dominated by NGS-based and PCR-based technologies that detect ctDNA in blood (or other fluids).	2010s	• Pros: Non-invasive and easy for patients; can capture the mutational landscape of all metastatic lesions; enables improved detection of resistance mutations, minimal residual disease assessment, and early cancer detection. • Cons: High sequencing depth is often required, driving up costs compared to tissue NGS. Sensitivity is not 100% compared to tissue NGS, even in patients with metastatic disease. Sensitivity in early-stage disease is more limited, although rapidly improving.

3.3.2 Regulation of diagnostic assays

The regulation of diagnostic assays has evolved significantly over the years, reflecting the growing complexity of molecular diagnostics, the need for robust clinical validation, and safe and appropriate use. Historically, diagnostic assays, including in vitro diagnostics (IVDs), were subject to less stringent regulatory oversight than medicines and medical devices. Many laboratory-developed tests (LDTs) were created by individual laboratories without the need for external approval, especially in the context of academic and hospital settings. In the US, diagnostic assays were initially regulated under the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act. However, for many years, LDTs were mostly unregulated by the US FDA and instead under the oversight of the Clinical Laboratory Improvement Amendments. The FDA currently oversees IVDs, including companion diagnostics and other molecular assays, under the Federal Food, Drug, and Cosmetic Act and related amendments using a risk-based classification where IVDs are classified into three categories:

- Class I: Low risk, often exempt from premarket approval (e.g., some pregnancy tests).
- Class II: Moderate risk, requiring premarket notification (510(k)) to demonstrate substantial equivalence to a legally marketed device.
- Class III: High risk, requiring premarket approval, including companion diagnostics and tests for life-threatening conditions.

The FDA's role in companion diagnostics has expanded in recent years, with these tests becoming essential for selecting patients for targeted therapies. Companion diagnostics must undergo a rigorous premarket approval process to ensure appropriate performance. The FDA has historically taken a hands-off approach to LDTs, but there has been increasing pressure to

bring these tests under stricter regulatory oversight due to concerns over inconsistent quality and validation. Efforts such as the VALID Act aim to reform LDT regulation in the US.

In the EU, the In Vitro Diagnostic Directive (IVDD) was introduced in 1998 (Directive 98/79/EC). It classified assays into four categories based on risk, with most tests subject to self-certification by manufacturers. Only a few high-risk diagnostics, such as those for HIV and hepatitis, required Notified Body review. As molecular diagnostics have advanced, the need for more comprehensive regulatory frameworks has evolved. Diagnostic tests, not least in oncology (e.g., companion diagnostics), have become necessary to identify appropriate patients for many medicines. This has led to a shift toward tighter regulatory control to ensure test accuracy, clinical relevance, and assay overall performance.

The In Vitro Diagnostic Medical Devices Regulation (IVDR) represents a major shift in the EU's regulatory landscape (Regulation (EU) 2017/746), replacing the IVDD with more stringent requirements for IVDs. The regulation applies uniformly across all EU member states, with an emphasis on safety, clinical performance, and post-market surveillance. Under IVDR, devices are classified into four risk classes (A, B, C, D), with higher-risk diagnostics requiring Notified Body oversight. Companion diagnostic assays now also face higher regulatory scrutiny, including consultations with medical authorities to ensure that the tests have sufficient performance.

The introduction of the IVDR has many implications. The regulation enhances patient safety by requiring manufacturers to provide more clinical evidence and better post-market surveillance. The introduction of unique device identifiers (UDI) and more stringent documentation requirements also make it easier to trace IVDs and their performance. By raising the bar for clinical evidence and safety, this may foster higher-quality innovations in molecular diagnostics. The framework ensures that the rules for in vitro diagnostics are standardized across all EU member states, simplifying the process for manufacturers seeking to market their devices across Europe. However, the increased regulatory burden and complexity of the regulation is hampering the development of IVDs in combined studies involving the medical product and the related IVD. It also increases the cost for manufacturers (and thereby payers), as more clinical evidence is required and a higher regulatory burden needs to be managed. There is also a limited number of designated notified bodies capable of certifying under IVDR, which has created a bottleneck with delays in product certification and access to novel tests for patients (267, 268). The European Commission has acknowledged these challenges and introduced extensions to the transition periods for IVDR compliance, with deadlines now staggered until December 2029, depending on the device class (269).

3.3.3 Future directions in molecular diagnostics

The field of molecular diagnostics in oncology and hematology has advanced dramatically over the last decades. Since the Human Genome Project (completed in 2003), the cost of DNA sequencing has decreased from USD 3 billion to under USD 600 today (270). NGS and new applications of NGS in, e.g., liquid biopsies have already changed how oncology is practiced in many indications. Importantly, these innovations have helped in identification of new targets and thereby enabled medicine development, but they have also been pivotal in the implementation of precision medicine as they enable identifying patients for targeted therapies, early cancer detection, and treatment monitoring. The coming years will see continued efforts on early detection assays that can help identify patients at a stage where they are potentially curable. With more and more targeted agents requiring specific biomarker analysis, we will also see continued increased use of predominantly large NGS panels in patients diagnosed with cancer to identify patients that can benefit from these medicines.

In many parts of the world (including Europe), the costs associated with NGS testing and limited reimbursement by payers as well as the lack of parallel reimbursement of the testing method and the medicine are restricting the use and systematic implementation of NGS. Continuous innovations in sequencing chemistry, nanotechnology, and computational power will keep driving the cost of sequencing further down (271). The integration of AI and machine learning into sequencing workflows will also lower costs by improving the accuracy and efficiency of data analysis (272). As data interpretation and storage costs decrease, the overall cost of sequencing is likely to continue to fall. Looking forward, it is likely that WGS could soon cost as little as USD 100 and this would allow making genomic testing routine practice in healthcare, enabling widespread use of precision medicine and preventive genomics. However, while the cost for sequencing might further decrease, the full costs of providing actionable and timely NGS results to patients also include the cost of sample acquisition and processing, logistics, initial setup and maintenance of the NGS (purchasing of equipment, laboratory and IT infrastructure, personnel, validation, participation in ring trials, quality controls, updates of software, etc.) (273). The latter costs might increase or stay stable over time, and adequate reimbursement for these services is vital for broad adoption.

Importantly, WGS will include both somatic and germline analysis which will also enable assessment of predisposition to diseases. It should be emphasized that WGS at large scale is not without complexities. There will be concerns about the risk of data security breaches, psychological stress from incidental findings, and the potential for genetic discrimination. Misinterpretation of genetic data and the implications for family members also raise ethical questions. Regulatory frameworks will thus need to evolve to address these risks, ensuring WGS is implemented responsibly in clinical settings.

As sequencing costs fall and novel technologies mature, we may also eventually see a transition to point-of-care diagnostics that could have significant impact on cancer care by offering rapid results in clinical environments without the need for centralized laboratory facilities and long turnaround times. Other technologies, such as CRISPR-based diagnostic tools (274), also hold promise for rapid nucleic acid detection in clinical settings, that could potentially enable rapid detection of mutations to guide treatment decisions.

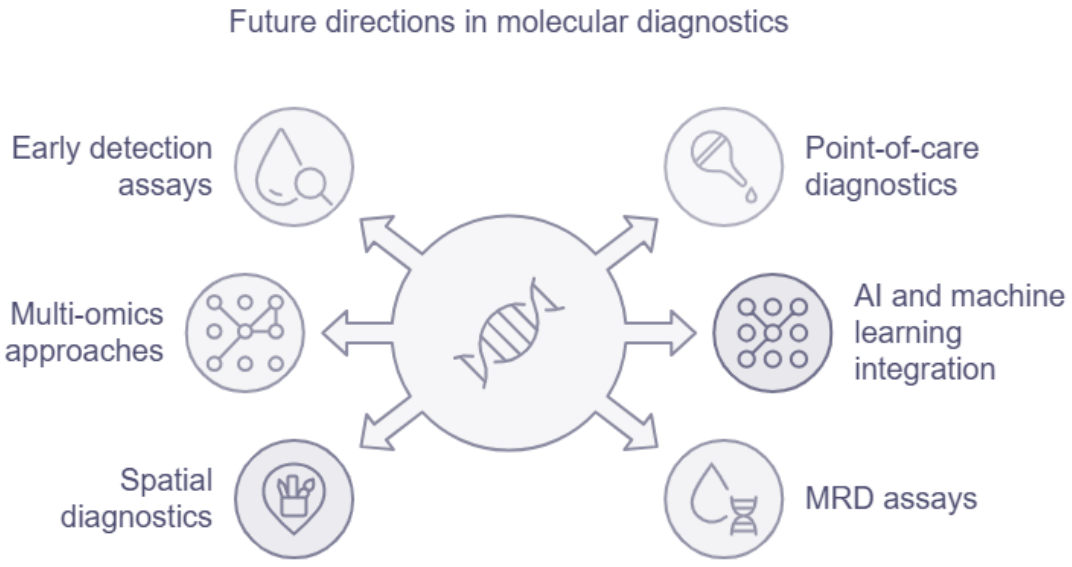


Figure 38: Future directions in molecular diagnostics.

MRD assays have been developed and validated, and the FDA recently accepted MRD as a surrogate endpoint in multiple myeloma based on robust evidence (254). In the coming years, we will see increasing clinical use of MRD assays in both hematologic and solid malignancies. Sensitivity will determine the clinical utility of these assays - limited sensitivity will limit use to choose active treatment in positive MRD patients and very high sensitivity will enable withholding therapy. The price of assays, and, not least, the price of multiple tests in the monitoring setting will also be important variables that determine how widely these assays are used.

Other trends for the future include the integration of multi-omics approaches, advances in spatial diagnostics, AI, and increasingly sensitive liquid biopsy technologies enabling earlier detection, improved disease monitoring, and more tailored treatments.

Multi-omics will allow for integrating data from genomics, transcriptomics, proteomics, and metabolomics, that contain orthogonal information to create a deeper understanding of cancer biology, which will drive further target identification and medicine discovery. Multi-omics approaches may also help drive sensitivity of assays for MRD and early detection. Whether multi-omics approaches will become applicable in the clinic or if it will mainly be limited to research and medicine development is hard to tell. Clinical utility and cost will be the drivers of clinical implementation.

Traditional molecular diagnostics such as PCR and NGS often focus on the analysis of bulk tissue, where spatial information is lost during sample preparation. However, the tumor micro-environment plays a crucial role in cancer development, progression, and response to therapy. Spatial molecular diagnostic technologies allow assessment of the complex relationships between tumor cells, immune cells, and the surrounding stromal components within their original tissue architecture. Spatial transcriptomics (275-277) and multiplex imaging technologies (278) allowing for a combined assessment of both proteins and nucleic acids are already relevant in medicine development but the future may see such analysis to be integrated in clinical care.

The growing complexity of molecular diagnostics requires advanced computational tools. AI and machine learning are becoming critical in analyzing large datasets, identifying patterns, and enhancing diagnostics. They are increasingly being integrated into molecular diagnostics, to help improve detection, analysis, and interpretation. One key area is the use of AI for genomic data interpretation. Tools have been developed to enhance the detection of genetic variants from NGS data with greater sensitivity and specificity than traditional methods (279). Similarly, AI is used in liquid biopsy for analyzing ctDNA to improve early cancer detection, particularly in identifying rare mutations in blood. For instance, CancerSEEK used AI to combine ctDNA and protein biomarker analysis to detect multiple cancers at early stages (259). AI is also applied to help integrate molecular data and histopathological image analysis (280). In predictive biomarker analysis, AI algorithms have been applied to analyze molecular profiles to predict patient response to treatments like for instance immunotherapy by evaluating biomarkers such as PD-L1 expression and TMB (281). AI is also applied to metabolomics and proteomics to detect metabolic biomarkers for diseases, allowing more personalized diagnostics, as seen in metabolomic studies on early-stage lung cancer detection (282). Finally, although radiology is not a molecular diagnostic method, AI has been applied for interpretation in radiology and more elaborate ways to integrate it in workflows have been developed (282).

AI and machine learning will continue to be applied to molecular research, development, analysis, and interpretation. The limitations currently are that most large datasets have been

generated using different methods, assays, and samples that have been processed/handled differently. Finally, the clinical annotation and follow up are frequently characterized by substantial missingness and heterogeneity in follow up. Development of high-quality datasets with consistent sample management/analysis and with homogenous, standardized follow-up will be key to the development of high-quality AI tools.

3.4 Medicine development

Background

Cancer is a complex, heterogeneous group of diseases and even if there has been huge progress in the development of treatments in oncology and hematology in the last decades, we still have large gaps in our understanding of cancer biology. The "hallmarks of cancer" were first conceptualized by Hanahan and Weinberg in 2000, and later updated and extended in 2011 and 2022 (283). The current ten hallmarks describe the essential biological capabilities that cancers have. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing or accessing vasculature (angiogenesis), activating invasion and metastasis, avoiding immune destruction, deregulating cellular metabolism, genome instability and mutation, and tumor-promoting inflammation. Different classes of medicines have been developed that target these hallmarks; see Figure 39. These medicine classes include, for instance, small molecular targeted therapies, angiogenesis inhibitors, immune checkpoint inhibitors, chimeric antigen receptor T-cell therapies (CAR-Ts), ADCs, but also novel medicine classes.

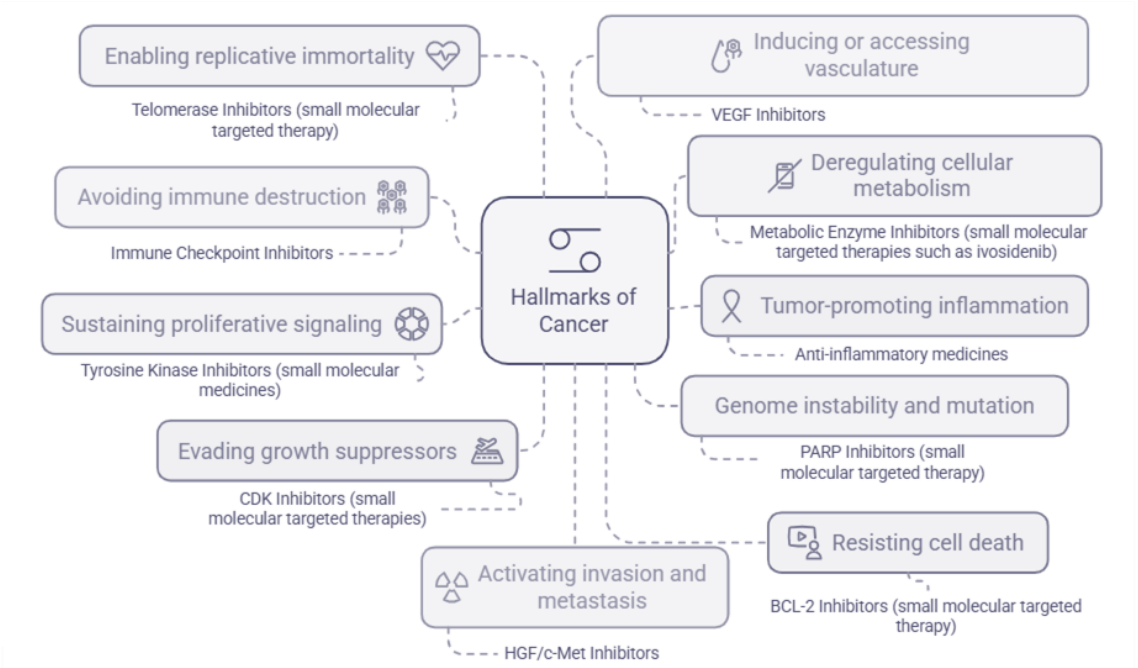


Figure 39: Hallmarks of cancer.

Source: (283).

The development of new therapeutics in oncology/hematology has accelerated in the last two decades. Oncology trials represented 29% of all initiated trials across all therapeutic areas in 2023 (up from 27% in 2018), with 44% of those trials being phase I trials reflecting a high number of new agents and combinations in development (284). This development is set to continue accelerating, fueled by improved methods and integration of AI across all areas of R&D,

including characterization of cancer host biology, target identification, medicine design, candidate medicine selection, and refined clinical trial designs (see also section 3.5). With improved methods available to a large number of biotech companies, we are likely to see continued development with a brief first-in-class exclusivity followed by very rapidly emerging me-too medicines for the same target(s). Progress in diagnostic methods in recent years, for instance in the area of early detection and MRD, will likely lead to a shift towards a higher proportion of patients diagnosed with early-stage disease and translate to increased efforts to develop medicines for approval based on MRD positivity which opens many previously unavailable indications (e.g., MRD positivity post adjuvant treatment).

Over the last years we have also seen an impressive increase of medicine development in China both of "me-too medicines" and of molecules with novel targets. Between 2013 and 2023, there has been an increase in trials initiated in China compared to the global total from 5% to 35% (285); see also section 5.4. In the coming decade, we should therefore expect to see increasing competition from medicines developed outside the US, Europe, and Japan.

From a medicine development point of view, the last few years have seen a shift towards a rapidly increasing focus on the development of immune checkpoint inhibition in combination with existing and novel agents, ADCs, bi-specific antibodies, cell therapies, but also continued development with kinase inhibitors and novel medicine classes such as PROTACs.

3.4.1 Small molecular targeted therapies

The human genome encodes more than 500 protein kinases. Mutations, overexpression, and dysregulation of some of these kinases have been identified as involved with cancer initiation and progression; see Figure 40.

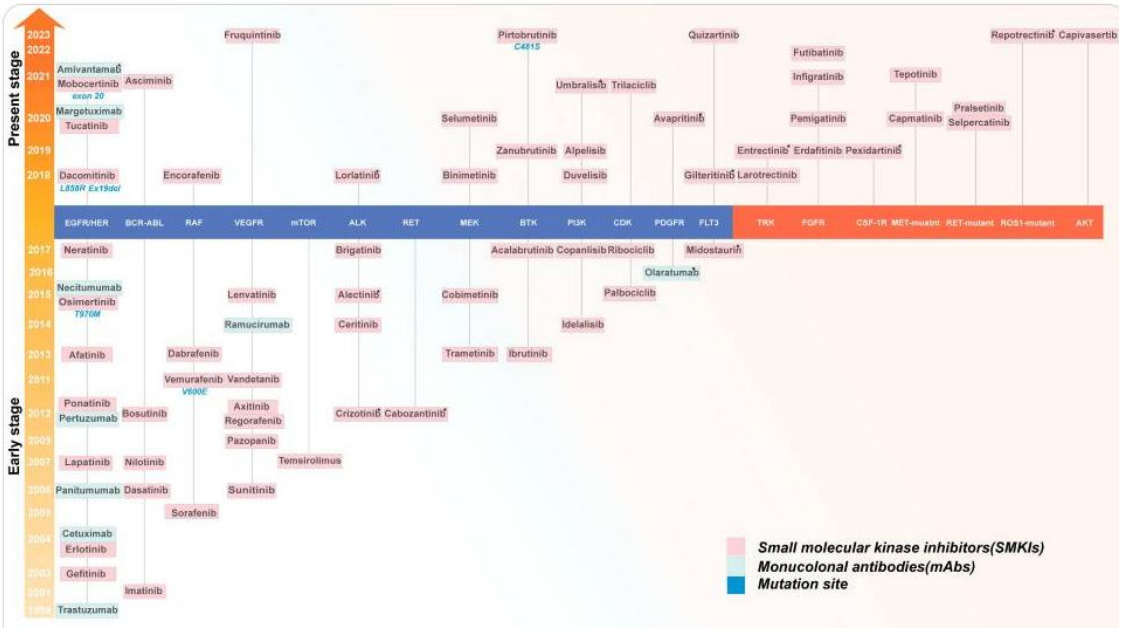


Figure 40: Approval history of FDA-approved small-molecular kinase inhibitors.

Note: This figure is adapted from Figure 2 in Li et al. 'Kinase Inhibitors and Kinase-Targeted Cancer Therapies: Recent Advances and Future Perspectives.' *Int J Mol Sci*. 2024; 25(10):5489. doi: 10.3390/ijms25105489. This material is licensed under CC BY, allowing for redistribution and adaptation. Source: (286).

There are currently around 70 FDA-approved kinase inhibitors used in oncology/hematology (286, 287). Although kinase inhibitors have not consistently proved to be the "magic bullets"

as they had been anticipated to be at the arrival of imatinib, they provide significant value in indications such as melanoma, GIST, hematologic malignancies, cholangiocarcinoma, lung-, renal-, breast- and bladder cancer. Over time, there has been a clear trend towards novel kinase inhibitors with more potent inhibition of driver mutations and activity in gate keeper mutations (that are associated with resistance), with less off-target toxicity than older agents, and with penetration to the brain, making these agents more effective and less toxic. For instance, osimertinib has rapidly become a frontline therapy in EGFR-mutant NSCLC, as it is a potent inhibitor of the most common EGFR alterations but also EGFR T790M, the most common alteration associated with resistance to the earlier EGFR inhibitors such as erlotinib and gefitinib. Similar examples exist in other alterations such as ALK and ROS1.

The most impressive progress in recent years has been the approval of kinase inhibitors in NSCLC in rare alterations such as ROS1 (288), RET (289), NTRK (290), BRAF (291), HER2 (292), cMET exon 14 skipping mutation (293), and KRAS G12C (294), where clinical trials have become feasible only with the introduction of broad NGS mutation panels. Other kinases have also been targeted successfully in more recent years. Multiple CDK4/6 inhibitors have for instance demonstrated significant value in ER-positive breast cancer in combination with endocrine therapy and are now first-line option for many patients with metastatic disease and also in the adjuvant setting of early-stage disease (295). Ongoing studies are assessing these agents in further indications. PI3K inhibition has succeeded after moving from pan-PI3K inhibitors to more isoform selective PI3K inhibitors and there are now several approved agents covering all PI3K (296) except the beta isoform and the number of indications are expected to increase. Other targets in other diseases have also been successfully targeted such as for instance FGFR in urothelial carcinoma (297) and cholangiocarcinoma (298), IDH1 in cholangiocarcinoma (299) and AML (300), IDH2 in AML (301), FLT3 in AML (302), BCL2 in AML (303), HER2 in colorectal cancer (304), multitarget kinase inhibitors in both first-line and second-line hepatocellular carcinoma (305), multiple, primarily VEGF-targeted agents (306) and HIF-2α in renal cancer (307), and most recently AKT in breast cancer (308).

An increasing number of tyrosine kinase inhibitors (TKIs) have received approval also in the adjuvant setting to reduce the risk of recurrence after early-stage disease. There are for instance approvals for osimertinib in EGFR-mutant NSCLC (309), alectinib in ALK fusions in NSCLC (310), dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) in high risk BRAF-mutant melanoma (311), imatinib is approved for high-risk patients with GIST (312), abemaciclib and ribociclib in ER-positive, HER2-negative breast cancer (313, 314), and sunitinib in high-risk renal cancer (only in the US) (315). For other rarer targets, adjuvant studies may be challenging from a feasibility perspective, and they would require global concerted efforts to include the number of patients required.

Another area that is being explored is the combination of TKIs with immune checkpoint inhibitors and with other types of agents where more than 400 trials are ongoing (316). Approvals include for instance axitinib with pembrolizumab in first-line renal cancer (317). Other combinations have had issues with toxicity that to some extent has been unexpected: durvalumab in combination with osimertinib was for instance associated with pneumonitis (318), tremelimumab and sunitinib was associated with renal failure (319), nivolumab and crizotinib (320) and pazopanib in combination with nivolumab (321) was associated with hepatic toxicity. The final role of combinations of TKIs with immune checkpoint inhibitors is unclear at this point.

In addition to kinase inhibitors, other types of small molecular medicines like for instance PARP inhibitors have in recent years been proven effective in patients with BRCA-mutant and HRD-

positive ovarian (322) and prostate cancer (323) and BRCA-mutant breast (324) and pancreatic (325) cancer, and DNA methyltransferase inhibitors in myelodysplastic syndromes (326), chronic myelomonocytic leukemia (327), AML (328) and BCL-2 inhibitors with approvals in AML (303), CLL (329), and small lymphocytic lymphoma (330).

Future directions for small molecular targeted therapies

Small molecular kinase inhibitors have been central to medicine development for more than two decades. Although only around 50 of the 500 known kinases are currently targeted in oncology, it is believed that the number of new targets will grow less rapidly in the future. Nevertheless, more than 150 new TKIs are in clinical trials, with many additional molecules in preclinical development (331, 332).

The current focus is primarily on developing therapies that are more potent inhibitors of their targets, as well as molecules capable of inhibiting gate-keeping mutations and other mutations associated with resistance. Additional objectives include improving adverse event profiles, enhancing combinability with other medicine classes, and achieving penetration across the blood-brain barrier to prevent and treat brain metastases, which is a significant clinical challenge in multiple indications (332).

There are still novel targets where molecules are in development, however. Some key targets with ongoing efforts include common KRAS mutations like KRAS G12D which is present in about 40% of pancreatic cancer (333, 334) and also pan-KRAS inhibitors that could benefit patients across many indications including pancreatic, NSCLC, and colorectal cancer (335). Importantly, there are also immunotherapy approaches that may enable targeting tumors with at least some of these KRAS alterations (336). Other new targets with medicines in development include for instance inhibitors of class II-III BRAF mutations, NRG1, WEE1, CHK1.

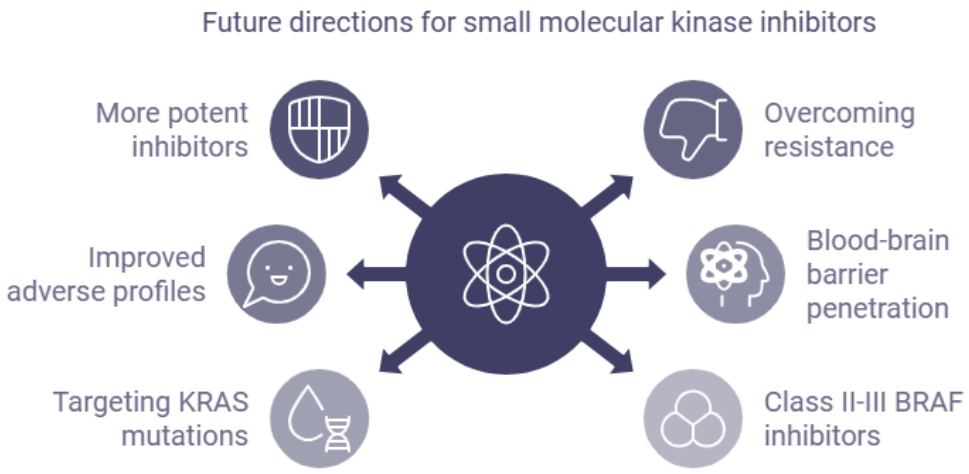


Figure 41: Future directions for small molecular kinase inhibitors.

3.4.2 Antibodies

Antibodies constitute a cornerstone of modern cancer therapy and are in many ways ideal cancer medicines by their high specificity, biological background, favorable pharmacokinetics, and potential for multiple modes of actions depending on construction and binding epitope. Antibodies have been developed against both ligands and receptors. They have been designed so that the binding of the antibody can shut down or activate the signaling of a receptor due

to a conformational change, inhibit ligand binding, inhibit receptor dimerization, or to predominantly activate the immune system to kill the cell they are binding to or as in the case of immune checkpoint inhibitors, modulation of the immune system itself. There are currently over 50 approved antibodies in oncology/hematology with approvals ranging from the late-stage metastatic to the early-stage neo/adjuvant setting and from monotherapy to combination with other therapies. Antibodies have over the years had a higher rate of success compared with small molecular medicines when assessing the rate of candidate medicines entering phase I to regulatory approval with an overall rate of about one in five compared with one in eight (337), which has triggered significant investments. There are currently several hundred antibodies targeting cancer in clinical development (338). Although some have targets that already have approved antibodies (not least immune checkpoint inhibitor targets) many have new targets, identified through advances in the biological understanding of cancer. In recent years, there have also been substantial developments in the antibody field with the development of ADCs and bispecific antibodies (BsAbs).

Antibody-drug conjugates (ADCs)

There are more than 100 ADCs in clinical development (339) with over 60 unique targets (340). A total of 13 ADCs have been approved so far; see Table 9. ADCs consist of monoclonal antibodies that are linked to an anticancer agent (currently usually a cytotoxic agent) by a synthetic linker. The idea is to enable highly selective delivery where the agent is cleaved off when internalized, thereby increasing the anti-tumor efficacy but at the same time also decreasing the off-target toxicity that is usually significant for cytotoxic therapies. The development of novel cytotoxic payloads and improved linkers are being explored to enable improved safety profiles, as systemic toxicity due to linker instability, target expression at low but insignificant levels in normal tissue has remained an issue with the currently approved agents (341). Other obstacles to ADCs include tumor heterogeneity and resistance due to single target.

Another emerging field related to antibodies are so-called nanobodies and antibody mimetics. Nanobodies are fragments of antibodies consisting of a single monomeric variable antibody (most frequently derived from llamas or camels), whereas antibody mimetics are proteins with binding properties similar to antibodies. Like an antibody, they can thereby bind selectively to a specific antigen. The potential advantage of a nanobody is that it is much smaller and has a lower molecular weight (12–15kDa) than common antibodies (150–160 kDa). Penetration to the interstitial space is thus higher but half-life typically very short compared to antibodies. Nanobodies also lack the immune-activating region of an antibody, which is advantageous in some (but not all) contexts. The first approval for a nanobody came in 2018 (342), and although it was not in oncology (caplacizumab in acquired thrombotic thrombocytopenic purpura) it represented an important milestone and has been followed by other approvals (343). Nanobody-based multiple nanobodies and antibody mimetic are in development in oncology both for imaging purposes and as therapies, and it is reasonable to assume that some will result in further approvals in the coming years (344). Yet another similar concept to ADCs are peptide-drug conjugates (PDCs). Instead of antibodies, smaller peptides are used to which medicines are linked. PDCs have the advantage of being smaller molecules that may be associated with higher penetration in tissues compared to ADCs but there are also potential challenges, in particular with short half-life. There is currently one approved PDC, melphalan flufenamide, in the EU (345), but it has been withdrawn from the US in 2024 due to failed confirmatory studies (345).

Table 9: ADCs with approvals in the EU and the US

Generic name	Characteristics	FDA-approved indications (Year of approval)	EMA-approved indications (Year of approval)
Gemtuzumab ozogamicin	Anti-CD33 antibody with acalicheamicin payload	CD33+ AML 2000 (original approval), withdrawn 2011 2017 (re-approved)	CD33+ AML: 2018
Brentuximab vedotin	Anti-CD30 antibody with an MMAE payload	Hodgkin lymphoma: 2011 Mycosis fungoides: 2017 Anaplastic large cell lymphoma: 2017 CD30-expressing lymphomas with chemotherapy: 2018 Hodgkin lymphoma with chemotherapy (pediatric): 2022	Hodgkin lymphoma: 2012 CD30-positive cutaneous T-cell lymphoma: 2018 Anaplastic large cell lymphoma: 2020
Trastuzumab emtansine	Anti-HER2 antibody with a DM1 payload	HER2+ breast cancer: 2013	HER2+ breast cancer: 2013
Inotuzumab ozogamicin	Anti-CD22 antibody with an N-acetyl calicheamicin payload	CD22 pos B-ALL: 2017	CD 22 pos B-ALL: 2017
Moxetumomab pasudotox	Anti-CD22 antibody with a Pseudomonas exotoxin payload	Hairy cell leukemia: 2018 Withdrawn 2022	Hairy cell leukemia: 2021 Withdrawn 2021
Polatuzumab vedotin	Anti-CD79b antibody with an MMAE payload	Diffuse large B cell lymphoma: 2019	Diffuse large B cell lymphoma: 2020
Belantamab mafodotin	Anti-BCMA antibody with an MMAF payload	Multiple myeloma: 2020, Withdrawn 2023	Multiple myeloma: 2020 Withdrawn 2024
Trastuzumab deruxtecan	Anti-HER2 antibody with a DXd payload	HER2+ breast cancer: 2019 HER2+ gastric or gastroesophageal cancer: 2021 HER2 mutated NSCLC: 2022 HER2 low breast cancer: 2022 HER2+ unresectable or metastatic solid tumors: 2024	HER2+ breast cancer: 2021 HER2+ gastric cancer: 2022 HER2 mutated NSCLC: 2023 HER2 low breast cancer: 2023
Enfortumab vedotin	Anti-nectin-4 antibody with an MMAE payload	Urothelial carcinoma: 2019 Urothelial carcinoma in combination with pembrolizumab: 2023	Urothelial carcinoma: 2022 Urothelial carcinoma in combination with pembrolizumab: 2024
Sacituzumab govitecan	Anti-TROP2 antibody with an SN-38 payload	Triple-negative breast cancer: 2020 Urothelial carcinoma: 2021 ER+, HER2− breast cancer: 2023	Triple-negative breast cancer: 2021 ER+, HER2− breast cancer: 2023
Loncastuximab tesirine	Anti-CD19 antibody with a PBD dimer payload	Large B cell lymphoma: 2021	B-cell lymphomas: 2022
Tisotumab vedotin	Anti-TF antibody with an MMAE payload	Cervical cancer: 2021	Cervical cancer: (2025)
Mirvetuximab soravtansine	Anti-FRα antibody with a DM4	Ovarian, fallopian tube and peritoneal cancers: 2022	Ovarian, fallopian tube and peritoneal cancers: 2024

Notes: There are additional approved ADCs in China only (iodine I-131 metuximab for liver cancer (2011), disitamab vedotin for gastric cancer (2021)). Source: (346).

Future directions for ADCs

With more than 100 different agents covering 60 unique targets in clinical development (339), there will be continued advances with novel targets, payloads, and improved linkers in the coming years. Multiple new ADC concepts are being explored ranging from bispecific, conditionally active (probody-drug conjugates), protein-degrader, dual-drug, and immune-stimulating ADCs. These concepts are believed to have different advantages. Probody-drug conjugates may enhance tumor specificity, bispecific ADCs, dual-drug, and protein degrader ADCs may address resistance and heterogeneity. Bi-specific ADCs are developed that target different epitopes of the same antigen (biparatopic ADCs) and bispecific ADCs that target two different antigens. Bi-paratopic ADCs have shown clinical efficacy with a response rate of 41% in pre-treated patients (347), and other concepts such as MET-directed agents are in pre-clinical testing (348). Bi-specific antibody ADCs targeting different antigens are being developed using for instance EGFR/MET (349), EGFR/ MUC1 (350), and EGFR/HER3 (351). The emerging data support efficacy but there are also relatively pronounced toxicities in some cases, indicating that further work is required. Probody-drug conjugates represent a version of "pro-drugs", i.e., the concept is to make the ADC active only in the tumor environment. This can be done by either masking moieties that are removed or the antigen-binding site changing conformation in response to certain tumor or tumor environment-associated factors like acidic conditions or proteases. Probody-drug conjugates with masking moieties that are removed by proteases are in clinical trials and have reported initial efficacy and safety data in heavily pre-treated patients that support the concept although the response rates so far are modest (352), and the concept of ADCs with conformational change in acidic environment is also in clinical trials (353).

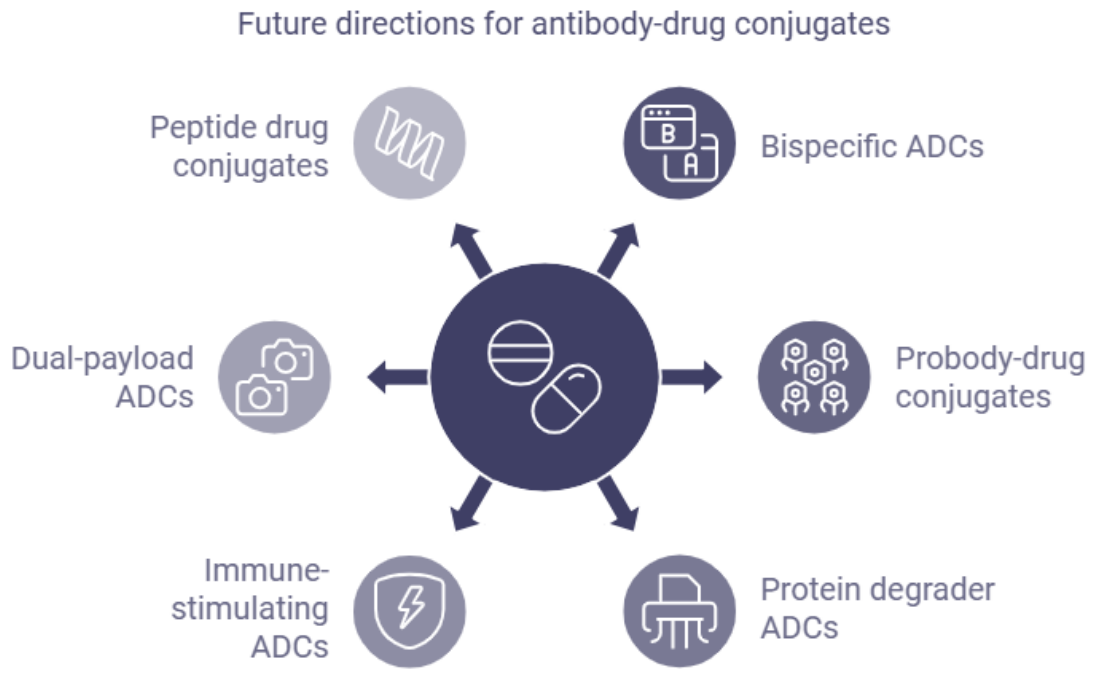


Figure 42: Future directions for antibody-drug conjugates.

Protein degrader ADCs (also called degrader-antibody conjugates, DACs) have for instance been developed against ER alpha (354), HER2 (355) and GSPT1 (356). ADCs designed to improve immune therapy have also been explored. Triggering innate immunity specifically in the tumor is a concept that will require administration that is highly exclusive to tumor sites. ADCs could

potentially ensure local administration and attempts at including agonists for toll like receptors. Initial data has been a mix of failed trials but also some trials showing activity, supporting that the concept in refined form is likely viable (357). Another avenue that is explored is ADCs where the payload is a stimulator of interferon genes (STING) agonist. There is compelling data in pre-clinical models (358), but the initial clinical trial has been on temporary hold which is now lifted, however. Finally, there are efforts to develop ADCs that carry two different payloads at the same time in order to address tumor heterogeneity and decrease risk of resistance. Initial data indicate that this is a viable approach (359, 360). There are also about 100 clinical trials with PDCs underway.

Bispecific antibodies (BsAbs)

Another rapidly emerging area within the antibody field are antibodies with two different binding epitopes, so-called bispecific antibodies (BsAbs). Unlike monoclonal antibodies, which typically target a single antigen, bispecific antibodies are designed to bind to a tumor-specific antigen (e.g., BCMA on multiple myeloma cells) and an immune cell receptor (e.g., CD3 on T-cells), or to a second tumor antigen, which may enhance specificity and reduce the likelihood of antigen escape/resistance (361). Bispecific antibodies represent a novel class of immunotherapies that are rapidly gaining traction, particularly in hematologic cancers although there are also approved agents in solid tumors. There are currently 12 bispecific antibodies approved in oncology globally, 10 of which were approved in 2021 or later; see Table 10.

Table 10: Bispecific antibodies with global approvals

Generic name	Target	Mode of action	Year of approval	Indication
Catumaxomab	EpCAM and CD3	TDCC	2009, withdrawn EU 2013	Ovarian ascites intraperitoneal
Blinatumomab	CD19 and CD3	TDCC BiTE	2014 (US, EU, Japan)	ALL
Amivantamab	EGFR and MET	Duobody, signaling inhibition + ADCC	2021 (US, EU)	NSCLC exon 20 insertion (2021) NSCLC in combination with lazertinib (2024)
Tebentafusp	gp100-HLA-A*02 and CD3	TDCC scFv-TCR fusion	2022 (US, EU)	Uveal melanoma
Mosunetuzumab	CD20 × CD3	TDCC KiH	2022 (US, EU)	Non-Hodgkin lymphoma
Cadonilimab	PD1 × CTLA4 Dual checkpoint inhibition	Tetrabody	2022 (China)	Hepatocellular carcinoma
Teclistamab	BCMA × CD3	TDCC Duobody	2022 (US, EU)	Multiple myeloma
Glofitamab	CD20 × CD3	TDCC CrossMAb	2023 (US, EU)	DLBCL
Epcoritamab	CD20 × CD3	TDCC Duobody	2023 (US, EU, Japan)	DLBCL
Talquetamab	GPRC5D × CD3	TDCC Duobody	2023 (US, EU)	Multiple myeloma
Elranatamab	BCMA × CD3	TDCC bsAb	2023 (US, EU)	Multiple myeloma
Odronextamab	CD20 × CD3	TDCC Duobody	2024 (EU), denied US 2024	Follicular lymphoma, DLBCL

Notes: TDCC = T cell-dependent cellular cytotoxicity. Source: (362, 363).

Bispecific antibodies have seen high complete response rates in hematologic cancers like B-cell lymphomas, ALL, and multiple myeloma. In some indications, bispecific antibodies have emerged as an alternative to existing treatments, specifically CAR T-cell therapies, with the advantages of being off-the-shelf products that can be administered immediately (as opposed to CAR-Ts that take weeks), cheaper to produce, and with less logistical challenges (364). There has also been progress in solid tumors, most notably with a recent approval in NSCLC (365) and a recently reported first-line trial where the bispecific antibody amivantamab in combination with an EGFR inhibitor had superior progression-free survival (23.7 vs. 16.6 months) compared to current standard of care (osimertinib monotherapy) (366), and another in uveal melanoma (367).

While bispecific antibodies hold great promise, there are also several challenges. Cytokine release syndrome is a relatively common serious toxicity caused by massive T-cell activation, which limits the use of bispecific antibodies in community oncology settings. Strategies to mitigate cytokine release syndrome have been identified, such as pretreatment with steroids, step-up dosing, subcutaneous administration, modification of CD3 affinities and prodrug concepts. The first generation of bispecific antibodies also had a relatively short half-life. Furthermore, tumors can develop resistance by tumor antigen escape where tumor cells can downregulate or lose expression of the target antigen. Finally, in solid tumors there are unique challenges due to the immunosuppressive tumor microenvironment which can inhibit the activity of bispecific antibodies.

Future directions for BsAbs

In total, there are more than 200 bispecific antibodies in clinical development, with 60 different targets and more than 100 target combinations (368). 25% of these agents are in development for hematology, while 75% target solid tumors. Among them, 5% are approved, 5% are in phase III trials, and 40% are in phase II. There are multiple types of bispecific antibodies ranging from dual modulators of signaling pathways such as EGFR/MET (365), HER2/HER3 (369), EGFR/HER2 (370), HER2/HER2 (371), tumor-targeted receptor agonists, bispecific ADCs (347), bispecific T cell engagers (372), bispecific natural killer cell engagers (373), bispecific innate immune cell engagers (374), bispecific checkpoint inhibitors (375), and co-stimulators (376). There are also developments with bispecific ADCs that include both cytotoxic payloads and, e.g., PROTACs. The success of the field will soon likely be driven by the identification of tumor-specific antigens (as even low levels of expression on normal cells are associated with toxicity) and combination therapies. There are also multi-specific and oligoclonal antibodies in development, but these have not yet entered late-stage clinical trials in oncology (377).

3.4.3 Immuno-oncology

In the last decade, immunotherapy with immune checkpoint inhibitors has become a cornerstone of cancer therapy with therapies targeting CTLA-4, PD-1, and LAG-3. PD-1 treatments, for example, work by targeting the interactions between proteins on the surface of T cells and tumor cells that normally inhibit the immune response against cancer (378, 379). By blocking these interactions, checkpoint inhibitors effectively unleash the immune system to attack and destroy cancer cells, providing a groundbreaking alternative to more conventional therapies; see Figure 43.

Many patients have substantial benefits from these therapies and a subset of patients with metastatic disease in indications like melanoma, lung, and renal cancer and are likely cured from their disease (380). The longest documented follow-up of 10 years is in patients with

metastatic melanoma randomized to ipilimumab (a CTLA-4 antibody) and nivolumab (a PD-1 antibody), ipilimumab alone, or nivolumab alone. The median melanoma-specific survival was more than 120 months for the combination (with 37% of the patients alive at the end of the trial), and among patients who were progression-free at 3 years, 10-year melanoma-specific survival was 96% with nivolumab plus ipilimumab, 97% with nivolumab, and 88% with ipilimumab (381). In other indications, the benefit is not as high, but nevertheless these agents have significantly improved outcomes across many indications.

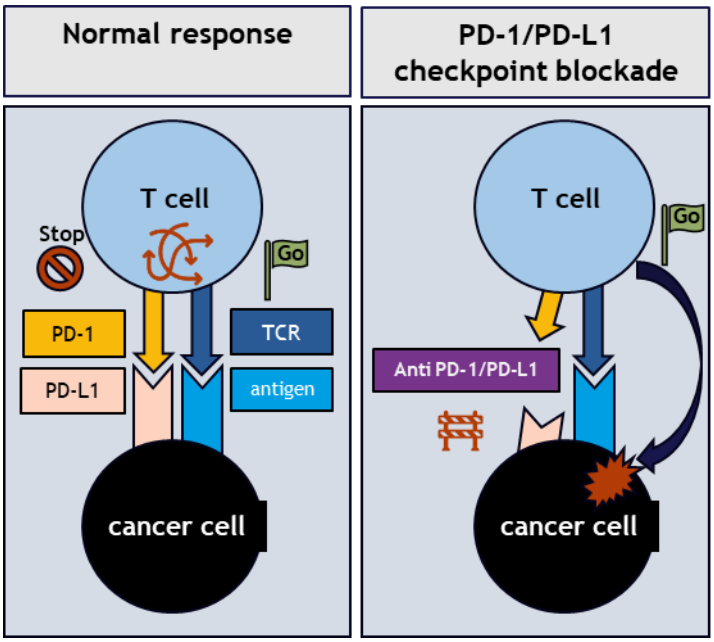


Figure 43: Mechanism of PD-1/PD-L1 immune checkpoint inhibition.

Notes: figure adapted from (378) and (379).

Immune checkpoint inhibitor antibodies against CTLA-4 (ipilimumab, tremelimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab, dostarlimab), PD-L1 (atezolizumab, durvalumab, avelumab), and LAG-3 (relatlimab) have been approved across more than a dozen solid malignancies (melanoma, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, lung, renal, urothelial cancer, mesothelioma) and Hodgkin and primary mediastinal large B-cell lymphoma. The position of these therapies has also moved rapidly to front-line metastatic therapy in several indications and to neo/adjuvant approvals in patients with early-stage melanoma, renal cancer, NSCLC, esophageal cancer, urothelial carcinoma, and triple-negative breast cancer. An indication-agnostic approval has been granted by the FDA in patients with MSI-H status (382) and high TMB, as these patients have a higher likelihood of benefit from PD-1 targeted therapy (383). The success of the initial immune checkpoint inhibitors has led to the development of multiple PD-1/PD-L1 antibodies globally, with multiple approvals in Europe (see Figure 44) and the US, as well as multiple China-only[22] approvals. A recent advance was an approved combination of the first LAG-3 antibody (a novel immune target) in combination with a PD-1 antibody in melanoma (384).

[22] Examples are candonilimab, envafolimab, penpulimab, serplulimab, sintilimab, sugemalimab, tislelizumab, zimberelimab, and the PD-1/VEGF bispecific antibody ivonescimab.

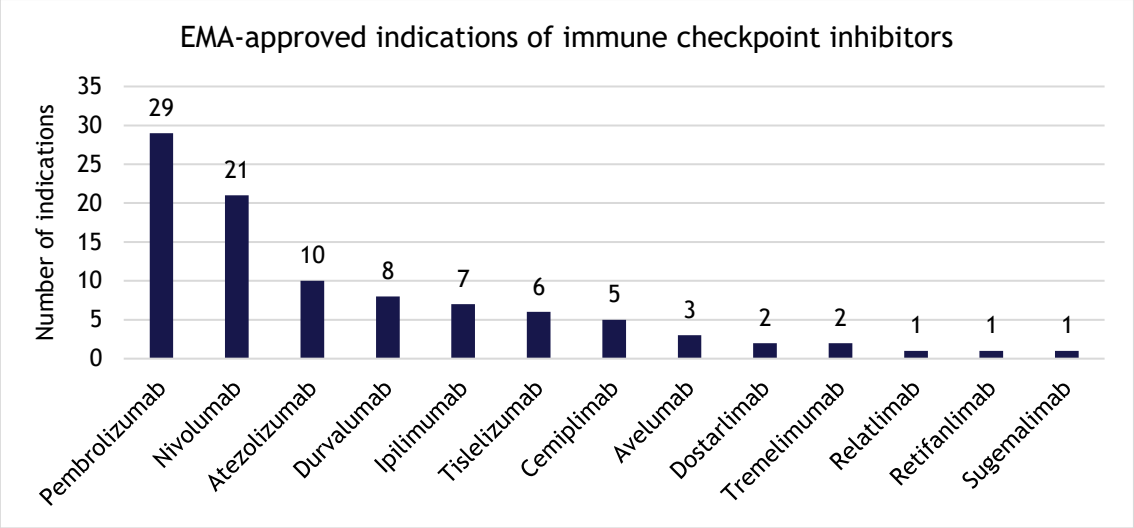


Figure 44: Number of EMA-approved indications of immune checkpoint inhibitors on December 31, 2024.

Source: EMA (385).

The introduction of immune checkpoint inhibitors has opened up a wealth of studies to assess the added value of these agents in combinations with other medicine classes ranging from chemotherapies to targeted therapies. This has resulted in approvals in a large number of indications; e.g., in metastatic NSCLC, the majority of patients without driver mutations are eligible for PD-1 antibody in combination with standard platinum doublet and only a minority of patients receives PD-1 antibody monotherapy in the first-line setting (386). There are also approvals for combinations with TKIs such as for instance cabozantinib/nivolumab and axitinib/pembrolizumab in first-line metastatic renal cancer (387, 388). Currently, there is a trend that a subset of patients appears to benefit from monotherapy with these agents while a larger subset derives benefit from the combination with other agents. Single-agent checkpoint inhibition has in general a good safety profile, but the combination of PD-1 or PD-L1 inhibitors with CTLA-4 inhibitors is associated with a relatively high frequency of immune-related toxicity that needs careful management (389).

Future directions for immune checkpoint inhibitors

The success of PD-1/PD-L1 and CTLA-4 targeted antibodies has highlighted the importance and potential of our immune systems in oncology. It has validated immune escape as a phenomenon and that it is possible to target and reverse immune escape in some patients. Despite more than a decade of intense activities with PD-1/PD-L1 and CTLA-4 antibodies, it is still, however, an area under development. Ongoing and future challenges include elucidating the value of different combinations and selecting patients appropriately. The last decade has been dominated by thousands of clinical trials assessing PD-1/PD-L1 in combination with different therapies. However, in 2022 after a decade of year over year increases, there was for the first time a decrease in the number of trials primarily driven by a reduction in phase II studies including anti-PD-1/PD-L1 mAbs (although still close to 1200 new phase II trials were initiated) (390). This may be due to both a saturation of approvals for PD-1/PD-L1 targeted agents but may also relate to several PD-1 agents coming off patent in a few years. There is however an increase in the number of phase I trials of newer theories such as different types of cell therapies and bispecific antibodies, and a growth in the number of targets for new agents (390).

There are still thousands of ongoing immune therapy trials that are yet to be read out and they are dominated by trials of antibodies against PD-1/PD-L1 followed by CTLA-4, TIGIT, LAG-3 and then a string of many other targets. Evidently not all these targets will proceed to have approved medicines. For example, there have recently been set backs in trials with TIGIT-targeted agents (391, 392). Even with a 10% success rate, we should expect many new agents, as there are close to 200 different targets being assessed.

Future challenges also include improved biomarkers to enable more appropriate patient selection. Since the immune system has the ability to remember and destroy new tumor clones as they emerge, immunotherapy is likely to remain a cornerstone in almost all areas of oncology. These therapies have in recent years gained several approvals in the neo/adjuvant setting after years of increasing indications within metastatic disease. We are likely to see many more neo/adjuvant indications with immune checkpoint inhibitors alone as well as in combination with other agents. Importantly, these new neo/adjuvant indications will represent opportunities for developing new indications for patients that have recurred after neo/adjuvant immunotherapy.

Immune modulation, provided that the therapies have a good safety profile, may also become important in the prevention of cancer as our immune systems change with aging, which is likely a strong contributing factor to the high incidence of cancer in the elderly.

3.4.4 Cell-based therapies

There are three types of autologous T cell immunotherapy that have reached approvals in the last few years: 1) tumor-infiltrating lymphocyte (TIL) therapies, 2) genetically engineered T cell receptors T cell therapies (TCR-T cell therapies), and 3) CAR T-cell therapies. TIL therapy received its first approval for lifileucel in 2024 (FDA only) for the treatment of advanced melanoma (393). There are also compelling data for cervical cancer (394), and ongoing trials in for instance ovarian cancer and NSCLC. This strategy is particularly promising for “hot tumors”, characterized by a tumor microenvironment (TME) enriched with tumor-infiltrating lymphocytes, indicating a preexisting immune response (395). TCR T-cell therapies involve expanding T cells with genetically encoded TCRs directed toward specific targets. Importantly, the targets can be intracellular as opposed to CARTs that are limited to cell surface proteins. The first approval for a TCR came in 2022 for tebentafusp in uveal melanoma (367), which is a TCR-based bispecific molecule that targets the GP100 peptide presented by HLA-A*02:01 on melanoma cells while simultaneously binding to and activating T cells to kill the tumor cells. This is not a conventional TCR-T therapy but a fusion of a TCR targeting a cancer antigen and a T-cell engager. A second approval came in synovial sarcoma in 2024 (FDA only) for afamitresgene autoleucel (396). The treatment includes collecting T cells from a patient’s blood, genetically engineering them in a lab, and then infusing them back. Genetic engineering produces a T-cell receptor that is better able to recognize and bind to a protein called MAGE-A4 in cancer cells. Ongoing trials in other indication also show promising activity in for instance urothelial carcinoma (397), indicating that we will likely see more approvals in the coming years in different indications.

In contrast, CAR T-cell therapy involves expanding genetically engineered T cells equipped with synthetic receptors (CARs) that recognize specific antigens on cancer cells (398). There are currently six FDA and EMA-approved CAR T-cell therapies; see Table 11. Four of the platforms are targeting CD19 in B-cell malignancies and 2 are targeting BCMA in multiple myeloma. Response rates are impressive in these heavily pre-treated patients but there are also complexities with these agents. Some patients experience cytokine release syndrome and

transient neurological adverse events making administration complex. Importantly, CD19-targeted CARTs can lead to B cell aplasia which requires maintenance therapy of intravenous immunoglobulins from normal donors (as all B cells express CD19). Although very rare, secondary malignancies of T-cell origin, including chimeric antigen receptor (CAR)-positive malignancies, have also been reported within weeks and up to several years after treatment of hematologic malignancies with BCMA- or CD19-targeted CAR T-cell therapy (399).

Table 11: Cell therapies in oncology with approvals in the EU and the US

Generic name	Type of therapy	Target	EMA approval	FDA approval	Indications
Tisagenlecleucel	CAR-T	CD19	Aug 2018	Aug 2017	ALL DLBCL Follicular lymphoma (FDA only)
Axicabtagene ciloleucel	CAR-T	CD19	Aug 2018	Oct 2017	DLBCL PMBCL Follicular lymphoma 2nd-line LBCL (FDA only)
Brexucabtagene autoleucel	CAR-T	CD19	Dec 2020	Jul 2020	Mantle cell lymphoma ALL (FDA only)
Lisocabtagene maraleucel	CAR-T	CD19	Apr 2022	Feb 2021	DLBCL PMBCL HGBCL Follicular lymphoma grade 3B 2nd-line LBCL (FDA only)
Idecabtagene vicleucel	CAR-T	BCMA	Aug 2021	Mar 2021	Relapsed/refractory multiple myeloma
Ciltacabtagene autoleucel	CAR-T	BCMA	May 2022	Feb 2022	Relapsed/refractory multiple myeloma
Tebentafusp	TCR-based bispecific molecule	GP100 peptide presented by on melanoma cells (HLA restricted)	Apr 2022	Jan 2022	Metastatic uveal melanoma (HLA restricted)
Lifileucel	TIL		Not approved	Feb 2024	Metastatic melanoma
Afamitresgene autoleucel	TCR	MAGE-A4 (HLA restricted)	Not approved	Aug 2024	Synovial sarcoma (HLA restricted)

Future directions for cell-based therapies

Cell-based therapies represent a significant advance in oncology with multiple approvals in hematology and very recently also in solid tumors. A current research direction is the development of CAR-Ts with novel targets (other than CD19 and BCMA) that can potentially expand the use to other indications, with targets such as CD20, CD22, CD30, CD33, CD123, EGFR, HER2, WT1, GPC3, CD38, MUC1, mesothelin, GD2, and neoantigens being explored (400). Some of these have already demonstrated clinical efficacy, e.g., CAR-Ts with CD22 in ALL and non-Hodgkin lymphoma (401), CD30 in Hodgkin lymphoma (402), CD123 in myelodysplastic syndrome (403).

There are also multiple efforts to design safer and more effective CAR-T strategies. More sophisticated engineered T cells, such as synthetic TCR and antigen receptor (STAR) (404), HLA-

independent T cell receptors (405), and alternative antigen receptor designs (406), to help improve the issue of low antigen sensitivity and a gradual loss of effector functions that limit clinical applicability of CAR-modified T cells are being developed. Furthermore, gene editing has also been used to make the CAR-Ts without PD-1 expression and to secrete antibodies against PD-L1 or secrete other immune modulating agents locally in the tumor that may help overcome potential resistance mechanisms (407). There are also developments in using CAR-natural killer (CAR-NK) cells which may offer some advantages as they do not require HLA compatibility and exhibit low safety concerns (408). CAR designs are also being introduced in other immune cells, such as dendritic cells, macrophages, regulatory T cells.

There have been doubts concerning the role of cell-based therapies in solid tumors as it has been a challenge to find antigens that are consistently expressed in a similar way to CD19 in B-cell malignancies and due to a different tumoral stroma. Recent data and approvals for TILs and TCRs strongly support a future with many cell-based therapies also in solid tumors. Multiple factors, including identification/validation of targets, solving regulatory compliance requirements, logistics, costs, and efficacy of other types of therapies such as bispecific antibodies will determine the ultimate role of cell therapy in solid malignancies.

BsAbs are perhaps in the short term the biggest competitive "threat" to cell-based therapies, as BsAbs are off-the-shelf products that enable immediate treatment whereas CAR-Ts take five to six weeks to produce for each patient (409-411). With BsAbs, older patients who are not eligible for CAR-Ts are able to be treated and adverse events might be fewer with BsAbs. However, BsAbs require regular administration whereas CAR-Ts are a one-time treatment. CAR-Ts require that patients have access to specialized care centers, but this might not be the case with BsAbs.

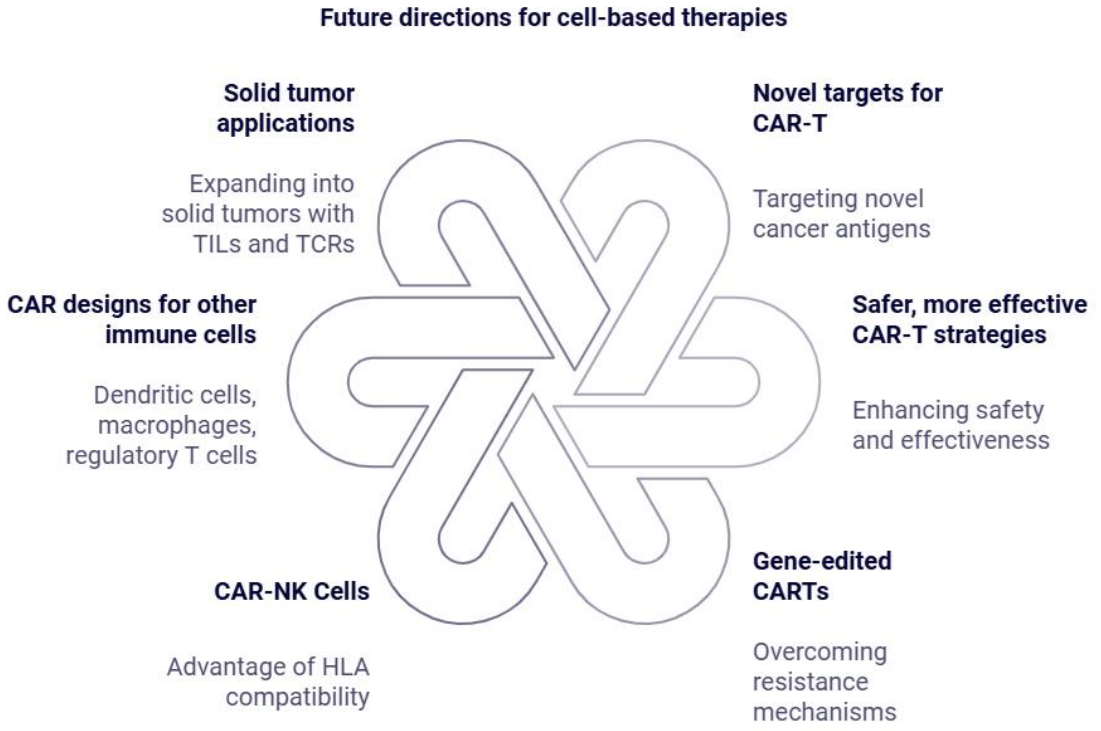


Figure 45: Future directions for cell-based therapies.

3.4.5 Radioligand therapy

A radioligand consists of a targeting molecule (often a small molecule or peptide) that binds specifically to a receptor or antigen on cancer cells (412). The ligand is attached to a radioactive isotope, which, upon binding to the cancer cell, emits radiation that damages the cell's DNA, ultimately killing it. In recent years, there have been two EMA approvals in 2017 and 2022 with agents targeting the somatostatin receptor in neuroendocrine tumors (403) and PSMA in prostate cancer (413). The use of radioligands has implications for treating centers as logistics and handling of radioactive waste materials is different from other antitumoral therapies, requiring additional site infrastructure and staff capabilities (414, 415).

Radioligand therapy is an emerging field with increased development activities and where we will likely see further approvals in the coming years, given the about 40 initiated trials in 2023 (416). There are also ongoing studies with the approved Lutetium Lu 177 dotatate to assess activity in breast cancer and Merkel cell carcinoma. Novel agents are being tested with the majority of efforts taking place in prostate cancer, neuroendocrine cancer, NSCLC, pancreatic cancer but also non-Hodgkin lymphoma (416, 417).

3.4.6 Novel medicine classes and challenging targets

Although the last two decades have seen a wealth of novel agents targeting kinases and immune checkpoints, most of our proteome is currently not "targetable" (therapeutically actionable), and many interesting targets that are common in cancer have remained elusive. Common drivers such as RAS, MYC, and other transcription factors have proved difficult to target, owing to large protein–protein interaction interfaces and/or lack of deep protein pockets and a complex biology with mechanisms of action requiring association with many co-factors.

Novel medicine classes are likely to enable the targeting of targets that have been out of reach so far. This includes the following classes:

- **PROTACs (proteolysis-targeting chimeras):** They are a class of compounds that tag specific proteins for degradation. Although challenges remain with PROTACs before they are in the clinic, there is substantial evidence supporting the concept (418-421), and it is likely to enable targeting previously therapeutically inactionable targets. PROTACs are also being developed as payloads for ADCs and for bispecific ADCs.
- **Gene editing / therapy**: This technology has started to become a reality in mono-genic diseases with the introduction of the CRISPR/Cas9 method. The first successful CRISPR/Cas9 technology therapeutics represent important milestones in medicine development and there are already approvals in sickle cell disease and beta thalassemia (422, 423). By contrast, cancer is characterized by alterations in many genes that cause abnormal behavior. The path to treating diseases like cancer will be long, as correcting a single gene will typically not be sufficient. CRISPR technology is however already accelerating our biological understanding of cancer, mechanisms of variants, and implications of therapies, as the technique enables the development of models that were previously unavailable to us (424).
- **Oncolytic virotherapy**: Oncolytic viruses are a form of immunotherapy that uses modified viruses to infect and destroy cancer cells (425). A genetically modified version of the virus is injected into the tumor. When the virus enters the cancer cells, it makes a copy of itself, which causes the cancer cells to burst and die. As the cells die, they release proteins that trigger the immune system to target any cancer cells in the body that have the same proteins, while the virus does not enter healthy cells. Oncolytic

viral therapy is an emerging area with a single approval for talimogene laherparepvec in melanoma in the EU in 2015 (426), two approvals in the US (melanoma and bladder cancer) (426, 427), and an approval in glioblastoma in Japan (428). There are multiple ongoing trials with oncolytic viral therapies, and we should expect further approvals in the coming years.

- **siRNA / RNA interference**: This is another rapidly developing area with four approved agents in the last years (429-432), although progress in oncology is yet to materialize.
- **Therapeutic cancer vaccines**: Some cancer cells have certain molecules, called cancer-specific antigens, on their surface that healthy cells do not have. Therapeutic cancer vaccines aim to stimulate an immune response against these antigens. Cancer vaccines may be non-personalized (i.e., targeting cancer antigens not specific to an individual person) or personalized with vaccines that are specifically tailored to each patient's mutational profile (433, 434). The first and thus far only cancer vaccine is sipuleucel-T for prostate cancer, approved by the FDA in 2010 and by the EMA in 2013 but withdrawn in Europe in 2015 (435, 436). Since then, progress has unfortunately been slow. However, with advances in mRNA vaccine technology that spurred the development of the COVID-19 vaccines in record time during the pandemic, the field of personalized cancer vaccines has accelerated. The development of personalized vaccines that are created based on the selection of the most likely immunogenic mutations of each patients' tumor is now in larger scale clinical trials. If the approach is effective, it has the potential to truly make cancer treatment personalized. Results have been somewhat mixed so far but in 2024, an investigational personalized mRNA cancer vaccine, in combination with the immune checkpoint inhibitor pembrolizumab, indicated positive results in adjuvant melanoma compared with pembrolizumab alone in a phase II trial (437), but definitive data that can lead to approval remain to be presented. Key challenges likely relate to predicting immunogenicity of epitopes presented (to select the best targets for the vaccine) and potentially addressing immune escape mechanisms that are present by adding other therapies such as immune checkpoint inhibitors for instance (437).

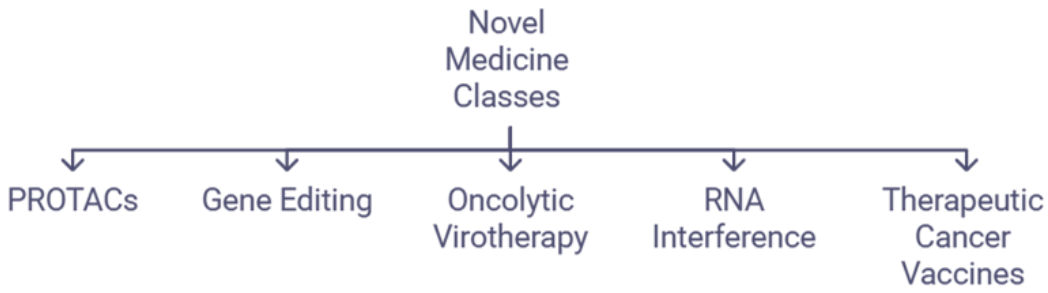


Figure 46: Novel medicine classes in oncology.

Some of the most common alterations in cancer such as mutations in TP53 are still elusive, but there are ongoing efforts ongoing that hold promise. Successfully targeting KRAS mutations would open up for significant advances in treating, e.g., pancreatic ductal adenocarcinoma and colorectal cancer where around 85% and 43% of patients, respectively, have KRAS mutations (438). TP53 is also one of the most mutated genes in cancer and the ability to target it would be another significant advance. Similar to with KRAS, there are multiple different approaches explored for TP53, ranging from small molecules (439-441) to immune therapeutic approaches (442, 443). Although many other targets in cancer remain elusive, there are reasons to be optimistic. These targets are likely only challenging to target but not untargetable.

3.5 Artificial intelligence in cancer care

Health care is becoming increasingly rich in data generated from patients, healthcare records that have transitioned to digital format, and new technologies like NGS that are providing detailed genomic/molecular characteristics of patients. Furthermore, imaging and pathology is used in digital format and wearable technologies are starting to enable capturing data from patients that have previously not been possible – ranging from vital parameters to the spoken word. The amount of data generated requires computer-assisted analysis in the form of AI/deep learning in order to make sense and develop understandable output that can help clinicians and patients in a meaningful way.

Machine learning has been extensively applied to image analysis and current data support that it can have a high accuracy in diagnosis of various medical conditions (444). In cancer, it has been applied to for instance diagnosis of melanoma, where the performance was similar to trained dermatologists (445), or better (446). Machine learning has also been applied to various areas of radiology imaging including mammography interpretation (447), thoracic screening imaging (448), and as a tool to help improve monitoring and control (449). The application of AI/deep learning to radiology is clearly starting to show interesting results, not least as it may assist in decreasing the interobserver variability of radiology assessments. Implementation will also require standardization, using similar formats and actual pipes and structure for large volume data sharing/computation (450).

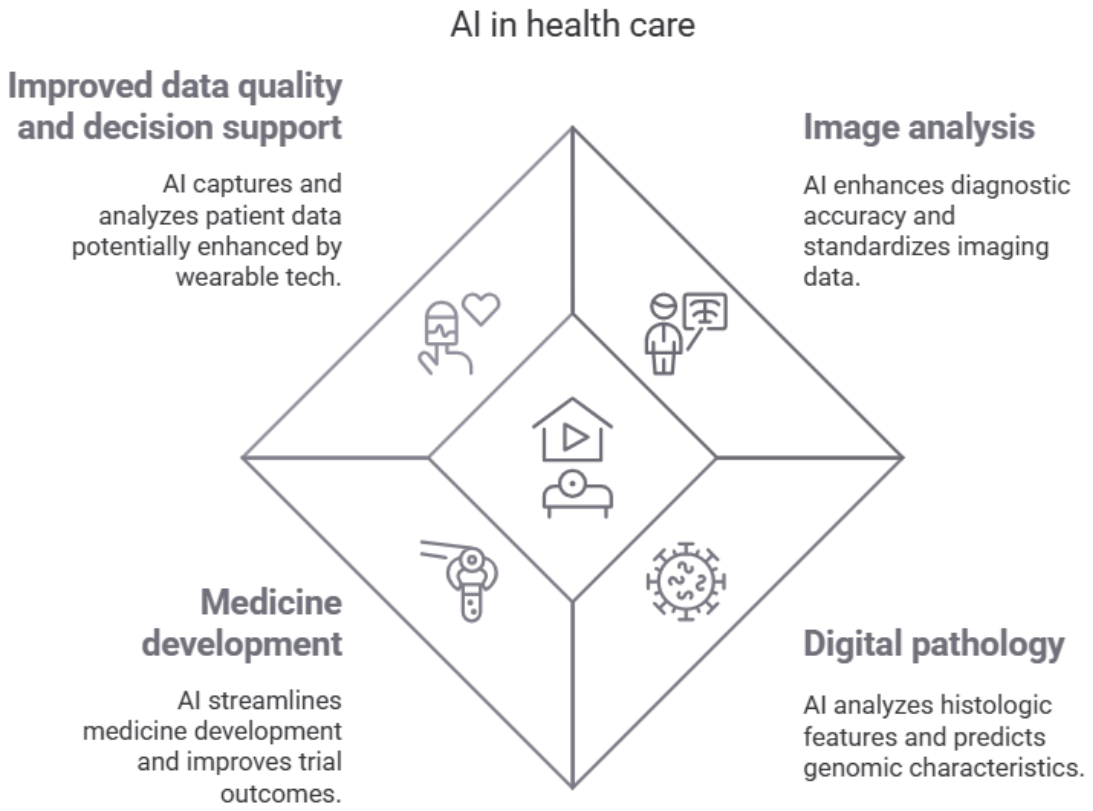


Figure 47: Broad areas of AI application in health care.

In digital pathology, AI has demonstrated accurate mitosis detection, characterization of histologic features such as nuclei, tubules and epithelium, count events, and characterization and classification of tissue (451-454). Deep learning has also helped to identify some features that are currently not used and that may be prognostic, such as stromal features (455), tumor-adjacent benign tissue in prostate cancer (456), and nuclear shape/orientation (457). Deep learning in digital pathology has been shown to be able to predict specific genomic/molecular characteristics such as mutations in lung cancer (458), MSI status (459, 460), and PD-L1 status (461). For some parameters in pathology such as determination of grade, there is substantial interobserver variability (462). One of the most likely first broad clinical uses of deep learning in digital pathology will be the standardization of such parameters.

AI is also being applied in medicine development, a process that used to be cumbersome and time intensive. The process typically begins with identifying a potential medicine target, followed by the design and testing of compounds/molecules that may bind to it. For example, the first mechanisms behind immune-checkpoint inhibition were already identified in 1974, but it took more than 20 years to study and show promising effects of immune checkpoint inhibitors in mice in 1996, followed by phase I/II studies in humans starting in 2001 and the first regulatory approval in 2011 (463). Although many breakthroughs have improved our understanding of cancer biology, the success rates for screened molecules entering phase I studies with eventual regulatory approval was 3.4% in oncology trials conducted in 2000–2015 (464). With low success rates and long development times, there is a strong interest in applying deep learning to various steps of the medicine development process. Machine learning is now increasingly being applied to almost all stages of medicine discovery and development as well as biomarker and clinical follow up data. In medicine discovery, it is being tested for target identification and validation, primarily based on gene-disease associations (465-468), but also on prediction of target therapeutic addressability (469-471). In compound screening and lead discovery, it has been applied to compound design and ligand-based compound screening (472). In preclinical development, it is applied to biomarker identification, predictive signatures, and prediction. In clinical development, it is being applied to for instance digital pathology and biomarker assessments as well as assisting to identify patients for clinical trials.

In the coming years, AI will be included in various aspects of clinical care. Applying AI to imaging analysis in radiology, skin diseases/retina, and digital pathology will help to standardize and potentially improve assessments. It can also improve quality of care and reduce stress for physicians by assisting in treatment decisions. AI analysis of data from wearable technologies has the potential to improve quality of care by identifying situations where the patient needs medical assistance and by providing more granular information on a patient’s symptoms and quality of life. It should also be emphasized that the successful application of AI to these areas will require large and high-quality clinical datasets, as the quality of the datasets determines the performance of the results. Rigorous validation in different datasets to prove performance will be key before clinical use. Another key aspect for the application of these products in clinical care is to respect patient integrity and confidentiality in line with privacy regulations such as GDPR in the EU. Unlike the application of AI to many technology products where consumer data are used without much concern for privacy, inappropriate use in health care will be detrimental and may severely damage and delay the integration of these technologies in clinical care.

3.6 Surrogate endpoints in clinical studies

Most cancer medicines are introduced in the treatment of patients with late-stage or metastatic disease. Their use may lead to improved survival, but the magnitude of the effect is seldom known when the medicine is first introduced, as surrogate endpoints, such as progression free survival (PFS) and objective response rate (ORR), are often used in clinical trials. Surrogate endpoints trade the advantage of reducing the time needed to conduct clinical trials (and hence accelerating patient access to new treatment options) for the disadvantage of greater uncertainty regarding patient-centered outcomes (e.g., overall survival (OS) and quality of life). Analyzing trials of 188 indications of 107 cancer medicines approved by the US FDA in 2006-2017, a study showed that the use of ORR or PFS as the primary endpoint was associated with 19 months or 11 months, respectively, shorter study duration compared to using OS (473). This can be compared to the average development time of a medicine – from early clinical trials to medicine approval – of about 6 to 15 years in the US (474).

The debate about appropriate endpoints for medicine approval in oncology has been going on for almost two decades and much has been learned (475). In general, the use of ORR alone is not enough, and the use of PFS is only suitable if it is strongly associated with OS (476). Surrogate endpoints are essential in certain settings, e.g. when the assessment of OS takes several years (e.g. early-stage cancers) and when crossover and the number of lines of therapy administered after the study medicine can dilute the chances of demonstrating clinically relevant effects on OS (477, 478). It is important to note that in late-stage disease PFS and OS may not differ much (479). A statistically significant increase in PFS with borderline clinical relevance (fewer than 2 months) that does not translate into a similar or larger impact on OS is not useful. However, it might happen that there is a modest median PFS benefit but a substantial effect on OS. For instance, in the pivotal study for ipilimumab there was no benefit in median PFS but a significant median OS benefit of close to 4 months difference favoring ipilimumab, with a continuous survival advantage and 20 percent survival at 7–8 years follow-up (480, 481). A recent important advance in surrogate endpoints from a regulatory point of view is the acceptance of MRD in multiple myeloma, where the FDA has formally accepted the marker based on robust evidence (254). A challenge with surrogate endpoints is also their transferability to routine practice, as they need to be easily measured to inform stopping or switching of therapy (482).

Many recent medicines target rare alterations. In these small indications it is not feasible to perform large-scale randomized phase III clinical trials to gain regulatory approval. Instead, approvals must be based on smaller phase II trials using PFS as primary endpoint, in order to not delay patient access to these medicines. Furthermore, tumor heterogeneity is a challenge when treatments are entering clinical practice. Tumor development is also an important difficulty which may include selection of clones that can be treatment related. Thus, demonstrating OS advantage can be very challenging in heavily pre-treated patients, and PFS may be a more useful endpoint. Also, evasion of immune response can be difficult to study as patient groups are small and heterogenous.

Ways to improve the robustness of the demonstration of clinical benefit compared to historical controls include the development of “synthetic” control arms, based on data from clinical registries capturing outcome (483). In theory, this may also become an option for other medicines with more common targets provided that the synthetic-control-arm data are robust and from high-quality sources.

3.7 Clinical effectiveness and real-world evidence

If a new medicine demonstrates efficacy in a randomized controlled trial (RCT), it means that the medicine works under controlled conditions and pre-defined endpoints. A patient treated in clinical practice does not necessarily fit the inclusion and exclusion criteria of clinical trials, however, as many patients are older and have more co-morbidities. Co-morbidities, treatments for co-morbidities, and dose reductions may influence the outcome for patients. Furthermore, the sequence and combinations of treatments may differ from what is permitted in protocols for clinical trials.

The discrepancy between treatment in an RCT and in clinical practice is the main argument for conducting clinical effectiveness studies. These studies include different aspects of effectiveness and safety from the perspective of the individual patient, the healthcare system, and of the broader society. Clinical effectiveness studies use data from clinical practice, usually extracted from patient charts (real-world data, RWD). In Europe, RWD is increasingly used as supportive evidence for regulatory approvals by the EMA (484). The European Organization for Research and Treatment Consortium (EORTC) has recently published their position on development of RWD evidence (485).

Clinical effectiveness studies can demonstrate which treatments are effective in real-world settings, providing insights into outcomes and long-term effects across different patient groups. They may also uncover previously unknown aspects that warrant further research. While the volume of data collected for each patient is often substantial, RWD frequently lack completeness and exhibit significant variability in assays, scan intervals, and terminology compared to clinical trials.

Efforts are underway to create extensive datasets combining clinical follow-up information with comprehensive genomic profiling (486, 487). These datasets have the potential to transform treatment by enabling the identification of therapies tailored to specific patient subgroups. Moreover, they could prove invaluable in medicine development, serving as synthetic control arms for rare patient populations where randomization is not feasible, and supporting label expansions to include subgroups not represented in pivotal trials. To realize their full potential, these datasets must include relevant variables and maintain high completeness rates. If achieved, they can provide high-quality RWD that supports evidence-based medical practice and facilitates reimbursement decisions.

4. Access to cancer medicines and molecular diagnostics

Key messages of this chapter

Comprehensive patient access to new cancer medicines requires three key steps.

Before cancer medicines reach patients, they must undergo regulatory approval, receive public reimbursement, and achieve uptake in clinical practice. Regulatory approval ensures safety, quality, and efficacy, reimbursement secures financial access through healthcare payers, and uptake in clinical practice enables actual usage by patients. These steps – at the European, country, and local/hospital level – illustrate the complexity and dependencies in patient access.

The EMA has approved 194 new cancer medicines since 1995, with a marked acceleration in approvals after 2012.

From 1995 to 2024, the EMA approved 194 new cancer medicines. The number of approvals has increased significantly from on average one new medicine per year in 1995-2000 to around 14 medicines per year in 2021-2024. In addition, there were 318 approvals of new indications of previously approved medicines. New medicine approvals consisted mostly of targeted therapies and immunotherapies. Most medicines were approved for use in solid tumors (62%), but a considerable share was approved in hematology (38%). An increasing number of new medicines has an orphan designation (37% in 2015-2024), demonstrating a strong focus on less prevalent cancer types.

Stark country inequalities in reimbursement of new cancer medicines exist.

Countries in Western Europe tend to reimburse more cancer medicines and reimburse them faster than countries in Central and Eastern Europe and smaller countries. For example, Germany reimbursed nearly all cancer medicines with EMA approval in 2019-2022 within 100 days, whereas countries such as Malta, Estonia, Slovakia, and Romania reimbursed fewer than 20% of new medicines and the average time to reimbursement was close to 900 days in Latvia and Lithuania, leading to stark inequalities in patient access to new treatments.

Molecular diagnostics is critical for the implementation of precision oncology, yet its availability differs widely between countries.

With nearly half of EMA-approved indications for solid tumors in 2015-2020 being linked to a biomarker, the availability and uptake of biomarker testing is crucial to enable patient access. This is also reflected in the launch of the first recommendation by ESMO in 2020 to use NGS testing in certain clinical settings. Single-gene techniques, such as immunohistochemistry, are usually available for most cancer types in all countries, although Bulgaria and Romania and to a lesser extent also Spain and Greece have some limitations. In contrast, for smaller NGS panels in lung cancer, only a few countries such as Luxembourg, Denmark, Switzerland ensure consistent availability, while access is greatly restricted in most Central and Eastern European countries and Malta, acting as a bottleneck in the widespread adoption of precision oncology.

The real size of cancer medicine expenditure is unknown, but - based on list prices - the expenditure almost tripled from 2014 to 2023 and varied six-fold between countries.

- Between 2014 and 2023, cancer medicine sales in Europe rose from €24.9 billion to €64.3 billion (based on list prices). This growth was driven by a combination of price and volume effects.
- Cancer medicine expenditure varied six-fold across countries in 2023, ranging from €31 per capita in Latvia to €195 per capita in Austria. Wealthier countries in Western Europe spent significantly more per capita on cancer medicines than countries in Central and Eastern Europe, yet there was some convergence from 2014 to 2023.
- The share of chemotherapy in total cancer medicine sales declined from 22% in 2014 to 6% in 2023 in Europe, replaced by targeted therapies and immunotherapies. Immunotherapies alone now account for 29% of total sales. Medicines used in the treatment of solid tumors accounted for 66-70% of sales in 2014-2023, while medicines used in the treatment of hematologic malignancies accounted for the remaining 30-34%.

- In 2023, around 250 different cancer medicines (with unique active substances) were sold in at least some quantities across European countries. Yet 10 medicines represented 44% of the total market sales (based on list prices).
- The latest cancer medicines only represent a small proportion of the total sales. Medicines approved by the EMA within the last 0 to 2 years accounted for 3-13% of total sales (based on list prices) in 2014-2023. The small share reflects that the average time from EMA approval to reimbursement exceeds one year in most European countries, which restricts usage.

The uptake of new cancer medicines has converged across countries over time, narrowing the access gap for patients.

- Austria, Switzerland, and France lead in adopting newer cancer medicines in clinical practice, while many Central and Eastern European countries, in particular Latvia, Poland, Estonia, and Slovakia, have the lowest uptake levels. Notable exceptions to this geographic pattern are the Netherlands and Portugal with uptake below the EU average and Bulgaria and Lithuania with uptake on par with the EU average, although the latter might be caused by inaccurate data and/or parallel trade of medicines not captured in the data used.
- Country differences have, by and large, grown smaller compared to the last Comparator Report. Overall, there was a 5.3-fold difference in uptake levels between the two countries with the highest and lowest uptake in 2018, which declined to a 3.3-fold difference in 2023. Immune checkpoint inhibitors saw a decrease from a 49-fold to an 8-fold difference, and breast cancer from a 9-fold to a 2.5-fold difference.
- Cancer types with a clear regional divide and lower uptake in Central and Eastern European countries are gynecological cancers and lung cancer, both of which are cases where biomarker testing is required for the administration of medicines. This is consistent with the lower availability and uptake of biomarker testing in this region.
- Non-Hodgkin lymphoma and leukemia are the only examples of similar or even higher uptake of newer cancer medicines in Central and Eastern European countries than in the Big Five countries and other countries in Northern and Western Europe.
- The newest cancer medicines (approved since 2020) mostly only had noticeable use in Austria, France, Germany, and Switzerland. The higher uptake aligns with faster reimbursement decisions (and probably the use of the early access program in France) in these countries.
- There are clear disparities in the speed of uptake across the Big Five countries. France and Germany achieve quicker uptake following EMA approval, indicating a favorable environment of funding, technology and capabilities (biomarker testing), quick integration in clinical guidelines, and well-trained healthcare professionals. The UK tends to lag behind, often resulting in considerable and persistent gaps in uptake levels.

Many root causes for country differences in patient access to new cancer medicines have been identified.

Beyond the common regulatory approval through the EMA, disparities in reimbursement and uptake affect cancer patients' chance to obtain access to new medicines. On the reimbursement side this includes differences in the initiation of the pricing and reimbursement process and the speed of national timelines and adherence. During the HTA process, there might be misalignment on evidence requirements and on value and price, differences in preferences regarding product differentiation and choice, and anticipation of an insufficient budget to implement decisions. Barries to uptake include insufficient budget to fully implement reimbursement decisions, suboptimal healthcare infrastructure and resources for biomarker testing and its reimbursement, infrequent updates of clinical guidelines, narrow treatment eligibility criteria, and limited continuing medical education.

The development and introduction of new cancer medicines have been among the most transformative aspects of cancer care in recent decades, playing an essential role in improving patient outcomes (216, 488-491). As a result, the landscape of cancer treatment has evolved significantly, with an increasing number of innovative therapies gaining approval and integration into healthcare systems; see Info box 7. However, the central question is to what extent patients have access to (new) medicines according to their needs. In general, full access to cancer medicines is attained when every patient that may benefit from a certain medicine will receive the appropriate medicine (492).

Info box 7. Major classes of cancer medicines

• **Chemotherapy** was initially tested at the beginning of the 20th century and more broadly introduced in the 1940s (147, 491). Even today, it remains the backbone in the treatment course of many cancer types. Chemotherapy can cause toxic side effects, as it attacks both (rapidly multiplying) healthy cells alongside malignant cells in the body.

• **Hormone therapy** (also called endocrine therapy) was first discovered in the 1940s for prostate cancer and in the 1970s for breast cancer (147). It is still the standard-of-care treatment modality in most patient subgroups of these cancer types, aiming to reduce the levels of estrogen in breast cancer and androgens such as testosterone in prostate cancer (493).

• **Targeted therapy** was introduced at the end of the 1990s (147). It targets molecular characteristics of the tumor and acts on specific molecules or proteins involved in the growth and spread of cancer cells. Newer types of targeted therapy in the form of ADCs combine the properties of targeted therapy that blocks tumor growth signals and chemotherapy.

• **Immunotherapy** in the form of immune checkpoint inhibitors, CAR T-cell therapies, and bispecific T-cell engager (BiTE) therapies was introduced in the 2010s (147). Immunotherapy agents help the body's own immune system (mostly T cells) to recognize and attack cancer cells.

• **Radiopharmaceutical therapy** relies on radiopharmaceuticals which contain radioactive forms of chemical elements called radioisotopes. They deliver radiation therapy directly and specifically to cancer cells, where the emitted radiation helps to destroy cancer cells (412, 494).

The continuous development of new and more effective cancer medicines is essential for improving patient outcomes. Before newly developed cancer medicines can reach patients in clinical practice in a country, they need to go through three main stages; see Figure 48. These are regulatory approval by the regulatory body for medical products after an evaluation of safety, quality, and efficacy, reimbursement by the public healthcare payer(s) which is most often preceded and informed by a more or less rigorous process of health technology assessment (HTA), and uptake in clinical practice.[23]

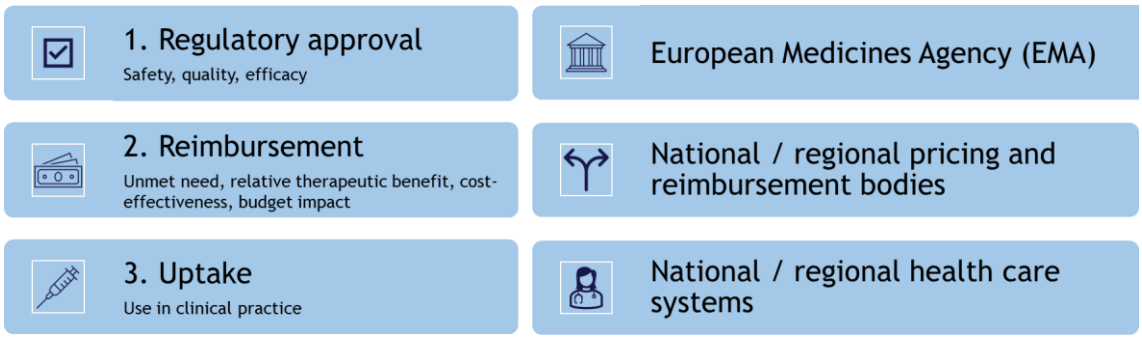


Figure 48: Main stages for patient access to new medicines and responsible institutions.

The following sub-sections provide an extensive analysis of the three main stages of patient access to new medicines. Section 4.1 provides a comprehensive analysis of the cancer medicines approved by the European Medicines Agency (EMA) from 1995 to 2024. Section 4.2 focuses on the second stage of gaining reimbursement in European countries. As many new medicines require biomarker testing to guide patient selection and their administration, section 4.3 focuses on availability and section 4.4. on uptake of these essential tests. The third stage of

[23] In practice, there are ways for patients to get access before regulatory approval (through clinical trials, compassionate use programs, early access programs, off-label use), after regulatory but before reimbursement (early access programs, off-label use, private purchases).

patient access – uptake of cancer medicines in clinical practice – is analyzed in value terms in section 4.5 and in volume terms in section 4.6 by country.

It is important to emphasize the difference in analyzing patient access measured as reimbursement (the second stage) and uptake (the third stage). Reimbursement is a prerequisite to use a medicine in clinical practice, but it does not mean that the medicine is actually used. Indeed, reimbursement means that a medicine has found its way on a (national/regional) list of prescribable medicines, whereas uptake means that a medicine is prescribed and reaches the patient. Nevertheless, even the analysis of uptake in this report is only an approximation of patient access. As in previous Comparator Reports, this report uses aggregate medicine sales on the country level as a proxy for patient access to cancer medicines; see Appendix C for the precise methodology and sources used. In this sense, access to cancer medicines is equated with market uptake, i.e., total annual sales (in volume and value) of medicines in a country. The gold standard of measuring patient access would be based on patient-level data from clinical cancer registries for the entire population of a country. This would allow for an exact analysis of prescribed medicines. The data could then be aggregated to the country level, providing knowledge on treatment patterns, length of usage, doses used, side effects of treatment, etc. It would also enable a comparison of actual and recommended treatment patterns, which can help to measure the quality of care and adherence to clinical guidelines.

4.1 Approval of new medicines

Newly developed cancer medicines have to obtain regulatory approval by the responsible regulatory authority before they can be prescribed to patients. The European Commission issues a centralized marketing authorization – after a recommendation by the EMA[24] (the regulatory body) – for new cancer medicines in the EU as well as Iceland, Liechtenstein, and Norway. Since 1995, the EMA has overseen the scientific evaluation of applications for centralized marketing authorizations for medicines. The EMA evaluates the safety, quality, and efficacy of new medicines (495). Since 2004, the process of centralized marketing authorization by the EMA has been mandatory for all new cancer medicines.

Between 1995 and 2024, 194 new cancer medicines (medicines with new active substances) were granted centralized marketing authorization by the EMA. There has been a marked increase in the number of approved medicines over time; see Figure 49. Four distinct periods are noticeable. Between 1995 and 2000, on average one new cancer medicine was approved per year. Between 2001 and 2011, the average annual number was close to four. Around ten new medicines were approved per year between 2012 and 2020. The year 2021 saw a record number of 17 approvals, lifting the average annual number to 14 medicines for the period 2021 to 2024. In 2024, new cancer medicines accounted for 28% of all medicines with new active substances recommended for approval by the EMA (496), which closely mirrors the share of oncology trials among initiated trials across all therapeutic areas (27% in 2018 and 29% in 2023; see section 3.4) (284). Figure 49 also illustrates important milestones in the introduction of new classes of medicines.

[24] The Committee for Medicinal Products for Human Use (CHMP) of the EMA is the body that issues a recommendation for authorization.

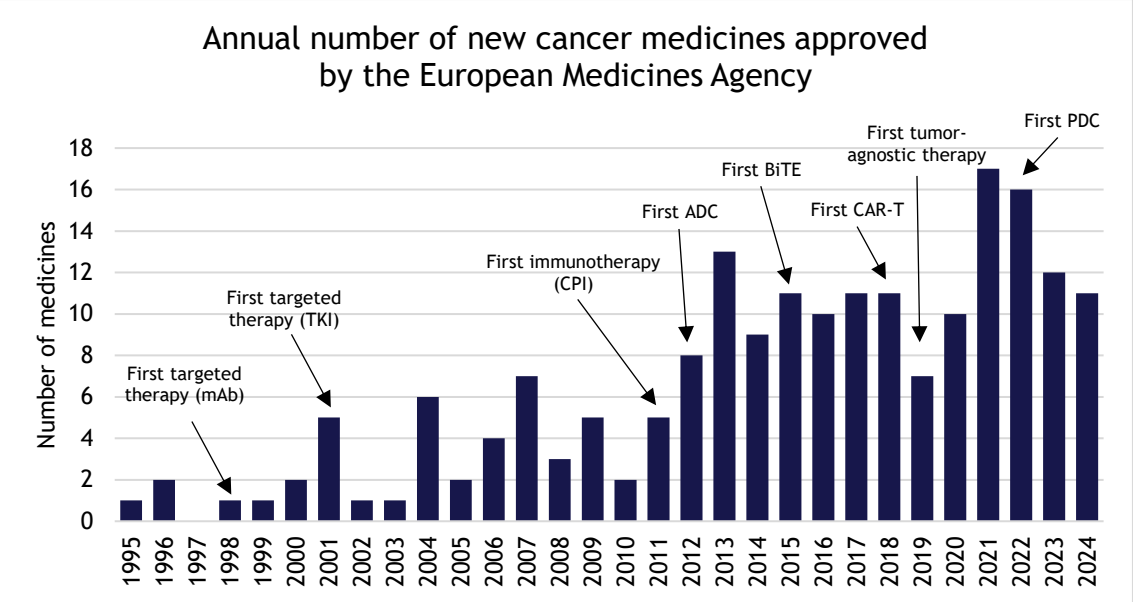


Figure 49: Annual number of new cancer medicines approved by the EMA, 1995-2024.

Notes: Medicines used with a therapeutic intent in cancer patients in the groups WHO ATC groups L01, L02, L03, L04, and V10 are included; see Table C1 in Appendix C for a detailed list. Medicines with identical active substances have only been included at their first instance of marketing authorization. Medicines that had their authorization withdrawn after initial approval are included. The approval dates reflect the decision date by the European Commission and not the CHMP recommendation date. mAb = monoclonal antibody, TKI = tyrosine kinase inhibitor, CPI = checkpoint inhibitor, ADC = antibody-drug conjugate, BiTE = bispecific T cell engager, CART-T = chimeric antigen receptor T cells, PDC = peptide-drug conjugate. Source: own calculations based on information from the EMA (497).

Besides the approval of new medicines, extensions of the use of previously approved medicines to new indications (i.e., new patient groups) are common.[25] These extensions are also subject to approval by the EMA. There has been an increasing trend in the number of extensions of indications of previously approved medicines, totaling 318 between 1995 and 2024. In many periods shown in Figure 50, the number of new indications was similar or outnumbered the number of new medicines. There was a notable increase in extensions, particularly after 2015 where there were twice as many new indications as new medicines. This coincides with the introduction of immune checkpoint inhibitors. For instance, nivolumab and pembrolizumab were both initially approved for the treatment of advanced melanoma in 2015, but had 21 and 29 approved indications, respectively, as of December 2024 (385). In comparison, targeted therapies typically see fewer extensions over their product cycle due to their targeted nature. The year 2024 saw a record number of 36 new indications approved, which was as many as during the whole five-year period in 2010-2014 and underlines the acceleration of new approvals in oncology.

[25] New cancer medicines can go through a sequence of label extensions following initial approval (498). Most often a new medicine is initially approved in a single cancer type, in advanced disease stage, as last line treatment. Label extensions over time may include earlier treatment line in advanced disease (e.g., first line), earlier disease stage in a curative setting (neoadjuvant and/or adjuvant treatment), change in treatment regimen (e.g., from use as monotherapy to combination with other medicines, or vice versa), treatment of other cancer types, and wider age bracket (e.g., pre-menopausal women, or children as of age 12).

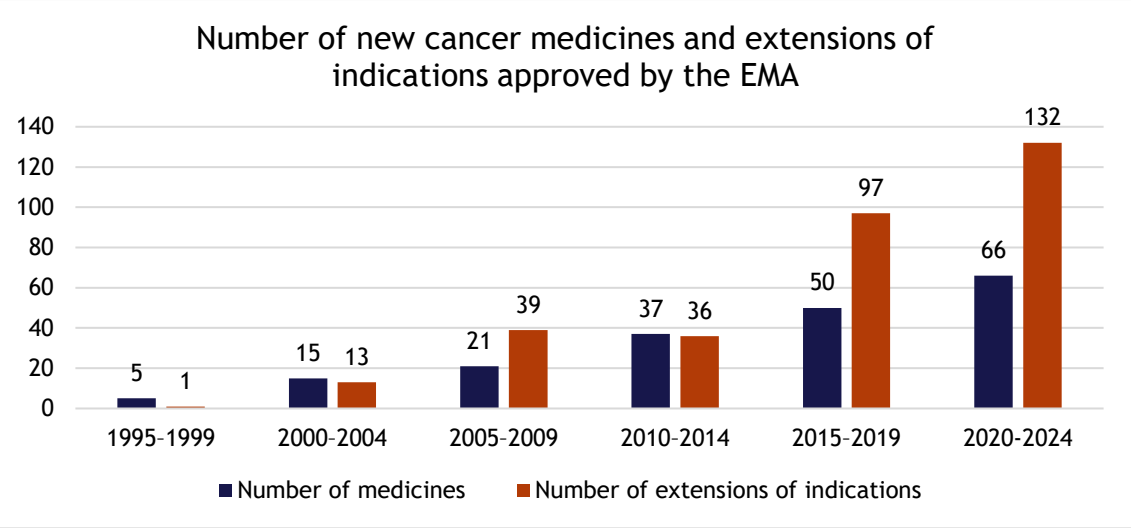


Figure 50: Number of new cancer medicines and extensions of indications approved by the EMA, 1995-2024.

Notes: See Figure 49 for inclusion criteria for new medicines. The number of extensions of indications covers only medicines that had been previously approved by the EMA and included in Appendix C for the full list of medicines. An extension of a combination of medicines where the EMA changed the label of each of the combined medicines was only counted as one extension. The dates for the extensions reflect the CHMP recommendation date (except for 1995-2002 where the decision date by the European Commission was used). Source: own calculations based on information from the EMA (499).

Figure 51 illustrates a significant shift in medicine classes of new therapeutic approaches over the past few decades. Since the early 2000s, there has been a marked transition from chemotherapy to targeted therapies. More recently, the introduction of immunotherapies has further diversified treatment options. The overall increase in the number of EMA-approved cancer medicines from 1995 to 2023 has been primarily driven by the rise of targeted therapies, with a notable contribution from immunotherapies, after 2015. There have only been a handful of new hormone therapies and radiopharmaceutical therapies since 1995.

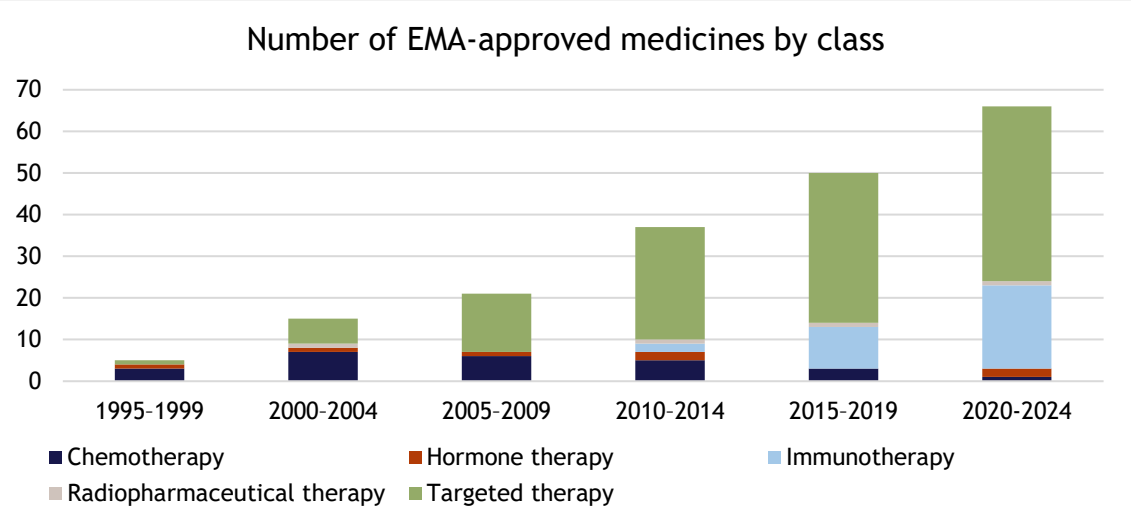


Figure 51: Number of EMA-approved medicines by class.

Notes: See Figure 49 for inclusion criteria for new medicines and Appendix C for the full list of medicines.

A variety of medicines for different cancer types have been approved by the EMA between 1995 and 2024, as shown in Figure 52. Most medicines were approved for use in solid tumors (62%),

but a considerable share was approved in hematology (38%) during the entire period, with almost the same number of approvals in 2020-2024. Breast cancer has seen a continuous introduction of new medicines. After 2005, the number of approvals began to rise particularly for lung cancer and leukemia. Melanoma saw many approvals between 2010 and 2019, while there were many approvals for multiple myeloma in 2015-2024. The most recent period from 2020-2024 shows many approvals for lymphoma. Nevertheless, this comparison only focuses on the first approved indication of a new medicine and therefore does not show the full picture. The class of immune checkpoint inhibitors has gradually witnessed the approval across dozens of mostly solid tumor types.

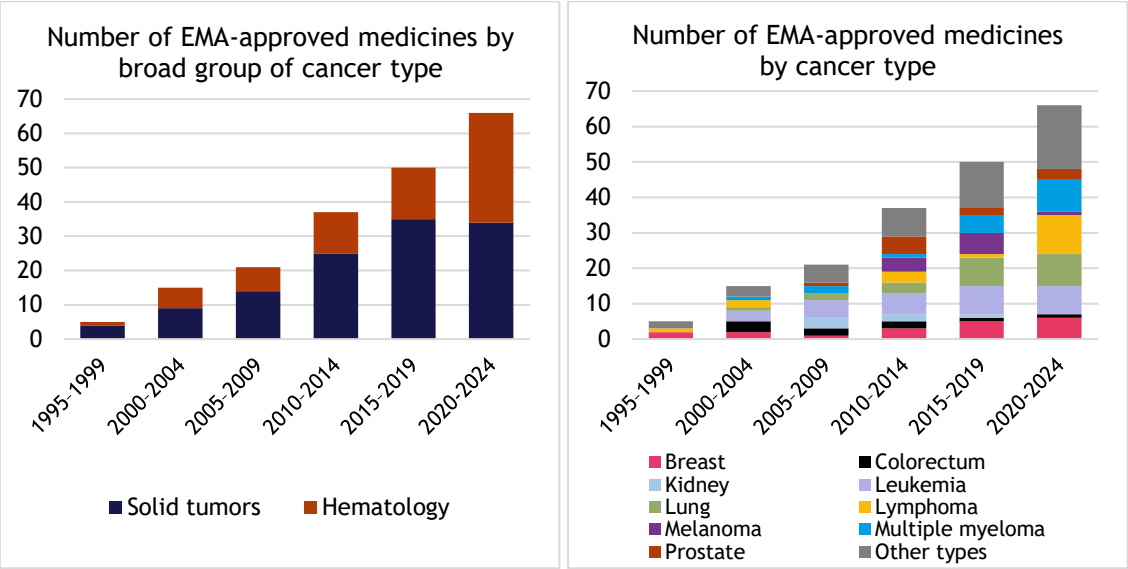


Figure 52: Number of EMA-approved medicines by cancer type.

Notes: See Figure 49 for inclusion criteria for new medicines and Appendix C for the full list of medicines. Only the first approved indication of a new medicine was considered.

The introduction of the monoclonal antibodies rituximab in 1998 and trastuzumab in 2000 heralded a new era in the targeted treatment of cancer. Over time, the growing number of monoclonal antibody approvals by the EMA suggests a certain shift in the focus of medicine development towards biologic therapies in contrast to small molecules; see Figure 53. Monoclonal antibodies composed 35% of all approvals in 2015–2024 compared to 19% in 2005-2014. Another trend shown in Figure 53 is the increasing number of medicines approved with an orphan designation[26] by the EMA - 37% in 2015–2024 compared to 29% in 2005-2014. The growth in orphan medicine approvals is likely the result of a combination of factors, such as the incentives for companies to develop orphan medicines by offering longer market exclusivity and fee reductions for applications through existing EU legislation (Regulation (EC) No 141/2000 on orphan medicinal products) (501), as well as advancements in biotechnology that have improved the identification of rare cancer subtypes and the therapeutic possibilities.

[26] To qualify for orphan designation by the EMA, a medicine (i) must be intended the treatment, prevention or diagnosis for a disease that is life-threatening or chronically debilitating, (ii) the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development, and (iii) no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition (500).

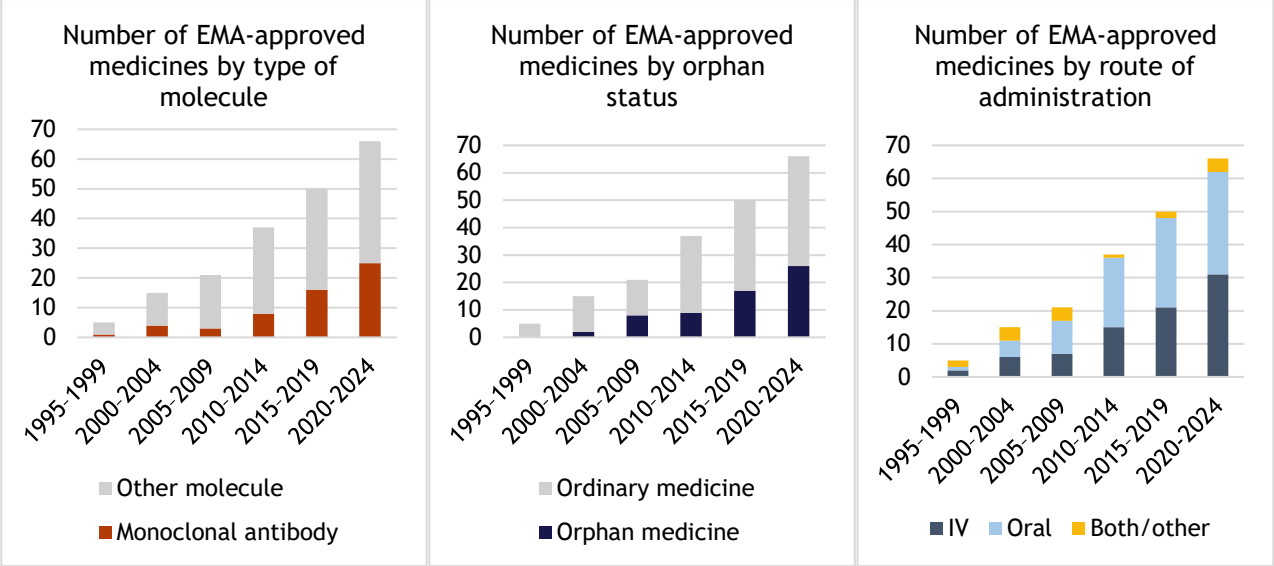


Figure 53: Number of EMA-approved medicines by type of molecule, orphan status, and route of administration.

Notes: See Figure 49 for inclusion criteria for new medicines and Appendix C for the full list of medicines. The orphan status refers to the time of EMA approval. The route of administration refers to the initial formulation approved by the EMA. IV = intravenous. Other forms of administration include intramuscular injections, subcutaneous injections, intraperitoneal injections, and topical applications.

Figure 53 also highlights a trend relevant to the analysis of costs associated with medicine administration. Before 2000, most approved medicines were administered intravenously, often necessitating extended ambulatory care visits or even inpatient stays due to long administration times of up to 24 hours and/or the need for monitoring side effects. With the rise of small-molecule targeted therapies, oral administration has become increasingly common. Newer hormone therapies (e.g., androgen receptor blockers for prostate cancer) are also taken as pills. In contrast, immunotherapies are typically administered intravenously, and their introduction has countered the trend towards more frequent oral administration. Nevertheless, the first subcutaneous form of an immune checkpoint inhibitors was approved by the EMA in early 2024 (502). Evidence from HER2-targeted therapies for breast cancer has shown that subcutaneous injection compared to intravenous infusion results in lower direct medical costs and indirect costs, partly explained by a higher time consumption for nurses and patients with intravenous administration (124). In addition, a majority of breast cancer patients preferred subcutaneous to intravenous administration (124).

Comparisons of approvals by the EMA and the US FDA generally find that the FDA approves cancer medicines earlier by around 8-10 months (503, 504). A minor part (around 20%) of the time difference is explained by earlier submission of applications by pharmaceutical companies, while the major part is due to a longer review time by the EMA (503). This in turn seems to be driven by a greater use of expedited review pathways by the FDA (82% of cancer medicines received priority review in 2007-2020) than by the EMA (17% received accelerated assessment) (503). In 2023, the EMA launched the Cancer Medicines Pathfinder project which aims to accelerate the approval timelines of cancer medicines (505).

4.2 Reimbursement of new medicines

After EMA approval, the second key stage for newly developed medicines to reach patients is reimbursement by public payers in the publicly funded healthcare systems of European countries. Over the past decade, regular publications of the EFPIA Patients WAIT Indicator Survey have highlighted significant inequalities between countries in this regard.[27] These inequalities manifest in both the number of new cancer medicines that are reimbursed (see Figure 54) and the time it takes for these medicines to receive reimbursement (see Figure 55).

Wealthier Western European countries generally reimburse more cancer medicines and do so more quickly than less affluent countries in Central and Eastern Europe as well as smaller countries (507). For example, in Malta no medicines approved by the EMA between 2019 and 2022 were reimbursed at the beginning of 2024, and in Estonia, Slovakia, and Romania, fewer than 20% of medicines were reimbursed, while in Germany almost all medicines (96%) were reimbursed. The average time to reimbursement was fewer than 150 days in Germany and Denmark but extended to close to 900 days in Latvia and Lithuania. A recent analysis of the OECD of selected EMA-approved medicines in 2016-2023 yielded similar results of enormous inequalities, with Malta at the bottom (0%) and Germany on top (100%) of the ranking (29).

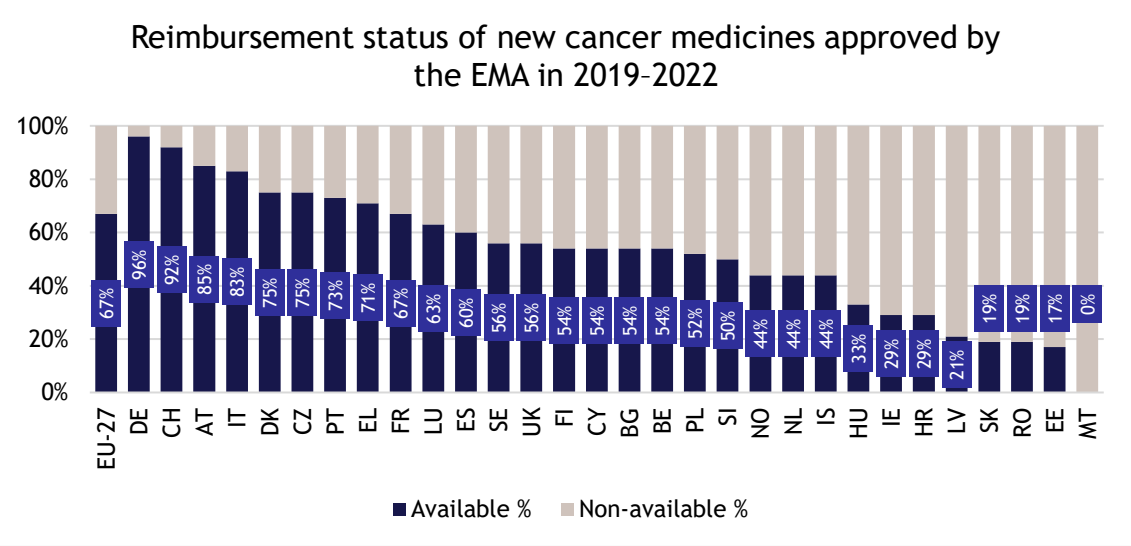


Figure 54: Reimbursement status of new cancer medicines approved by the EMA in 2019-2022 in January 2024.

Notes: UK refers to England. Data for CY and HR are incomplete and might not be fully representative. In most countries, availability is determined by inclusion on the reimbursement list. However, in DK, FI, LU, NO, and SE, certain hospital products are excluded from the general reimbursement scheme. In Spain, the data do not account for medicinal products that may be accessible earlier under Spain's Royal Decree 1015/2009, which governs Medicines in Special Situations. The EU-27 figure is a weighted average of all EU member states. Source: (507).

A potentially important aspect for patient access not shown in Figure 54 is the extent of reimbursement in relation to the eligible patient population. The EFPIA Patients WAIT Indicator

[27] A caveat of the EFPIA Patients WAIT Indicator Survey is its focus on products (and their first EMA-approved indication) rather than new EMA-approved indications. This might distort the overall picture, because medicines can gain many extensions to new indications over time; see section 4.1. A recent study for Czechia, Hungary, Poland, Slovakia showed that an indication-based analysis of cancer medicines yields fairly similar results compared to the product-based analysis of the EFPIA Patients WAIT Indicator Survey for the proportion of reimbursed medicines/indications but that the reimbursement delays are underestimated in these four countries (506).

Survey makes a distinction between full and limited reimbursement, where limited reimbursement is defined as limiting provisions (e.g. specific subpopulations of an approved indication, a provision on a national named-patient basis) being applicable (507). All countries, except for Belgium, Germany, Luxembourg, Netherlands, and Norway, had at least some new medicines with limited reimbursement in 2024, and in 11 EU countries half or more than half of the new medicines had limited reimbursement. A recent OECD report of selected EMA-approved medicines in 2016-2023 also found that there are some countries (Croatia, Czechia, Estonia, France) where half or more than half of indications faced restrictions to the eligible patient population in their indication text in the public reimbursement list compared to the EMA-approved indication (29).

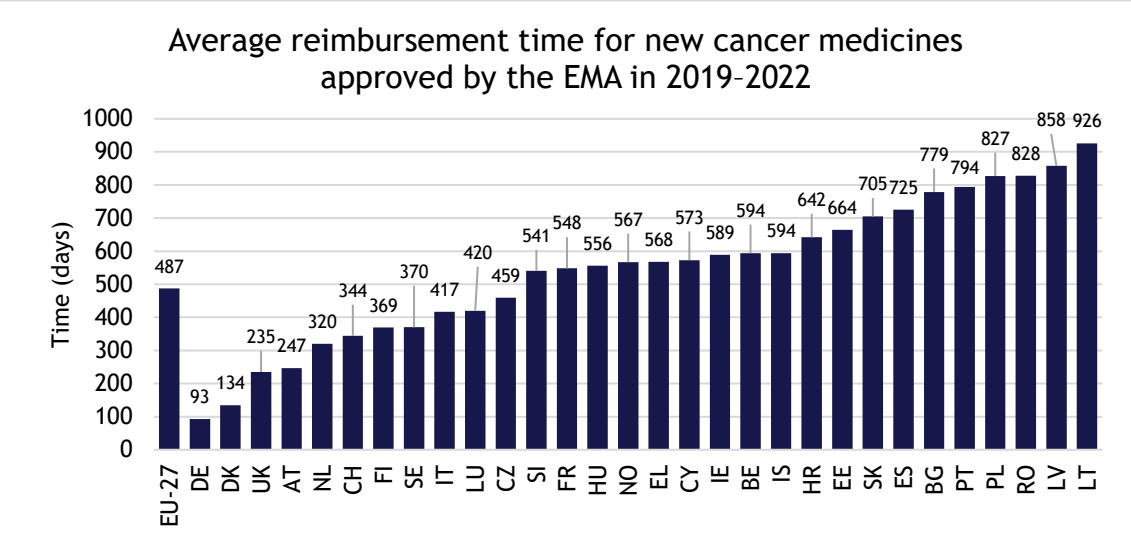


Figure 55: Average reimbursement time for new cancer medicines approved by the EMA in 2019-2022 (follow-up until January 2024).

Notes: See notes for Figure 54. The 'reimbursement time' is defined as the time between EMA marketing authorization and the time point when a medicine gains access to the public reimbursement list (except in DK, FI, and SE for some hospital medicines) with full or limited reimbursement. Early access schemes, such as the ATU/AAP program in France and the EAMS in the UK, are not taken into account in this analysis. Malta is not included because it did not reimburse any medicines. UK refers to England. The EU-27 figure is a weighted average of all EU member states. Sources: (507).

From a policy perspective, a central question is what the causes of these huge inequalities between countries are. EFPIA has previously published a list of root causes (508). The initiation of the pricing and reimbursement process as well as the speed of national timelines and adherence are among the causes. Indeed, the delays in reimbursement are the sum of delayed applications by pharmaceutical companies and delays in the assessment and decision making by relevant authorities in the countries. A recent analysis by the OECD showed that there is a tendency of pharmaceutical companies to submit applications earlier in high-income countries where price expectations and willingness/ability to pay higher prices are greater (29). Countries such as Austria, Belgium, Denmark, France, Germany, and Norway tend to receive applications within a month of EMA approval (or even prior to EMA approval), while the average time of applications in Latvia, Greece, and Cyprus exceeded 500 days. In some countries, administrative rules lead to late applications, such as if applications can only be filed once a positive reimbursement decision has been reached in a certain number of other EU countries. Nevertheless, most of the total delay seems to stem from the time it takes to successfully complete the assessment and decision-making process by the relevant authorities in the countries. This is also confirmed by a recent analysis of the European Access Hurdles Portal maintained by EFPIA that found that of medicines (including non-oncology ones) with

reimbursement, 29% of the total time between EMA approval and reimbursement is attributed to delays in applications by companies and the remaining 71% is attributable to the time between application and reimbursement decision at the country level (509); see section 5.1 for a more detailed discussion of policy implications around the EU HTA regulation and the Joint Clinical Assessment.

Other root causes for country differences identified by EFPIA relate to the HTA process that informs the reimbursement decision (508). This includes misalignment on evidence requirements (the extent to which evidence for the clinical assessment is considered robust or acceptable varies greatly between countries), misalignment on value and price (misalignment leads to long negotiations between payers and pharmaceutical companies, especially in the absence of established mechanisms to deal with uncertainty). The value assigned to product differentiation and choice might also affect the approval of new medicines that are similar to previously reimbursed ones. Finally, the anticipation of an insufficient budget to implement reimbursement decisions might lead payers to reject applications or delay the HTA process.

4.3 Availability of molecular diagnostics

Biomarker testing to guide the therapeutic approach in cancer treatment has a long history dating back to the introduction of tamoxifen for hormone-sensitive breast cancer at the end of the 1970s (147). To avoid prescribing tamoxifen to patients who would not respond to it, prior biomarker testing (so-called predictive biomarker testing) started to become a requirement for breast cancer patients. As described in section 4.1, the past decade has witnessed a significant increase in the approval of new cancer treatments, specifically molecularly targeted therapies and immunotherapies. These advancements have been driven by a deeper understanding of the biological and molecular mechanisms that cause and sustain tumors. Between 2015 and 2020, nearly half (47%) of the EMA approvals of new indications for solid tumors were linked to a biomarker (214).

In an effort to facilitate the implementation and prioritization of biomarkers for genomic testing in oncology, ESMO launched the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) in 2018 (510).[28] It defines clinical evidence-based criteria to prioritize genomic alterations as biomarkers to select patients for targeted therapies. Based on the ESCAT classification, ESMO subsequently issued its first recommendation to use NGS in the treatment of certain cancer types in 2020 (28) and extended it to more cancer types in 2024 (219); see section 4.3.2. ESMO has also started to incorporate the ESCAT level in its clinical practice guidelines. The ESMO recommendations on the use of NGS in a certain cancer type took into account a public health perspective, the perspective of academic clinical research centers, and an individual patient perspective (28). Moreover, in 2022, ESMO issued a recommendation on liquid biopsies as an alternative option to tissue-based testing in patients with advanced cancer where validated and adequately sensitive ctDNA assays have utility in identifying actionable mutations to direct targeted therapy, and also when faster results will be clinically important, or when tissue biopsies are not possible or inappropriate (511).

A variety of genomic biomarker testing methods are available. They can be broadly grouped into single-gene testing methods and multigene testing methods. In cancer types with multiple potential mutations that are targetable by available medicines, single-biomarker testing has

[28] The ESCAT defines six levels of clinical evidence for molecular targets according to the implications for patient management; ESCAT I = Target ready for routine use, ESCAT II = Investigational target, ESCAT III & IV = Hypothetical target, ESCAT V = Combination development, and ESCAT X = Lack of evidence.

become impractical. Instead, multigene biomarker testing methods, in particular NGS, is increasingly becoming standard of care in several cancer types (512).

Info box 8. Predictive biomarkers, companion diagnostics, and testing technology

Biological markers (biomarkers) have a broad range of applications along the patient pathway, from cancer risk assessment, screening and early detection of cancer, accurate diagnosis, patient prognosis, prediction of therapeutic response, to cancer surveillance and monitoring response (513). Biomarker testing is the cornerstone of personalized/precision medicine. It allows the treatment to become increasingly individualized and departs from the previous one-size-fits-all approach based on the organ site where the tumor started to form.

Testing material: Material for biomarker testing is typically collected through biopsies that obtain tumor tissue, but minimally-invasive means, such as blood, saliva, stool, or urine samples, are also being studied and used (513).

Predictive biomarker testing: Before administering certain therapies, patients are tested for specific biomarkers to determine whether they are likely to benefit from a therapy. For example, HER2 is a predictive biomarker for the administration of HER2-targeted therapies.

Examples of (predictive) biomarkers:

- **Breast cancer:** Around 15-20% of breast cancers express a protein called HER2 (human epidermal growth factor receptor 2) (514). These cancers can be treated with anti-HER2 medicines, which specifically target this protein. Around 3-5% of breast cancers have BRCA1/2 gene mutations (515, 516). These cancers can be treated with PARP inhibitors, which specifically target these mutations.
- **Non-small cell lung cancer (NSCLC):** Tumors of NSCLC can have many (often mutually exclusive) mutations for which multiple targeted therapies have been introduced in the last 15 years (517-521). This includes EGFR (occurring in about 10-15% of cases), ALK (3-5%). ROS1 (1-2%), BRAF (≈3%), NTRK (0.2-0.3%), KRAS G12C (10-13%), MET (≈3%), RET (1-2%), HER2 (2-4%).

Companion diagnostics: These are the specific diagnostic tests used to identify patients who are suitable for a particular therapy. For example, an immunohistochemistry (IHC) test or fluorescence in situ hybridization (FISH) test is used to find out if cancer cells have a high level of the HER2 protein in breast cancer patients to determine if they should receive HER2-targeted therapies.

Testing methods: The technology for biomarker testing has evolved rapidly during the past decades. Previously, tests would analyze one biomarker at a time (single-gene techniques), which required sequential testing if testing for multiple biomarkers needed to be done. Nowadays, it is possible to analyze multiple biomarkers simultaneously with multiplex tests and next-generation sequencing (NGS) technology (multi-gene techniques) (215). NGS can be used for small hotspot panels (<50 genes), larger panels (>50 genes) or for whole genome sequencing (WGS) and whole exome sequencing (WES).

4.3.1 Availability of single-gene techniques

As of September 2024, the ESMO clinical practice guidelines recommended the following single-gene techniques for specific solid tumor types:

- **Breast cancer:** Single-gene testing is crucial for determining the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) using IHC (522). These biomarkers help guide decisions on hormone therapy, targeted therapies, and immunotherapies (522). FISH is recommended for cases with an equivocal HER2 IHC score (HER2 2+) to confirm HER2 status. Additionally, BRCA1/2 mutation testing is advised for patients meeting national criteria – typically based on factors such as family history, age at diagnosis, and ethnicity – as well as for patients eligible for PARP inhibitors (522) as explained in Info box 8. In the metastatic setting, PD-L1 status testing is important to assess the potential benefit of incorporating immune checkpoint inhibitors (523). Furthermore, metastatic patients with PIK3CA-mutated tumors may benefit from specific targeted therapies.

- **Non-small cell lung cancer:** Single-gene testing for EGFR mutations and for PD-L1 in unresectable NSCLC is mandatory (524). These tests are usually performed using polymerase chain reaction (PCR) or IHC techniques and are essential for identifying patients who might benefit from targeted therapies or immunotherapies. In metastatic NSCLC lacking identifiable driver mutations, PD-L1 IHC testing is recommended (525). Conversely, in cases of metastatic NSCLC driven by specific genetic mutations, targeted gene testing is essential for identifying actionable mutations that inform the selection of appropriate targeted therapies. Next-generation sequencing (NGS) is the preferred method for this testing, as it allows for the simultaneous analysis of multiple genes, such as EGFR, ALK, ROS1, NTRK, RET, MET, KRAS, BRAF, and HER2 (526). However, if resource limitations preclude NGS, alternative single-gene testing strategies should be used, including EGFR mutation testing, ALK rearrangement testing, and ROS1 rearrangement testing.
- **Colorectal cancer:** Testing for MSI/MMR deficiency is key and typically done through IHC, PCR, or NGS assays (527). MSI/MMR status helps determine prognosis, guide adjuvant therapy decisions, and identify patients who may have Lynch syndrome, a hereditary condition associated with a higher risk of colorectal and other cancers (527). Similar to early-stage colorectal cancer, MMR/MSI status testing is recommended for metastatic patients (528). Testing for mutations in KRAS, NRAS, and BRAF is recommended for all patients at the time of diagnosis (528). These mutations are typically identified using PCR. Identifying HER2 amplification, often performed using IHC or FISH, is recommended in RAS wild-type patients. For rare cases, NTRK gene fusion testing is recommended, starting with IHC screening followed by confirmation through NGS.
- **Gastric cancer:** HER2 status should be assessed using IHC and/or amplification by in situ hybridization (ISH) (529). HER2-positive status is a critical predictor for the effectiveness of HER2-targeted therapies. PD-L1 testing by IHC is recommended (529), as PD-L1 expression helps identify patients who may benefit from immunotherapy. Testing for MSI/MMR status (usually done with PCR and IHC) is also recommended to guide administration of immunotherapy.
- **Melanoma:** BRAF mutation status (usually assessed with PCR techniques) is used to identify patients who are candidates for BRAF-targeted therapies (530).

Two comprehensive studies – one lead by IQN Path and EFPIA, and one led by ESMO – have in recent years assessed the pan-European landscape of biomarker testing (531-533). The study by ESMO provides more up-to-date information from the end of 2021. One aspect considered in this study was the availability of various testing methods for different cancer types in routine practice. The study indicated if the method was “available always, usually, or occasionally in routine practice, only in trial or research, or never”. Note that “availability” was not defined as “reimbursement” as the costs for a test might be covered by the general hospital budget (especially for research purposes) or a pharmaceutical company rather being a specific reimbursable service through a third-party payer. As an example of a common single-gene technique, Table 12 shows the availability of IHC for different cancer types. The main findings are the following:

- **Variation in availability by cancer site:** IHC testing for lung, breast, and colon cancer was always available in nearly all 31 countries, indicating that these tests are standard practice across Europe. IHC testing for prostate, gastric, pancreatic cancer, hepatocellular carcinoma (HCC), and bile duct carcinoma was slightly less widely available. 18 countries indicated that IHC was always available across all cancer types.

- **Limited access in some countries:** A few countries, particularly Bulgaria and Romania and to a lower extent also Spain and Greece, had limited availability of IHC testing for many cancer types. This could indicate potential areas where diagnostic capabilities might need to be expanded.

Table 12: Availability of immunohistochemistry (IHC) in routine practice by cancer type and country at the end of 2021

Country	Lung	Breast	Colon	Prostate	Gastric	Pancreatic	Hepatocellular	Bile duct
Austria								
Belgium								
Bulgaria								
Croatia								
Cyprus								
Czechia								
Denmark								
Estonia								
Finland								
France								
Germany								
Greece								
Hungary								
Iceland								
Ireland								
Italy								
Latvia								
Lithuania								
Luxembourg								
Malta								
Netherlands								
Norway								
Poland								
Portugal								
Romania								
Slovakia								
Slovenia								
Spain								
Sweden								
Switzerland								
UK								

Color labels

	Always
	Usually
	Occasionally
	Research only
	Never

Notes: The table was sourced from the supplemental material (section 2.2.1) in Bayle et al (2023). The original data includes responses from 201 field reporters across 48 European countries. Bile duct cancer is also referred to as cholangiocarcinoma. Sources: ESMO (531).

4.3.2 Availability of multigene techniques

In 2020, ESMO started to recommend the routine use of NGS for managing several cancer types cancer (28). Specifically, ESMO advised NGS for advanced-stage tumors in non-squamous non-small cell lung cancer, prostate cancer, ovarian cancer, and bile duct cancer. For colon cancers, ESMO recommended that NGS could be an alternative to PCR testing. The recommendations also included assessing tumor mutational burden (TMB) status in cases of cervical cancer, well- and moderately differentiated neuroendocrine tumors, and cancers of the salivary gland,

thyroid, and vulva. Driven by the increasing availability of new targeted medicines, ESMO expanded its recommendations for routine use NGS testing in 2024 (219). The latest recommendations include advanced-stage breast cancer and several rare cancers, including sarcoma, GIST, thyroid cancer, and a heterogeneous group of cancers where metastatic tumors are present, but the original (primary) site of the cancer cannot be identified. NGS testing for detecting tumor-agnostic alterations in patients with metastatic cancers where matched therapies are accessible also started to be recommended.

Table 13: Availability of NGS panels (<50 genes) in routine practice by cancer type and country at the end of 2021

Country	Lung	Prostate	Bile duct	Colon	Breast
Austria	Usually	Occasionally	Usually	Usually	Occasionally
Belgium	Usually	Occasionally	Occasionally	Usually	Occasionally
Bulgaria	Occasionally	Research only	Research only	Research only	Research only
Croatia	Occasionally	Never	Never	Occasionally	Never
Cyprus	Occasionally	Occasionally	Occasionally	Occasionally	Occasionally
Czechia	Usually	Occasionally	Occasionally	Usually	Occasionally
Denmark	Always	Research only	Research only	Usually	Occasionally
Estonia	Research only	Research only	Research only	Research only	Occasionally
Finland	Usually	Occasionally	Occasionally	Usually	Occasionally
France	Usually	Occasionally	Research only	Usually	Occasionally
Germany	Usually	Research only	Research only	Occasionally	Occasionally
Greece	Occasionally	Occasionally	Research only	Occasionally	Occasionally
Hungary	Occasionally	Occasionally	Occasionally	Occasionally	Occasionally
Iceland	Usually	Occasionally	Usually	Usually	Occasionally
Ireland	Usually	Research only	Research only	Usually	Research only
Italy	Occasionally	Research only	Occasionally	Occasionally	Occasionally
Latvia	Occasionally	Never	Never	Occasionally	Never
Lithuania	Occasionally	Occasionally	Never	Occasionally	Occasionally
Luxembourg	Always	Occasionally	Occasionally	Occasionally	Occasionally
Malta	Occasionally	Research only	Research only	Research only	Research only
Netherlands	Usually	Occasionally	Occasionally	Usually	Usually
Norway	Usually	Research only	Occasionally	Occasionally	Occasionally
Poland	Occasionally	Research only	Research only	Occasionally	Occasionally
Portugal	Occasionally	Occasionally	Occasionally	Occasionally	Occasionally
Romania	Research only	Research only	Occasionally	Research only	Research only
Slovakia	Occasionally	Research only	Research only	Occasionally	Occasionally
Slovenia	Research only	Never	Never	Never	Research only
Spain	Occasionally	Occasionally	Research only	Occasionally	Occasionally
Sweden	Usually	Occasionally	Occasionally	Occasionally	Occasionally
Switzerland	Always	Usually	Usually	Usually	Occasionally
UK	Usually	Occasionally	Research only	Occasionally	Occasionally

Color labels

	Always
	Usually
	Occasionally
	Research only
	Never

Notes: The table was sourced from the supplemental material (section 2.2.4) in Bayle et al (2023). The original data includes responses from 201 field reporters across 48 European countries. Bile duct cancer is also referred to as cholangiocarcinoma. Sources: (531).

Despite the recent recommendation by ESMO to start using NGS, the availability differed widely across European countries at the end of 2021, according to the above-described study coordinated by ESMO (531). Table 13 shows whether a small NGS panel (<50 genes) was "available always, usually, or occasionally in routine practice, only in trial or research, or never". Note that "availability" was not defined as "reimbursement" as the costs for a test

might be covered by the general hospital budget (especially for research purposes) or a pharmaceutical company rather being a specific reimbursable service through a third-party payer. The main findings are the following:

- **Great variation in availability by country:** Only a few countries, Luxembourg, Denmark, and Switzerland, indicated consistent availability to NGS panels for lung cancer. In several other countries, including Austria, Belgium, Iceland, Czechia, Finland, and the Netherlands, access to NGS was common but not universal across cancer types, indicating relatively good, though not comprehensive, availability. Across all cancer types and countries, NGS testing for lung cancer was most widely available.
- **Research-only access or no access is common:** In certain countries, such as Bulgaria, Estonia, Malta, and Romania, NGS panels were available mostly only for research purposes. In Slovenia, Croatia, Latvia, and Lithuania, NGS was never available across several cancer types.
- **Barriers to utilization:** For multigene techniques, the main barriers were reimbursement of the tests, reimbursement of approved medicines, ability to prescribe a suitable medicine, and ability to find a suitable trial.

4.4 Uptake of molecular diagnostics

Uptake and utilization of biomarker testing may differ from the sheer availability discussed above. The actual use of biomarker testing may be restricted by the human and technical capacity (number of pathologists and biomedical scientists, molecular testing labs with adequate equipment) to run and interpret tests on tumor samples (533). The price of testing can also play a role, as single-gene techniques such as IHC, FISH, and PCR cost between a few tens of euros to at most EUR 200 per test, while NGS costs between EUR 500 and EUR 1,800 per test according to a pan-European study by ESMO from 2021 (531). In certain clinical settings, such as advanced NSCLC, NGS-based comprehensive genomic profiling might be a cost-saving alternative to single-gene testing because of the large number of actionable mutations that would need to be tested (for) one by one (534).

Out-of-pocket payments for biomarker tests have also been found to be significant across European countries by ESMO (531), which may hamper their use. Indeed, many European countries do not have a system of joint/parallel reimbursement of a new medicine together with its companion diagnostic. A analysis among OECD countries (mostly from Europe) found that fewer than half of countries (11 out 24 European countries) stated having an automatic link between the reimbursement decision for a medicine and its companion diagnostic in 2023 (29). This can result in a paradoxical situation where public healthcare payers decide to reimburse a medicine but not its companion diagnostic, necessitating out-of-pocket payments or support from pharmaceutical manufacturers to cover testing costs (535).

International data on the uptake of different testing methods in various cancer types is generally scarce. Part of the reason might be the difficulty of defining clear metrics that do not only cover a single testing method in a certain cancer type and a distinct therapeutic setting. In addition, the swift development in the field of biomarker testing means that statistics on the uptake of testing methods run the risk of becoming outdated quickly. A collaboration of several stakeholders led by IQN Path and EFPIA assessed the status of uptake of NGS testing across European countries in 2020 (533). It found great disparities. Table 14 shows that Denmark and the Netherlands had the highest uptake of NGS, with more than half of biopsies analyzed with this technique. Most countries had a low uptake (0-24%) and Czechia and Slovakia had zero uptake. The same study also provided a qualitative analysis of the low

use of NGS tests in EU countries. It identified several determinants, including lack of diagnostic laboratory infrastructure with NGS testing capabilities, inefficient organization of diagnostic testing, financial constraints, and failure to include NGS testing in local guidelines (533).

Table 14: Uptake of biomarker testing with NGS in Europe in 2020

Access dimension	Access level	Country
Uptake (% of all biopsies analyzed with NGS tests)	0-24%	Belgium, Croatia, Czechia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Slovakia, Spain, UK
	25-49%	Austria, Cyprus, Portugal, Sweden
	Less than 50%	Bulgaria, Estonia, Luxembourg, Romania, Slovenia
	50% or more	Denmark, Netherlands

Notes: The uptake was calculated as the percentage of all biopsies analyzed using NGS technology. Information for Malta was not available. Information for the "less than 50%" group was not granular enough to group them into either the 0-24% group or the 25-49% group. Sources: (533).

After 2020, the use of NGS testing in oncology has expanded, driven by the increasing adoption of gene panels for personalized cancer treatment. For instance, all children diagnosed with a primary or relapsed solid tumor in Sweden have been offered up-front WGS complemented by whole-transcriptome sequencing (RNA-Seq) since 2021 (536). In France, the National Authority for Health (HAS) started to reimburse targeted high-throughput sequencing (NGS) of gene panels in the management of lung cancer, GIST, and chronic lymphocytic leukemia (CLL) in 2024 (537). The increasing adoption of NGS is also facilitated by a decrease in testing costs. An analysis of the test costs for WGS in leukemia in Sweden in 2023 found that WGS was still more costly than standard of care tests (€3,472 vs. €1,207-2,465), but it concluded that the costs can be reduced by utilizing laboratories with higher throughput and by the expected decline in cost of reagents (538).

The uptake of predictive biomarker testing can also be inferred indirectly to some extent by looking at the uptake of medicines that require biomarker testing prior to administration. An example of the medicine pemigatinib is shown in Figure 56. This medicine received EMA approval in March 2021 for the treatment of locally advanced or metastatic cholangiocarcinoma (bile duct cancer) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy (539). FGFR2 fusions/rearrangements are present in about 10-16% of intrahepatic cholangiocarcinoma cases (540). Predictive biomarker testing is mandatory before prescribing pemigatinib. NGS is the recommended standard because it can identify both known and novel FGFR2 fusions, yet simpler, less comprehensive methods such as FISH or PCR may also be used to detect some FGFR2 gene rearrangements and when NGS is not available (541). Figure 56 shows that 17 out 27 countries had at least some uptake of pemigatinib in 2021-2023, with little or no uptake in Central and Eastern European countries, Spain, and several smaller countries in Northern and Western Europe. Austria had the highest uptake and was also a country where NGS testing was "usually" available for cholangiocarcinoma patients in 2021, whereas Iceland and Switzerland which had indicated a similar testing availability had no or little uptake. Germany, Denmark, and France were countries with comparatively high uptake, but NGS testing was available for in "research only" settings in 2021. Latvia is a country where NGS testing was "never" available in 2021, but still achieved some uptake in 2021-2023 (in fact all of the uptake occurred in 2023). Overall, information on biomarker testing availability from ESMO from 2021 does not seem to be a good predictor of the uptake of pemigatinib in 2021-2023. As emphasized above, testing standards have evolved quickly since 2020/2021, which impacts on the possibility for patients to receive new therapies.

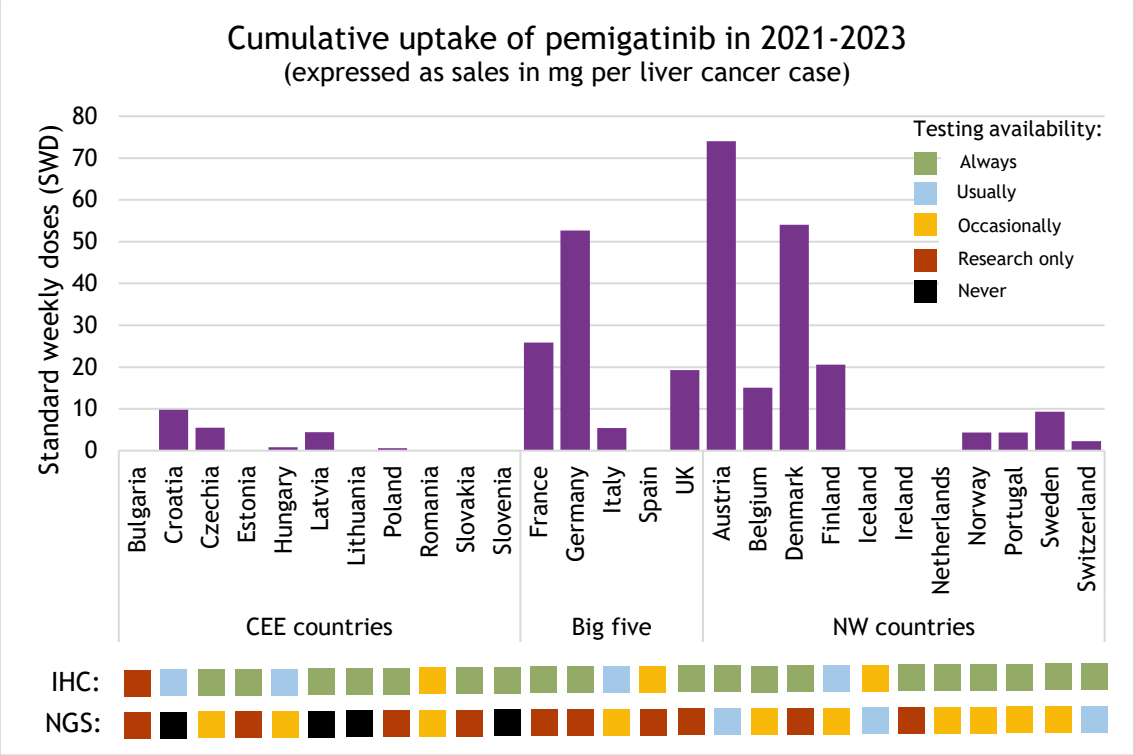


Figure 56: Cumulative uptake of pemigatinib in 2021-2023 expressed as sales in SWD per liver cancer case and availability of biomarker testing technologies for cholangiocarcinoma in 2021.

Notes: Liver cancer case refers to liver cancer deaths in 2022, which includes deaths from cholangiocarcinoma. Sales data in milligram (mg) are shown. BG, EE, LT, RO, SK, SI, ES, IS, IE, and NL had no sales in 2021-2023. CEE = Central and Eastern European, NW = Northern and Western European, IHC = immunohistochemistry, NGS = next-generation sequencing. Source: see Figure 70 for sales and Table 12 and Table 13 for testing.

4.5 Uptake of medicines in value

The third and final key stage for newly developed medicines to reach patients is the uptake in clinical practice. As emphasized before, the analysis of uptake in this report is only an approximation of patient access due to the nature of available data. This sub-section uses total annual sales in value terms (in euros), whereas sub-section 4.6 looks at sales in volume terms (in milligrams). A major challenge in country comparisons of sales data in euros is the lack of net expenditure data. Available international sales data are based on list prices of medicines, which are higher than the real (net) prices that payers actually pay pharmaceutical companies for their products; see Info box 9. Consequently, the use of sales data based on list prices overestimates the true cancer medicine expenditure in all statistics presented below.

4.5.1 Overall pharmaceutical expenditure

Cancer medicine expenditure is part of pharmaceutical expenditure, which in turn is part of health expenditure. While reliable data on health expenditure are readily available from all statistical authorities in European countries, complete data on pharmaceutical expenditure (and therefore also cancer medicines) are not available. Medicines that are administered in an inpatient setting at hospitals might be counted towards hospital inpatient expenditure rather than pharmaceutical expenditure reported by the OECD and Eurostat (138, 542). In the oncology sector, for instance, the hospital share of the total pharmaceutical expenditure was estimated to average 70% in 2021 (543). This data situation is not desirable, because in the public debate,

the growth in pharmaceutical expenditure is a frequent concern among European payers (543). An informed debate should be based on real numbers.

Figure 57 shows the proportion of healthcare expenditure allocated to pharmaceuticals (covering prescribed medicines, over-the-counter medicines, other medical non-durable goods) across countries in 2022 as reported by Eurostat. There is significant variation, with Denmark, the Netherlands, and Norway reporting the lowest proportions, where medicines account for 6-7% of healthcare spending (544). In the middle range, countries such as Austria, France, and Germany spend 12-14% on pharmaceuticals. At the higher end, Bulgaria has the largest share, with 31% of healthcare expenditure going toward pharmaceuticals, followed by Romania, Greece, and Hungary, which range between 24 and 27%. Over time, many high-income countries, such as Belgium, Denmark, the Netherlands, and Sweden, have seen a gradual decline in the proportion of healthcare spending devoted to pharmaceuticals (544). For example, the Netherlands' share dropped from over 11% in the early 1990s to below 7% in 2022. Meanwhile, countries like Germany and France have maintained relatively stable expenditure levels, consistently ranging between 13 and 15%, with only minor fluctuations. In Central and Eastern Europe, countries such as Bulgaria, Romania, and Slovakia exhibited high shares of pharmaceutical expenditure in the early 2010s, followed by gradual decreases in recent years. Romania, for instance, spent at 38% on pharmaceuticals in 2011 before declining steadily to 24% in 2022.

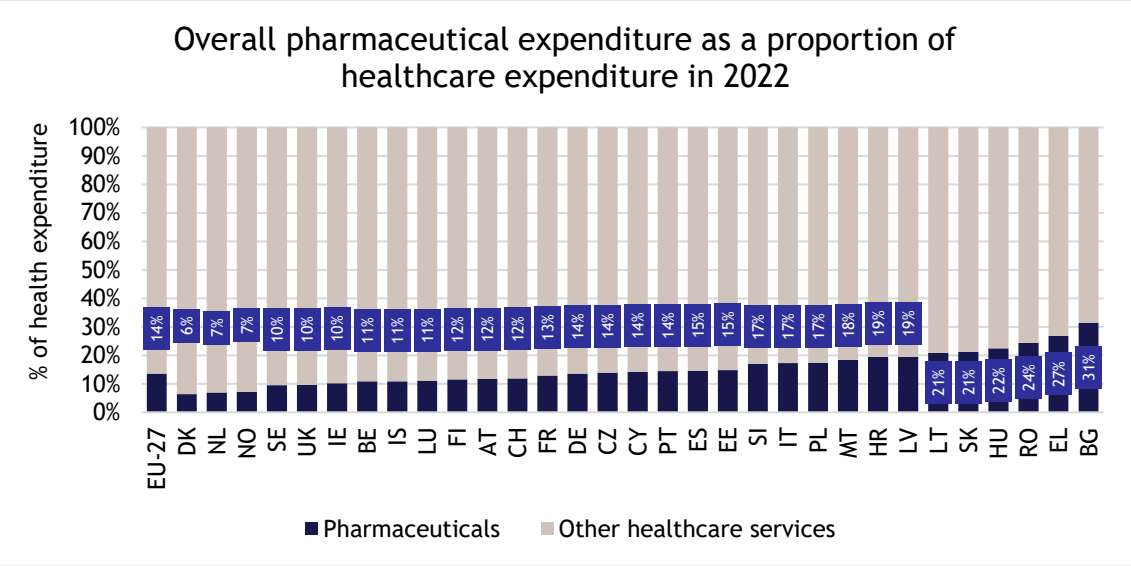


Figure 57: Proportion of healthcare expenditure on pharmaceuticals by country.

Notes: The share of pharmaceutical expenditure for the UK is based on the most recent data available from 2021. Medicines that are administered in an inpatient setting at hospitals might not be fully included in the presented number, leading to an underestimation of the proportion of overall spending on pharmaceuticals. Source: (544, 545).

While the aforementioned statistics from Eurostat indicate that pharmaceutical expenditure does not seem to be the main driver of the growth of overall health expenditure, cancer medicines have been a driver of pharmaceutical expenditure. The previous Comparator Report showed an increase in the share of cancer medicine expenditure as part of the total pharmaceutical expenditure in France, Germany, Sweden, and the UK from 1995 to 2015, rising from approximately 3% in 1995 to 12% in 2015 (46). As described in Table 15, the share of cancer medicine expenditure in Sweden continued to grow and reached 17% in 2022. Similarly, Belgium and Spain had a share of 25% and 17%, respectively in 2021. As the share of cancer medicine expenditure expanded across European countries since 1995, the share of medicines for other

major disease areas such as cardiovascular diseases, ulcers, and pain management declined (546). This mirrors the research activity in the development of new medicines, where oncology accounted for the largest proportion of product-indication pairs that entered pre-clinical or clinical development in every year since 2011, with its proportion growing from 27% of all product-indication pairs in 2011 to 40% in 2021, according to the OECD (547).

Table 15: Share of cancer medicine expenditure on total pharmaceutical expenditure in selected countries

Country	Amount spent on cancer medicines	Source
Belgium	In 2021, cancer medicines accounted for 25% of the gross budget of the Institut national d'assurance maladie-invalidité (INAMI) for reimbursable pharmaceutical specialties.	(548)
Spain	In 2021, spending on cancer medicines through hospitals and pharmacies amounted to €3.11 billion, equivalent to 16.9% of the total expenditure on medicines.	(549)
Sweden	In 2018, cancer medicines accounted for 12% of the total pharmaceutical expenditure, amounting to SEK 5.9 billion out of a total of SEK 47.9 billion spent on medicines (all based on list prices). By 2022, this share had increased to 17%, with SEK 9.6 billion spent on cancer medicines out of total pharmaceutical expenditure of SEK 57.9 billion (all based on list prices).	(550-552)

4.5.2 Cancer medicine expenditure

The real size of cancer medicine expenditure is unknown, because many national sources and all international sources (such as from IQVIA) report cancer medicine expenditure based on list prices. Because of the existence of confidential financial agreements between payers and pharmaceutical companies, there is an important difference between list prices and net prices; see Info box 9. There is some evidence that the size of the rebates (i.e., the difference between list and net prices) has been growing over time and might nowadays be around 50% in Europe for new cancer medicines, making statistics based on list prices increasingly futile. The absence of real data on cancer medicine expenditure also complicates an informed public debate on the cost of cancer medicines. Indeed, the significant progress made in the launch of new cancer medicines over the past two decades has brought increased attention to the price of medicines and expenditure on medicines. Yet public discussions are usually focused on the list prices, which overestimate the net prices and hence do not reflect the truth.

Info box 9. Differences between net prices and list prices of cancer medicines

The presence of confidential financial agreements (such as discounts, rebates, clawback payments, volume caps, etc.) between payers and pharmaceutical companies hampers comparisons of expenditure data both across countries and across years. Available evidence on differences between the (higher) list prices of medicines and the (lower) net prices is sketchy due to the confidential nature of the agreements. Analyses of single (often patent-protected) cancer medicines have found differences in the range of 40-50% in various European countries, although these differences varied significantly by medicines and countries (553, 554). In the US, the size of the rebates for cancer medicines has increased over time, with list prices of branded medicines increasing almost twice as much as net prices (+59% vs. +35%) between 2007 and 2018 (555). It is unclear to what extent the same growing pattern applies to European countries.

There are also some statistics on the size of rebates in cancer medicine expenditure as a whole. For instance, an analysis by the OECD for Italy for the years 2013-2018 found a gap of around 15-25% between cancer medicine expenditure based on list prices and net expenditure (556). In Bulgaria, the National Health Insurance Fund reported net spending on cancer medicines of BGN 385 million in 2018 and BGN 764 million in 2023 (557). Expenditure based on list prices from the MIDAS database shown in section 4.5.2 in this report are 13% higher than net spending in 2018 and 47% higher in 2023, indicating a considerable increase in the size of rebates over time.

Previous Comparator Reports showed that absolute expenditure on cancer medicines has followed an increasing trend (based on list prices). New data for this report indicate a continuation of this upward trend. The combined cancer medicines sales in Europe in current prices increased from €19.5 billion to €64.3 billion between 2014 and 2023 (based on list prices). In per-capita terms, sales rose from €30 to €97, meaning expenditure more than tripled over this ten-year period. Adjusting for inflation and exchange rates, the expenditure in 2014 amounted to €24.9 billion (€46 per capita), indicating that even in constant prices, cancer medicine expenditure more than doubled to €64.3 billion (€118 per capita) by 2023; see Figure 58. The five most populous countries in Europe (the "Big Five") accounted for nearly 73% of all sales in both 2014 and 2023, which is more than the just over 60% of Europe's population they represent. Germany was the largest spender in 2014, accounting for 24% of total sales, but its share declined to 19% in 2023, while other Big Five countries except the UK saw their shares increase. The country-specific total sales and per-capita sales for all years are summarized in Appendix C. They show that year-by-year sales grew quite constantly in many countries, while some countries, such as Bulgaria, Croatia, France, Latvia, Lithuania, and the UK, experienced accelerated growth rates after 2018 or 2019.

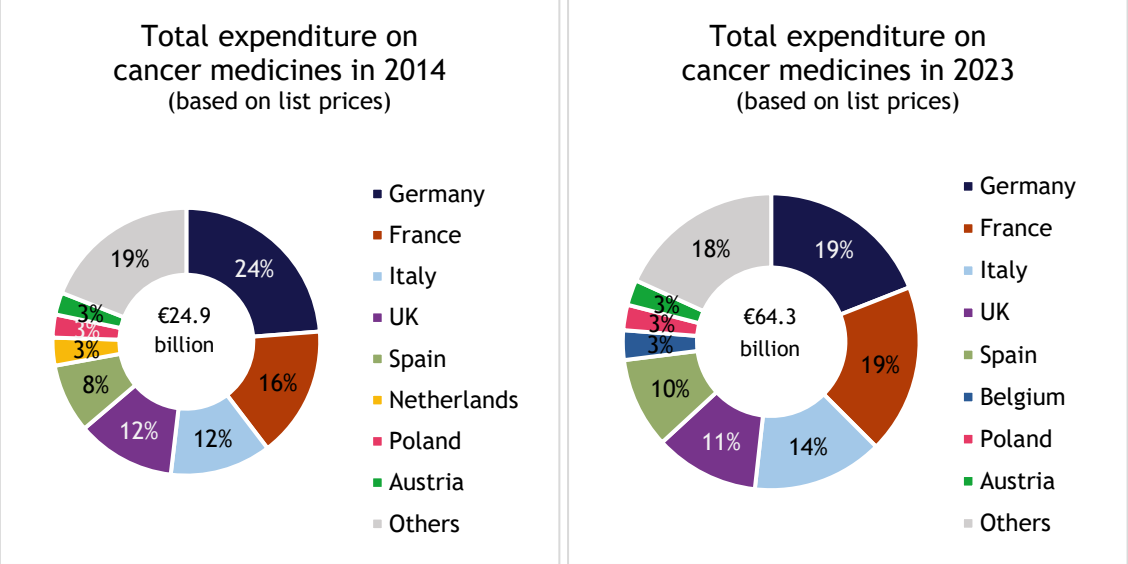


Figure 58: Total expenditure of cancer medicines (in constant prices and exchange rates; based on list prices) in Europe, 2014 and 2023.

Notes: Sales data are based on list prices, leading to an overestimation of the true expenditure. Source: Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Frumtök for Iceland, Signum Life Science for Denmark, and Ravimiamet for Estonia. Exchange rate and inflation rate sources: (64, 114).

The strong growth in cancer medicine sales between 2014 and 2023 is a product of several factors relating to prices and volume. Table 16 lists factors which might have played a role in this development.

Table 16: Potential reasons for growing cancer medicines sales

Area	Reason	Rationale
Price	Higher list prices and net prices of newly introduced medicines (monthly/annual costs per treatment)	Price developments of cancer medicines in European countries are not well documented, whereas more comprehensive data exist for the US which might also be relevant for Europe (yet not the absolute value of prices). For instance, IQVIA reports that of new cancer medicines launched in 2019-2023 in the US, 85% had an annual cost of over USD 100,000, whereas of new medicines launched in 2009-2013 only 35% had such a high annual cost (285). Similarly, the OECD found that median monthly costs of new cancer medicines in the US have doubled from around USD 8,000 in 2005-2010 to USD 16,000 in 2015-2019 (556).
Volume	Rising number of cancer patients	Incidence; see chapter 2.
	Increasing treatment duration of first-line therapy	For instance, chemotherapy is administered for a fixed number of cycles typically lasting less than half a year in the metastatic treatment setting of solid tumors. When chemotherapy was replaced by targeted therapies and checkpoint immune inhibitors, the treatment duration changed, as they typically are administered until disease progression or unacceptable toxicity, which can last for more than a year.
	Increasing patient numbers reaching subsequent lines of therapy	Increasing survival leads to a growing number of prevalent cases that can receive longer-term treatment and more rounds of treatment. For instance, more patients can continue to four lines of therapy in multiple myeloma whereas in the past most patients had died after the second line.
	Increasing use of combination therapies	For instance, many times, new indications of immune checkpoint inhibitors entail a combination with a chemotherapy regimen that was the previous standard of care. Multiple myeloma is another example where new treatments tended to be added to the previous standard of care rather than replacing it.
	Increasing number of new cancer medicines and indications	See section 4.1; The growing number means that more medicines are gaining market exclusivity than the number of older medicines losing it.
	Introduction of cancer medicines for previously untreated patient groups	For instance, the use of immune checkpoint inhibitors and PARP inhibitors as adjuvant therapy in triple-negative breast cancer.
	Introduction of cancer medicines that are increasingly used in a neo/adjuvant setting instead of just in a palliative setting	For instance, CDK4/6 inhibitors in breast cancer, EGFR and ALK inhibitors in lung cancer, and immune checkpoint inhibitors are used in a growing number of solid tumors.

Figure 59 compares the cancer medicines expenditure per capita (adjusted for inflation and in 2023-exchange rates; based on list prices) in each country in 2014 and 2023. In the EU-27[29] as a whole, the expenditure more than doubled from €49 to €126 per capita. All countries with complete data recorded increased expenditure. The biggest increases in expenditure in relative

[29] The numbers do not include CY, EL, LU, and MT due to unavailable or missing data.

terms between 2014 and 2023 were recorded in Lithuania (five-fold increase from €12 to €62) and Croatia (five-fold increase from €21 to €102). The smallest increases were observed in Slovakia (+35% from €38 to €51) and in Hungary (+53% from €46 to €71). Austria had the highest per-capita expenditure in 2014 and 2023, and Latvia had the lowest expenditure in both years, yet the relative difference between those countries became smaller (from an 8-fold to a 6-fold difference), indicating some convergence. In general, the pattern follows income levels, with countries with higher GDP capita in Western Europe also seeming to have higher expenditure levels, and vice versa for countries in Central and Eastern Europe. Nevertheless, the expenditure levels of Croatia (being higher than three Nordic countries, Ireland, and the Netherlands) and Bulgaria (the poorest country in the sample) are surprising and may partly indicate inaccurate data and/or parallel trade with other countries that is not captured in the data.

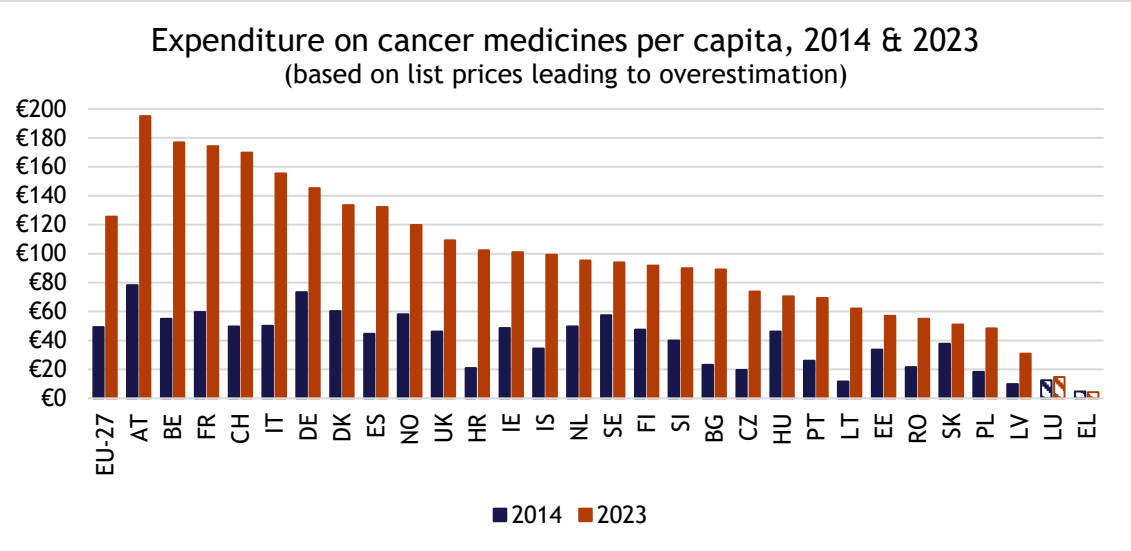


Figure 59: Expenditure on cancer medicines per capita (in 2023 price levels and exchange rates; based on list prices), 2014 and 2023.

Notes: Sales data are based on list prices, leading to an overestimation of the true expenditure. Hatched bars indicate that data for EL and LU only comprise retail sales. CY and MT are missing due to lack of data. The EU-27 average excludes EL and LU. Source: Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Frumtök for Iceland, Signum Life Science for Denmark, and Ravimiamet for Estonia. Exchange rate and inflation rate sources: (64, 114).

As shown in chapter 2, the per-capita numbers of cancer patients differ between countries. Therefore, expenditure on cancer medicines should also be considered in relation to the disease burden, as the latter dictates the demand for cancer medicines. Figure 60 compares the cancer medicine expenditure in constant prices per new cancer case and per cancer death between 2014 and 2023. Overall, cancer expenditure per new case in the EU-27 roughly doubled from €9,281 to €20,539 (+121%) between 2014 and 2023 and per death from €19,491 to €43,644 (+124%). The most notable increases were observed in Lithuania, where expenditure more than quadrupled, and in Croatia, Bulgaria, Czechia, and Belgium where they roughly tripled. In contrast, Estonia, Hungary, and Slovakia saw small relative increases of around 10-40%.

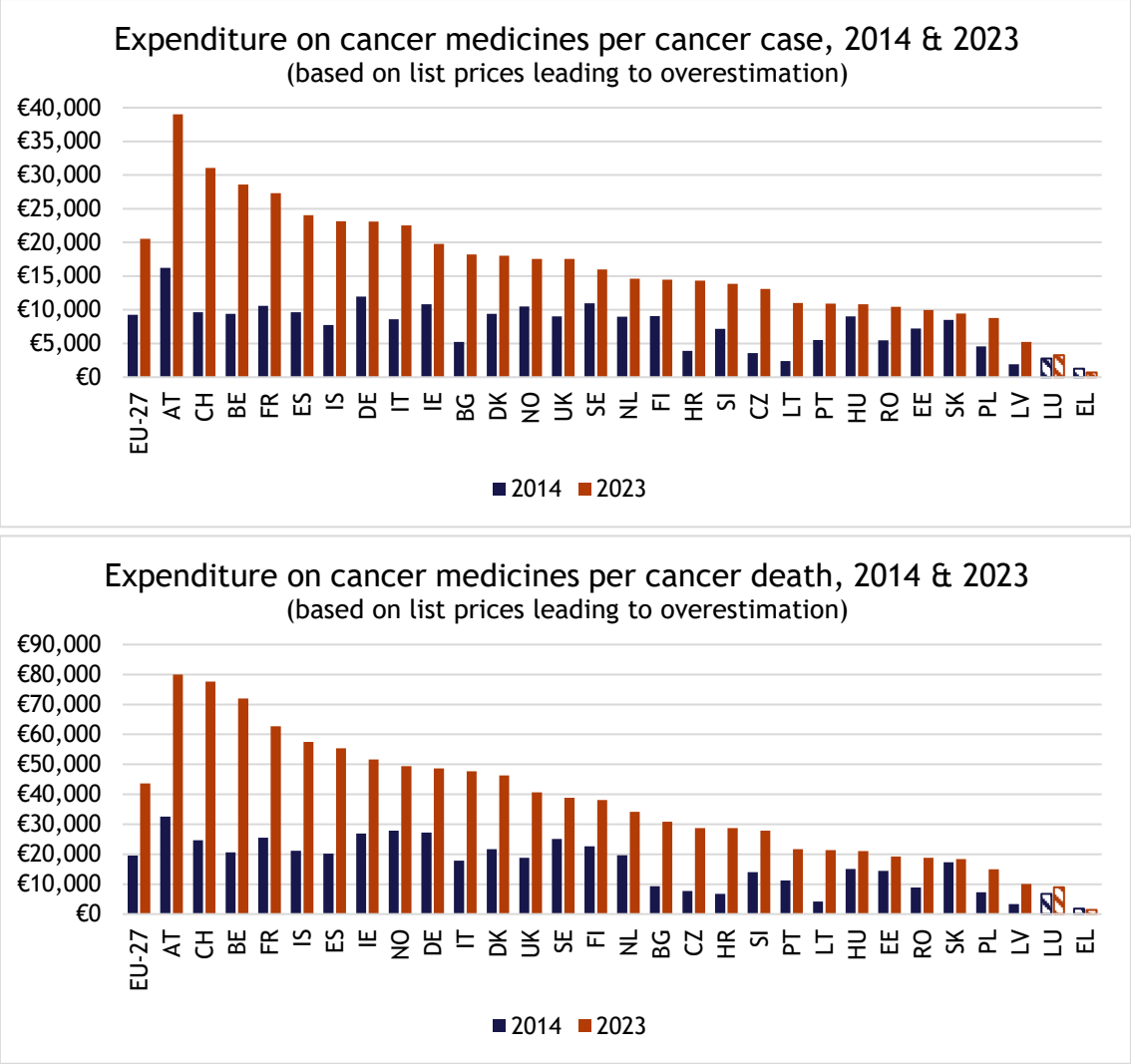


Figure 60: Expenditure on cancer medicines per new cancer case (top figure) and per cancer death (bottom figure) (in 2023 price levels and exchange rates; based on list prices), 2014 and 2023.

Notes: Sales data are based on list prices, leading to an overestimation of the true expenditure. The 2023 sales data were divided by the number of new cancer cases or deaths (excluding non-melanoma) in 2022 (nearest available year) from IARC, and 2014 sales data were divided by new cancer cases or deaths in 2012. Hatched bars indicate that data for EL and LU only comprise retail sales. CY and MT are missing due to lack of data. The EU-27 average excludes EL and LU. Source: Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Frumtök for Iceland, Signum Life Science for Denmark, and Ravimiamet for Estonia. Exchange rate and inflation rate sources: (64, 114).

As already described in section 2.5.1, expenditure on cancer medicines has been representing a fast-growing component of the cancer care expenditure, yet with limited impact on the overall growth of the relative share of health spending on cancer care. Previous Comparator Reports found that cancer medicine costs in Europe amounted to 9% of the direct costs of cancer in 2002/2003 (45), 13% in 2004 (48), 18% in 2007 (49), 23% in 2014 (47), and 31% in 2018 (46). Figure 61 shows that the increase continued until 2023, with the share growing from 21% in 2014 (recalculated with newer data) to 45% in 2023. Because of the use of list prices, the true share is lower.

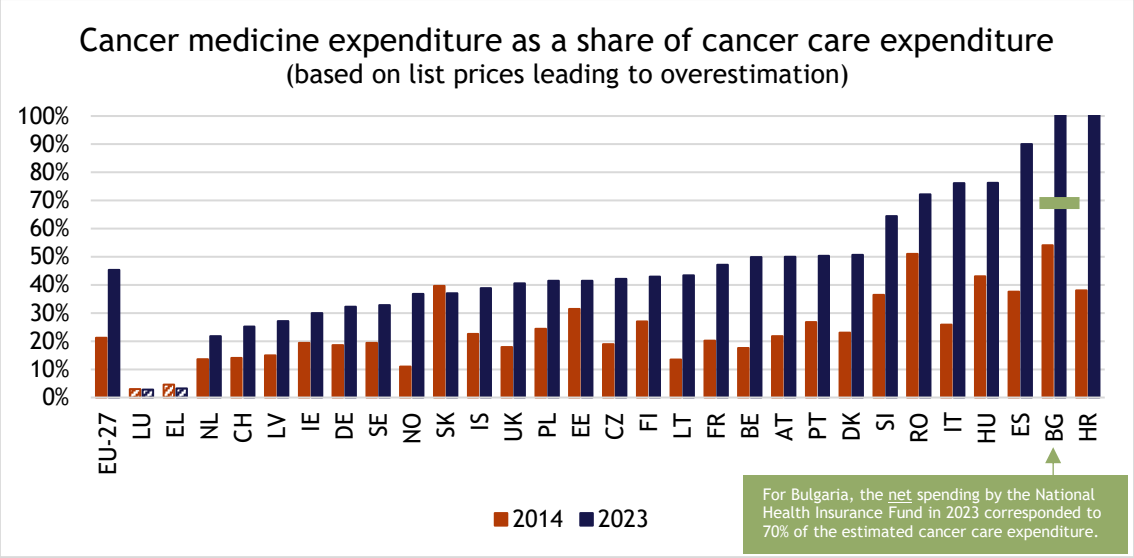


Figure 61: Cancer medicine expenditure (based on list prices) as a share of cancer care expenditure, 2014 & 2023.

Notes: Eur. = Europe. Hatched bars indicate that data for cancer medicines for EL and LU only comprise retail sales. CY and MT are missing due to lack of data on cancer medicine sales. Sources: own calculations, see Figure 59 and Figure 24.

The share of cancer medicine expenditure (based on list prices) increased in all countries with complete data, except in Slovakia, and showed wide variation between countries. Cancer medicine expenditure accounted for 30% or less of cancer care expenditure in Ireland, Latvia, Switzerland, and the Netherlands in 2023. Yet they accounted for 50% or more in 11 countries, with the share estimated at over 100% in Bulgaria and Croatia. The latter is of course impossible, and either explained by an underestimation of the costs of cancer care (in both countries no local data were identified and had to be estimated) and/or by an overestimation of the costs of cancer medicines. Indeed, net spending data on cancer medicines in Bulgaria in 2023 were much lower than those based on list prices (see also Info box 9). If net spending data were applied in Bulgaria, the share of cancer medicine expenditure would be 70%. This is still a very high share compared to, e.g., the 32% in Germany, yet one reason for this pattern is that there is a greater difference in relative prices of "local" cancer care services (e.g. the salaries of physicians and nurses) and "international" cancer medicines in Central and Eastern European countries. The results for Sweden of a 32%-share in 2022 based on IQVIA (not shown in Figure 61) can also be compared to the results of a local report that drew on real spending data and estimated a 26% share of cancer medicines that year (see Figure 23), equal to a relative difference of 23% of spending based on list prices versus net prices.

4.5.3 Composition of cancer medicine expenditure

In 2023, around 250 different cancer medicines (with unique active substances) were sold in at least some quantities across European countries. However, a small number of these medicines account for a significant portion of total sales. The top 10 medicines in terms of sales in 2023 represented 44% of the total market; see Table 17. In 2019, the corresponding number was 46% and 52% in 2014. This noteworthy drop in the proportion of the top 10 medicines is probably a result of the strong increase in the number of cancer medicines approved since 2010 (see Figure 49).

Table 17: Top ten highest-selling medicines (based on list prices) in Europe

2014		2019		2023	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Trastuzumab	9.0%	Pembrolizumab	7.7%	Pembrolizumab	14.6%
Rituximab	8.2%	Lenalidomide	6.3%	Daratumumab	6.5%
Bevacizumab	8.0%	Nivolumab	6.0%	Nivolumab	5.0%
Imatinib	6.2%	Trastuzumab	4.4%	Enzalutamide	3.7%
Lenalidomide	4.6%	Bevacizumab	4.1%	Ibrutinib	3.3%
Abiraterone	4.4%	Rituximab	3.9%	Atezolizumab	2.4%
Pemetrexed	3.3%	Ibrutinib	3.8%	Osimertinib	2.3%
Bortezomib	3.2%	Palbociclib	3.4%	Bevacizumab	2.1%
Leuprorelin	2.6%	Enzalutamide	3.3%	Palbociclib	2.1%
Paclitaxel	2.5%	Abiraterone	3.2%	Ruxolitinib	2.0%
Total	52.1%	Total	46.3%	Total	44.1%

Notes: Sales data are based on list prices and do not account for variations in confidential discounts and rebates across products. For EE, EL, and LU, only retail data were included. Source: see Figure 58.

There have been significant changes among the top 10 best-selling cancer medicines in Europe over time; see Table 17. Of the top 10 list in 2014, only bevacizumab retained a spot in the list until 2023, despite facing competition from biosimilars towards the end of the period. Moreover, four medicines that were in the top 10 in 2019 had dropped from the list in 2023 (abiraterone, lenalidomide, rituximab, trastuzumab), all of which faced competition from generics or biosimilars in 2023. Pembrolizumab has taken a clear lead in terms of sales since its approval in 2015, accounting for one seventh of all cancer medicines sales in 2023. The top 10 list looks largely similar in the Big Five countries and countries in Northern and Western Europe whereas the ranking in Central and Eastern European countries differs more; see Appendix C.

In general, the latest cancer medicines only account for a small proportion of the total sales of cancer medicines. Figure 62 shows that the share of sales from medicines approved by the EMA within the last 0 to 2 years is relatively small each year, fluctuating between 3% and 13% from 2014 to 2023. This is not surprising given that the average time from EMA approval to reimbursement exceeds one year in most EU countries, as shown before in Figure 55. Even after reimbursement, it takes time for newer medicines to be adopted in clinical practice as shown in section 4.6. By contrast, the proportion of sales from medicines approved more than 10 years ago has decreased from 44% in 2014 to 26% in 2023. This aligns with data from Table 17 indicating that older medicines, including those once in the top 10, are losing market share to newer therapies as patents expire and cheaper generics and biosimilars enter the market. Figure 62 also shows how medicines approved in the last 3 to 5 years saw a considerable increase in their sales share until 2021 before declining again. The reverse pattern is visible for medicines approved in the last 6 to 10 years. Much of this pattern is driven by nivolumab and pembrolizumab which were approved in 2015 and hence switched from the 3–5-year group to the 6–10-year group in 2021.

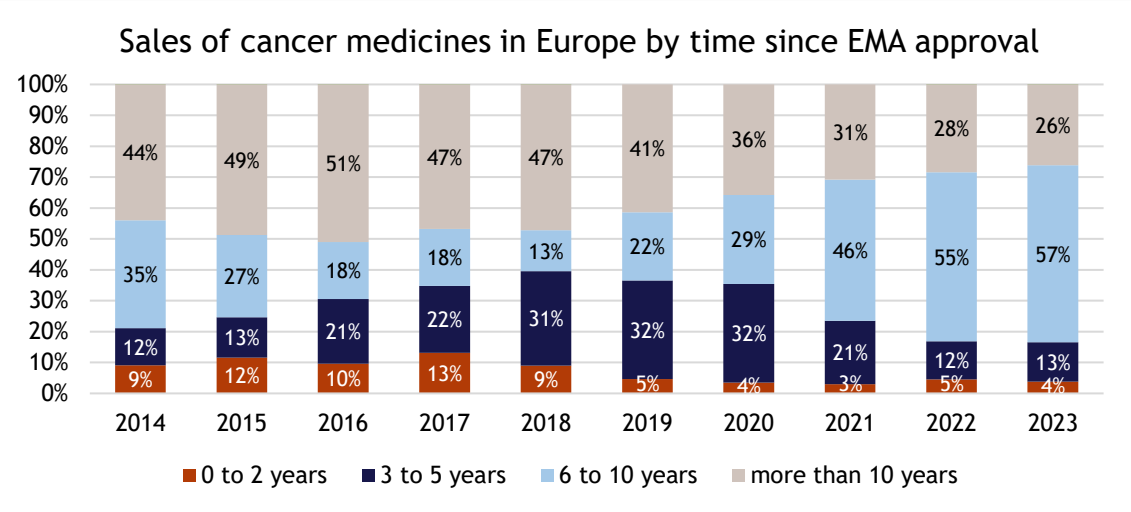


Figure 62: Sales of cancer medicines (in % of total sales in euros; based on list prices) in Europe by time since EMA approval.

Notes: Sales data are based on list prices, which do not take into account the varying presence and size of confidential discounts and rebates between products. For EE, EL, and LU, only retail data were included. Source: (497) and see Figure 58.

Figure 63 shows the breakdown of cancer medicine sales by five major medicine classes across Europe. Chemotherapy medicines have seen a gradual decline over the period from 22% in 2014 to 6% in 2023, largely due to the lack of new launches of new products, the expiration of patents of existing products, and their replacement by other medicine classes. In contrast, targeted cancer therapies have consistently accounted for more than half of the sales each year between 2014 and 2023. Immunotherapy medicines have seen a notable increase in sales, particularly after 2015, following the approval of nivolumab and pembrolizumab, reaching a sales share of 29% in 2023. Hormone therapies have seen a slow but steady decline in the sales share from 15% to 8% over the period. Meanwhile, radiopharmaceuticals maintained the lowest sales figures of less than 1% in all years, mirroring their limited application and approval numbers in oncology.

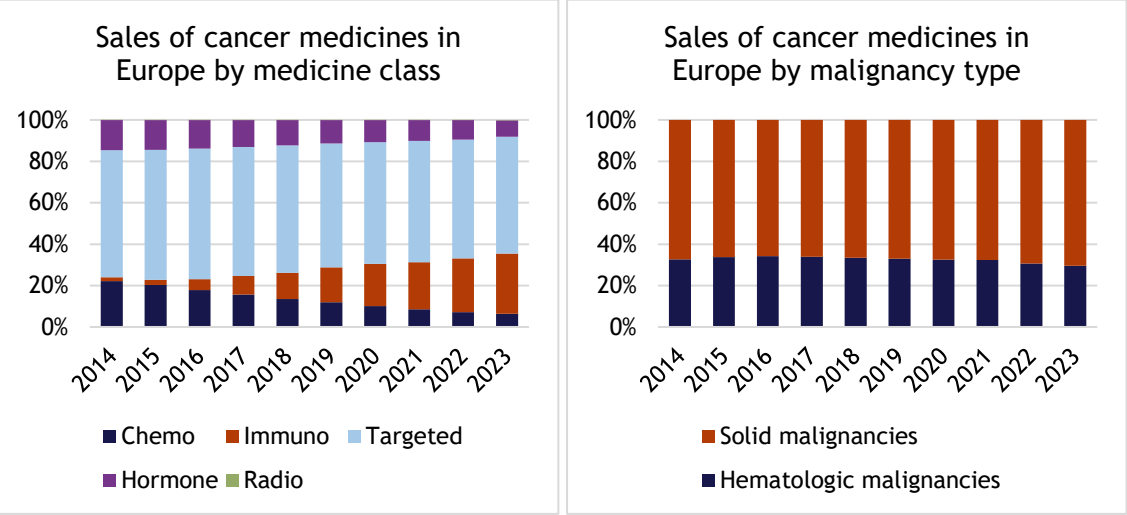


Figure 63: Sales of cancer medicines (based on list prices) by medicine class and malignancy type in Europe.

Notes: Sales data are based on list prices, which do not take into account the varying presence and size of confidential discounts and rebates between products. Medicines used in both solid tumors and hematology were classified according to their main therapeutic area. For EE, EL, and LU, only retail data were included due to limited data availability, likely underestimating total sales. Source: see Figure 58.

Figure 63 also shows the sales of cancer medicines categorized by broad therapeutic areas. Medicines used in the treatment of solid tumors represented a very consistent sales share of 66-70% in 2014-2023, while medicines used in the treatment of hematologic malignancies accounted for the remaining 30-34%. The sales share of hematology is considerably higher than the disease burden of these cancer types. As shown in section 2.3, hematologic malignancies accounted for around 8% of new cancer cases and 8% of cancer deaths in 2022.[30]

4.6 Uptake of medicines in volume

As new treatments are launched, understanding their uptake in clinical practice is crucial for evaluating their integration into healthcare systems and anticipated potential to improve patient outcomes. This subsection examines the sales volume of cancer medicines in milligrams. The consideration of milligrams overcomes the issue of varying medicine prices, discounts and rebates, and exchange rates between countries and over time in section 4.5 (47).

As in previous Comparator Reports, two analyses of the uptake of newer medicines are made. Firstly, the uptake of a selected medicine per cancer type is considered over time for the five most populous countries in Europe. This analysis is based on the annual sales of milligrams of the active ingredient in the medicine; see Appendix C for the sources. Secondly, the uptake of multiple medicines per cancer type is considered for 2023, the latest available year with data. This analysis requires a standardization of the milligrams required per patient and per time period for each medicine. A measure called the standard weekly dose (SWD) per patient – which is similar to the measure of defined daily dose (DDD) used by the WHO for many non-cancer medicines – was used; see Appendix C for the SWD per medicine. Annual sales in milligrams were divided by the SWD for every medicine to get the number of weekly doses sold. The weekly doses sold were then summed up across cancer medicines. In both analyses, the number of milligrams or weekly doses were divided by the number of cancer patients[31] in a country (rather than by the total population) in order to put the uptake in closer relation to the actual demand for cancer medicines.[32] The resulting measure of uptake is the number of milligrams or standard weekly doses sold per cancer patient.

For the analysis of the uptake of newer cancer medicines, the following cancer types or medicine classes were considered:

1. **Solid tumors**: breast cancer, prostate cancer, lung cancer, gastrointestinal cancers (including colorectal cancer), melanoma of the skin, urinary tract cancers (bladder and kidney cancer), gynecological cancers, tumor-agnostic therapies targeting specific molecular markers, and immune checkpoint inhibitors as a separate category as they are used across multiple solid tumors.

[30] It should be noted that cancer medicines are the main treatment modality in hematology together with stem-cell therapy, whereas surgery and radiation therapy are used alongside cancer medicines in the treatment of solid tumors. A joint consideration of all treatment modalities would probably rebalance the distribution of costs between solid tumors and hematologic malignancies compared to the pattern shown in Figure 63.

[31] Cancer patients were either defined as the number of new cases or deaths from a certain cancer type in 2022, based on the most recent data from IARC. The choice between incidence and mortality varied depending on if most considered medicines were only used in the metastatic/palliative setting (mortality was chosen as a proxy for incurable disease) or also in the early-stage/curative setting (incidence was chosen).

[32] What this analysis cannot tell is how many milligrams or doses are needed, i.e., the optimal level of uptake given the patient needs. An analysis of uptake in relation to patient needs would require a consideration of (local) clinical guidelines and a closer definition of the target patient group (e.g. castration-resistant metastatic prostate cancer rather than only prostate cancer as in this report).

2. **Hematology**: non-Hodgkin lymphoma, leukemia, multiple myeloma, and CAR T-cell therapies as a separate category as they are used across all hematologic malignancies.

For each cancer type or medicine class, a number of newer cancer medicines were selected based on the following three criteria: (i) up to seven medicines, (ii) highest sales volume in EUR in Europe in 2023, (iii) EMA approval in 2010 or later; see Appendix C for the selected list of medicines.

Some of the medicines analyzed in a specific cancer type also have approved indications in other cancer types, e.g., use in both non-Hodgkin lymphoma and leukemia. IQVIA MIDAS sales data before 2018 do not contain a split by indication, whereas after 2018, only estimations of the broad use by cancer type (but not by subtypes or lines of treatment) are available. For countries not covered by IQVIA MIDAS sales data, an indication split is not available. Therefore, no split of product sales into indications was used in this section. Products were allocated to the cancer type with the supposedly biggest use.

For the comparisons in this section, the 27 countries with complete sales data were divided into three groups, as shown in Table 18. The EU-27 average in this section is the population-weighted average of all member states (excluding Cyprus, Greece, Luxembourg, and Malta).

Table 18: Three main groups of countries

Countries in Central and Eastern Europe (CEE)		Big Five countries	Smaller countries in Northern and Western Europe (NW)	
Bulgaria	Lithuania	France	Austria	Netherlands
Croatia	Poland	Germany	Belgium	Norway
Czechia	Romania	Italy	Denmark	Portugal
Estonia	Slovakia	Spain	Finland	Sweden
Hungary	Slovenia	United Kingdom	Iceland	Switzerland
Latvia			Ireland	
This group includes countries from Central and Eastern Europe. They are generally characterized by lower overall healthcare spending than other countries.		This group consists of the most populous countries. They represent a significant share of the European cancer medicine market.	This group includes small and medium-sized high-income countries in Northern and Western Europe. They are generally characterized by high overall healthcare spending.	

Notes: No complete sales data by product were available in Cyprus, Greece, Luxembourg, and Malta. These countries are excluded from the EU average in all uptake graphs.

The interpretation of the numbers in the following sections for each cancer type is important. First of all, it should be emphasized that the focus here is on access to newer medicines. A low uptake of newer medicines does not mean that patients receive no medicines at all. They might simply receive older, potentially less effective medicines. The central question here is whether a higher uptake of newer medicines is desirable or not. The following points are worth considering:

- As explained above, the uptake of new medicines is set in relation to the approximative demand by patients in this section. Nevertheless, both the numbers used for volume sales and the patient demand might not be perfectly accurate. In terms of patient demand, this is partly because they rely on estimations from IARC and partly because they are defined in a broad way by tumor type whereas most medicines only are given to certain subgroups within a tumor type and a certain disease stage. Therefore, small country differences in uptake of, e.g., ±20% should not be overinterpreted.

- All else equal, countries that manage to detect a higher number of patients in early stages would need less use of new medicines, as these are mostly restricted to the metastatic setting.
- For solid tumors, the selected list of medicines shows high agreement with the scoring of the ESMO-MCBS (Magnitude of Clinical Benefit Scale) framework, as nearly all medicines have a score of 3 or higher in the metastatic setting of the respective cancer type.[33] Since its launch in 2015, the ESMO-MCBS has found its way into the clinical practice guidelines by ESMO in order to guide the use of medicines in daily practice. Given the clinical recommendation for the newer cancer medicines considered in this section, higher uptake numbers might generally be more desirable than lower numbers.

4.6.1 Breast cancer

After the introduction of trastuzumab in 2000 for HER2-positive breast cancer, which represents about 15% of primary breast cancer cases, pertuzumab was approved in 2013. The dual HER2 blockade resulted in a significant prolongation of survival. At the same time trastuzumab emtansine was introduced as a second-line treatment for HER2-positive cases following trastuzumab failure. Since 2021, trastuzumab deruxtecan has started to replace trastuzumab emtansine in this setting. Trastuzumab deruxtecan also made inroads as the first treatment of metastatic HER2-low breast cancer. The years 2016-2018 witnessed the introduction of CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) in HR-positive, HER2-negative metastatic breast cancer, which represents around 75% of all metastatic breast cancer patients. In 2022, abemaciclib received approval for early-stage treatment, which significantly increased the number of eligible patients as most breast cancer patients are diagnosed in early stages. Sacituzumab govitecan was approved in 2021 for later-line treatment of metastatic triple-negative breast cancer, which accounts for around 10% of primary breast cancer cases, but received an extension to metastatic HER2-negative breast cancer in 2023.

There is a relatively uniform uptake of newer medicines in 2023 in all three groups of countries, yet a more than two-fold difference between countries with the lowest uptake (Poland and Slovakia) and the highest uptake (Croatia, France, Spain, Switzerland) is visible; see Figure 64. The joint uptake of the CDK4/6 inhibitors dominates the picture, due to the larger underlying patient population. The low uptake of abemaciclib in relation to the other CDK4/6 inhibitors is surprising, given its extension of use to the early-stage setting in 2022, but probably a sign of delayed reimbursement. The analysis of the trend in uptake of the Big Five countries in Figure 65 shows that abemaciclib experienced a steady increase in use over time, with a slight acceleration in use from 2022 to 2023. Among the HER2 targeted therapies, trastuzumab emtansine has a similar uptake in nearly all countries in 2023; see Figure 64. For pertuzumab, comparisons a more complicated due to the introduction of a fixed-dose combination with trastuzumab, which is included here. The uptake of the two latest medicines, trastuzumab deruxtecan and sacituzumab govitecan, was highest in the Big Five countries and NW countries with the exception of the Netherlands (no uptake for both) and Ireland (no uptake for one).

[33] The only exception are two medicines in the section on gastrointestinal cancers.

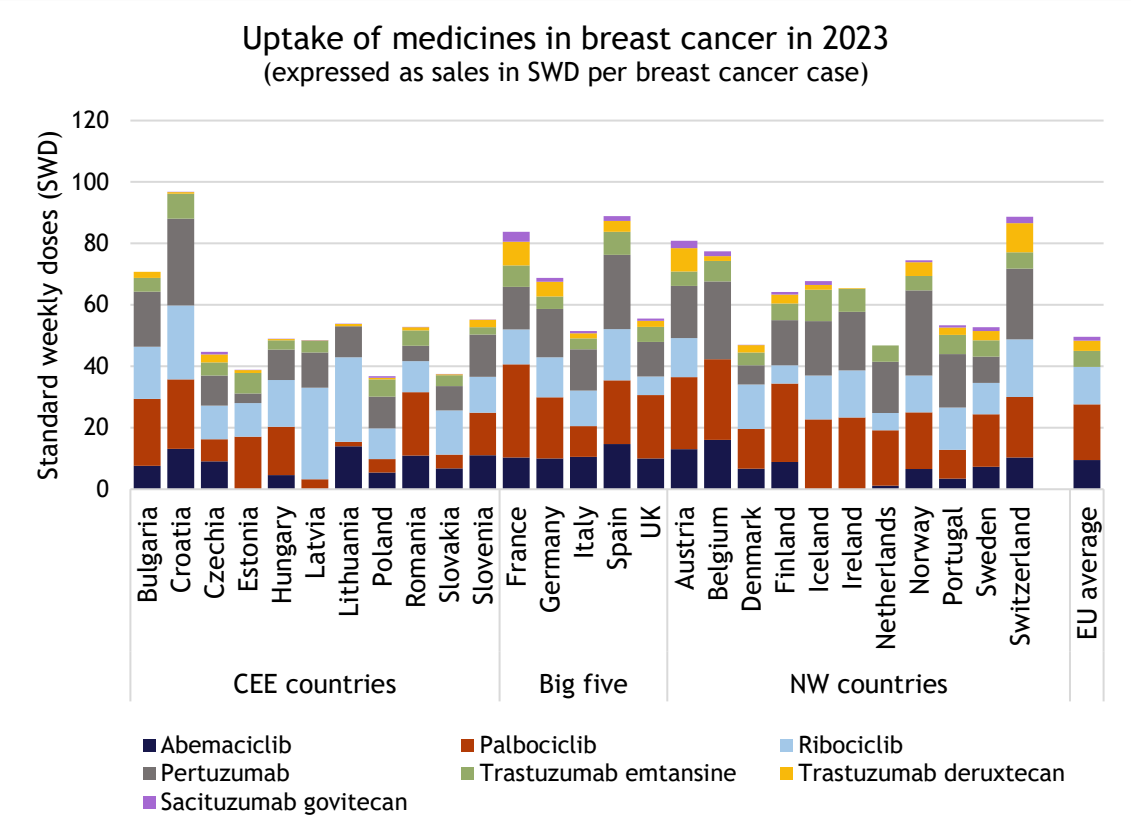


Figure 64: Uptake of breast cancer medicines in 2023 expressed as sales in SWD per breast cancer case.

Notes: Breast cancer case refers to breast cancer deaths in 2022. Pertuzumab includes both pertuzumab monotherapy and the fixed-dose pertuzumab-trastuzumab combination, yet BE, EE, HU, IS, and PL had no sales of the combination. Abemaciclib had no sales in EE, LV, IS, and IE. Ribociclib had no sales in BE. Trastuzumab emtansine had no sales in LT. Trastuzumab deruxtecan had no sales in NL. Sacituzumab govitecan had no sales in BG, IE, and NL.

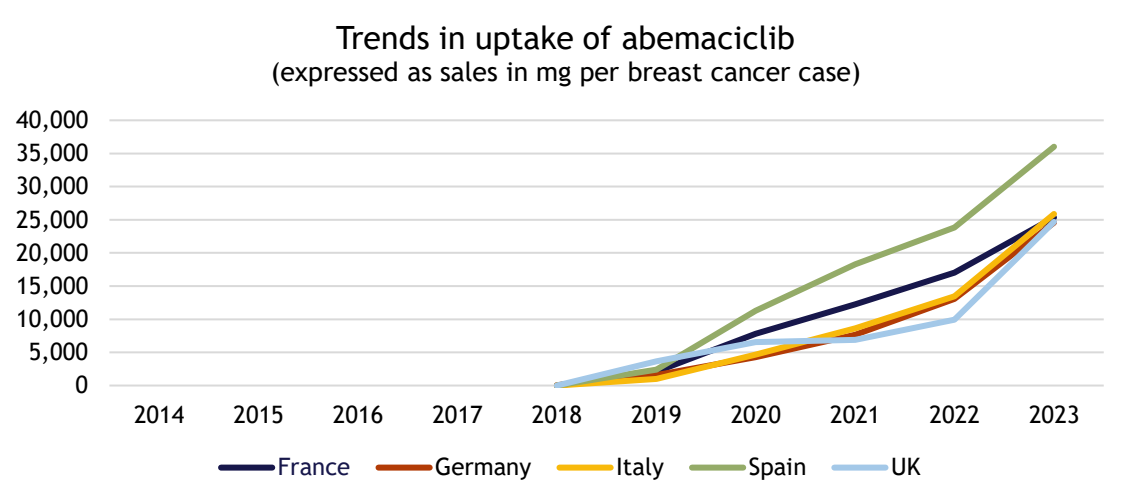


Figure 65: Trends in uptake of abemaciclib expressed as sales in mg per breast cancer case.

Notes: Breast cancer case refers to breast cancer deaths in 2022.

4.6.2 Prostate cancer

The introduction of new medicines for prostate cancer, called androgen receptor pathway inhibitors, started in 2011 with the approval of abiraterone. This was followed by the approval of enzalutamide in 2013, apalutamide in 2019, and darolutamide in 2020. Initially their use was in metastatic castration-resistant prostate cancer (mCRPC) but later expanded to metastatic hormone-sensitive prostate cancer (mHSPC), non-metastatic hormone-sensitive prostate cancer (nmHSPC), and non-metastatic castration-resistant prostate cancer (nmCRPC).

The overall uptake of the four medicines in 2023 differed considerably between country groups, with CEE countries experiencing lower uptake; see Figure 66. There was also a marked difference in the uptake within country groups, e.g., twofold differences between Slovakia and Poland, between France and the UK, and between Ireland and the Netherlands and Portugal. The uptake of abiraterone (which had already seen the introduction of generics in 2023) and enzalutamide (which is the only medicine with approval in all four prostate cancer subtypes described above) was roughly equal within most countries. Apalutamide has a much higher uptake than darolutamide in all countries expect in Denmark and Ireland in 2023, despite those two medicines having nearly identical approved indications (with the approval in mHSPC being three years apart however). Trends in the uptake of apalutamide in the Big Five countries show a big divergence, with a low uptake level in the UK that in 2023 resembled the level that France and Germany had in 2021; see Figure 67. Italy also saw a slow uptake compared to France and Germany.

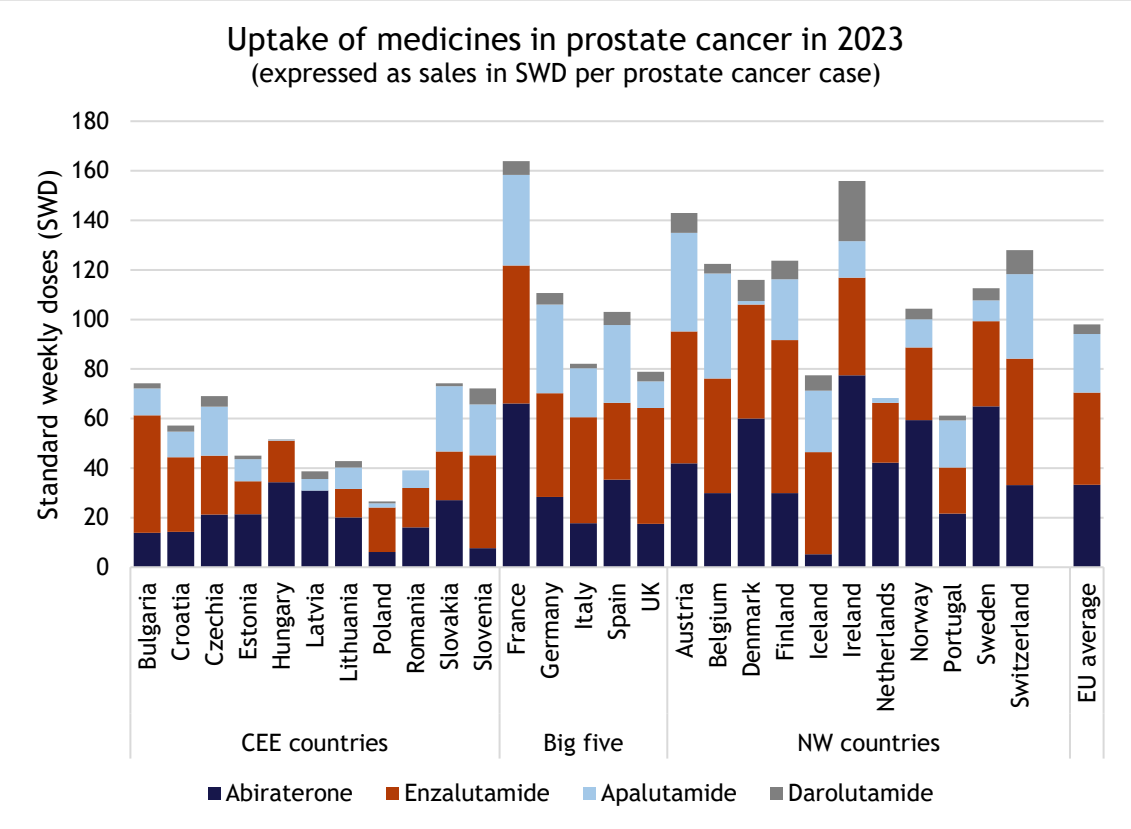


Figure 66: Uptake of prostate cancer medicines in 2023 expressed as sales in SWD per prostate cancer case.

Notes: Prostate cancer case refers to prostate cancer deaths in 2022. Darolutamide had no sales in RO and NL. Enzalutamide had no sales in LV.

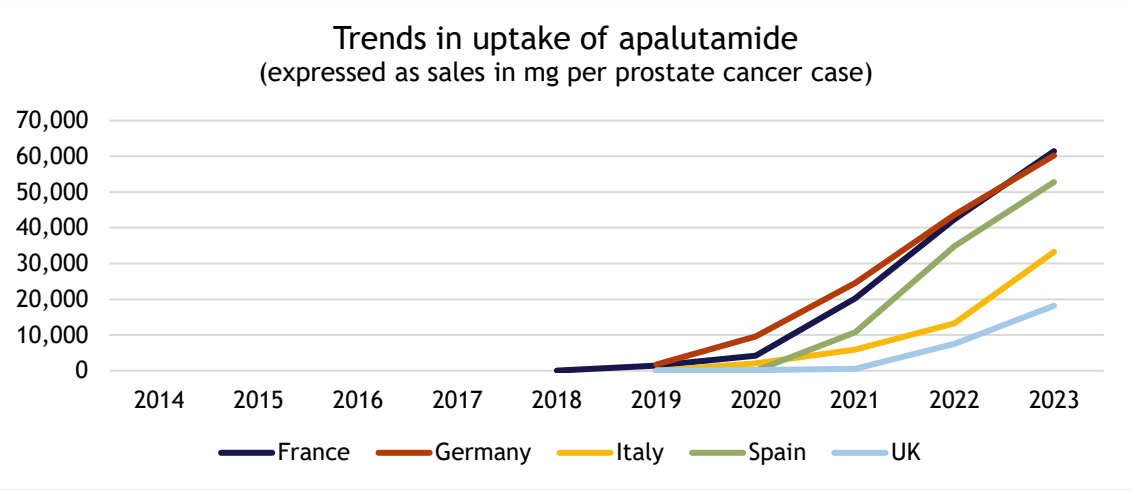


Figure 67: Trends in uptake of apalutamide expressed as sales in mg per prostate cancer case.

Notes: Prostate cancer case refers to prostate cancer deaths in 2022.

4.6.3 Lung cancer

The landscape of lung cancer treatment has changed entirely over the last 15 years, from previously being treated with chemotherapy alone. For the NSCLC subtype, which accounts for approximately 85% of all new cases, more than a dozen targeted therapies for various mutations have been introduced, in addition to the introduction of immune checkpoint inhibitors (see section 4.6.9). The latter have also been introduced in the treatment of the subtype SCLC, which accounts for the remaining 15% of new cases. In terms of targeted therapies for NSCLC, EGFR inhibitors were introduced first, with osimertinib, a third-generation inhibitor, being standard of care not only in metastatic disease (since 2018) but also in early-stage disease (since 2021). This was followed by the introduction of ALK inhibitors, starting with crizotinib in 2012 and later superseded by second-generation inhibitors (alectinib, brigatinib, ceritinib) and third-generation inhibitors (lorlatinib). Crizotinib was also approved as a targeted therapy for ROS1 mutations in 2016. BRAF-targeted therapies, approved for NSCLC in 2017, are discussed in section 4.6.5. NTRK-targeted therapies, approved in 2019-2020, are discussed in section 4.6.8. The first RET inhibitors (pralsetinib and selpercatinib) were approved in 2021. The first KRAS G12C inhibitor (sotorasib) and MET inhibitors (tepotinib and capmatinib) were all approved as second-line treatment in 2022. Trastuzumab deruxtecan (already discussed in section 4.6.1) was approved as a HER2 inhibitor in 2023.

Country differences in uptake for lung cancer medicines are high in 2023, with lower uptake in CEE countries, especially Hungary, Latvia, and Poland; see Figure 68. The UK has a comparatively low uptake among its peers and is on par with Romania. Looking at the specific medicines, osimertinib dominates the picture, which is expected as the EGFR mutation is much more common than other mutations (and similar to the prevalence of KRAS G12C) and its use in both the early-stage and metastatic setting. While the use of osimertinib across the Big Five and NW countries is comparatively uniform (apart from two-fold differences between France and the UK and Ireland and Switzerland), the use is low in many CEE countries. The latter countries might still be using older inhibitors such as afatinib, erlotinib, or gefitinib. The trend in the uptake of osimertinib was very uniform in the Big Five except the UK until 2020, after which the gap with the UK widened and also Germany saw much slower growth at the time when the extension to the early-stage setting had happened; see Figure 69. Alectinib is the most used ALK inhibitor in all countries; see Figure 68. The combined use of all considered ALK

inhibitors is highest in Austria, Sweden, and Switzerland, whereas there is almost no use in Romania. The low use of crizotinib in most countries in CEE except Slovenia and Slovakia probably reflects the limited access to comprehensive biomarker testing in these countries, as shown in section 5.3. The use of selpercatinib and sotorasib was very limited in almost all CEE countries except Slovenia, and Italy and Spain had negligible uptake among the Big Five, whereas Austria and Switzerland had high uptake.

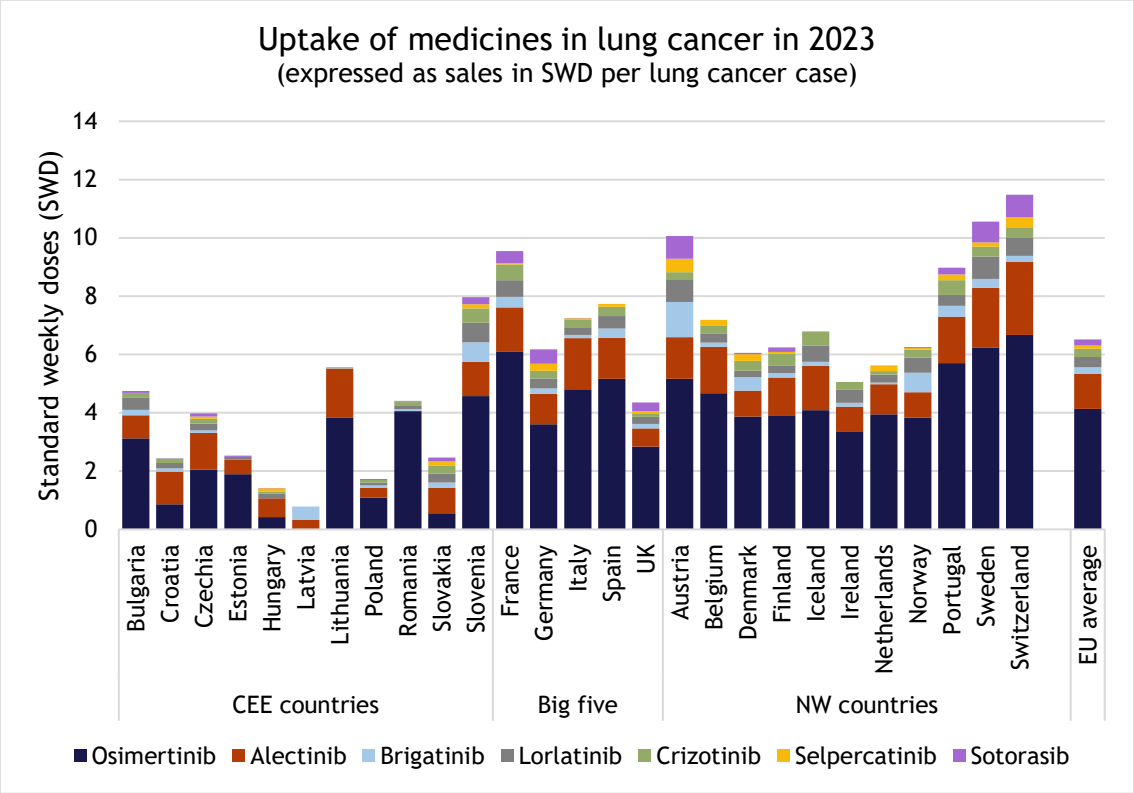


Figure 68: Uptake of lung cancer medicines in 2023 expressed as sales in SWD per lung cancer case.

Notes: Lung cancer case refers to lung cancer deaths in 2022. Alectinib had no sales in RO. Brigatinib had no sales in EE. Lorlatinib had no sales in LV and LT. Crizotinib had no sales in EE and LV. Selpercatinib had no sales in BG, HR, EE, LV, LT, RO, IS, and IE. Sotorasib had no sales in LV, LT, ES, BE, IS, and IE.

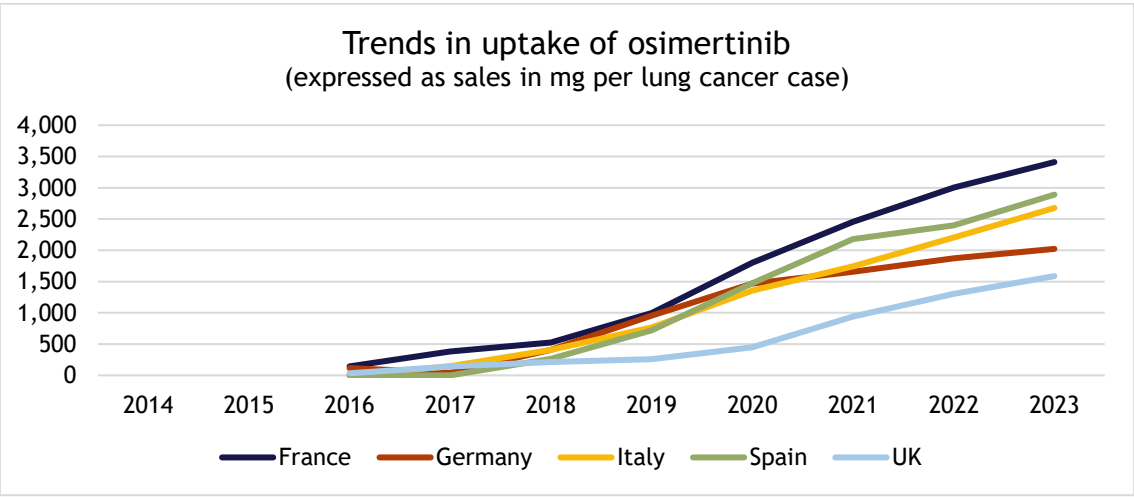


Figure 69: Trends in uptake of osimertinib expressed as sales in mg per lung cancer case.

Notes: Lung cancer case refers to lung cancer deaths in 2022.

4.6.4 Gastrointestinal cancers

Compared to many other solid tumor types, gastrointestinal cancers have seen limited introduction of new medicines since 2010. One big exception is the use of immune checkpoint inhibitors (considered in section 4.6.9), which have been introduced in the metastatic setting of colorectal cancer (limited to cases with MSI-H/dMMR status), gastric cancer, hepatocellular carcinoma (HCC, which accounts for 90% of liver cancers), esophageal cancer (also in the early-stage setting), and biliary tract cancer. Apart from the use of immune checkpoint inhibitors, colorectal cancer saw the approval of the fixed-dose combination trifluridine / tipiracil, ramucirumab, and regorafenib as later-line treatments in the metastatic setting. The former two medicines were also approved as later-line treatments of metastatic gastric cancer, whereas the latter two medicines were approved as second-line treatments in metastatic HCC. Cabozantinib is also approved as second-line treatment in metastatic HCC, whereas lenvatinib is approved as a first-line treatment (considered in section 4.6.6). For the treatment of metastatic bile duct cancer (cholangiocarcinoma), two FGFR2 inhibitors, pemigatinib and futibatinib, were approved in 2021 and 2023, respectively, and ivosidenib, an IDH1 inhibitor, in 2023. Pancreatic cancer only saw the approval of the targeted therapy olaparib (considered in section 4.6.7) for BRCA-positive metastatic cases in 2020. Three medicines for the treatment of GIST – regorafenib in 2014, avapritinib in 2020, and ripretinib in 2021 – were approved.

The uptake of new medicines in gastrointestinal cancers varies widely between countries, although there is no discernible pattern between the three groups of countries; see Figure 70. Lithuania and Austria recorded the highest uptake and Denmark and Norway the lowest uptake among countries with complete data. The uptake trend of the combination of trifluridine / tipiracil in the Big Five countries is also rather unique; see Figure 71. There was a quick jump in uptake from 2015 (year of approval in colorectal cancer) to 2016, whereupon the use remained stable in the UK and Spain at a low level until 2023 (despite the approval of use in gastric cancer in 2019), whereas in Italy and France, the initial uptake was delayed by a year but then reached double the level of Spain and the UK in the following years. Pemigatinib as well as avapritinib and ripretinib have a low uptake compared to the other medicines, which relates to the much smaller patient pool with cholangiocarcinoma and GIST, respectively; see Figure 70. Among the CEE countries, only Slovenia has a noticeable use of avapritinib in 2023, and France, Germany, and Austria are the only other countries with a visible use of both avapritinib and ripretinib. For pemigatinib, only Austria, Denmark, and Germany have a comparatively high uptake.

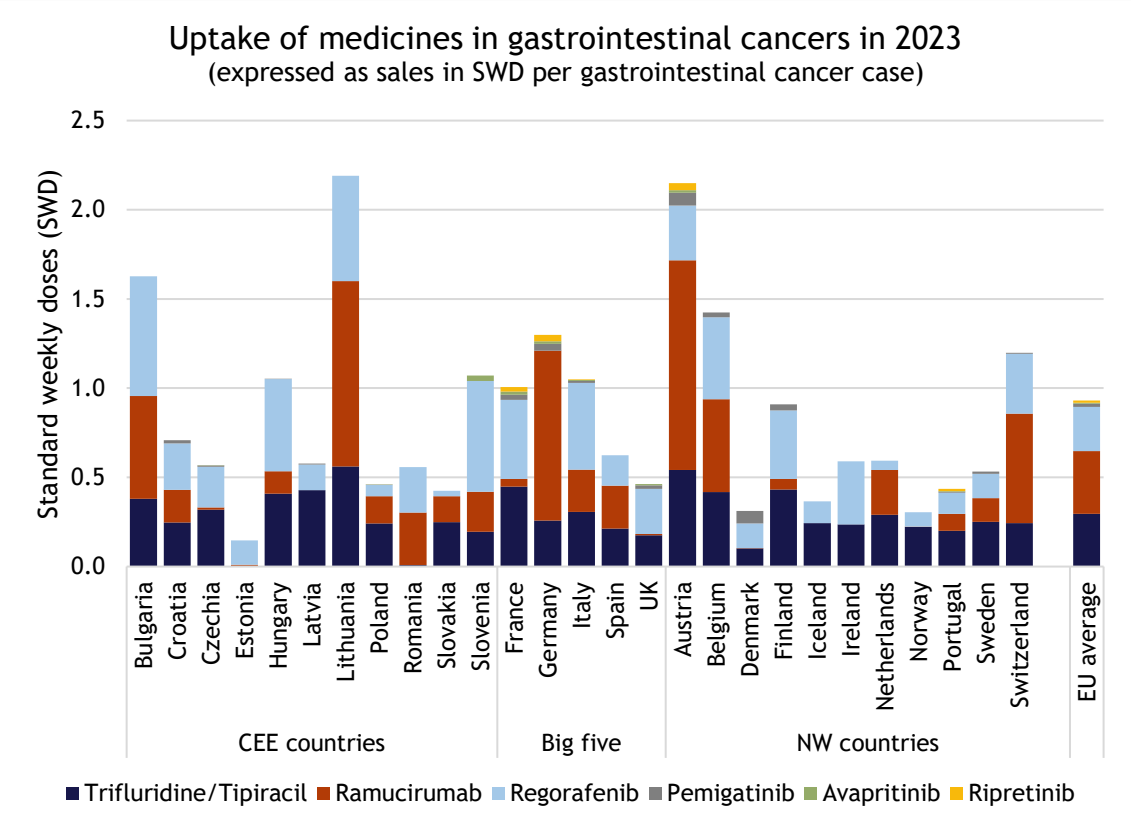


Figure 70: Uptake of medicines in gastrointestinal cancers in 2023 expressed as sales in SWD per gastrointestinal cancer case.

Notes: Gastrointestinal cancer case refers to gastrointestinal cancer deaths in 2022. Gastrointestinal cancer includes cancers of the esophagus, stomach, pancreas, colorectum, anus, liver, and gallbladder. Sales data for trifluridine/tipiracil in EE are omitted due to variation in volume sales. Ramucirumab had no sales in LV, IS, and IE. Pemigatinib had no sales in BG, EE, LT, RO, SK, SI, ES, IS, IE, NL, and NO. Avapritinib had no sales in BG, HR, HU, LV, LY, RO, SK, ES, EE, BE, DK, FI, IS, IE, NL, NO, SE, and CH. Ripretinib had no sales in BG, HR, CZ, EE, HU, LV, LT, PL, RO, SK, SI, ES, UK, BE, DK, FI, IS, IE, NL, NO, SE, and CH.

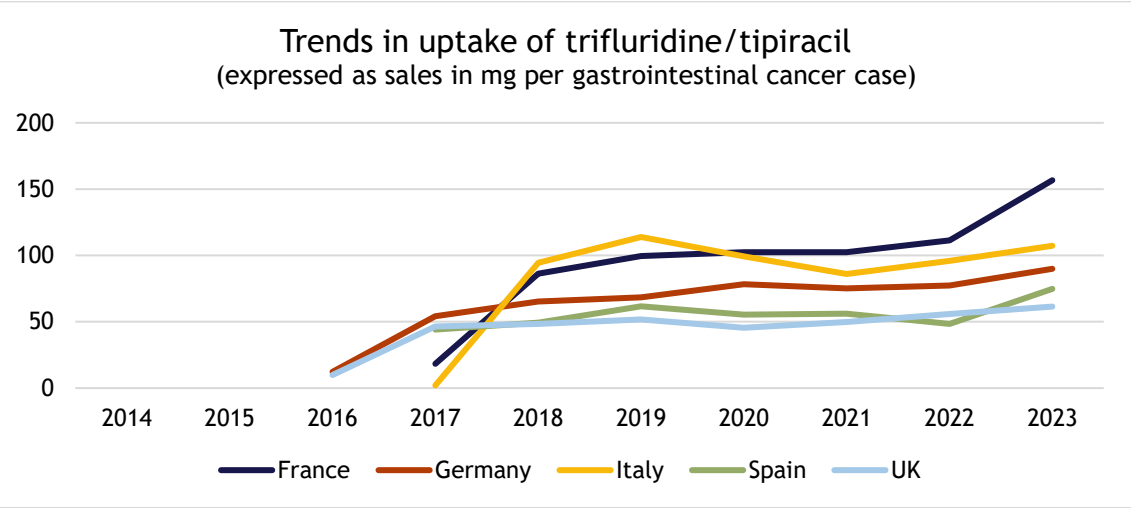


Figure 71: Trends in uptake of trifluridine/tipiracil expressed as sales in mg per gastrointestinal cancer case.

Notes: Gastrointestinal cancer case refers to gastrointestinal cancer deaths in 2022. Gastrointestinal cancer includes cancers of the esophagus, stomach, pancreas, colorectum, anus, liver, and gallbladder.

4.6.5 Melanoma

The treatment of melanoma of the skin has been revolutionized with the introduction of immune checkpoint inhibitors since 2011, expanding from the metastatic setting to the early-stage setting (considered in section 4.6.9). They are nowadays the cornerstone of medical treatment in melanoma. At the same time, several targeted therapies for the subgroup of patients with BRAF V600 mutations have been introduced. This started with vemurafenib, introduced in 2012, which was largely replaced by dabrafenib, introduced in 2013. These BRAF inhibitors were later combined with MEK inhibitors (cobimetinib and trametinib, respectively), both approved in 2015. Another combination of a BRAF and a MEK inhibitor, encorafenib and binimetinib, was approved in 2018, which demonstrated better outcomes than vemurafenib monotherapy. Initially, all combinations were restricted to the metastatic setting, but dabrafenib and trametinib were in 2018 also approved as adjuvant treatment for stage III melanoma. The combinations of dabrafenib and trametinib in 2017 and encorafenib and binimetinib in 2024 were also approved in the treatment of metastatic BRAF V600-positive NSCLC (considered in section 4.6.3). Encorafenib without binimetinib was also approved for metastatic BRAF V600-positive colorectal cancer in 2020 (considered in section 4.6.4).

The uptake of BRAF-MEK inhibitors is very similar in all NW countries as well as the Big Five countries in 2023, with dabrafenib and trametinib dominating picture followed by encorafenib and binimetinib and very little use of vemurafenib and cobimetinib; see Figure 72. The highest overall uptake of all countries is found in Lithuania and Hungary and the lowest one in Poland and Slovenia. A higher uptake of BRAF-MEK inhibitors could partly compensate for a lower uptake of immune checkpoint inhibitors in BRAF V600-positive melanoma cases, as, e.g., treatment guidelines from ESMO leave some room for BRAF-MEK inhibitors being used as first-line treatment in the metastatic setting if immune checkpoint inhibitors are not available or patients are considered ineligible for their use (558). While all Big Five and NW countries (except Iceland) use the latest combination of encorafenib and binimetinib, only four out of the eleven CEE countries use it. The uptake of encorafenib in the Big Five countries saw a slow start from 2018 to 2019 except for Germany, after which uptake grew most rapidly in France, whereas there was a slow uptake in Italy that eventually converged to other countries until 2023; see Figure 73. It is also interesting to note that Spain and France show a quite flat uptake in 2021-2023, possibly indicating limited use of encorafenib in colorectal cancer after its approval in 2020.

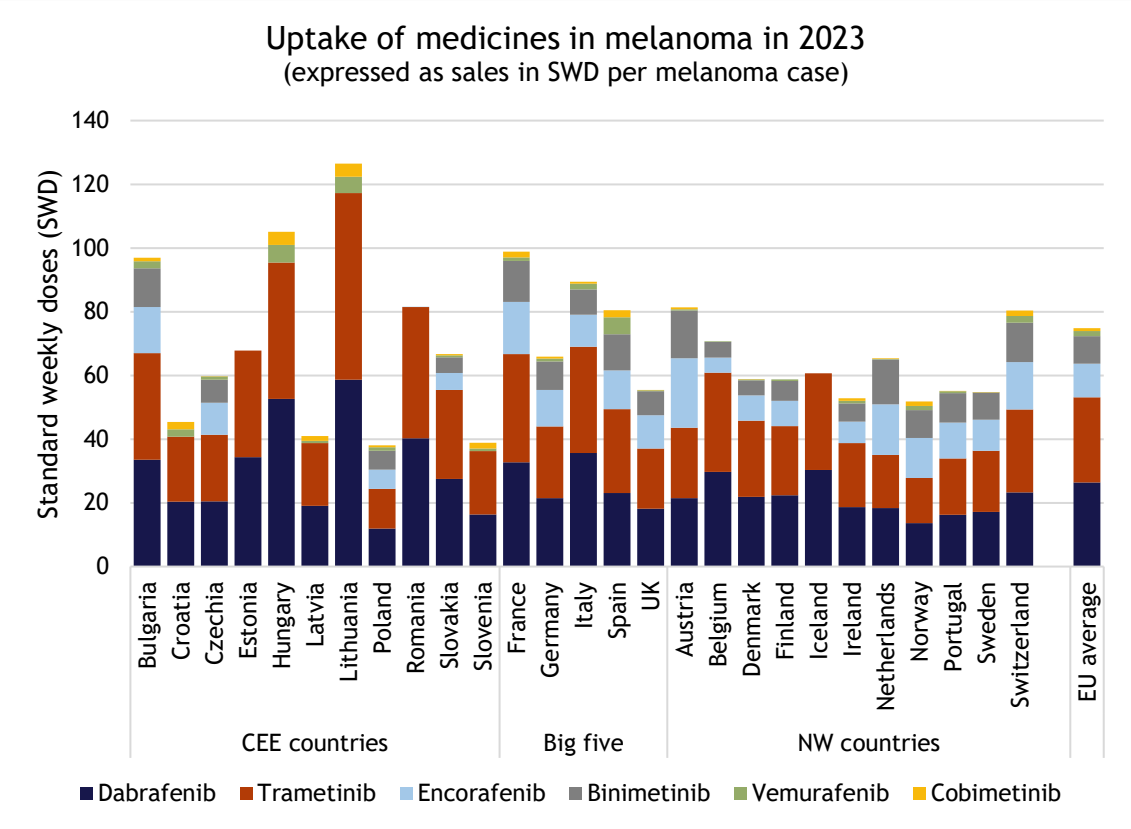


Figure 72: Uptake of medicines in melanoma in 2023 expressed as sales in SWD per melanoma case.

Notes: Melanoma case refers to melanoma deaths in 2022. Encorafenib had no sales in HR, EE, HU, LV, LT, SI, and IS. Binimetinib had no sales in HR, EE, HU, LV, LT, RO, SI, and IS. Vemurafenib had no sales in EE, RO, and IS. Cobimetinib had no sales in EE, RO, BE, FI, and IS.

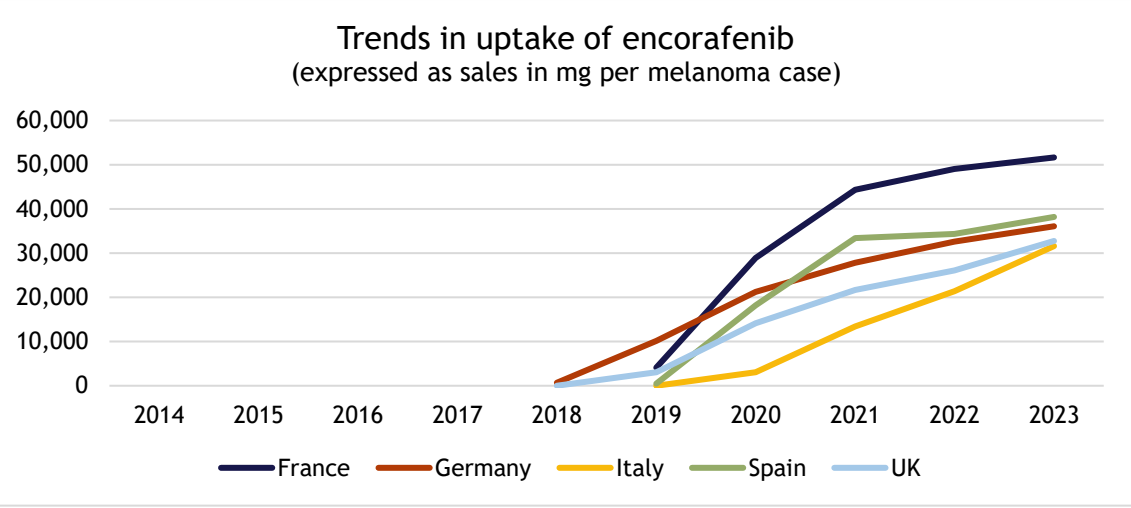


Figure 73: Trends in uptake of encorafenib expressed as sales in mg per melanoma case.

Notes: Melanoma case refers to melanoma deaths in 2022.

4.6.6 Urinary tract cancers

Urinary tract cancers, here defined as bladder cancer (specifically urothelial carcinoma) and kidney cancer (specifically renal cell carcinoma, RCC), have undergone profound changes in treatment standards since 2010. Much of this is owed to the introduction of immune checkpoint

inhibitors (considered in section 4.6.9), initially limited to the metastatic setting but since 2022 also approved for use in early-stages of urothelial carcinoma and RCC. While immune checkpoint inhibitors are used as adjuvant monotherapies in early-stage urothelial carcinoma and RCC, they are often combined with targeted therapies or chemotherapy as first-line treatment in the metastatic setting. RCC has seen the approval of immune checkpoint inhibitors in combination with axitinib in 2019, lenvatinib in 2021, and cabozantinib in 2021. Pazopanib is a somewhat older agent that can also be given as first-line or later-line treatment as monotherapy in RCC. In metastatic urothelial carcinoma, enfortumab vedotin as monotherapy was approved as a second-line treatment in 2022, before becoming standard of care in first-line treatment in combination with pembrolizumab in 2024.

The uptake of newer medicines for urinary tract cancers varies a lot between countries, with a somewhat higher uptake in NW and the Big Five countries compared to the CEE countries; see Figure 74. Nevertheless, the Netherlands has the lowest overall uptake. France has the highest uptake, which is mostly driven by a high uptake of enfortumab vedotin, whereas France's uptake of the medicines in RCC was more similar to other Big Five countries. All CEE countries except Slovenia had no or little uptake of enfortumab vedotin. The trend in the uptake of cabozantinib reveals some divergence between the Big Five countries; see Figure 75. Following the initial approval in metastatic medullary thyroid carcinoma in 2014, there was little uptake. After the approval as second-line monotherapy in metastatic RCC in 2016, the uptake increases (with a one-year delay in Italy) even beyond the approval as first-line monotherapy in metastatic RCC in 2018 (and also second-line therapy for metastatic HCC in the same year). Yet a two-fold difference between France (highest uptake) and Spain (lowest uptake) remains until 2023. The 2021-approval of cabozantinib in combination with nivolumab in first-line metastatic RCC had no major visible impact except in France and Spain.

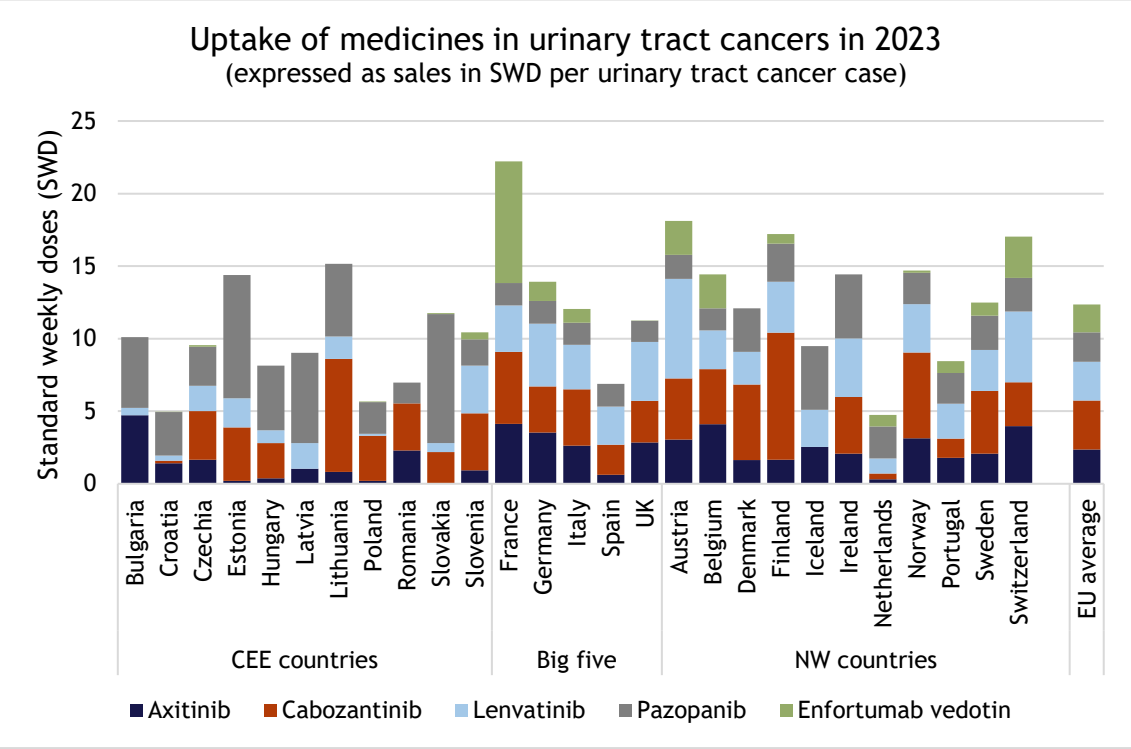


Figure 74: Uptake of medicines in urinary tract cancers in 2023 expressed as sales in SWD per urinary tract cancer case.

Notes: Urinary tract cancer case refers to urinary tract cancer deaths in 2022. Urinary tract cancers include kidney and bladder cancers. Enfortumab vedotin had no sales in BG, EE, HU, LV, LT, RO, ES, DK, IS, and IE. Cabozantinib had no sales in BG, LV, and IS. Lenvatinib had no sales in RO.

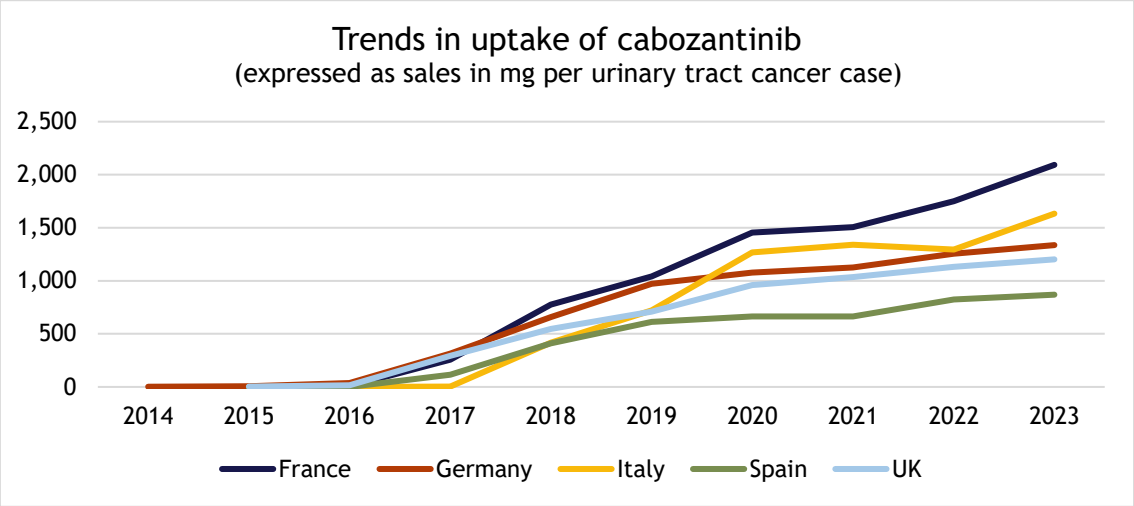


Figure 75: Trends in uptake of cabozantinib expressed as sales in mg per urinary tract cancer case.

Notes: Urinary tract cancer case refers to urinary tract cancer deaths in 2022. Urinary tract cancers include kidney and bladder cancers.

4.6.7 Gynecological cancers

Gynecological cancers include cancers of the cervix, uterus, ovaries, vagina, and vulva. There has been comparatively little progress in the medical treatment of all these cancer types. For ovarian cancer, the first PARP inhibitor for BRCA-mutated cases was olaparib, introduced in 2014, followed by niraparib in 2017 and rucaparib in 2018. Olaparib has since then been approved for several other solid tumors with a BRCA mutation, including breast cancer in 2019, pancreatic cancer in 2020, prostate cancer in 2020 (and in 2022 without BRCA mutation), endometrial cancer in 2024 (without BRCA mutation). For cervical cancer, immune checkpoint inhibitors (considered in section 4.6.9) were introduced in 2022 as first-line and second-line treatments of metastatic disease. For uterine cancer (specifically endometrial cancer), immune checkpoint inhibitors were introduced in 2021 as second-line treatments of metastatic disease (one of which combined with lenvatinib considered in section 4.6.6) but moved to first-line treatment for dMMR/MSI-H cases in 2023.

The uptake pattern of PARP inhibitors shows a clear divide of lower uptake in CEE countries and higher uptake in other countries in 2023; see Figure 76. A notable exception among the CEE countries is Slovenia with the third-highest uptake after Austria and Switzerland, whereas Slovakia and Portugal only had a fifth of their uptake level. Olaparib has the highest uptake in all countries. The Big Five countries are the only countries with a noticeable uptake of rucaparib. The trend in the uptake of olaparib in the Big Five countries was almost identical until 2018, with the exception of the UK which always had lower uptake; see Figure 77. After 2018, uptake was highest in Germany and continued to rise until 2023, likely driven by the continuous expansion of the medicine to new indications.

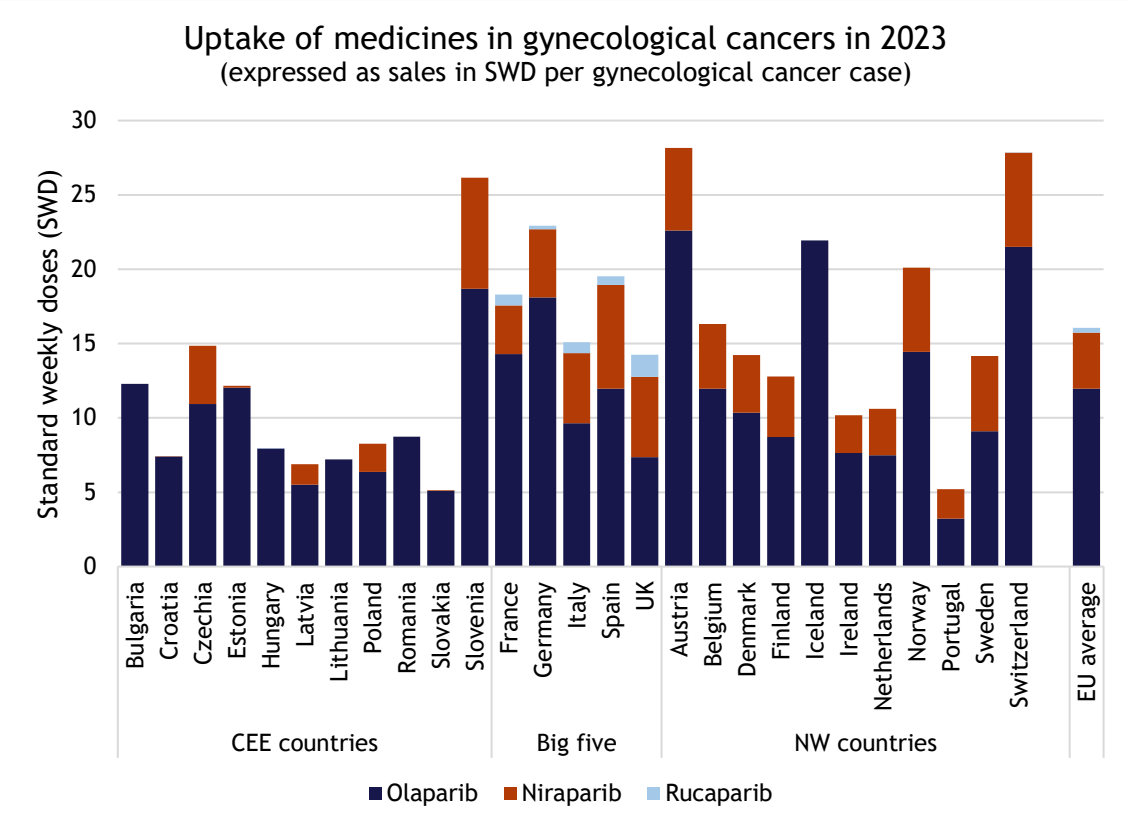


Figure 76: Uptake of medicines in gynecological cancers in 2023 expressed as sales in SWD per gynecological cancer case.

Notes: Gynecological cancer case refers to gynecological cancer deaths in 2022. Gynecological cancers include cancers of the cervix, uterus, ovaries, vagina, and vulva. Niraparib had no sales in BG, HU, LT, RO, and IS. Rucaparib had no sales in BG, EE, HR, CZ, LV, LT, PL, RO, SK, SI, AT, BE, DK, FI, IS, IE, NL, NO, PT, and SE.

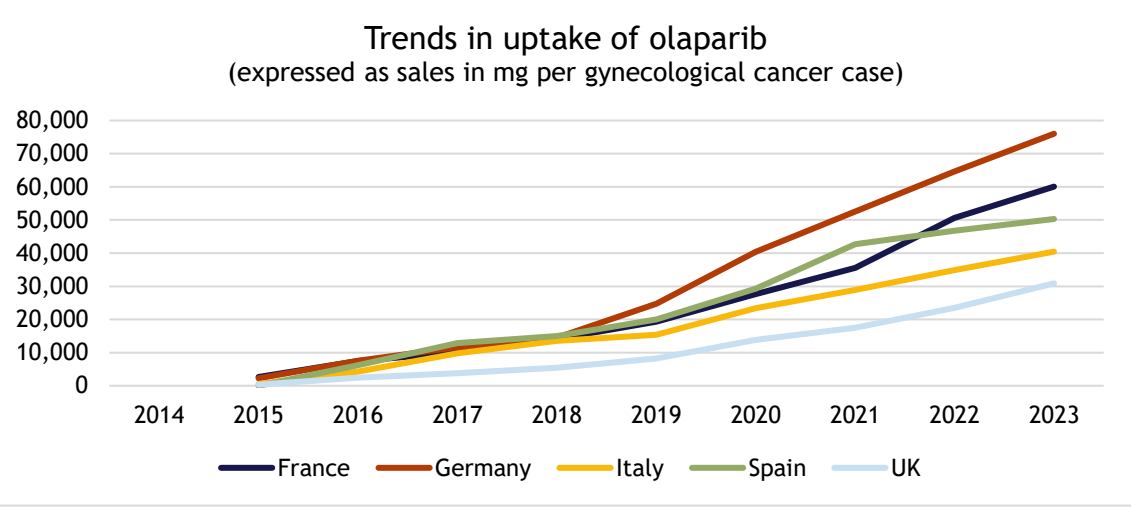


Figure 77: Trends in uptake of olaparib expressed as sales in mg per gynecological cancer case.

Notes: Gynecological cancer case refers to gynecological cancer deaths in 2022. Gynecological cancers include cancers of the cervix, uterus, ovaries, vagina, and vulva.

4.6.8 Tumor-agnostic therapies

Therapies that are not tied to a specific organ site but rather to the molecular features of a tumor irrespective of the site of origin are called tumor-agnostic therapies (559). Larotrectinib in 2019 and entrectinib in 2020 were the first two approved therapies for NTRK-positive solid tumors. Their use is restricted to metastatic tumors when no other treatment options have worked or are available. Compared to larotrectinib, entrectinib has also an approved indication in ROS1-positive NSCLC (considered in section 4.6.3). In 2022, pembrolizumab was the first immune checkpoint inhibitors approved in a tumor-agnostic way for several solid tumors with dMMR/MSI-H status in the second-line or later-line metastatic treatment setting.

Biomarker testing with NGS is typically a prerequisite for the administration of NTRK inhibitors. The low prevalence (<1%) of NTRK in solid tumors renders biomarker testing for that specific mutation a low priority (560). This naturally restricts the use of these medicines in clinical practice. The vast country differences with zero uptake in several countries in 2023, shown in Figure 78, are therefore not surprising. It is also interesting to note that Czechia and Slovenia achieve a higher uptake than all Big Five countries. Trends in the uptake of entrectinib differ vastly between the Big Five countries, with no use at all in France and very little use in Spain until 2023; see Figure 79. Italy had initially a slow uptake but then jump ahead of Germany and UK in 2023.

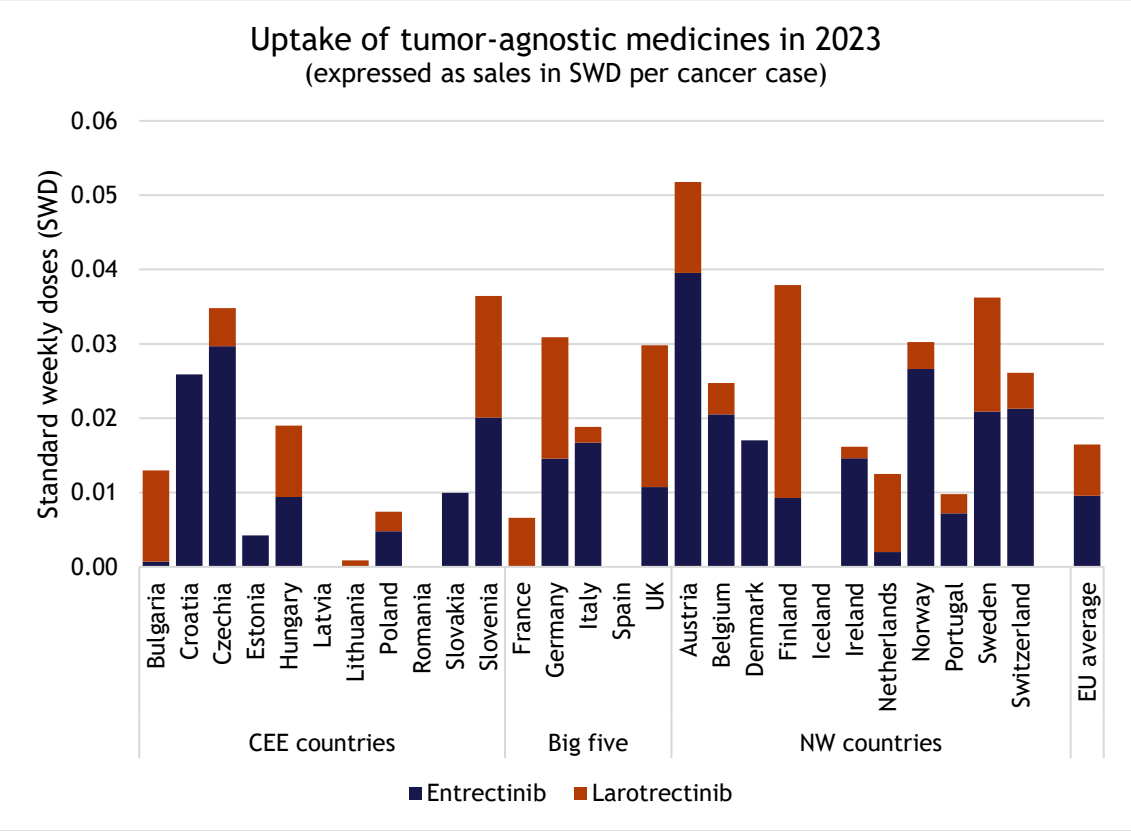


Figure 78: Uptake of tumor-agnostic medicines in 2023 expressed as sales in SWD per cancer case.

Notes: Cancer case refers to total cancer deaths (excl. non-melanoma skin cancer) in 2022. Entrectinib had no sales in LV, LT, RO, FR, and IS. Larotrectinib had no sales in HR, EE, LV, RO, SK, ES, DK, and IS.

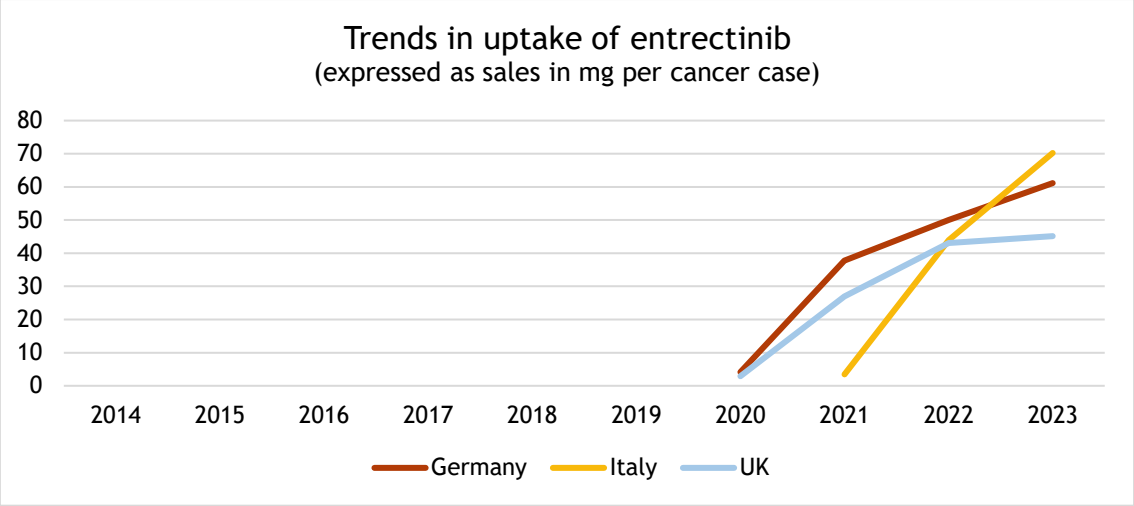


Figure 79: Trends in uptake of entrectinib expressed as sales in mg per cancer case.

Notes: Cancer case refers to total cancer deaths (excl. non-melanoma skin cancer) in 2022. No sales in France and only minor sales (<0.2 mg per cancer case) in Spain in 2023.

4.6.9 Immune checkpoint inhibitors

Immuno-oncology started with the introduction of the CTLA-4 inhibitor ipilimumab in 2011 but took off with the launch of more effective PD-1/PD-L1 inhibitors, nivolumab and pembrolizumab, in 2015. Six additional PD-1/PD-L1 inhibitors have been added to the immuno-oncology arsenal until 2023, along with one LAG-3 inhibitor in 2022 and a second CTLA-4 inhibitor in 2023. The combined use of these immune checkpoint inhibitors stretches across more than a dozen solid tumor types and even some hematologic malignancies. They also saw an expansion of use from the metastatic setting to the early-stage setting in an increasing number of cancer types, starting with melanoma in 2018. Ipilimumab and nivolumab (a PD-1 inhibitor) are also used in combination for “dual immune checkpoint blockade” which has proven more effective (but also more toxic) in certain subgroups of patients.

The uptake of immune checkpoint inhibitors differs almost 8-fold between countries with the lowest uptake, Latvia and Slovakia, and countries with the highest uptake, Belgium, Austria, and France; see Figure 80. A large number of CEE countries has very similar overall uptake levels, on par with the UK, Denmark, Ireland, and Portugal. Finland has an exceptionally low uptake among the NW countries. Most of the uptake in all countries is concentrated in two PD-1 inhibitors, pembrolizumab and nivolumab, which are also the two medicines with the broadest approved use across cancer types and disease stages. Looking at trends in the uptake of these two medicines in Figure 81, it is noticeable that pembrolizumab follows a linear or almost exponential curve, while growth in the use of nivolumab has stalled after 2019. The UK has the lowest uptake for both medicines in all years and Germany and France the highest, resulting in a three-fold difference between the UK and France in 2023. The use of ipilimumab increased in all Big Five countries after 2016-2018, indicating increased use of dual immune checkpoint blockade. The same is true for most other countries, although Croatia, Latvia, Finland, and Slovakia had very limited uptake of ipilimumab.

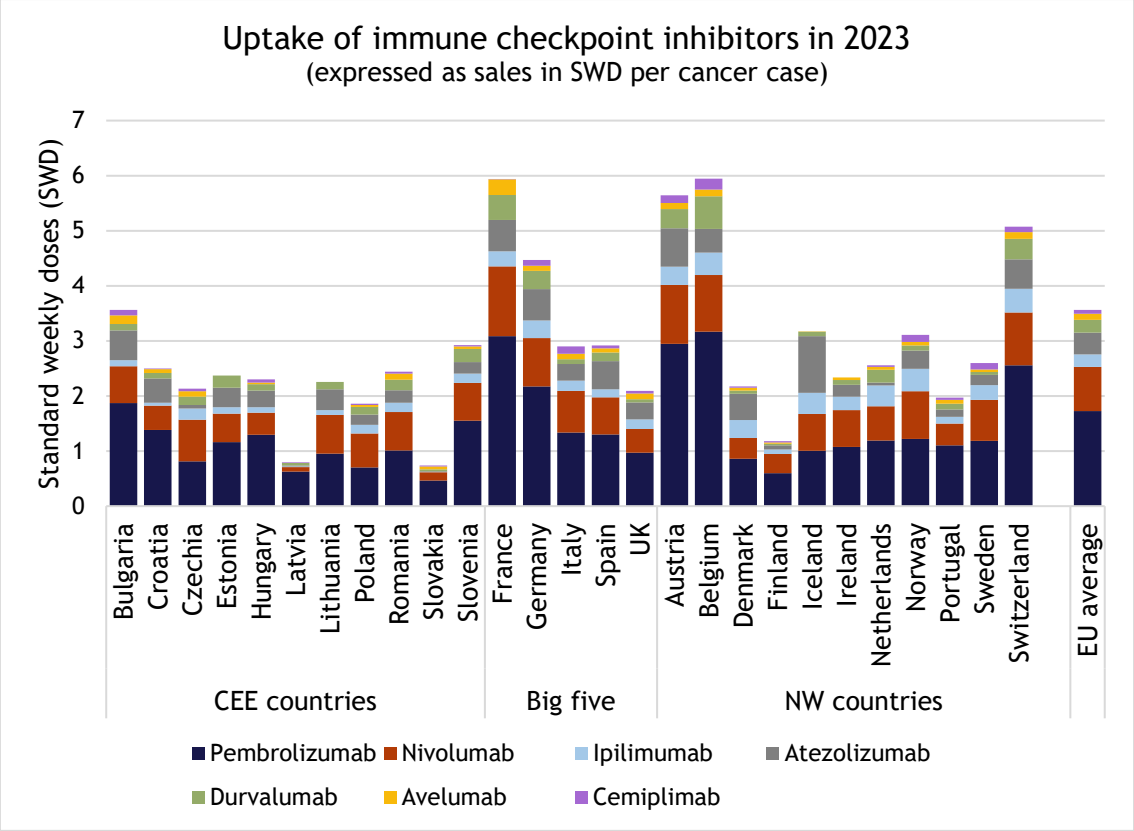


Figure 80: Uptake of immune checkpoint inhibitors in 2023 expressed as sales in SWD per cancer case.

Notes: Cancer case refers to total cancer incidence (excl. non-melanoma skin cancer) in 2022. Avelumab had no sales in EE, LV, and LT. Cemiplimab had no sales in EE, LT, IS, and IE.

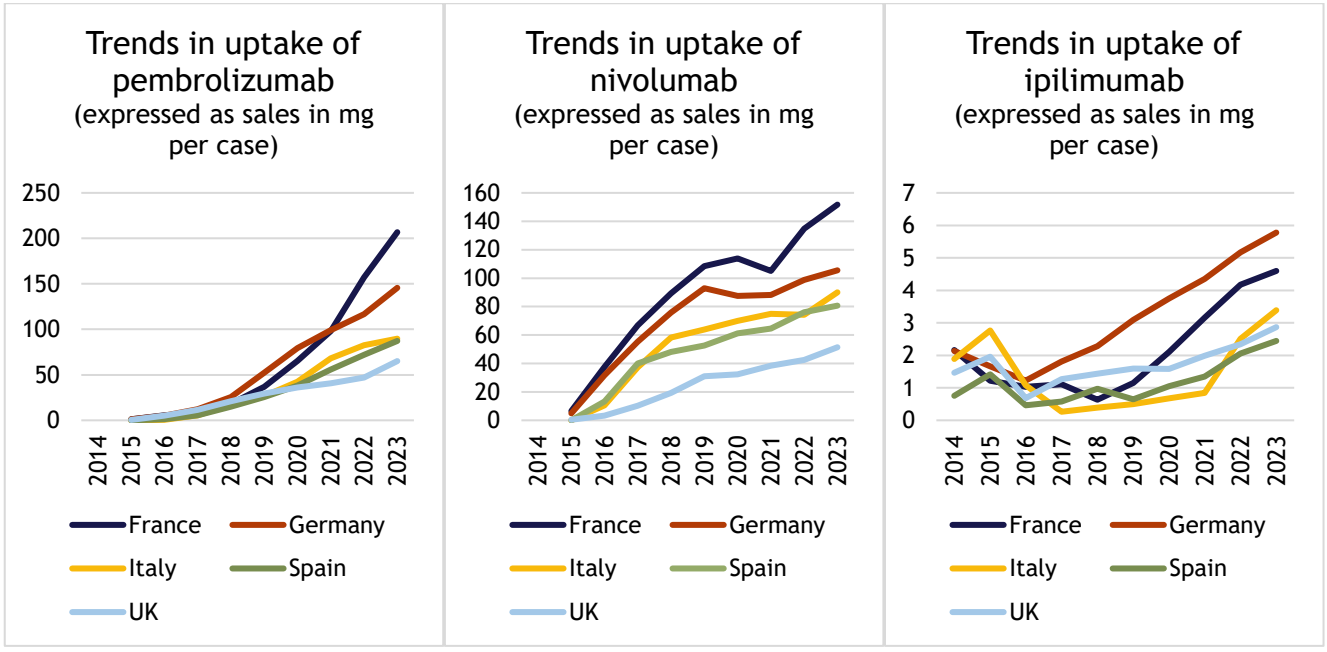


Figure 81: Trends in uptake of pembrolizumab, nivolumab, and ipilimumab expressed as sales in mg per cancer case.

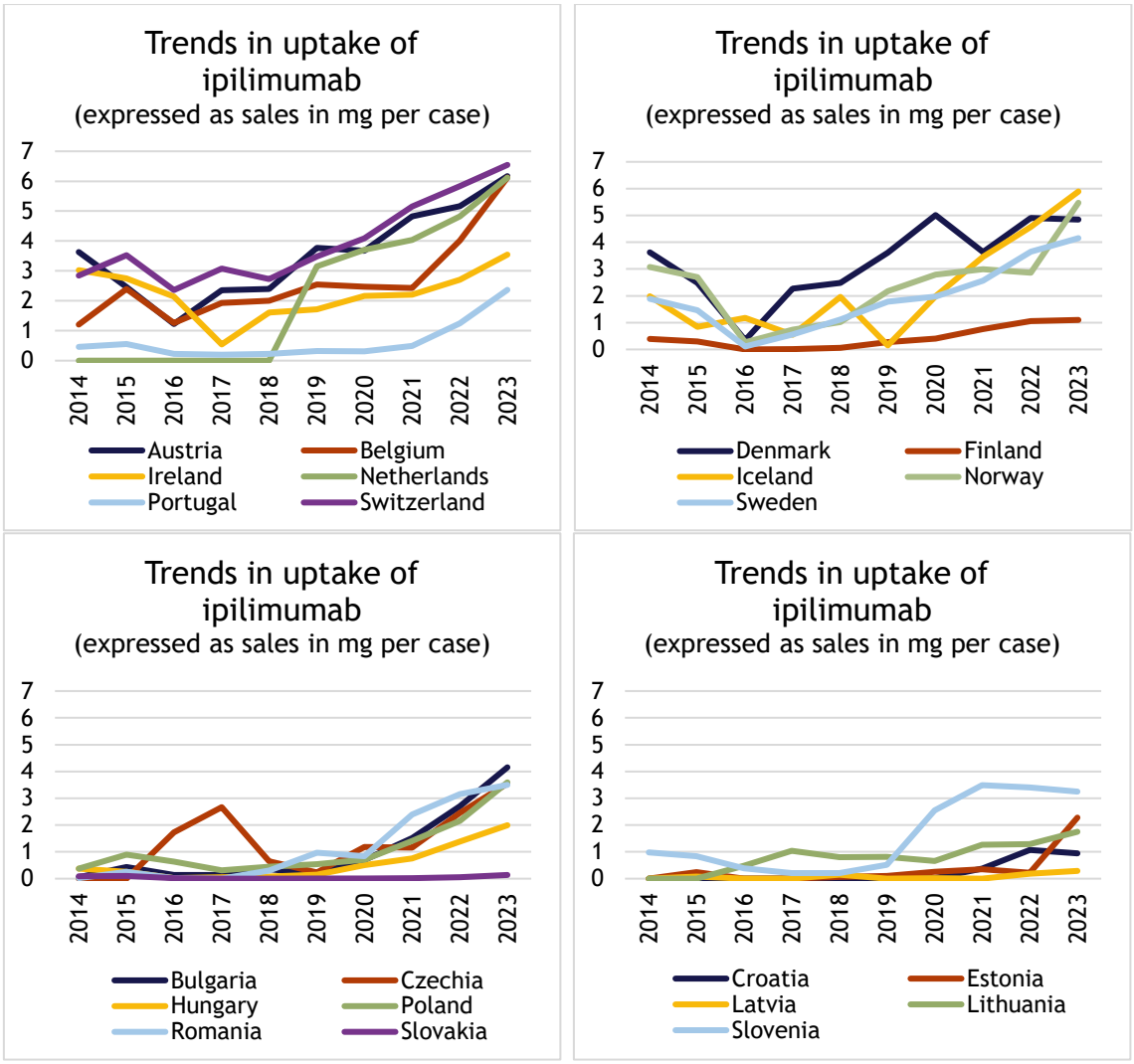


Figure 81 (continued): Trends in uptake of pembrolizumab, nivolumab, and ipilimumab expressed as sales in mg per cancer case.

Notes: Cancer case refers to total cancer incidence (excl. non-melanoma skin cancer) in 2022.

4.6.10 Non-Hodgkin lymphoma

Treatment advances in non-Hodgkin lymphoma have been recorded across many different subtypes of the disease, including bigger ones, such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), and smaller ones, such as mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), high-grade B-cell lymphoma (HGBCL), primary mediastinal large B cell lymphoma (PMBCL), anaplastic large-cell lymphoma (ALCL), cutaneous T-cell lymphoma (CTCL), and Waldenström macroglobulinemia (WM). For instance, brentuximab vedotin was approved for ALCL in 2012 and CTCL in 2017. A major leap in the treatment of MCL was the introduction of ibrutinib in 2014. Ibrutinib was also approved for WM in 2015 and was joined in this indication by zanubrutinib in 2021. Zanubrutinib was also approved for MZL in 2022 and FL in 2023. Obinutuzumab (considered in section 4.6.11) was approved for FL in 2016. Polatuzumab vedotin in 2020, tafasitamab in 2021, glofitamab in 2023 were all approved for DLBCL. In addition, four CAR T-cell therapies (axicabtagene ciloleucel and tisagenlecleucel in 2018, brexucabtagene autoleucel in 2020, lisocabtagene maraleucel in 2022; considered in section 4.6.13) have been approved for various subtypes.

The overall uptake of newer medicines for non-Hodgkin lymphoma looks very different from any other cancer type, with the highest use in the CEE countries highest, followed by the Big Five countries and the NW countries in 2023; see Figure 82. Lithuania has the highest use whereas the five Nordic countries together with the Netherlands and Portugal have the lowest use. The overall picture is entirely overshadowed by ibrutinib, which is also extensively prescribed outside of non-Hodgkin lymphoma for the treatment of CLL. The trend in the uptake of ibrutinib in the Big Five countries started with a one-year delay in Italy and Spain but was then fairly uniform, with Spain taking the lead; see Figure 83. Zanubrutinib had no or only little uptake in all CEE countries, but much higher uptake in the Big Five countries (except France) and the NW countries; see Figure 82. Tafasitamab had only some noticeable uptake in France, Germany, and Austria.

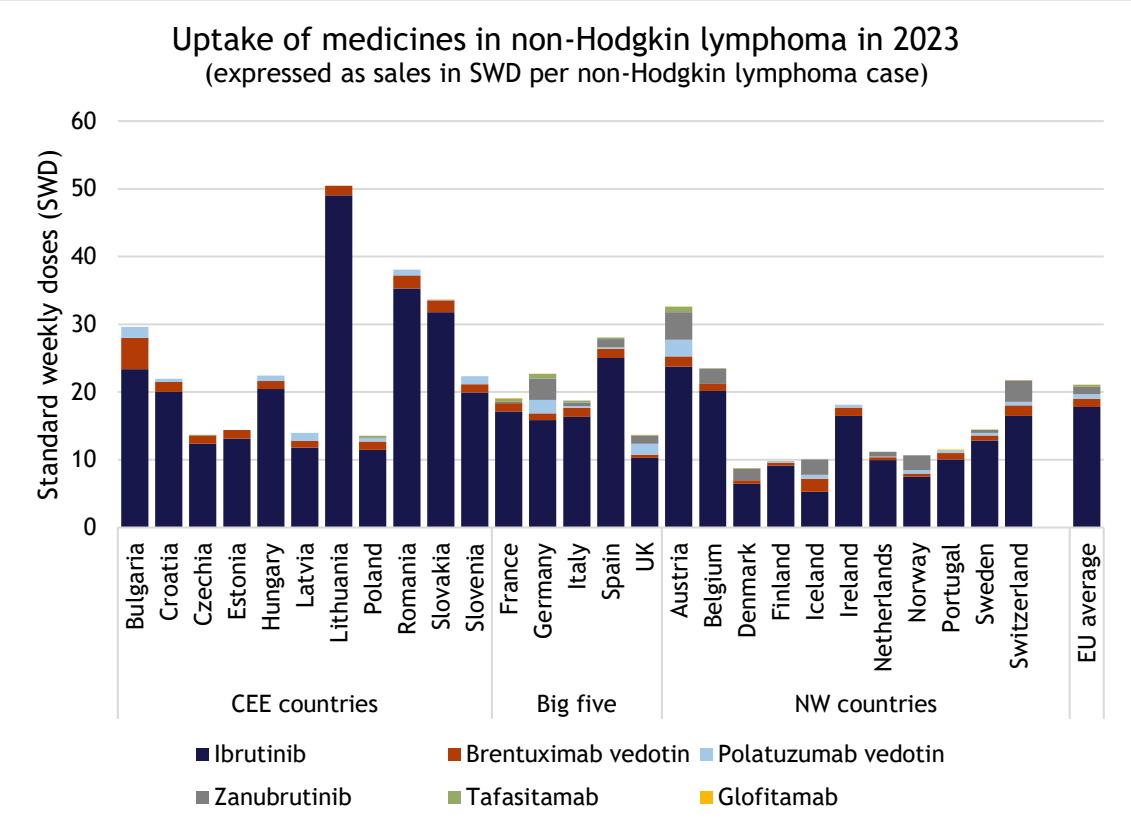


Figure 82: Uptake of non-Hodgkin lymphoma medicines in 2023 expressed as sales in SWD per non-Hodgkin cancer case.

Notes: Non-Hodgkin lymphoma case refers to non-Hodgkin lymphoma incidence in 2022. Polatuzumab vedotin had no sales in CZ, EE, LT, BE, and DK. Zanubrutinib had no sales in BG, HR, EE, HU, LV, LT, RO, SK, SI, IE, and PT. Tafasitamab had no sales in BG, HR, EE, HU, LV, LT, RO, SK, SI, IS, IE, NL, NO, and CH. Glofitamab had no sales in BG, HR, CZ, EE, HU, LV, LT, PL, RO, SI, IT, ES, BE, FI, IS, IE, NL, and NO.

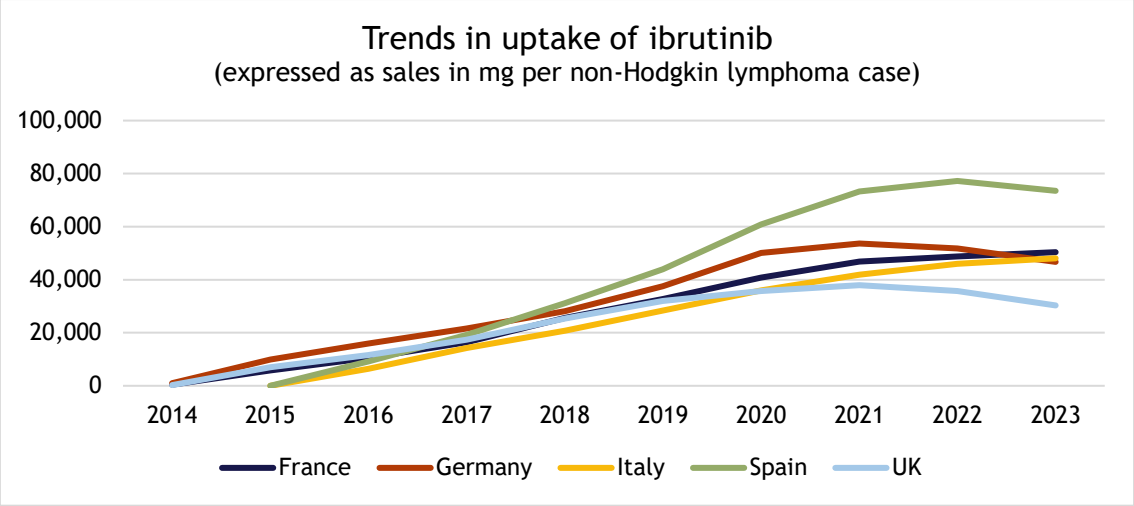


Figure 83: Trends in uptake of ibrutinib expressed as sales in mg per non-Hodgkin lymphoma case.

Notes: Non-Hodgkin lymphoma case refers to non-Hodgkin lymphoma incidence in 2022.

4.6.11 Leukemia

Leukemia has seen the introduction of many new medicines during the last two decades, which target all four major subtypes (acute lymphoblastic leukemia, ALL; acute myeloid leukemia AML; chronic lymphocytic leukemia CLL; chronic myeloid leukemia; CML). The treatment of CLL was revolutionized by the introduction of rituximab in 1998. Further improvements were made by the introduction of obinutuzumab in 2014, ibrutinib (considered in section 4.6.10) in 2014, venetoclax in 2016, and acalabrutinib in 2020. For AML, the chemotherapy backbone treatments cytarabine and daunorubicin received reinforcement by the introduction of the hypomethylating agents azacitidine in 2008 and decitabine in 2012, with the two latter being combined with venetoclax in 2021. Midostaurin was approved in 2017 for a subgroup of AML patients with an FLT3 mutation as first-line treatment, later joined by gilteritinib in 2019 as second-line treatment. For CML, the approval of imatinib in 2001 marked a milestone, followed by second-generation TKIs dasatinib in 2006, nilotinib in 2007, bosutinib and ponatinib 2013, and asciminib in 2022. ALL has seen a somewhat different development with the approval of two CAR T-cell therapies (tisagenlecleucel in 2018 and brexucabtagene autoleucel in 2022; considered in section 4.6.13) in addition to imatinib and dasatinib as well as blinatumomab in 2015 and inotuzumab ozogamicin in 2017.

The uptake of all newer leukemia medicines is fairly uniform among the CEE countries (except Latvia) and on the same level as in the Big Five countries in 2023; see Figure 84. Much larger differences are noticeable among the NW countries, with high uptake in Austria, Ireland, and Switzerland and low uptake in the Netherlands, Norway, and Portugal. Much of these differences are driven by a lower use of acalabrutinib and obinutuzumab. For the AML treatments, midostaurin is being used in every country, yet there is a six-fold difference between Hungary (lowest use) and Austria (highest use). The CML treatment bosutinib had a very similar uptake level in the Big Five countries, but some NW countries had almost double the uptake level. The uptake trend of venetoclax was almost identical in all Big Five countries, with only Germany exhibiting a higher level in 2019-2023; see Figure 85.

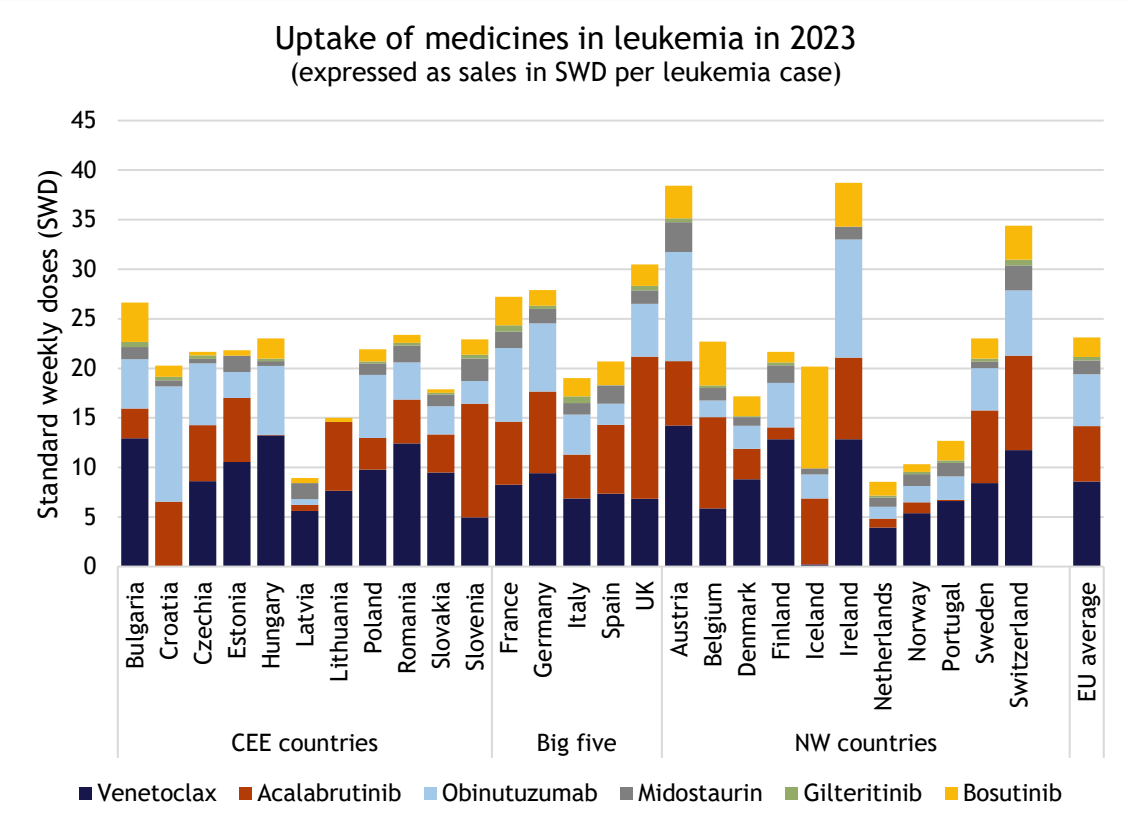


Figure 84: Uptake of leukemia medicines in 2023 expressed as sales in SWD per leukemia case.

Notes: Leukemia case refers to leukemia incidence in 2022. Venetoclax had no sales in HR. Obinutuzumab had no sales in LT. Midostaurin had no sales in LT. Gilteritinib had no sales in EE, LV, LT, IS, and IE.

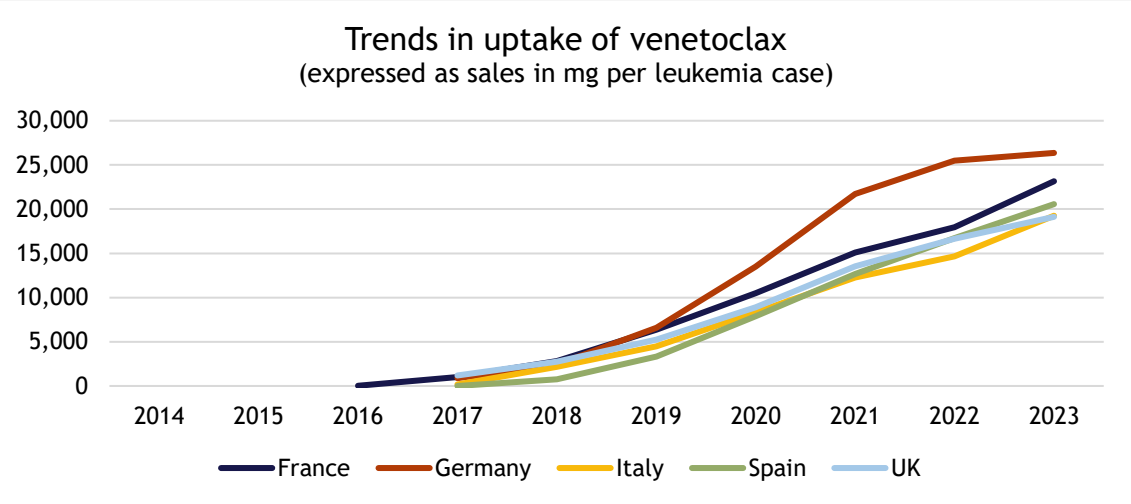


Figure 85: Trends in uptake of venetoclax expressed as sales in mg per leukemia case.

Notes: Leukemia case refers to leukemia incidence in 2022.

4.6.12 Multiple myeloma

Multiple myeloma represents a disease where effective medicines for both disease control and symptom control are key for quality of life and survival. Bortezomib and lenalidomide quickly became backbone treatments after their approvals in 2004 and 2007, respectively. Despite the

low number of patients, there have been continued research efforts, resulting in more than a dozen new medicines since 2010. The biggest breakthrough was daratumumab, approved in 2016, which quickly moved from a third-line or second-line treatment to a first-line treatment for all newly diagnosed patients, irrespective of their ineligibility for autologous stem cell transplant. In later lines of treatment, the approvals of pomalidomide in 2013, carfilzomib in 2015, elotuzumab and ixazomib in 2016, and isatuximab in 2020 are also notable. An additional breakthrough was the approval of two CAR T-cell therapies (idecabtagene vicleucel in 2021 and ciltacabtagene autoleucel in 2022; considered in section 4.6.13).

The overall uptake of newer myeloma medicines is highest in the Big Five countries and in many NW countries in 2023; see Figure 86. Latvia has an exceptionally low uptake but even Croatia, Estonia, Hungary, Lithuania, and Poland have only a fourth of the uptake of the leading countries, France, Austria, and Sweden. Much of these differences are caused by daratumumab, which dwarfs the use of all other medicines. The trend in the uptake of daratumumab in the Big Five countries shows that France and Germany adopted it quicker, with Italy and Spain only catching up with Germany in 2021-2023, whereas France further augmented its uptake level and created a three-fold gap to the UK until 2023; see Figure 87. The uptake level of second-line treatments also differs largely between countries, with, e.g., the highest uptake of isatuximab in the Big Five countries along with Austria and Finland.

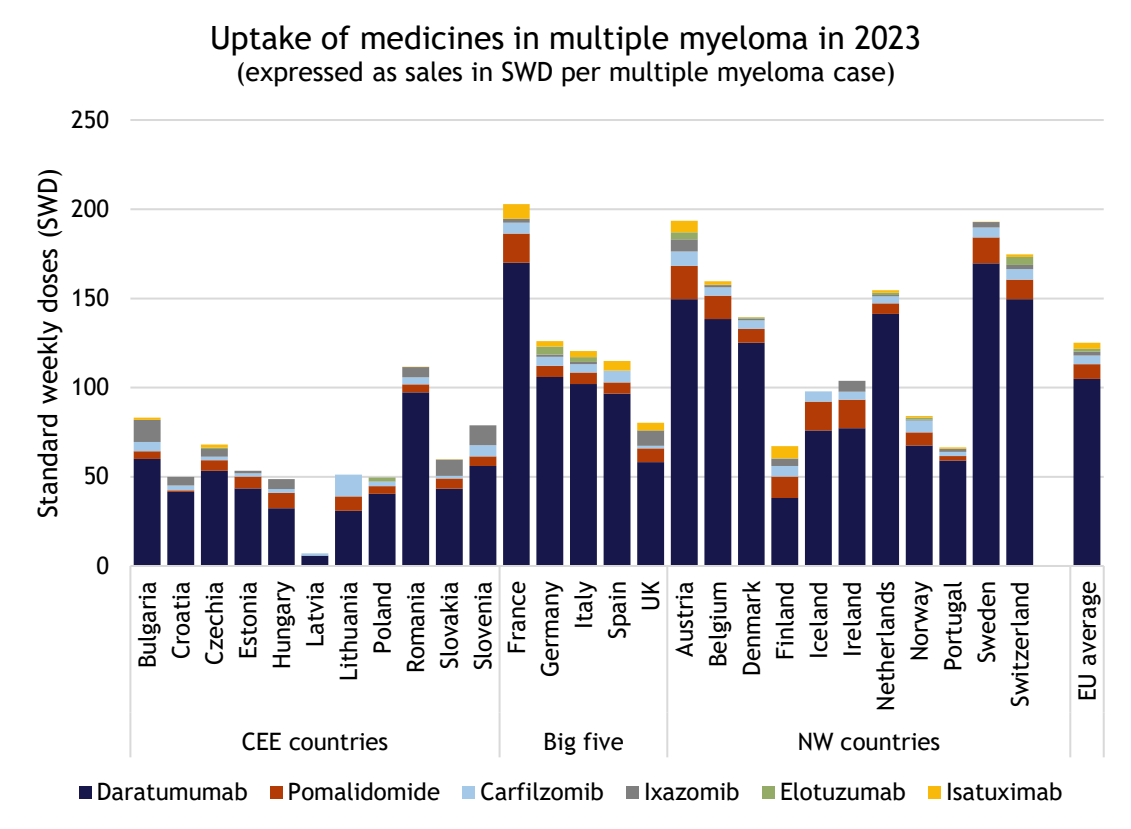


Figure 86: Uptake of multiple myeloma medicines in 2023 expressed as sales in SWD per multiple myeloma case.

Notes: Multiple myeloma case refers to multiple myeloma incidence in 2022. Pomalidomide had no sales in LV. Ixazomib had no sales in LV, LT, ES, and IS. Elotuzumab had no sales in BG, HR, EE, HU, LV, LT, RO, SK, SI, FR, ES, IS, IE, PT, and SE. Isatuximab had no sales in HR, EE, HU, LV, LT, PL, SI, IS, and IE.

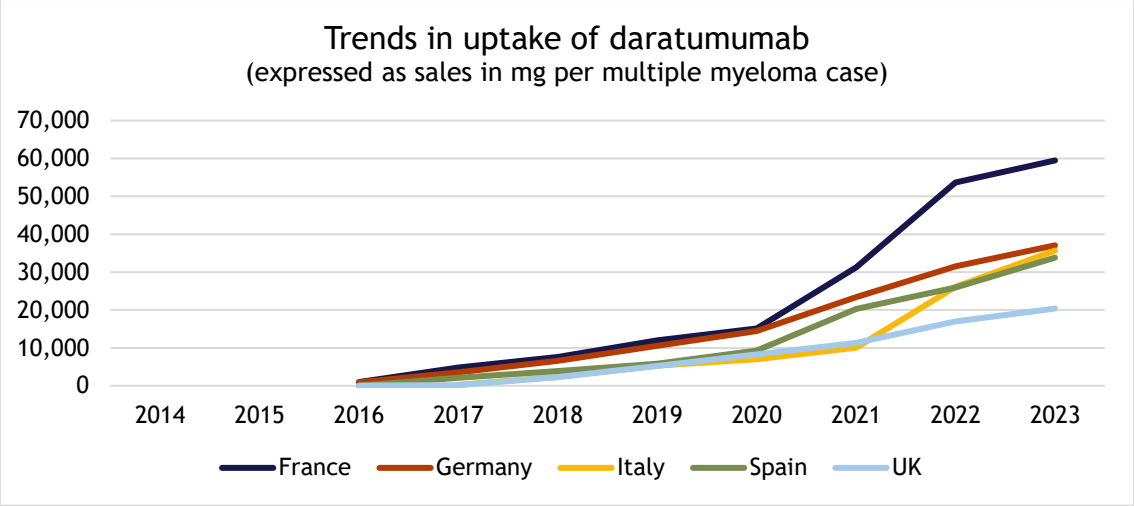


Figure 87: Trends in uptake of daratumumab expressed as sales in mg per multiple myeloma case.

Notes: Multiple myeloma case refers to multiple myeloma incidence in 2022.

4.6.13 CAR T-cell therapy

A total of six CAR T-cell therapies have been approved so far starting with the launch of tisagenlecleucel and axicabtagene ciloleucel in 2018 and followed by brexucabtagene autoleucel in 2020, idecabtagene vicleucel in 2021 and lisocabtagene maraleucel and ciltacabtagene autoleucel in 2022. Their therapeutic area covers several subtypes non-Hodgkin lymphoma (DLBCL, FL, MCL, HGBCL, PMBCL), leukemia (ALL) and multiple myeloma. Initially, they were approved as later-line or last-line treatments, but some of the therapies have moved into earlier lines, yet not first line.

The measurement of sales of CAR T-cell therapies in traditional databases is difficult because, unlike other types of cancer medicines, these therapies are not off-the-shelf products sold through wholesalers. CAR T-cell therapies are personalized one-time treatments administered at specialized hospitals. The uptake in volume terms would be equal to the number of patients treated. IQVIA MIDAS sales data do not contain such information. They only contain information on the sales in value terms for a limited number of countries. Total sales of the six therapies in 2023 in all European countries with data amounted to EUR 1.18 billion, of which EUR 1.11 billion came from the Big Five countries and Poland. In the latter six countries, the sales per cancer case in 2023 differed considerably; see Figure 88. The uptake per cancer case in France was around eight times higher than in Poland. Part of this large difference might relate to the late adoption of CAR T-cell therapy in Poland, with reimbursement for the first therapy for ALL starting in September 2021 and two therapies for DLBCL starting in May 2022 (561).

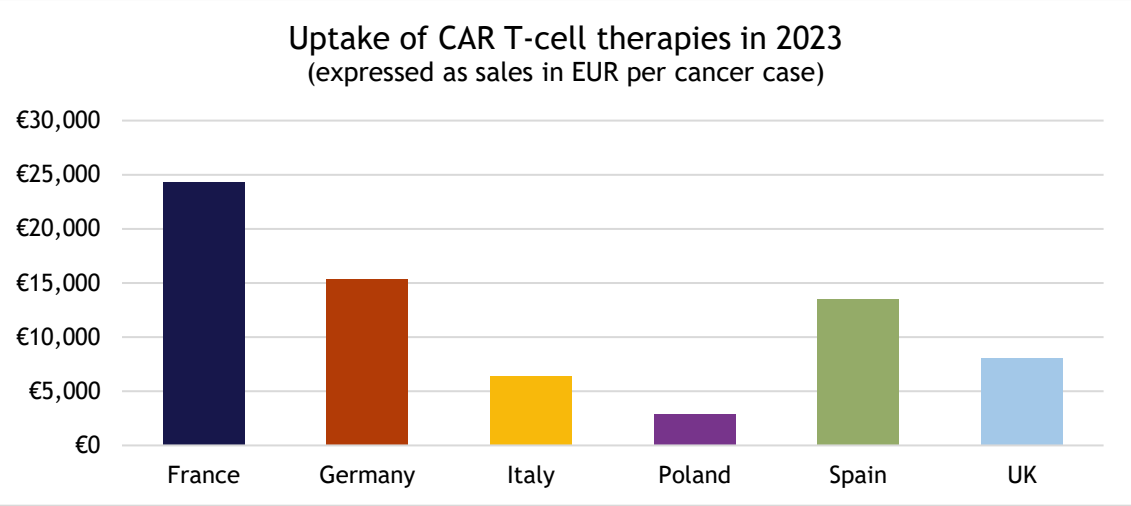


Figure 88: Uptake of CAR T-cell therapies in 2023 expressed as sales in EUR per cancer case.

Notes: Cancer case refers to the combined cancer deaths of non-Hodgkin lymphoma, leukemia, and multiple myeloma in 2022. No reliable data available for other countries.

4.6.14 Uptake of medicines without market exclusivity

After the loss of market exclusivity of new medicines, generics and biosimilars can enter the market. They offer the potential for cost savings over the original product, while providing the same (or nearly the same) benefit. Nevertheless, they differ in terms of development, production, and the scale of price reductions they typically achieve. Generics contain the same active ingredients of small-molecule medicines, which are chemically synthesized and have relatively simple structures. They are comparatively easy to manufacture, and because they are equivalent to the original product, they require less extensive clinical testing and can enter the market at a lower cost (562). Biosimilars are highly similar, but not identical, to original biologic medicines, which are large, complex molecules derived from living cells. Due to the inherent complexity of biologics, biosimilars take longer to develop, are more difficult to manufacture, need more extensive preclinical and clinical testing to demonstrate their similarity in terms of efficacy, safety, and immunogenicity, and require more rigorous post-marketing surveillance (pharmacovigilance) (562). As fewer companies manufacture biosimilars than generics due to the higher barriers to entering the market, there is less price competition.

Examples of the impact of the introduction of biosimilars and generics are shown below. They illustrate how the uptake in value and volume terms has changed for a selected number of previous “blockbuster medicines”.

Impact of biosimilars

The patents for rituximab, trastuzumab, and bevacizumab in Europe expired in 2013, 2014, and 2022, respectively (563). The EMA approved the first biosimilars for trastuzumab and rituximab in 2017 and the first biosimilar for bevacizumab in 2018 (564). As shown in Figure 89, sales in value were mostly saturated and peaked right before the entry of competitors, upon which they started to fall. For rituximab (which also has considerable use outside of oncology in the treatment of rheumatoid arthritis, multiple sclerosis, and some rare diseases), annual sales decreased by 41% in 2023 compared to 2016 (adjusted for inflation) along with a 48% drop in the implicit price (EUR per mg; based on list prices). For trastuzumab, the decline in annual sales was 49% in 2023 compared to 2016, along with a 43% drop in the implicit price. In contrast,

annual sales of bevacizumab fell only by 14% from 2021 to 2023, yet the decline in sales had already started after 2016, and the implicit price dropped by 32% from 2021 to 2023.

The trend in the volume uptake in Figure 89 shows different patterns across medicines. For rituximab, annual volume sales remained mostly stable after 2016 (+13% versus 2023). For trastuzumab, annual volume sales initially continued to grow after 2016 but then started to decline after 2020 (part of which is probably caused by the introduction of a fixed-dose combination with pertuzumab not considered here). The annual volume sales of bevacizumab were stable until 2020 but then increased sharply until 2023 (+45% versus 2020), which might relate to the approval of new indications of combinations (especially with atezolizumab) during this period.

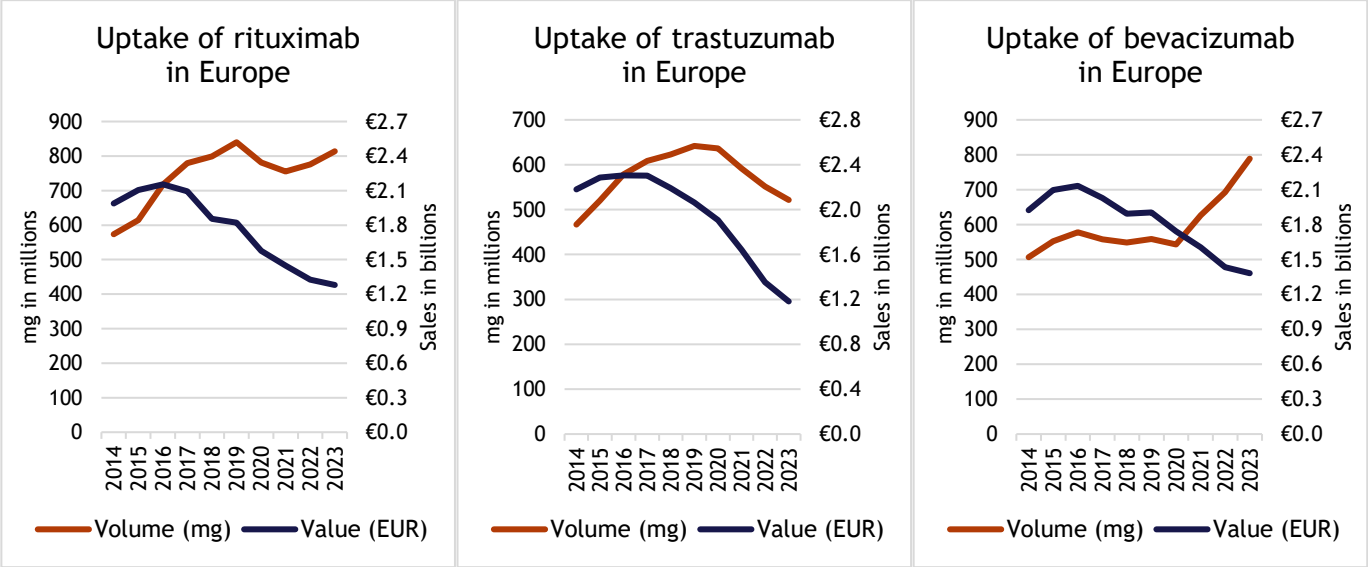


Figure 89: Trends in uptake of rituximab, trastuzumab, and bevacizumab in Europe in 2014-2023 (sales in constant prices and exchange rates).

Notes: No data were included for EE, EL, and LU. Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Frumtök for Iceland, and Signum Life Science for Denmark. Sales data is presented in constant 2023 prices and exchange rates. For trastuzumab, part of the decline in sales in both value and volume after 2020 is caused by the introduction of a fixed-dose combination of trastuzumab and pertuzumab (EMA approval in December 2020) which was not included here.

Impact of generics

Changes in the sales in value for products with competition from generics are generally expected to be greater than for products with competition from biosimilars, due to the higher research and development costs as well as manufacturing costs associated with biosimilars that lead to fewer producers (565). Imatinib, which lost its patent in Europe in 2016 and had its first generic already approved in 2012 (566, 567), saw an 83% decline in annual sales from 2015 to 2023 (adjusted for inflation), along with a 84% drop in the implicit price (EUR per mg; based on list prices); see Figure 90. By comparison, lenalidomide, which lost its patent in Europe in 2022 and saw several generics approved that same year (566, 567), experienced a 65% reduction in annual sales from 2021 to 2023, with the implicit price dropping 71%.

The trend in the volume uptake of the two medicines shows two different patterns. For imatinib, there seems to have been a saturation of the market already before the entry of generics, resulting in no major volume changes after 2015. In contrast, the volume uptake of lenalidomide grew constantly before 2022 and continued its upward trend seemingly unaffected

by the price drop until 2023. The lower price might have allowed a greater share of the eligible patient population to be treated.

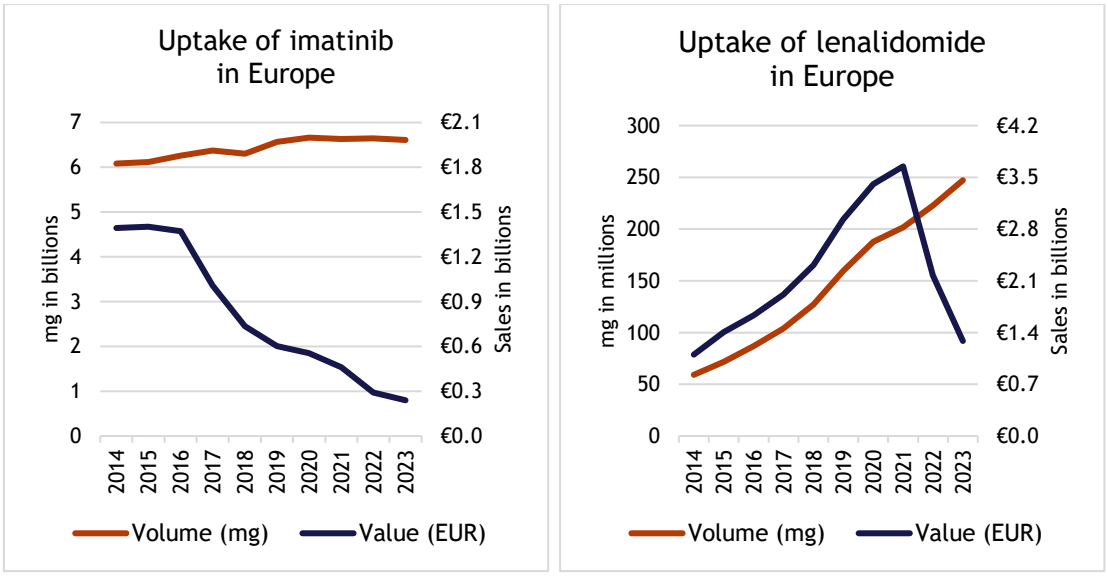


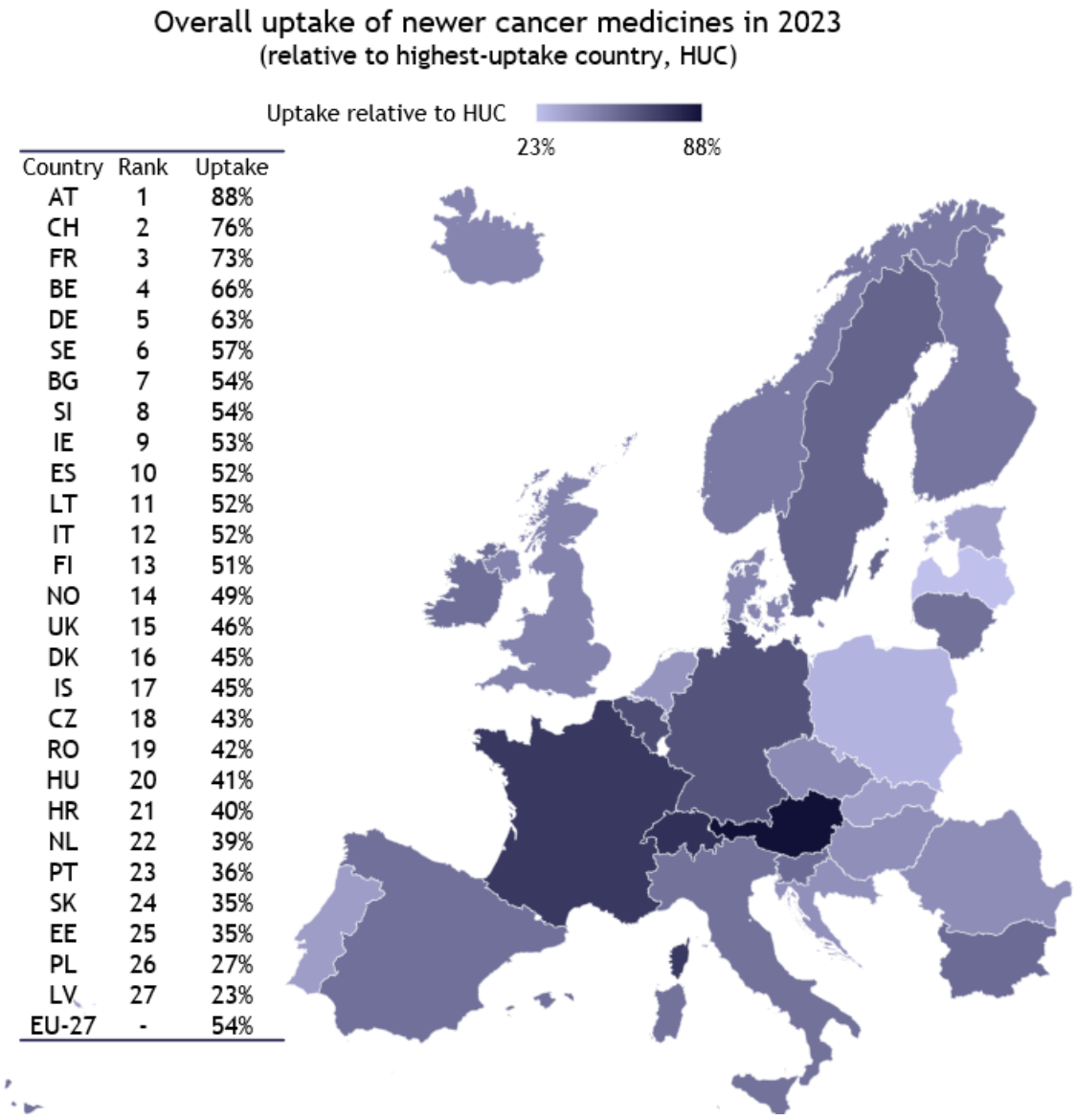
Figure 90: Trends in uptake of imatinib and lenalidomide in Europe in 2014-2023 (sales in constant prices and exchange rates).

Notes: No data were included for EE, EL, and LU. Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Frumtök for Iceland, and Signum Life Science for Denmark. Sales data is presented in constant 2023 prices and exchange rates.

4.6.15 Overall uptake of new medicines

A country ranking of the overall uptake of newer cancer medicines in 2023 is illustrated in Figure 91. This ranking aggregates information from the analysis of uptake across twelve cancer types and medicine classes (sections 4.6.1 to 4.6.12), with each country's uptake level expressed relative to the country with the highest uptake level. As stated before, it should be stressed that the focus here is on access to newer medicines (with EMA approval in 2010 or later). A low uptake of newer medicines does not mean that patients do not receive any medicines, as they instead might receive older, potentially less effective medicines.

Austria leads in the uptake of newer cancer medicines (with an 88% score out of the theoretical maximum of 100%), followed by Switzerland (76%) and France (73%). The treatment of patients from other countries (medical tourism) might play some role in the high numbers for Austria. At the opposite end of the ranking are Slovakia and Estonia (both 35%), Poland (27%), and Latvia (23%). In general, Northern and Western European countries tend to rank higher, whereas countries in Central and Eastern Europe rank lower; see Figure 91. Yet there are notable exceptions, with Bulgaria ranking seventh (54%), Slovenia eighth (54%), and Lithuania eleventh (52%). As noted before, the high ranking of Bulgaria may partly stem from inaccurate data on medicine sales and/or considerable parallel export, with the latter also having attracted the attention of Bulgarian authorities in 2023/2024 (568, 569). Other notable exceptions are the Netherlands ranking in 22nd place (39%) and Portugal in 23rd place (36%). For the Netherlands, the comparatively low ranking might relate to the introduction of the "lock" system in 2015 and a stricter focus on only accepting overall survival as a valid endpoint in HTA (570-572). Among the Big Five countries, the UK ranks lowest in 15th place (46%), reflecting a pattern already documented in the previous Comparator Report and despite the existence of the Cancer Drugs Fund since 2011. A full overview can be found in Appendix C.



Country	Rank	Uptake
AT	1	88%
CH	2	76%
FR	3	73%
BE	4	66%
DE	5	63%
SE	6	57%
BG	7	54%
SI	8	54%
IE	9	53%
ES	10	52%
LT	11	52%
IT	12	52%
FI	13	51%
NO	14	49%
UK	15	46%
DK	16	45%
IS	17	45%
CZ	18	43%
RO	19	42%
HU	20	41%
HR	21	40%
NL	22	39%
PT	23	36%
SK	24	35%
EE	25	35%
PL	26	27%
LV	27	23%
EU-27	-	54%

Figure 91: Overall uptake of newer cancer medicines in Europe in 2023.

Notes: The rank is based on an index that considers the uptake of newer cancer medicines across 12 categories (breast cancer, prostate cancer, lung cancer, gastrointestinal cancers, melanoma, urinary tract cancers, gynecological cancers, tumor-agnostic therapies, non-Hodgkin lymphoma, leukemia, and multiple myeloma), each expressed as sales in SWD per cancer case. For each category, the uptake in a country compared to the country with the highest uptake (highest-uptake country, HUC) was calculated. The arithmetic mean of the relative uptake across all 12 categories was calculated to determine the overall ranking of a country. The theoretical maximum uptake is 100% if a country had the highest uptake across all 12 categories, while the theoretical minimum is 0% if a country had no uptake across all 12 categories. The maximum uptake was 88% (Austria) and the minimum uptake was 23% (Latvia).

Regional disparities in the level of uptake

Great regional disparities exist in the uptake of cancer medicines across Europe. The three German-speaking countries, France, and Belgium are on top. The five Nordic countries together with Ireland and UK are in the middle of the ranking, with a notable negative outlier being the Netherlands in this region. In Southern Europe, Italy and Spain perform rather similar, whereas there is a distinct gap down to Portugal. In Southeastern Europe, Bulgaria and Slovenia perform well and much better than their neighbors Romania and Croatia, respectively. The four Visegrád countries are rather similar with a below-average uptake level. In the Baltic countries, Lithuania greatly outperforms Estonia and Latvia.

Similar regional disparities are visible for most cancer types and medicine classes considered, with lower uptake in CEE countries than in the Big Five countries and the NW countries. For example, there was an 8-fold difference in uptake of immune checkpoint inhibitors between the two lowest-uptake countries, Slovakia and Latvia, and the two highest-uptake countries, Belgium and France. For medicines in prostate cancer and multiple myeloma, the gap between the CEE countries and other countries was also pronounced (5-fold difference for prostate cancer and 7-fold difference for multiple myeloma between the top-two and bottom-two countries). Other cancer types with a clear regional divide and lower uptake in CEE countries are gynecological cancers (only PARP inhibitors) and lung cancer (only targeted therapies), both of which are cases where biomarker testing is required for the administration of the medicines. This is consistent with the lower availability and uptake of biomarker testing in CEE countries found in sections 4.3 and 4.4.

There are some examples of similar or even higher uptake of newer cancer medicines in CEE countries compared to other countries in 2023. Rather similar uptake levels were observed for breast cancer (except the two ADCs), gastrointestinal cancers (yet with big differences between individual countries), melanoma, and urinary tract cancers (except targeted therapy for bladder cancer). For non-Hodgkin lymphoma and leukemia, the uptake levels in the CEE countries were on par with the Big Five countries and higher than the NW countries.

Medicines that have been approved by the EMA more recently since 2020 (such as the two ADCs in breast cancer, the RET and KRAS inhibitors in lung cancer, enfortumab vedotin in urinary tract cancers, zanubrutinib, tafasitamab, and glofitamab in non-Hodgkin lymphoma, isatuximab in multiple myeloma) mostly only had noticeable use in 2023 in the Big Five countries (and more so in France and Germany) and certain NW countries, mostly in Austria and Switzerland. The higher uptake aligns with faster reimbursement decisions (and probably the use of the early access program in France) in these countries, as shown in section 4.2.

Changes in the level of uptake between 2018 and 2023

A comparison of the results of the previous Comparator Report for the year 2018 and the new results for 2023 in this report indicates some convergence in uptake levels across countries; see Table 19. Overall, there was a 5.3-fold difference in uptake levels between the two countries with the highest and lowest uptake in 2018, which declined to a 3.3-fold difference in 2023. Immune checkpoint inhibitors are an example where uptake has become much more similar across countries, converging from a 49-fold difference in 2018 to an 8-fold difference in 2023. Breast cancer is another example of great convergence from a 9-fold to a 2.5-fold difference, mostly driven by a more equal uptake of CDK4/6 inhibitors, making breast cancer the disease group with the least unequal uptake. By contrast, uptake has become more unequal across countries in lung cancer and multiple myeloma. In the case of multiple myeloma this is driven by large differences in uptake of daratumumab, whereas in the case of lung cancer the differences might be influenced by varying levels of biomarker testing combined with the large influx of new medicines.

Table 19: Comparison of country differences in uptake of new cancer medicines in 2018 and 2023

	X-fold difference in uptake between top 2 and bottom 2 countries		Coefficient of variation	
	2018	2023	2018	2023
Breast cancer	9.0	2.5	43%	28%
Prostate cancer	6.5	4.9	50%	43%
Lung cancer	6.0	9.9	40%	49%
Gastrointestinal cancers	12.4	9.7	51%	64%
Melanoma	4.3	3.0	40%	31%
Urinary tract cancers	no data	3.9	no data	37%
Gynecological cancers	13.1	5.4	55%	47%
Tumor-agnostic therapies	no data	∞	no data	77%
Immune checkpoint inhibitors	48.7	7.7	71%	49%
Non-Hodgkin lymphoma	no data	4.8	no data	49%
Leukemia	no data	4.4	no data	35%
Multiple myeloma	5.7	7.1	47%	51%
Overall	5.3	3.3	40%	30%

Notes: The samples of "new" medicines analyzed in 2018 and 2023 are different. In 2018, gastrointestinal cancers only included medicines used for colorectal cancer. Czechia and Estonia are not part of the sample in 2018. A higher %-value of the coefficient of variation indicates greater differences between countries. ∞ = could not be calculated as the bottom 2 countries had zero uptake. Uptake for multiple myeloma and immune checkpoint inhibitors was standardized differently in 2018 (per cancer-specific mortality and per 100,000 inhabitants, respectively) than in 2023. Source: recalculations of results for 2018 from the 2019 Comparator Report and own calculations of sales for 2023.

Disparities in the speed of uptake in the Big Five countries

For most individually analyzed medicines in the Big Five countries, the uptake curve begins to rise slowly and increases year by year after EMA approval. This shape of the uptake curve is consistent with a gradual integration of medicines into treatment protocols and routine practice across treatment facilities in a country. For most medicines, it also reflects the extension of the medicine's usage to new indications over time.

Notable differences exist between the countries. France and Germany consistently lead in uptake across medicines following EMA approval, indicating a favorable environment of funding, technology and capabilities (e.g., biomarker testing), quick integration in clinical guidelines, and well-trained healthcare professionals. Italy and Spain tend to exhibit a pattern of more moderate uptake, characterized by an initial delay in adoption, followed by convergence to France and Germany. The UK tends to lag behind the other countries, both in the initial years after EMA approval and later on, often resulting in considerable and persistent gaps in uptake levels.

4.6.16 Explanations for differences in uptake

There are many potential explanations for the country differences in the uptake of newer cancer medicines. A key step before cancer medicines can reach patients is reimbursement by the public healthcare payer(s). The left graph in Figure 92 shows the association between the uptake level of newer cancer medicines in 2023 (from Figure 91) and countries' reimbursement status defined as the proportion of EMA-approved cancer medicines with reimbursement at the beginning of 2024 (from Figure 54). The upward-sloping trend line indicates a positive correlation between reimbursement status and uptake. Countries that reimburse a higher proportion of medicines tend to have a higher uptake of cancer medicines, while countries with a lower proportion of reimbursement medicines have a lower uptake. Nevertheless, the association is not very strong (R^2 of 0.39). The same is true for the right graph in Figure 92, which shows the association between the uptake level of newer cancer medicines in 2023 (from

Figure 91) and countries' average reimbursement time for EMA-approved cancer medicines at the beginning of 2024 (from Figure 55). While the downward-sloping trend line suggests that countries with faster reimbursement times tend to have a higher uptake of cancer medicines, the association is weak (R^2 of 0.22), as some countries with similar reimbursement times display widely different uptake levels.[34]

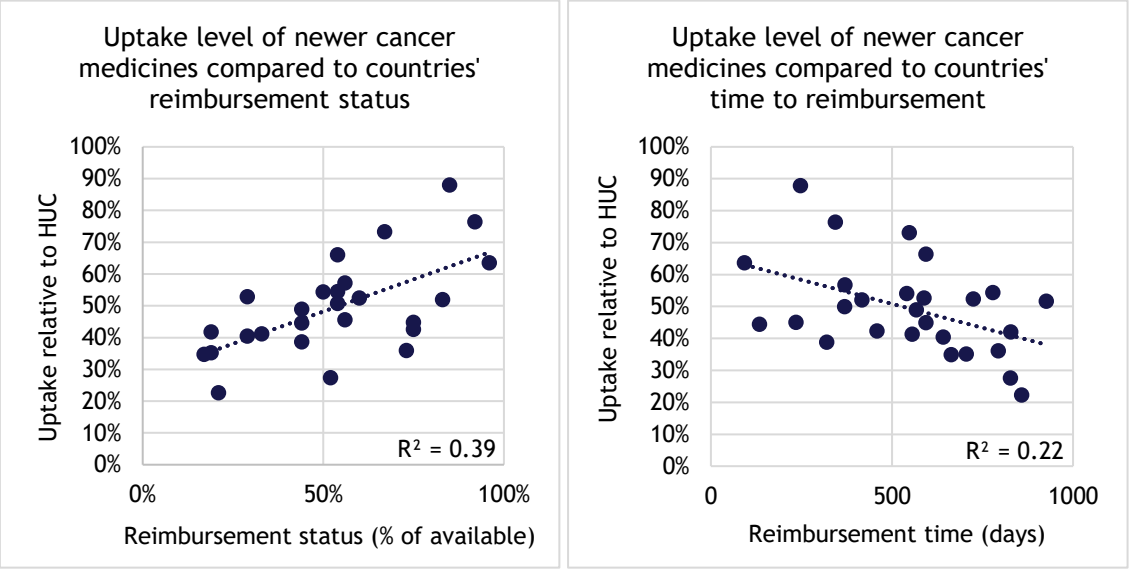


Figure 92: Correlation between countries' volume uptake of newer cancer medicines and reimbursement status (left graph) and time to get reimbursement (right graph).

Notes: See Figure 91 (volume uptake) and Figure 54 and Figure 55 (reimbursement).

While reimbursement of the cost of a cancer medicine is a necessary step for patient access in Europe's publicly funded healthcare systems, it is clearly not a sufficient step. Despite reimbursement, new medicines often take time – months or years – until they are used on a broad scale, as clinical routines need to be adapted, and medical staff needs to be trained on how to use the new medicines, and testing infrastructure needs to be established or extended and integrated into the care process. A better predictor of the level of uptake in volume is the money spent on cancer medicines. Figure 93 shows that this association is strong (R^2 of 0.74 for spending per capita, R^2 of 0.80 for spending per new cancer case, R^2 of 0.72 for spending per cancer death). The upward-sloping trend lines suggest that countries with higher spending on (any) cancer medicines (based on list prices) in 2023 also achieved a higher uptake of newer cancer medicines in 2023. For instance, Austria spent the most on cancer medicines (€195 per capita, €39,017 per cancer case, €79,989 per cancer death) and achieved the highest uptake level (88%), whereas Latvia spent the least (€31 per capita, €5,256 per cancer case, €10,028 per cancer death) and had the lowest uptake level (23%).

[34] A potential reason for the rather weak association between the uptake level of cancer medicines and the reimbursement status and the reimbursement time might be the way the two latter variables are measured. The EFPIA Patients WAIT Indicator Survey measures reimbursement on the product level, whereas the uptake of a medicine is influenced by the number of reimbursed indications.

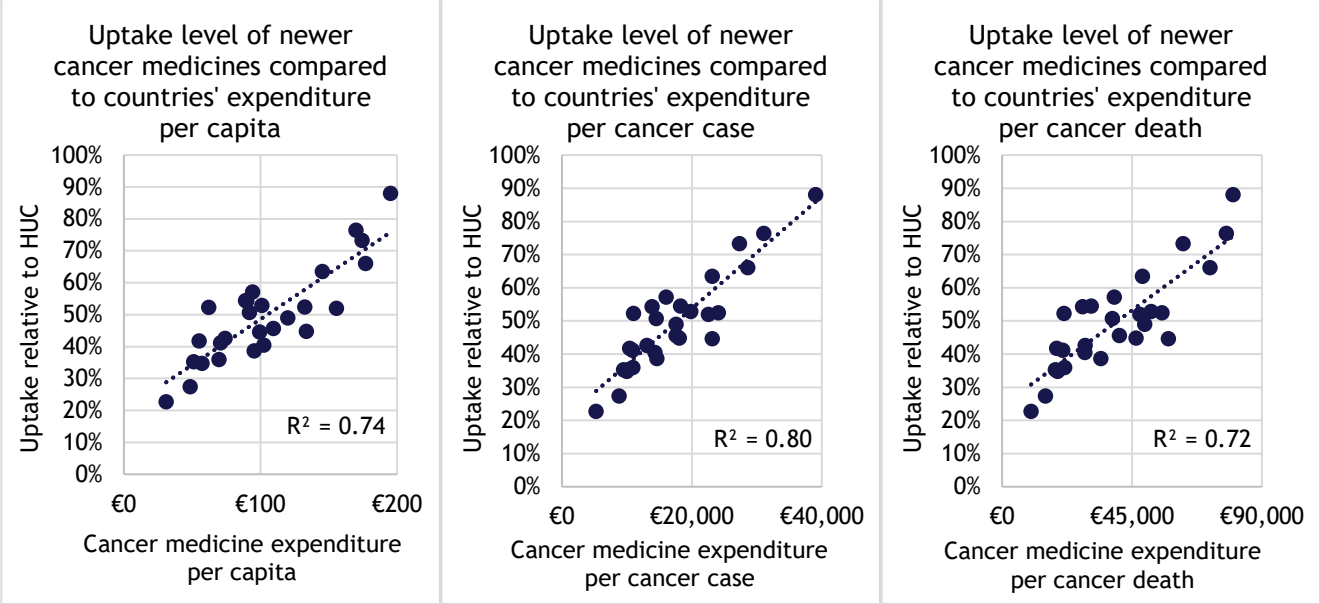


Figure 93: Correlation between countries' volume uptake of newer cancer medicines and expenditure on cancer medicines per capita (left graph) and per cancer case (right graph).

Notes: See Figure 91 (volume uptake) and Figure 59 and Figure 60 (expenditure). Cancer medicine expenditure are based on list prices, leading to an overestimation of the true expenditure.

A previous analysis of a multi-stakeholder group in Europe summarized challenges in patient access to new cancer medicines after reimbursement under the umbrella term of "health system readiness" (573). The following three barriers were identified to affect the extent stakeholders integrate a new therapy in clinical practice:

- **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 negative pressure on prescription and use.
- **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.
- **Suboptimal healthcare infrastructure:** Suboptimal organization of healthcare systems in general and oncology care pathways in particular may lead to problems in absorbing and using a new medicine in the most optimal way.

Another analysis of treatment patterns with cancer medicines in patients with advanced-stage NSCLC across 12 European countries in 2014-2020 also revealed several common reasons for suboptimal treatment (517). The analysis was based on a comparison of estimated treatment patterns in a country and recommended treatment patterns according to clinical practice guidelines from ESMO. Regarding the reasons for suboptimal treatment, a distinction was made between barriers that stood in the way of getting treated in the first place and barriers that made it difficult to receive newer, recommended medicines; see Table 20.

Table 20: Reasons for suboptimal treatment in advanced-stage NSCLC in Europe

Patients remain untreated because of …	Patients receive older, less effective treatment options because of …
Poor functional status at time of diagnosis Some patients are too sick to receive treatment with medicines, because they are diagnosed with very advanced disease. This can be compounded by the presence of co-morbidities and old age.	**Delays in reimbursement of new medicines** The local reimbursement of new medicines and new indications may often take 2-3 years, following EMA approval, during which older treatment options need to be prescribed.
Delays in time from diagnosis to treatment For cancers that progress quickly (such as lung cancer), several months of delay in the diagnostic process means that patients who would be fit enough to receive medicines at the time of diagnosis are no longer fit enough by the time of treatment initiation.	**Limited public budgets for medicines** Delays in reimbursement of new medicines might partly be caused by limited public budget. Yet even newly reimbursed medicines might not be available for all eligible patients due to constrained hospital budgets.
Narrow treatment eligibility criteria Local clinical guidelines or reimbursement guidelines might exclude certain patient subgroups from receiving treatment as compared to ESMO guidelines.	**Limited resources for biomarker testing** Comprehensive biomarker testing, which is a prerequisite for administering all targeted therapies in NSCLC, might not be performed because of practical reasons (lack of high-quality tumor tissue), limited testing capacity (both infrastructure and human resources), and financial reasons (no reimbursement of tests).
Treatment refusal by patients Some patients might not want to get treated, e.g., because of stigma among current/former smokers, fear of treatment and side effects, and low trust in healthcare professionals and services.	**Limited continuing medical education** The rapidly evolving treatment paradigm in some cancer types poses a challenge for the fast adoption of new treatment practices. University hospitals and leading cancer centers are often early adopters whereas healthcare professionals at other hospitals are typically slower.

Source: (517).

5. Policy implications

Key messages of this chapter

Sustaining Europe's momentum in the fight against cancer will be crucial in the coming years.

The EU has played a pivotal role in cancer control for over 40 years, culminating in the launch of the Europe's Beating Cancer Plan (EBCP) in 2021. Together with the EU Cancer Mission, the EBCP has driven research, policy action, and funding to improve cancer prevention, detection, diagnosis and treatment, and survivorship. However, with most EBCP actions concluding by 2025 and shifting EU priorities inside and outside healthcare, sustaining momentum is crucial. Key challenges include ensuring long-term funding, integrating new regulations on health technology assessment and medical devices, and using new opportunities such as the European Health Data Space.

Persistent inequalities in access to new cancer medicines and structural barriers require urgent action.

Despite 20 years of research highlighting disparities as part of the Comparator Reports, inequalities in access to new cancer medicines across Europe remain significant. While Central and Eastern European countries have made progress and started to catch up with Northern and Western European countries, reimbursement delays and budgetary constraints continue to limit timely access to effective treatments. Delayed adoption of new, effective medicines results in opportunity costs of a potential loss of life years for patients and society. Structural barriers include varying HTA criteria, subnational approval processes, limited diagnostic infrastructure, infrequent updates of clinical guidelines, and inadequate continuing medical education. The lack of joint/parallel reimbursement for companion diagnostics and medicines in many countries further complicates the adoption of precision medicine.

European-level policy efforts hold the potential to mitigate access disparities.

The new HTA Regulation (HTAR) and the proposed revision of the EU pharmaceutical legislation aim to accelerate reimbursement decisions and incentivize companies to market medicines in all EU countries. However, successful implementation of the HTAR depends on national acceptance of joint clinical assessments. In addition, the 2022-commitment by EFPIA member companies to file for pricing and reimbursement in all EU countries no later than two years from EMA approval could further reduce disparities. It remains to be seen to what extent all these efforts will indeed move the needle in the right direction, without unintended consequences of making Europe less attractive for pharmaceutical investment on a global scale.

The rising expenditure for cancer medicines calls for consistent use of HTA and optimization strategies of medicines use.

While new medicines contribute to reducing the disease burden, the rising expenditure on cancer medicines also poses affordability challenges. More stringent and consistent application of HTA plays a crucial role in evaluating cost-effectiveness and budget impact, ensuring that investments provide meaningful patient benefits while maintaining financial sustainability. In addition, optimizing cancer medicine usage can improve efficient use of resources without compromising patient outcomes. Approaches such as biomarker-driven patient stratification, optimizing treatment sequencing, minimizing overtreatment at end-of-life, reducing medicine spillage, and promoting adoption of generics and biosimilars can significantly reduce expenditure. The price drops of five blockbuster cancer medicines following patent loss and competition from generics and biosimilars have saved €21.9 billion in 2016-2023 (based on list prices). This creates financial headroom for new medicines without limiting patient access to existing treatments.

Understanding the value of new cancer medicines requires a comprehensive perspective to capture societal benefits beyond direct healthcare outcomes.

Discussions on the value of cancer medicines often focus on either clinical efficacy or price, but a more holistic perspective is needed. New cancer medicines not only improve survival but also contribute to societal and economic benefits, such as increased possibility to return to work for patients and reduced caregiver burden. Frameworks like the ISPOR Value Flower emphasize the broader impact of treatments, highlighting the need for HTA to adopt a societal perspective. Greater use of (performance-based) managed entry agreements (MEAs) and multi-speed HTA processes could help prioritize access to medicines with proven clinical benefit while ensuring follow-up for those with uncertain value.

The lack of systematic real-world data on treatment patterns and survival statistics from cancer registries hampers value demonstration of new technologies and evidence-based policymaking.

Comprehensive real-world data (RWD) on cancer treatment patterns are largely unavailable in most European countries, limiting the ability to assess and optimize care delivery. Few countries systematically track how cancer patients are treated across hospitals or regions on a national level. Additionally, up-to-date survival data is lacking – currently only 15 out of 31 European countries publish five-year survival rates for all cancers combined and by cancer type, 3 countries only publish survival rates by type but not combined, and 13 countries provide no survival data at all. RWD – as opposed to past predictions – indicate that cancer deaths in Europe have stopped to increase and started to stabilize at around 1.3-1.4 million annually since 2008, which signifies a turnaround in the battle against cancer. Strengthening data collection and accessibility is crucial for assessing treatment effectiveness, demonstrating value of new technologies, and guiding evidence-based policy decisions to improve patient outcomes. Without up-to-date survival data, policymakers are navigating efforts in cancer care without a clear compass.

Europe should reinforce its role as a global leader in cancer research and innovation

Europe's position in cancer research is declining, with its share of global clinical trial starts in oncology dropping from 41% in 2008 to 21% in 2023, while China's share has surged and surpassed Europe. Unequal access to clinical trials across European countries further exacerbates disparities in earliest possible patient access to new treatments. To maintain competitiveness, Europe should invest in research, safeguard intellectual property rights, and create a supportive policy environment. Strategic EU initiatives, including the "Draghi Report" and the Competitiveness Compass, recognize innovation in life sciences as a driver of economic growth and healthcare advancement, underscoring the need for urgent action to lift Europe to new heights.

The EU's role in the fight against cancer goes back 40 years. In 1985, the European Council endorsed the "Europe Against Cancer" program which ran from 1987 until 2000, with the aim to reduce cancer mortality in Europe by 15% until 2000 (574). Although this aim was not quite reached, the initiative made inroads in the common fight against cancer (575). In 2009, the European Commission reinforced its efforts to support member states in the fight against cancer by setting up the European Partnership for Action Against Cancer (EPAAC) for the period 2009-2013 (576). This initiative brought together different stakeholders in a joint response to prevent and control cancer, with the aim of all member states adopting integrated national cancer plans and the target to reduce cancer incidence by 15% until 2020 (577).

The biggest milestone for cancer in the EU came in 2021 with the launch of the Europe's Beating Cancer Plan (EBCP) (2). Backed by €4 billion funding, it established a comprehensive approach to address cancer from prevention, early detection, diagnosis and treatment to survivorship. This plan aligns with the EU Cancer Mission as part of the Horizon Europe research and innovation program for the years 2021–2027, reinforcing the Commission's commitment to addressing cancer as a major public health challenge (30). The Cancer Mission has set the ambitious overall aim – to be jointly achieved with the EBCP – of improving the lives of more than 3 million people by 2030,[35] through prevention and cure and for those affected by cancer including their families, to live longer and better, by accelerating cancer prevention and control programs and creating more equitable access to these programs.

The EBCP and the EU Cancer Mission have set in motion a plethora of European research initiatives and policy initiatives. As of September 2024, there were 137 cancer-related projects funded by Horizon Europe and EU4Health, of which 11 projects in the area of "Understanding", 26 in the area of "Prevention", 14 in the area of "Screening & early detection", 71 in the area

[35] The 3-million aim was based on an analysis of avoidable deaths by IARC.

of “Diagnosis & treatment”, and 15 in the area of “Quality of life” (578). In addition, the Council of the EU revised and extended its recommendation to member states on screening programs in December 2022 and issued a new recommendation on vaccine-preventable cancers in June 2024 (34, 35). In 2025, the publication of the fifth edition of the European Code Against Cancer is expected, which should encourage both member states and individuals to take action to prevent cancer and detect it early (579). Nevertheless, the implementation of recommendations and changes in care delivery rest with the member states, as the EU can only complement national policies and promote research but not organize and deliver health services and medical care or manage the allocation of resources according to Article 168 of the Treaty on the Functioning of the European Union. The efforts by the European Commission to create the ECIR in February 2022 (32), and the development of Country Cancer Profiles for all EU countries through the OECD in 2023 and 2025 (36), are supposed to stimulate action by member states.

With the strong focus on cancer at the EU level since 2021, there is a risk that this development abates and is superseded by other priorities in the coming years. Table 21 lists developments and initiatives that might represent tailwinds and headwinds in the coming years, with a focus on cancer medicines and molecular diagnostics.

Table 21: Selected EU-level policy developments related to cancer

Area	Description
Europe’s Beating Cancer Plan	Most of the 42 planned actions have a timeline that ends in 2025 (2). The only four exceptions are HPV vaccination (2030), an Occupational Safety and Health Strategic Framework (2027), Preventing cancers caused by infections (2030), Projects focusing on cancer diagnostics and treatment using high-performance computing and AI and new digital platforms (2027).
EU Cancer Mission	The Horizon Europe research and innovation program runs out in 2027 (30). It is yet unclear whether earmarked funding for cancer (one of five missions) will be available in the next program.
Health Technology Assessment Regulation (HTAR) (2021/2282)	The HTAR applies for cancer medicines from January 12, 2025 (580). This entails a joint (cross-country) clinical assessment of the effectiveness of new medicines. It is supposed to reduce duplication of efforts for both national HTA authorities and industry, facilitate business predictability, and ensure the long-term sustainability of EU HTA cooperation.
Reform of the EU pharmaceutical legislation	The European Commission proposed a revision of the EU pharmaceutical legislation in April 2023, where two main objectives are to reduce country differences in the availability of new medicines and to shorten the time from EMA approval until patient access while continuing to offer an attractive and innovation-friendly environment for research, development, and production of medicines in Europe (581).
Medical Devices Regulation (MDR) 2017/745 and In Vitro Diagnostic Medical Devices Regulation (IVDR) 2017/746	These regulations came into force in 2021 and 2022, respectively, to unify legislation for medical devices and ensure safety and innovation (582). The timelines for the gradual roll-out have been extended in 2024 and now run until 2029 (269). In addition, the European Parliament passed a resolution in October 2024 urging the Commission to address the most pressing challenges and bottlenecks in the implementation of the legislative frameworks and to propose the systematic revision of all relevant articles of these regulations, accompanied by an impact assessment (583).
Clinical Trials Regulation (536/2014)	This regulation became applicable on January 31, 2022 (584). It harmonizes the processes for assessment and supervision of clinical trials throughout the EU. It enables sponsors to submit one online application via the Clinical Trials Information System (CTIS) platform

Area	Description
	for approval to run a clinical trial in several European countries, making it easier to carry out such multinational trials and creating a favorable environment for conducting clinical research on a large scale.
European Health Data Space (EHDS) Regulation (2025/327)	This regulation entered into force on March 26, 2025 (and starting to apply two years later and with gradual enforcement of different provisions until 2035) to create a single market for electronic health record systems and facilitate the cross-border use of both primary data for individuals and secondary data for research, innovation, policymaking, and regulatory activities (585-587).
EU Competitiveness Compass	In January 2025, the European Commission outlined a broad strategy to enhance the EU's competitiveness, including the promise of a Life Sciences Strategy to be revealed later in 2025 (588).
Focus on other health areas	Inspired by the EBCP, the new EU Commissioner for Health announced in January 2025 that he intends to launch a European Cardiovascular Health Plan (589). There have also been calls to establish an EU Coordination Plan for the Brain (mental health and neurological diseases) led by the European Brain Council (590).
Focus on non-health areas	With the ongoing war in Ukraine and political developments in the United States, European NATO countries are ramping up public spending on defense. Unless taxes are raised, the NATO chief suggested for governments to reallocate money from welfare to defense in January 2025 (591).

The following sub-sections provide a synthesis and reflections on the analysis in chapters 2-4. While section 5.1 discusses ways to bridge inequalities in access to new medicines across Europe, section 5.2 focuses on the value of new medicines and their contribution to improving patient outcomes. Section 5.3 describes data needs for better decision-making in cancer care. Section 5.4 discusses Europe's role in a global context of conducting research and stimulating innovation.

5.1 Bridging inequalities in access to new medicines

The very first Comparator Report documented profound inequalities in the uptake of new cancer medicines across European countries in the early 2000s. Some 20 years later, this report shows that the situation is not very different, indicating rather persistent inequalities. Nevertheless, this report also finds some positive tendencies of a convergent pattern in recent years, with low-uptake countries in Central and Eastern Europe catching up with other countries. In a similar manner, the EFPIA Patients WAIT Indicator Survey has for more than a decade now tracked inequalities in reimbursement (which is a prerequisite for broad uptake) across Europe, finding large variations in the share of new cancer medicines that are reimbursed as well as in the time from EMA approval until reimbursement.[36] Info box 10 describes some of the health-related implications of these inequalities.

[36] It should be noted that a 100% reimbursement rate or an immediate reimbursement of EMA-approved medicines is not always necessary nor essential from a clinical perspective, as emphasized by both the OECD and EFPIA (508, 592). For instance, in a clinical setting where multiple medicines with similar effectiveness are available, it would be sufficient if patients have access to one medicine without impairing their health. An analysis by the OECD in 2023 found that differences between European countries in the reimbursement rate are smaller if specific indications with multiple, similar alternatives are considered (29). The analysis in this report about the uptake of medicines in section 4.6 addressed this issue, e.g., by jointly looking at all three CDK4/6 inhibitors in breast cancer.

Info box 10. Health-related implications of delayed access to new and effective cancer medicines

Existing inequalities in timely access to effective medicines have direct implications for the health of cancer patients. An analysis of 12 cancer medicines across 28 European countries in the period 2011-2018 found that the average time to market (defined as the time between EMA approval and first registered sales) was 403 days (range 17-1187 days) (593). For two medicines (ipilimumab and abiraterone, both with EMA approval in 2011), the recorded delay in patient access may have led to a potential loss of around 21,600 life years in the first year after EMA approval.

A similar analysis for Ireland of 11 cancer indications with EMA approval in 2015-2021 found that the time from EMA approval until reimbursement by the Health Service Executive (HSE) together accounted for 2,600 years of potential life lost, of which 1,000 years in working-age patients, corresponding to an economic loss of €34 million (12).

Potentially important aspects such as improved quality of life of patients or reduced numbers of adverse events were not taken into account in the two aforementioned analyses. Importantly, both analyses only focused on medicines with a statistically significant gain in median overall survival (OS) and clinical settings where no similar treatment alternatives existed. These settings should be prioritized by decision-makers to minimize detrimental effects for patients.

5.1.1 Barriers

Patient access to new medicines will remain unequal or become even more unequal in the future unless the root causes are addressed. The speed of innovation in oncology, with the number of new medicines coming to the market every year exceeding the number of medicines going off patent, might be too fast for less wealthy countries to catch up with wealthier countries. In fact, an analysis by the OECD in 2023 found that the budget impact of new cancer medicines has become more important for public coverage/reimbursement decisions in the last five years in most European countries (29). In addition, and as described in chapter 4, analyses by different stakeholders have pointed out many root causes such as (508, 517, 573):

- Timelines of the national pricing and reimbursement process
- Criteria used in the HTA / value assessment process
- Health system constraints and resources, including budget and infrastructure
- Subnational approval process
- Low frequency of clinical guideline updates
- Limited continuing medical education

For the uptake of NGS testing (which is a prerequisite for administering an increasing number of cancer medicines), identified barriers include lack of diagnostic laboratory infrastructure with NGS testing capabilities, inefficient organization of diagnostic testing, financial constraints, and failure to include NGS testing in local guidelines (533, 594). Unless NGS testing is reimbursed and used, the adoption of precision medicine will be stalled. A paradoxical situation identified in previous research is that in some European countries, public healthcare payers may decide to reimburse a medicine but not its companion diagnostic (535). Without access to the companion diagnostic, patients struggle to access targeted therapies even though they are reimbursed, unless patients are able to pay for the testing out-of-pocket or rely on pharmaceutical companies covering test costs (533). In 2023, only 11 out of 24 European countries automatically reimbursed a companion diagnostic when a medicine/indication was being reimbursed, meaning that in more than half the countries the reimbursement decisions were not aligned (29).

5.1.2 Facilitators

Although the root causes of inequalities in access to cancer medicines mostly seem to be found at the country level, there are efforts at the European level to bridge the gaps – especially concerning the reimbursement of new medicines; see Figure 94. One such effort comes from the pharmaceutical industry. In 2022, EFPIA member companies announced that they commit to filing for pricing and reimbursement in all EU countries no later than two years from EMA approval (595). A recent OECD report focusing on EMA-approved indications in breast and lung cancer between 2016 and 2023 found that this promise by EFPIA member companies is already fulfilled to a large extent, with the mean time from EMA approval to reimbursement application exceeding one year only in Cyprus, Greece, and Latvia (out of 20 EU countries) and not exceeding two years in any country (29). However, only 7 out of 23 EU countries reported receiving applications for all considered indications, and Malta, Hungary, and Cyprus had received applications for fewer than 40% of the indications. This indicates that there is still a considerable gap in living up to the EFPIA commitment.

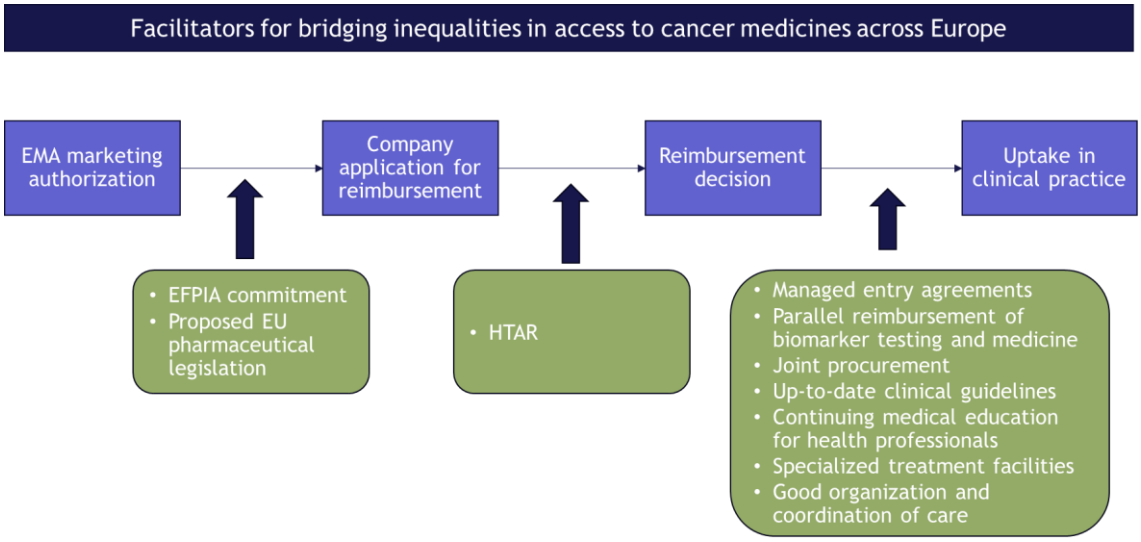


Figure 94: Facilitators for bridging inequalities in access to cancer medicines across Europe.

As noted in section 4.2, the greatest share of the delay in the time from EMA approval to local reimbursement is caused by the time between the application for reimbursement and the decision. This assessment period is regulated by EU law through the Transparency Directive (Council Directive 89/105/EEC), which imposes maximum time limits for pricing and reimbursement decisions (90 days for pricing, 90 days for reimbursement or 180 days for combined pricing and reimbursement decisions) from the time a pharmaceutical company applies (596). However, observed delays are often longer than the 180-day maximum, as clockstops may apply during which a company is asked to provide further information (597).

Two legislative changes at the EU level – the HTAR and the reform of the EU pharmaceutical legislation – might positively influence the speed of reimbursement decisions and the reimbursement application rate. For all new cancer medicines, the HTAR mandates joint clinical assessments (JCA) and joint scientific consultations which includes the involvement of patients, clinical experts, and other relevant experts since January 12, 2025 (580). The JCA is supposed to provide evidence on the relative effectiveness of a new medicine, yet it will not include any analysis of costs, as they may differ from country to country. National (or sub-national) assessments of cost-effectiveness and budget impact will still be required in countries where this is part of the HTA process. The crucial point for the assessment timelines is whether

countries accept the outcomes of the JCA as they are, or whether they still require their own assessment of relative effectiveness during the HTA process. The latter would result in duplication of work for both national HTA bodies and pharmaceutical companies and potentially prolong the entire timelines from EMA approval rather than shorten them.

The Commission proposal for the reform of the EU pharmaceutical legislation (from April 2023; still pending adoption) suggests linking medicine access to regulatory data protection (581). The idea is to address the situation with medicines being reimbursed at different times in different countries as well as to address cases where a medicine is never marketed in a country, which results in unequal patient access. Companies that provide access to their medicines in all member states will be rewarded with two extra years of data protection. Companies must provide actual access in all member states within two years of the marketing authorization (three years for smaller companies), unless a member state indicates no interest/need for the medicine. The Commission proposal has been met with concern from EFPIA, which points out that the conditionality of the two-year additional data protection is in reality in the hands of governments, payers, and providers and is not dependent on companies' willingness to submit a request for pricing and reimbursement (598). There might also be unintended consequences of making Europe less competitive in the global race to attract life science investments, deliver new treatments to patients first, and generate jobs and growth (598).

Faster reimbursement of new cancer medicines is one thing, but more focus in policy debates and effort is needed to achieve sufficient uptake and meet patient needs. This includes access to and reimbursement of molecular diagnostic testing, up-to-date clinical guidelines and their adherence, access to trained professionals and their continuing medical education, access to specialized treatment facilities, and good organization and coordination of care. Diagnostic testing was pointed out by the OECD as one area where imbalances exist in many European countries that do not reimburse medicines and their companion diagnostics in parallel (29). HTA processes should consider the additional costs of both the testing and the medicine in an integrated way, resulting in a decision to either reimburse both or neither. Other recommendations to facilitate the uptake of biomarker testing include establishing a centralized testing infrastructure with mandatory quality assurance, up-to-date guidelines on comprehensive testing, and stakeholder education on precision medicine (532, 533). Evidence-based tools such as the ESCAT developed by ESMO could be integrated into national considerations and guidelines on biomarker testing (531).

Managed entry agreements (MEAs) – both financial ones and performance-based ones – have for long been proposed and used to facilitate the reimbursement of new medicines that are characterized by uncertainties in clinical benefit, cost-effectiveness, and budget impact (556, 599-601). Financial MEAs (confidential rebates/discounts, price-volume agreements, expenditure caps, etc.) are commonly used for cancer medicines in nearly all EU countries according to the OECD (29). In contrast, performance-based MEAs (coverage with evidence development, payment-by-result, etc.) have been used by fewer EU countries for cancer medicines and mostly only in special cases because of challenges with defining "performance", administrative burden (both for companies and payers), lack of appropriate IT systems that can easily extract relevant data from medical records and have them processed by healthcare payers, and lack of staff to run and maintain the systems (29). The establishment of the European Health Data Space might nudge countries in a more favorable direction to improve the integration of IT systems and facilitate more widespread use of performance-based MEAs.

To address the budget impact of new cancer medicines across the EU, there is no one-size-fits-all solution given the diverse healthcare systems, health priorities, and budget processes. The

idea of joint procurement of cancer medicines has gained renewed attention, particularly following the experience with the joint procurement mechanism for COVID-19 vaccines by the European Commission to address the specific case of this cross-border health threat (602, 603). By leveraging collective purchasing power, joint procurement could enhance affordability and accessibility of high-cost medicines while reducing the budgetary impact on individual countries (604, 605). This approach aligns with the objectives of the EBCP, which emphasizes equitable access to innovative therapies across the EU (2). While joint procurement has been previously discussed, its practical implementation for cancer medicines remains uncertain and complex, given the diverse national pricing and reimbursement frameworks (606), and the need for flexibility to find local targeted solutions. A system of joint procurement with a uniform price in all EU countries would also undermine the principle of value-based pricing, although the addition of a system of tiered pricing could potentially address this shortcoming. Nonetheless, increased collaboration in this area could provide a more sustainable pricing model, benefiting both national healthcare systems and patients.

5.2 Value of new medicines

Cancer medicines constitute a growing share of cancer care spending in Europe as shown in section 4.5. While innovations in cancer care are key to reducing the disease burden, they require additional funding and raise budgetary concerns although they might lead to savings to the healthcare system and society in the long-term. The importance of applying rigorous HTA not just for new cancer medicines, but all novel technologies more generally, has never been greater. Yet the reality is that there are different approaches to HTA across European countries, taking into account varying criteria in the value assessment process (607, 608).

Through HTA, healthcare systems can weigh the costs from investing in novel technologies against the potential improvements in patient outcomes (i.e., cost effectiveness), ideally applying a societal perspective (including indirect costs of productivity losses and informal care cost) rather than a healthcare perspective. The estimation of incremental cost-effectiveness ratios enables a balanced consideration of the value (609); see Figure 95. At the same time, as noted before, considerations of the budget impact of new cancer medicines have grown in importance (29). Although a new medicine might be cost-effective, it might not be affordable for healthcare payers ("affordability barrier"). CAR T-cell therapies are an example which might be cost-effective but have a considerable incremental budget impact (610, 611).

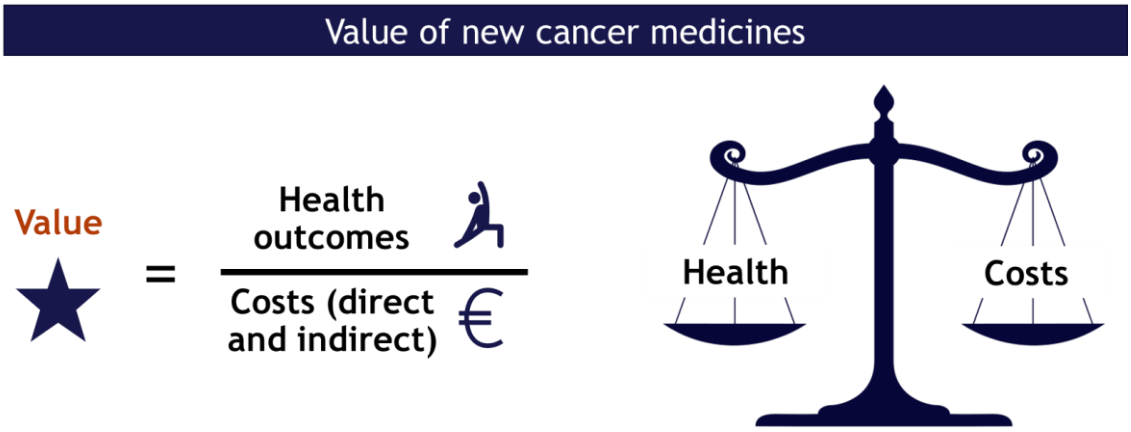


Figure 95: Value of new cancer medicines.

5.2.1 Perspectives on the value of new cancer medicines

Medical discussions about the value of new cancer medicines are typically limited to considerations of their efficacy or effectiveness, while political discussions may focus more on the price of medicines. From a health-economic perspective, the health aspects and the economic aspects should be considered jointly; see Figure 95. However, even in joint considerations of health outcomes and costs, the question is which perspective is taken on health outcomes (what are relevant outcomes?) and costs (costs for the healthcare payer or costs for society?).

For new medicines there is a well-known trade-off between providing early access and providing evidence on value to patients (612, 613). On the clinical side, regulatory approvals by the EMA are made based on trial data that involve a great amount of uncertainty about the effects in clinical practice. Clinical data used for approval are far from always based on the gold standard of large-scale phase III RCTs with long-term evidence on overall survival. The EMA considers OS as the primary clinical endpoint in clinical trials for cancer medicines and benefits proven for the medicine in OS is seen as the most "persuasive" outcome (614). In reality, pivotal clinical trials for regulatory approval may be single-arm phase II trials for therapies targeting rare cancer types or rare mutations of a cancer type, basket trials for tumor-agnostic medicines, or trials that show robust evidence on surrogate endpoints but where follow-up to get robust data on OS takes many years, such as in many early-stage cancer settings. An analysis of 199 cancer indications with EMA-approval in 2010-2019 found that 159 approvals (80%) were based on at least one RCT and the remaining 40 (20%) were not (9 of which had a post-approval RCT), and 63 approvals (32%) had at least one RCT with OS as the primary or co-primary endpoint (615).

Several studies have systematically examined the efficacy of cancer medicines approved by the EMA and US FDA; see section 5.4.3 in the 2019-Comparator Report for an overview. As in the past, newer studies show a mixed picture. Clinical trial data supporting FDA approvals of cancer medicines between 2003 and 2021 showed an increase in OS by a median of 2.8 months and by a median of 3.3 months for the surrogative endpoint progression-free survival (616). Similarly, a study of 132 EMA-approved indications for solid tumors in 2015-2020 showed that the median gain in OS was 2.8 months (214). Using the ESMO-MCBS, an analysis of 144 indications used in solid cancers with EMA approval between January 1, 2009 and October 31, 2020 showed that only 33% had a "substantial" clinical benefit (617). In Switzerland, a study of 92 cancer indications approved by the regulatory body (Swissmedic) in 2010-2019 found that 39% had a "substantial" clinical benefit according to the ESMO-MCBS (618). In general, the ESMO-MCBS for non-curative treatments considers the gain of ≥3 or ≥5 months in OS (depending on the median survival of control) as substantial (619). The challenge with the ESMO-MCBS is that all single-arm trials and basket trials cannot demonstrate a substantial benefit per default because of the lack of a comparator arm. Partly in response, ESMO released new guidance in 2024 on tumor-agnostic therapies, whose value can be classified based on the ESMO Tumour-Agnostic Classifier and Screener (ETAC-S), which defines minimum thresholds for establishing objective response in at least one out of five patients (ORR ≥ 20%) in two-thirds (≥4) of the investigated tumor types, with at least five evaluable patients in each tumor type (620).

Uncertain clinical data at the time of regulatory approval do not imply that a medicine will never turn out to be effective nor that it is not cost effective, but it complicates the subsequent HTA process at the country level and the evaluation of the medicines' cost-effectiveness. In order to share the uncertainty (and associated risk) between the pharmaceutical company and the healthcare payer, MEAs are often used; see section 5.1.2. Instead of providing equal access to all medicines with regulatory approval, countries ought to put a stronger focus on providing

greater access to the most valuable and cost-effective medicines and make access to medicines that have not yet been proven to be effective and cost-effective conditional on appropriate follow-up. This could take the form of a multi-speed approach in the national HTA process, where high priority is given to medicines with proven incremental clinical effectiveness (favorable OS data from an RCT), medium priority to medicines with possible incremental clinical effectiveness (favorable efficacy based on validated surrogate endpoints for OS from an RCT), low priority for medicines with unclear incremental clinical effectiveness (efficacy based on validated surrogate endpoints for OS from single-arm / basket trials). In the two latter cases, a system of conditional reimbursement with clawback payments (partly or in full) and automatic de-listing could be considered if incremental benefits from surrogate endpoints do not translate into an incremental benefit in OS in the pivotal trial or if the provision of RWD within a specific timeframe does not support an incremental gain in OS; see also section 3.7 on RWD. At least for solid tumor indications, the ESMO-MCBS could be used to guide a multi-speed approach in HTA (high priority for those with a high ESMO-MCBS score and vice versa).

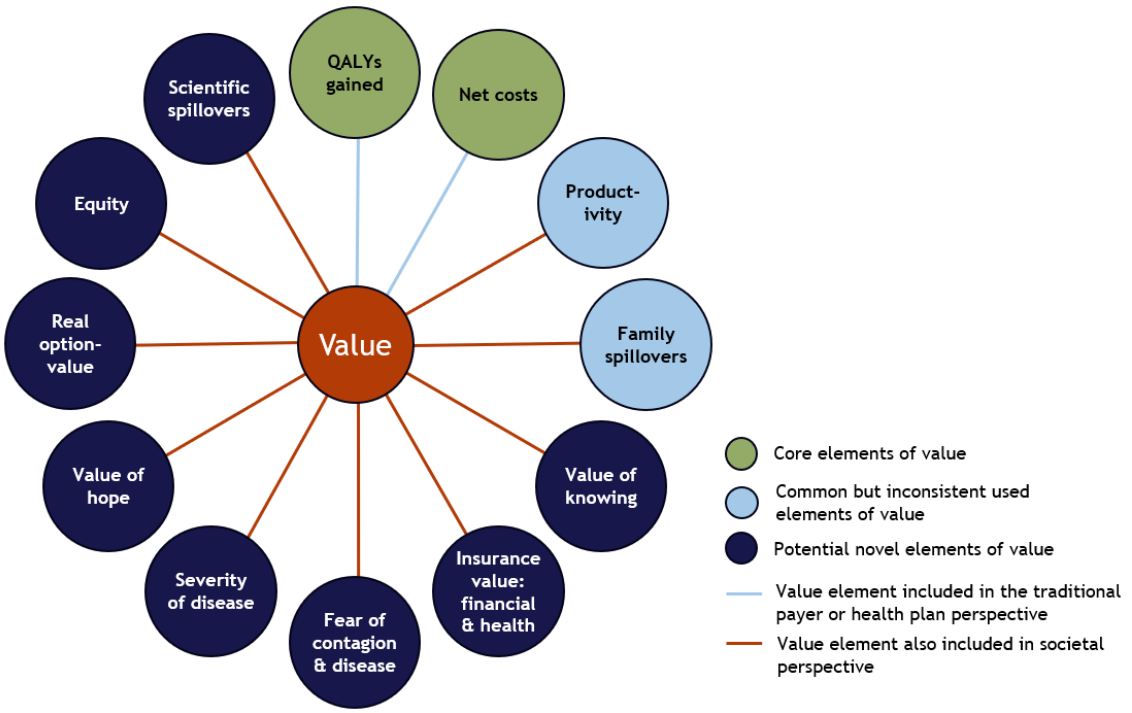


Figure 96: The ISPOR Value Flower for new medical technologies.

Notes: QALY = quality-adjusted life years. Source: Adopted from Lakdawalla et al. (2018) (621).

In 2018, the ISPOR Value Flower was launched as a comprehensive framework designed to capture the full value of new medicines beyond traditional cost-effectiveness analysis (621); see Figure 96. Often, the true value of a new medicine is underestimated due to a narrow focus on two health-economic factors, the direct healthcare costs and the clinical outcomes (OS and quality-adjusted life years, QALYs). The Value Flower expands this perspective by incorporating multiple "petals" representing diverse elements of value, including patient-centric metrics, and broader societal impacts. Recent discussions on this framework have highlighted the need for a more holistic evaluation of new medicines, ensuring that policymakers, payers, and healthcare systems recognize their full contribution. Research efforts have focused on providing more rigorous theoretical and mathematical foundations for certain novel value elements (e.g., severity of illness, value of insurance, value of hope) through "generalized risk-adjusted cost-effectiveness analysis" (GRACE) (622). More work will be needed before HTA bodies can

systematically integrate this broader view, yet some elements (e.g., disease severity modifiers to cost-effectiveness thresholds) have already been used by some bodies (e.g., NICE in England, TLV in Sweden) for many years (623, 624). By considering these multiple dimensions, the ISPOR Value Flower fosters a more balanced and informed approach to assessing new treatments, ultimately supporting better decision-making in healthcare.

As illustrated in the ISPOR Value Flower, while new medicines typically increase direct healthcare costs (net costs), they may provide indirect societal benefits regarding the patient's productivity (such as better employment outcomes, higher tax revenue, and lower social benefit payments) and family spillovers (informal caregivers' health-related quality of life (HRQoL), absenteeism and presenteeism at work). Taking a broader societal perspective on costs in health-economic evaluations might therefore have profound implications for whether a new medicine is deemed cost-effective or not.

- **Example of productivity**: A study of triple-negative breast cancer in Switzerland evaluated the potential fiscal benefits from the Swiss government's perspective of introducing neoadjuvant immunotherapy plus chemotherapy followed by surgery and adjuvant immunotherapy compared to the previous standard of care of neoadjuvant chemotherapy followed by surgery (625). It found that about 75% of the additional healthcare costs of the new treatment regimen were offset by increased tax revenue as improved clinical outcomes (longer event-free survival and reduced recurrence) helped mitigate negative employment outcomes for patients. However, while social benefit payments with the new treatment regimen were around 3% lower on an annual basis, the longer lifespan of patients resulted in an increase in total social benefit payments of 28%.
- **Example of family spillovers**: A review of all published technology appraisals (TAs) and highly specialized technologies (HSTs) by NICE in England from 2000 to 2019 found that only 12 of 414 TAs (3%) and 4 of 8 HSTs (50%) included carer HRQoL (626). A newer review covering the period 2019-2022 showed that the proportion of appraisals that included carer HRQoL had increased (6% [13/226] of TAs and 78% [7/9] of HST evaluations) (627). The newer review also noted that carer HRQoL was more often included in base-case analyses rather than scenario analyses, indicating a growing role of carer HRQoL in NICE appraisals. Appraisals that include carer HRQoL mostly concerned orphan indications, pediatric populations, and/or neurological conditions. An international systematic review of published cost-utility analysis across all therapeutic areas concluded that including carer HRQoL generally resulted in lower incremental cost-effectiveness ratios (628).

5.2.2 Real-world impact of cancer medicines

The significant improvements in cancer survival since the 1990s (see section 2.4) can be attributed to a combination of factors, including advances in early detection, diagnostics, and treatment. Early detection methods, such as screening programs and improved diagnostic technologies, allow cancers to be caught at earlier, more treatable stages; see section 3.2. Advances in diagnostic technologies, such as endoscopic ultrasound, positron emission tomography (PET) scans with radiotracers or combined with magnetic resonance imaging (MRI) or computed tomography (CT) and lately assisted by AI, allow for more accurate tumor localization and spread, better staging, and obtaining tissue samples for biopsy (629). All major treatment modalities have seen advances. For surgery, advances have been achieved through improved tumor imaging, better surgical techniques (minimally invasive surgery), surgical robots, AI-assisted surgery, and also by combining surgery with neoadjuvant systemic therapy

and/or radiation therapy to shrink the tumor before surgery (630). Radiation therapy has become more precise, focusing radiation beams more on the tumor and less on healthy tissue (631). Medical oncology has been the most dynamic area of cancer care, with the introduction of targeted therapies and immunotherapies, enabling more personalized and effective therapeutic approaches based on genetic and molecular profiling; see sections 3.3 and 3.4.

Because of the simultaneous improvement in all areas to detect, diagnose, and treat cancer, it is difficult to isolate the contribution of a certain component, such as cancer medicines. Unlike in the controlled settings of a clinical trial where the impact of a single intervention on survival is studied, the analysis of RWD on cancer survival will be the sum of all simultaneous improvements in clinical practice. The following observations can be made regarding the contribution of new cancer medicines to the development of survival rates in Europe since the 1990s (presented in section 2.4):

- Survival rates have improved most for hematologic cancers (+10 to 30 pp since the 1990s). Improvements in early detection, imaging diagnostics, surgery, and radiation therapy offer little explanation for the observed increase in survival of multiple myeloma, leukemia, and non-Hodgkin lymphoma, as there are no screening programs and the main treatment modality consists of cancer medicines and stem cell transplant (632-634). At the same time, the widespread use of stem cell transplants since the 1990s (635), together with the high number of new medicines in hematology (see Figure 52) that have been replacing each other as preferred front-line therapy and treatment of relapsed/refractory cases are the likely main drivers of the observed improvements in survival.
- Cancer types with little or no improvement in survival rates include brain cancer, laryngeal cancer, testicular cancer (where rates are already close to 100%), and to some extent also bladder cancer and gynecological cancers (cervical, ovarian, uterine cancer). A common observation across these cancer types are the low number of EMA-approved indications between 1995 and 2023, most of which are only used for the treatment of metastatic disease: brain cancer (3 indications, of which 1 approved in 2023), laryngeal cancer (7 indications, of which 3 approved since 2017; 1 indication in the curative setting), testicular cancer (0 indications), bladder cancer (8 indications, of which 7 approved since 2017; 1 indication in the curative setting), cervical cancer (4 indications, of which 2 approved since 2022), ovarian cancer (13 indications, of which 6 approved since 2018), uterine cancer (4 indications, of which all approved since 2021).

There are some US-based empirical studies that have tried to answer the question of the contribution of different components of cancer care to the observed decline in age-standardized mortality rates (thus not survival rates); see Table 22. One study for breast cancer found that 75% of the observed decline in mortality rates in 1975-2019 was attributable to improved treatment with cancer medicines (47% in early-stage, 29% in metastatic stage), while the remaining 25% were caused by earlier detection from mammography screening (88). However, improvements in surgery and radiation therapy during the observation period were not considered. Another study of five cancer types found that the estimated number of averted deaths in 1975-2020 was mostly explained by improved prevention and screening (80%) and to a lesser extent by better treatment (mostly with cancer medicines) (20%). A third study of a broader range of cancer sites estimated that the observed reduction in mortality rates in 2000-2009 was mostly caused by new medicines (58%), followed by better diagnostic imaging (29%) and a decline in incidence (9%). In sum, new and effective cancer medicines contribute to

decreasing mortality rates, although their exact contribution is difficult to ascertain and also differs by cancer type.

Table 22: Studies of explanatory factors for observed reductions in cancer mortality

Study	Caswell-Jin et al. (2024) (88)	Goddard et al. (2024) (636)	Lichtenberg (2014) (489)
Country	US	US	US
Cancer type	Breast cancer	Breast, cervical, colorectal, lung, and prostate cancers	~60 cancer sites
Time period	1975-2019	1975-2020	2000-2009
Population	Women aged 30 to 79 years	Men and women (different age ranges by cancer type)	all
Measure	Mortality (age-standardized rates)	Mortality (number of deaths averted)	Mortality (age-standardized rates)
Overall change	58% reduction in age-adjusted breast cancer mortality rate	5.94 million cancer deaths averted	13.8% reduction in age-adjusted cancer mortality rate
Contribution to the overall change by component (sum is 100%)	• 25% mammography screening • 47% treatment of stage I to III breast cancer with medicines • 29% treatment of metastatic breast cancer with medicines	Overall: • 80% prevention and screening • 20% treatment By cancer type: • Breast: 25% prevention and screening and 75% treatment • Cervix: 100% and 0% • Colorectum: 79% and 21% • Lung: 98% and 2% • Prostate: 56% and 44%	• 9% decline in incidence • 29% diagnostic imaging • 58% medicines • 4% other reasons

Notes: The study by Goddard et al. (2024) defined treatment differently for each cancer type; for breast, colorectal, and lung cancers only medicines were included, for cervical cancer no treatments were included, and for prostate cancer surgery, radiation therapy, and medicines were included.

5.2.3 Optimizing the efficient use of cancer medicines

Partly spurred by the rising expenditure on cancer medicines, a number of strategies have been advised to optimize their use in clinical practice in recent years. The intention is not to deny patient access to cancer medicines, but rather to maintain the same patient outcomes (or achieve even better ones) while reducing or altering the use of medicines.[37]

Use of prognostic biomarkers for patient stratification

Gene expression profiling tests in breast cancer have been used for more than a decade for risk stratification of women with lymph node-negative, estrogen receptor-positive, early-stage breast cancer who are most likely to benefit from adjuvant chemotherapy in addition to

[37] While these strategies focus on optimizing the use of medicines for existing patients, another way to decrease the use of medicines is to lower the overall demand. Through better prevention, fewer people would get cancer and require treatment. Through better early detection (screening and early diagnosis), more patients could be diagnosed in earlier disease stages, where the use of cancer medicines is less common – especially the use of newer cancer medicines which are most often only used in the metastatic setting.

standard adjuvant endocrine therapy to prevent recurrence (637, 638). Instead of giving chemotherapy to all patients, it helps to single out women who will not derive any benefits, saving medicine costs and costs for managing side effects.

Similar tests are also being developed for other cancer types and clinical settings. A recent example is a prognostic biomarker test (Prostatype score) for early-stage prostate cancer that reclassifies a higher proportion of patients into the low-risk category, making them eligible for active surveillance. A study in a Swedish setting showed that this test led to cost savings and generated an additional 0.19 QALYs compared to traditional risk categorization systems (639). The added costs of the test and higher costs of active surveillance and radiation therapy were counterbalanced by savings from reduced costs of surgery, treatment-related side-effects, and treatment of metastatic disease including medicines.

Optimization of treatment algorithms

As described in section 4.6.1, CDK4/6 inhibitors for the treatment of advanced breast cancer in combination with endocrine therapy have been introduced as first- and second-line therapy over the last decade. A recent study in the Netherlands found no statistically significant benefit of the use of CDK4/6 inhibitors in first-line compared with second-line treatment (640). This challenges the need for first-line use, which entails longer treatment duration with CDK4/6 inhibitors and results in more side effects and more hospital visits. Confining the use to second-line is estimated to achieve healthcare cost reductions of around EUR 30,000 per patient and over EUR 45 million per year in the Netherlands (641).

Perioperative immunotherapy (neoadjuvant immunotherapy followed by surgery and adjuvant immunotherapy) has in the last few years emerged as a common curative approach in several early-stage solid tumors. Yet is unclear to what extent patients benefit from neoadjuvant therapy alone and adjuvant therapy alone compared to the perioperative approach. A recent study of resectable NSCLC assessed whether the surrogate endpoints pathologic complete response (pCR) and major pathologic response (MPR) after neoadjuvant chemoimmunotherapy have prognostic significance for the surrogate endpoint event-free survival (EFS) and the impact of adjuvant immunotherapy (642). It was found that in patients who achieved either pCR or MPR after neoadjuvant chemoimmunotherapy, the use of adjuvant immunotherapy after surgery was not associated with improved EFS. If adjuvant immontherapy were skipped for this subset of patients, the treatment costs for around 9-12 months of immunotherapy could be saved.

Minimization of overtreatment at the end of life

Many cancer patients approaching the end of life (EOL) receive treatments that provide minimal benefit and may lead to harm (643). Such overtreatment at the EOL can result in side effects, higher healthcare costs, delayed EOL planning, and strained resources, while also causing moral distress among clinicians and treatment teams. Recommendations to avoid overtreatment at the EOL include enhancing communication, addressing cognitive biases, and limiting dependence on unproven technologies to reduce unnecessary interventions (643). In Ireland, the National Cancer Strategy (2017–2026) recommends that <25% of patients should receive cancer medicines in the last month of life (644).

Minimization of medicine spillages

Medicine spillage occurs in various settings. Cancellations by patients supposed to receive intravenous (IV) therapy, which has been prepared in advance, can lead to wastage. In the

Netherlands, the Erasmus MC schedules patients undergoing the same treatment on the same day, thereby being able to give the therapy to another patient when a patient cancels on short notice (645). Similarly single-patient vials often contain more product than a typical patient needs, and saving the excess amount from two or more vials to later formulate a dose for an extra patient ("vial sharing") treated on the same day can result in significant savings (644).

Another example from the Netherlands (Radboud UMC) is the reduction of spillage of oral cancer medicines. When patients need to stop treatment during a treatment course, large quantities of oral medicines may be left unused. Collecting and re-dispensing these unused medicines could save money (645). In Germany, a study among patients with newly prescribed oral cancer medicines found that almost 25% of patients discontinued treatment within 12 weeks. There were unused tablets/capsules worth around EUR 3,300 per patient (in total EUR 112,212 among 34 patients). For around 40% of the prescriptions, a smaller package size could have been prescribed, potentially avoiding wastage (646).

Efficient dosing

While many chemotherapies use weight-based dosing, immune checkpoint inhibitors originally also had a weight-based dosing (ipilimumab still has one in 2025) but then switched to fixed-dose regimens (e.g., pembrolizumab switched from a weight-base dose of 2 mg/kg Q3W to a fixed dose of 200 mg Q3W). However, it has been suggested that fixed-dose regimens were commercialized with reference weights higher than the accurate weight of patients with cancer in routine practice (647). Estimations of the extra cost attributable to fixed-dose regimens of nivolumab and pembrolizumab in France amounted to EUR 55 million in 2017 (647). Similar results have been reported for Ireland (644). However, the limited availability of appropriate vial sizes means that weight-based dosing might be logistically challenging.

Use of biosimilars and generics

The use of generics (copies of small-molecule medicines) and biosimilars (copies of biologics) can greatly increase efficiency in the use of cancer medicines (29). By stimulating competition between producers after the loss of market exclusivity, lower prices can be achieved. An analysis of biosimilars in oncology in Europe indicated reductions in list prices of 12% and rebates and confidential discounts of between 10% and 90% of the list price (648). Even greater price reductions are usually observed for generics (29); see also section 4.6.14.

A recent OECD analysis of the only three cancer medicines with biosimilars approved by the EMA until 2023 showed great variations in the reimbursement rate and the time to reimbursement across European countries (29). While all biosimilars were in principle available in Estonia, only one biosimilar was available per medicine in Malta (yet after a competitive procurement procedure). The mean time from EMA approval to reimbursement varied from around 200 days in Germany and Spain to between 700 and 835 days in Greece, Iceland, Latvia, Lithuania, and Slovenia and almost 1400 days in Cyprus.

The potential to achieve a more efficient use of resources through competition from biosimilars and generics can be illustrated based on the five medicines (rituximab, trastuzumab, bevacizumab, imatinib, lenalidomide) analyzed in section 4.6.14. After the year of patent loss, the implicit price of all marketed products for a certain medicine started to drop (based on list prices). This results in savings compared to if the price had remained unchanged, with the size of the savings increasing with the extent of the price drop and greater volume use. Figure 97 shows that €21.9 billion have been cumulatively saved due to price decreases after patent loss

across the five medicines in Europe until 2023. This is almost as much as the total cancer medicine expenditure in 2014 which was €24.9 billion (based on list prices); see section 4.5.2.

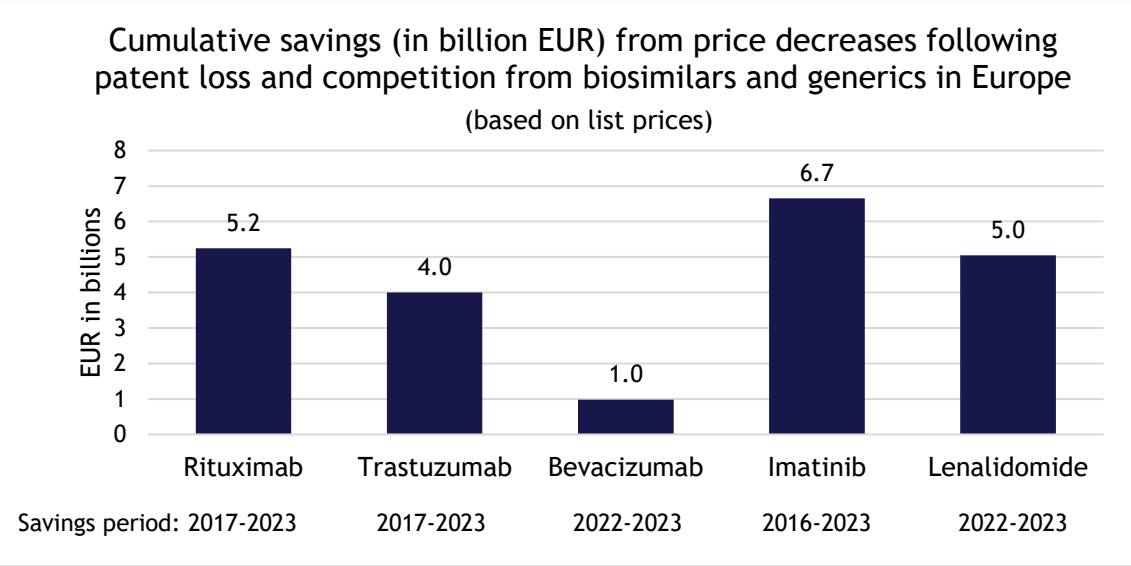


Figure 97: Cumulative savings (in billion EUR) from price decreases (based on list prices) following patent loss and competition from biosimilars and generics of selected blockbuster medicines in Europe until 2023.

Notes: No data were included for EE, EL, and LU. Sales data were adjusted for inflation and exchange rates to 2023 prices. The savings in each year were calculated as the volume use of a medicine (the sum of all products) in that year multiplied with the difference between the implicit price (defined as total sales in EUR divided by total sales in milligrams of all marketed products of a medicine) in that year and the implicit price the year before patent loss (2015 for imatinib, 2016 for rituximab and trastuzumab, 2021 for bevacizumab and lenalidomide). The calculated savings in each year of the savings period were summed up to obtain the cumulative savings. Source: Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Frumtök for Iceland, and Signum Life Science for Denmark; see also section 4.6.14 for uptake patterns.

With upcoming losses of market exclusivity of several blockbuster cancer medicines that were among the top 10 sellers in Europe in 2023, strategies to improve the availability and quick adoption of generics and biosimilars should be prioritized. Although mandatory generic/biosimilar substitution policies could be a strategy to realize the full potential of savings, a majority of countries in Europe does not mandate them for generics and few countries apply them for biosimilars. As shown in Figure 97, savings generated from the use of generics and biosimilars might create substantial budget headroom, which could be reinvested in new cancer medicines (29).

5.3 Data needs for better decision-making

Access to better and relevant data – on resource use, patient outcomes, and costs – are vital to identify current inefficiencies and shortcomings in the care process along the entire patient pathway. Discussions about access to cancer care should consider different quality aspects. A conceptual way to think about quality of care is the famous Donabedian model (649). This model postulates that quality of care is composed of three components: quality of structure (inputs), quality of process (actions), and quality of outcome (results); see Figure 98 for an illustration. Quality of structure refers to contextual factors or inputs (such as human resources, physical facilities, equipment) for the care process as well as organizational factors. Quality of process refers to all actions in healthcare provision (such as diagnosis and treatment) and is, among other things, shaped by clinical and health policy guidelines. Quality of outcome refers

to the results of healthcare provision for the patient (such as health status, HRQoL, patient satisfaction).

Figure 98: Donabedian-style model of dimensions in quality of cancer care.

Notes: HRQoL = health-related quality of life.

Data on the cancer care system are important for documentation, assessment, and communication of quality of care. They help to inform and plan the allocation of cancer resources, identify oversupply and undersupply of services, and detect regional differences in access to and quality of treatment. They are also fundamental to making comparisons over time in order to assess the progress and impact of policy measures. International data on variations between countries in the use of methods for prevention, screening and treatment would help to identify best practices for achieving an effective and cost-effective allocation of resources that maximizes patient outcomes.

The sources for relevant data on the cancer care system in a country should ideally be a country-wide system of an epidemiological cancer registry and a clinical cancer registry. These registries would not only register the number of people diagnosed with cancer and dying from cancer along with basic individual patient characteristics, but they would also collect data on the treatments and services provided from the first symptom-related healthcare visit to the completion of treatment or death.

Despite investments in cancer registries and healthcare statistics, the following three subsections show that there is still insufficient data to evaluate resource allocation, outcomes, and efficiency of spending in cancer care across countries. One lesson from the COVID-19 pandemic is that this bleak data situation with cancer is due to a lack of prioritization rather than a lack of ability to provide data. During the COVID-19 pandemic, we saw governments ramp up efforts to track resource utilization (the number of tests, the number and length of hospitalizations, the number of vaccines administered, etc.) and outcomes (number of new cases, recovered cases, deaths) in record time and in great detail, covering the entire country and providing daily updates. Yet it seems that this remains a one-time effort. Healthcare systems, responsible for both patient care and cost-effective spending, must ensure this information is available and used for cancer care as well.

5.3.1 Data on inputs and resources

Data on the most basic indicator of the input dimension – the amount of cancer care spending by healthcare systems – is often lacking on the country level. This report collected published evidence for 22 out of the 31 included European countries, which is more than the 20 countries with information in the two previous Comparator Reports; see Table 23. Smaller countries and countries in Central and Eastern Europe tended to have lower availability of such data.

However, in nearly all countries (except in Estonia and Poland) the available data is not up to date (year 2023) and newer data is only provided with a considerable delay. Many countries also do not provide a consistent time range of data; see section 2.5.1. To address this issue, disease-specific health accounts should be created by national statistical offices or similar bodies. The Federal Statistical Office of Germany (Destatis), the Estonian Health Insurance Fund (Tervisekassa), and the National Institute for Public Health and the Environment (RIVM) in the Netherlands provide such information based on the ICD-10 disease classification system. Furthermore, a disaggregation of costs into separate categories such as inpatient care, outpatient care, medicines, screening, prevention, etc. would be desirable. Not knowing how much money is spent on a particular disease and which specific resources the money is spent on obviously represents a significant limitation in informing health policy.

Table 23: Countries with available information on cancer care spending

2016 and 2019 Comparator Report	20 out of 31 countries. No data for Austria, Belgium, Bulgaria, Croatia, Ireland, Latvia, Lithuania, Luxembourg, Malta, Romania, Slovakia.
2025 Comparator Report	22 out of 31 countries. New data for Belgium and Lithuania.

Source: (46, 47).

One area with comparatively good information on resource use is cancer medicines. As shown in section 4.5, rather complete information on the sales of cancer medicines could be obtained for 27 out of the 31 European countries (incomplete data for Greece and Luxembourg, and no data for Cyprus and Malta). However, a major limitation is that the sales figures are based on list prices, which overestimates the true expenditure. Another limitation in the obtained data was the scarce information on cell therapies (CAR T-cell therapies) because the data are based on information from pharmaceutical wholesalers. Due to the unique manufacturing and administration process of cell therapies (and gene therapies), they do not pass through the same distribution channels as tablets, capsules, or vials.

Aggregated reimbursement data on cancer medicines for all 31 European countries are publicly available and provided on an annual basis by EFPIA through the Patients WAIT Indicator Survey (507). The European Access Hurdles Portal maintained by EFPIA has also started to publish some aggregate data on companies filing for pricing and reimbursement and the reimbursement decision (509). However, in both cases, no detailed data for a specific medicine for all countries are published, which would be needed to, e.g., better understand the uptake patterns shown in section 4.6. In addition, as the EFPIA Patients WAIT Indicator Survey tracks the reimbursement of the first EMA-approved indication of a new medicine, this is a limitation for most cancer medicines which tend to receive multiple extensions to new indications over time; see section 4.1.

For molecular diagnostics, the data situation is rather poor. The two studies from ESMO and IQN Path plus EFPIA presented in section 4.3 provide some information for selected types of tests and cancer types. Yet clear and comprehensive information on the reimbursement status of a certain companion diagnostic or, e.g., NGS testing in a certain clinical setting would be needed. Furthermore, as the development in this area proceeds very fast, yearly updates similar to the EFPIA Patients WAIT Indicator Survey would be desirable. This would provide deeper insights into understanding country differences in uptake patterns of medicines as shown in section 4.6.

5.3.2 Data on the care process

High-quality and international comparable data in the process dimension are limited to a few settings. Examples are HPV vaccination rates published by the WHO, cancer screening rates published by Eurostat, and the number of (non-cancer-specific) examinations performed by diagnostic imaging equipment (PET, MRI, CT scanners) by Eurostat. This report adds new data in the area of uptake of medicines for 27 out of the 31 European countries (section 4.6) and presents some older data on the uptake of molecular diagnostics (section 4.4).

The most desirable information for improving cancer care would be real-world information on treatment patterns for each type of cancer. Most countries are currently not able to provide structured and up-to-date RWD on how cancer patients are treated, be it in a single hospital, a cluster of hospitals within a region, or the entire country. A review of cancer treatment data in European cancer registries performed in 2022 found an increase in published data by population-based cancer registries over the years (650). Treatment data were most often collected for breast cancer followed by colorectal, prostate, and lung cancer. Another review of published treatment patterns for a distinct clinical setting – advanced non-small cell lung cancer – across 25 European countries performed in 2023 found that only two countries (Sweden and the UK) published annual, country-wide data on treatment patterns, 11 countries had at least some published evidence for a certain year from a single institution, whereas no published evidence was found for 12 countries – most of them located in Central and Eastern Europe (651). These findings highlight the dire need to improve data collection.

5.3.3 Data on outcomes

Survival data are the primary indicator for measuring outcomes in cancer care. They reflect both how early the cancer was detected and the effectiveness of cancer treatment. Patient-reported indicators in the form of patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) are other measures of outcomes. Few countries in Europe collected PROMs and PREMs systematically, e.g., only for some cancers either at the regional level (Denmark) or via clinical cancer registries (Sweden), according to a recent OECD report (652).

One of the most pressing challenges is the lack of survival data across European countries. Although the ultimate goal of cancer care arguably could be achieving a five-year relative survival rate of 100%, many countries struggle to measure how far away they are from this goal. In countries without a cancer registry that produces survival data, such as Greece, physicians cannot inform patients about their likely outcomes without referring to data from other countries. Even in countries with survival data, their timely publication is not always prioritized, resulting in a lack of up-to-date data. The level of detail of the survival data is another challenge. While survival rates are typically presented for distinct cancer types (breast cancer, lung cancer, etc.), this is out of sync with the treatment approach which targets distinct subgroups (e.g., hormone-receptor positive breast cancer or EGFR-positive lung cancer), which makes it difficult to closely track the impact of advances in treatment. Figure 99 shows a snapshot of publicly available national data on survival rates on national websites/reports (as of mid-January 2025). Out of the 31 countries, only 15 provide five-year survival rates for all cancers combined and various types, while another 3 countries provide survival rates only by cancer type but not combined. The remaining 13 countries provided no survival data.

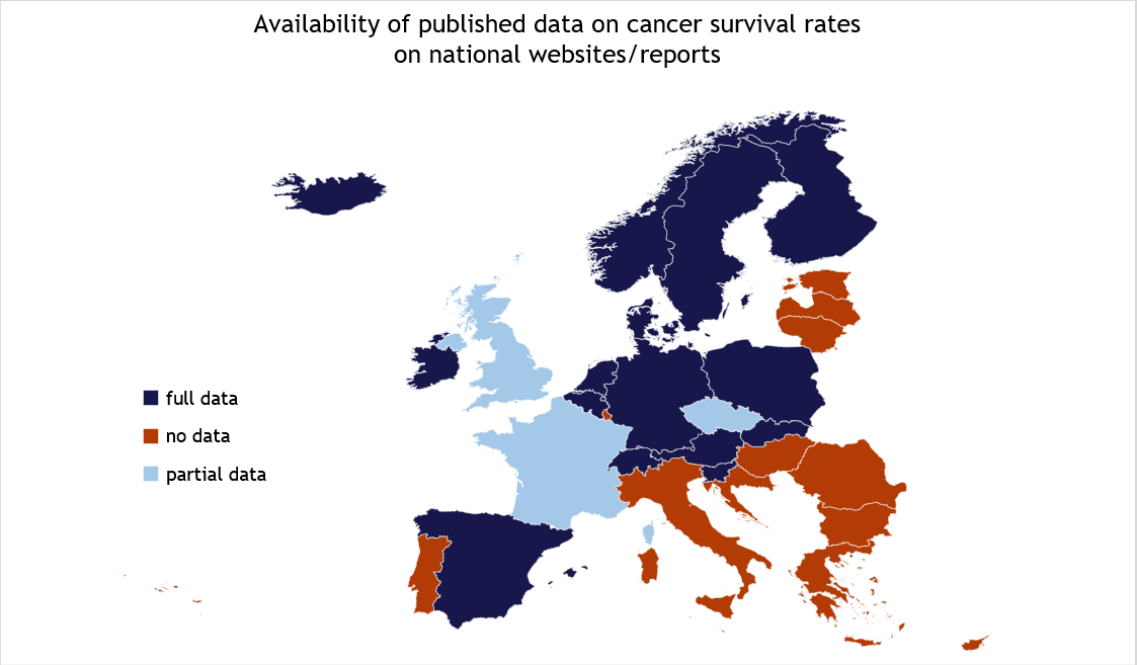


Figure 99: Availability of published national data on survival rates for all cancers combined on national websites/reports (as of mid-January 2025).

Notes: Countries were classified according to the availability of published, national five-year survival rates for all cancers combined (ICD-10 C00-97 or C00-97/C44 or similar) on national websites or annual reports of national cancer registries. Countries with "partial data" only published survival rates by cancer type but not for all cancers combined. Malta is not visible on the map but is classified as "no data". Note that as part of the CONCORD-3 study, many of the countries marked as "no data" were able to submit data that allowed for the estimation of survival rates. As part of the 2025 OECD Country Cancer Profiles, some newer survival data for Croatia, Estonia, and Latvia were published in February 2025, but they are not available on the national website. Source: authors' search of the respective websites of national cancer registries or similar in each country in mid-January 2025.

International comparable survival data often see major delays in publication – a situation which has not improved during the last ten years. A past report published in 2014 noted that the latest available survival data for 23 EU countries through the EUROCARE-5 project covered the period 2000-2007 and that these data had been published at the end of 2013, equaling an almost 6-year lag in between the date of publication and the end of the reference period (653).[38] Similarly, at the beginning of 2025, the latest available international comparative data come from the CONCORD-3 program, with survival rates covering the period 2000-2014. Since their publication in 2018, seven years have passed without any new international data. This situation brings disadvantages both for patients and policymakers. Health policymakers have to make decisions on improving cancer care based on outdated evidence, and patients' hopes will hinge on outdated numbers that might portray an overly negative picture of their survival prospects. Improving international measurement and monitoring of cancer survival should be a top priority. This could be an area where the European Commission through the EBCP and perhaps partnering with the European Network of Cancer Registries (ENCR) could initiate a permanent integration of data in Europe, similar to NORDCAN - Association of the Nordic Cancer Registries.

In the absence of robust and up-to-date data on survival, studies of the outcomes of cancer care tend to look at mortality (cancer deaths). Although the sole consideration of trends in mortality is not advised unless considered together with trends in incidence, they are often the

[38] The lag was not caused by the use of cohort analysis. EUROCARE-5 used period analysis with follow-up until the end of 2008. Thus, there was a gap of 5 years between the end of follow up and the publication in 2013.

only reliable source, coming from well-established cause-of-death registries. IARC has since the 1990s provided estimates on both cancer incidence and mortality for European countries, which are highly cited and used by policymakers in Europe. The accuracy of these estimates (or the fact that they are estimates and not real data) is sometimes overlooked. A comparison of estimated and observed cancer mortality data in Europe is shown in Figure 100. While mortality estimates by IARC were very accurate in 2008 and 2012, afterwards the gap between estimated and observed deaths has grown considerably larger. In fact, the trends in estimated and observed deaths tell a different story. Estimated deaths suggest a steady increase in cancer deaths from 2008 to 2022 ("We are still facing an uphill battle against cancer"), while observed data show a much more constant trend at around 1.3-1.4 million deaths per year ("We are starting to achieve a turnaround in the battle against cancer"). This observation also calls the prediction in the EBCP of cancer becoming the leading cause of death in the EU by 2035 into question, as these predictions were made based on data from IARC.

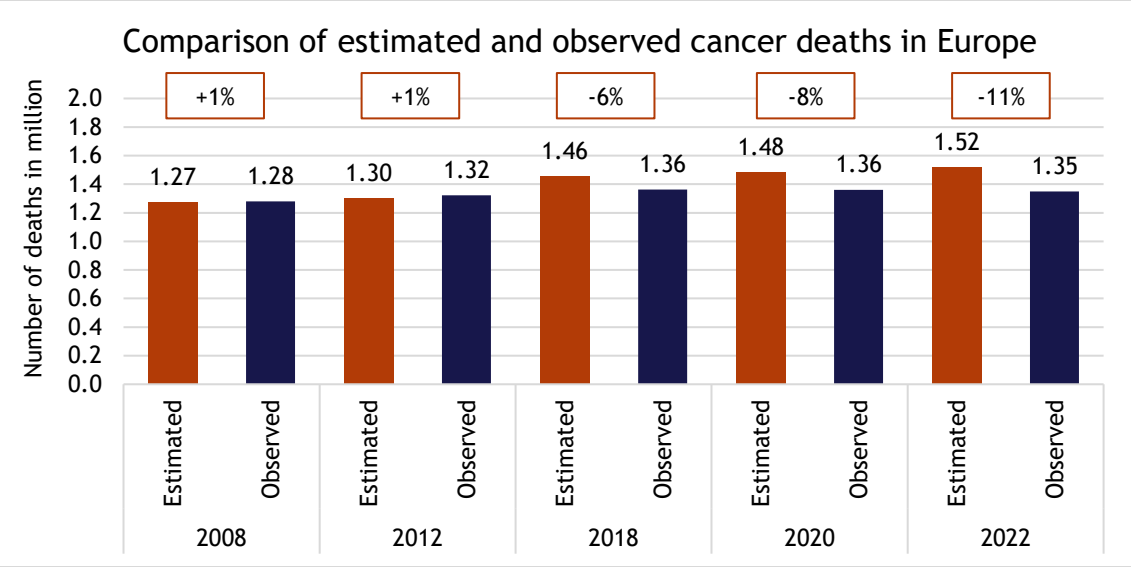


Figure 100: Comparison of estimated cancer deaths by IARC and observed cancer deaths by Eurostat in Europe, 2008-2022.

Notes: Cancer is defined as all sites (ICD-10 C00-97) in all years except for estimated deaths in 2008 and 2012 which exclude deaths of non-melanoma skin cancer (ICD-10 C00-96/C44), which in 2018-2022 only accounted for around 0.7-0.8% of all estimated cancer deaths. Estimated numbers for 2018 and 2020 were sourced from previous website information from IARC. Data for France only include Metropolitan France. Source: IARC (7-9, 52, 654), Eurostat (64, 69).

5.4 Europe in a global context

Europe has long been a leader in medical research, contributing significantly to advancements in cancer treatment and the development of new medicines. However, recent trends indicate that Europe is losing ground to the US and China in this critical area (655). To ensure that European patients continue to benefit from the latest therapeutic options and to maintain the region's economic vitality, it is imperative to reinvigorate Europe's commitment to clinical research and innovation.

Being at the forefront of clinical research offers numerous benefits, such as early patient access, professional development, elevating standards of care, and boosting economic activity. Cancer patients can gain access to cutting-edge treatments through clinical trials, potentially improving outcomes. Clinical trials have also clear financial benefits for health system payers, as the trial medicines are provided free of charge in industry-sponsored studies (644). However,

access to clinical trials in oncology is uneven across European countries, ranging from fewer than 2 trials per 100,000 inhabitants in Romania and Croatia to 10 or more trials per 100,000 inhabitants in Denmark and Belgium (29). For healthcare professionals, engaging in the latest molecular testing technologies and therapies helps to enhance their skills and knowledge early on. A robust research environment also fosters continuous improvements in medical practices and patient care. A strong clinical research environment drives innovation, creates jobs, attracts investments, and enhances Europe's global competitiveness. Strengthening policies supporting R&D, regulatory efficiency, and cross-border collaboration (such as through the Clinical Trials Regulation) can further amplify these benefits.

5.4.1 Current challenges

Europe's position in global clinical research in oncology has been diminishing over the last two decades. Although R&D activity in oncology has increased globally from around 1,500 clinical trial (phase I-III) starts in 2008 to 2,500 trial starts in 2023, the geographic footprint of companies headquartered in Europe has declined (285). Figure 101 shows how Europe's share of the number oncology trial starts accounted for 41% in 2008 and 2013, but then rapidly declined to 21% in 2023. The absolute number of trial starts by European companies decreased by 8% from 2008 to 2023. At the same time, China has skyrocketed from a share of 1% of all trial starts in 2008 to 35% in 2023, narrowly surpassing the US. With the massive wave of research coming from China, the coming years will likely see an increasing number of new cancer medicines being launched in a therapeutic area that was previously dominated by Europe, the US, and to a smaller extent also Japan.

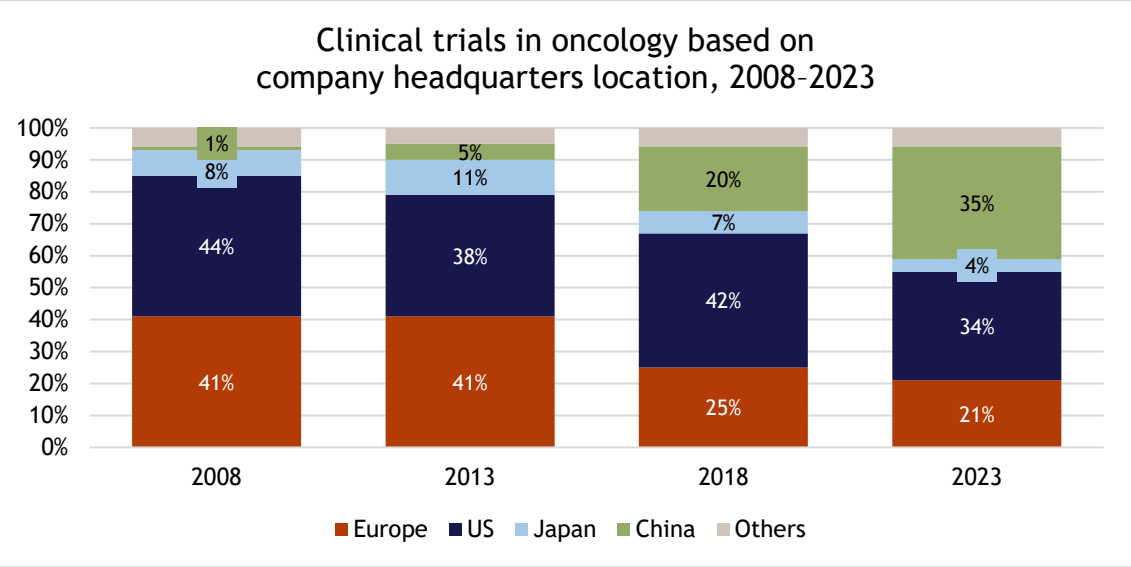


Figure 101: Country share of the number of phase I-III trials started in oncology based on company headquarters location, 2008-2023.

Source: IQVIA (285).

The situation looks similar when considering the country location of the clinical trials (285). Around 38% of clinical trials in oncology had participants from countries in Western Europe in 2014, but this share declined to around 25% in 2023. The share of trials with participants in Central and Eastern Europe halved from around 14% to 7% during this period. This mirrors to some extent the drop in European-headquartered companies' share of global trial starts. While the share of trials with participants in the US remained largely unchanged at around 20-25%, China's share increased from around 5% in 2014 to 22% in 2023.

5.4.2 Strategic initiatives

Investing in healthcare is not solely about patient well-being; it also bolsters the economy. According to EFPIA, the pharmaceutical industry is responsible for about 21% of global research expenditure (655, 656). It directly employs around 900,000 people across the European region and indirectly generates over 2.5 million jobs. A conducive research environment is also shaped by legislation on intellectual property rights. Strong intellectual property rights are crucial for fostering innovation, ensuring that new treatments are developed for patients today and in the future (657, 658).

A strategic view on research in life sciences has recently also taken hold at the EU level and might shape the work of the European Commission in its current term until 2029. This development is rooted in the "Draghi Report" published in September 2024. The Draghi Report provides recommendations to bolster the EU's competitiveness, highlighting the importance of innovation and reducing dependencies (659). An entire chapter on sectoral policies is focused on the pharma sector with nine proposals focusing on drawing novel R&D activities to the EU, helping expedite the access to markets for products, addressing options for increased and more focused R&D funding, and aiming at fostering business predictability in the longer run. In early 2025, Commission President Ursula von der Leyen unveiled the Competitiveness Compass, focusing on closing the innovation gap and driving productivity through innovation (588). It highlights life sciences as one of the areas of innovative technologies and potential growth engines.

To maintain its leadership in medical research and ensure that patients have access to the latest treatments, Europe should renew its commitment to clinical research and innovation. This involves not only investing in healthcare but also creating a policy environment that supports rapid development and deployment of new therapies. By treating healthcare expenditure as an investment, Europe can secure a healthier future for its citizens and a more robust economy.

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Appendix

A - Disease burden

Cumulative risk of getting cancer

Table A1: Cumulative risk of being diagnosed with cancer before the age of 85 for men and women in 2022

Country	Cumulative risk for men (%)	Cumulative risk for women (%)
Austria	41.8	31.7
Belgium	49.7	38.8
Bulgaria	39.2	27.5
Croatia	52.5	37.2
Cyprus	45.4	37.8
Czechia	46.9	35.4
Denmark	54.3	46.0
Estonia	52.3	33.8
Finland	46.8	37.3
France	51.4	38.7
Germany	46.7	36.2
Greece	47.5	33.6
Hungary	52.6	38.1
Iceland	43.8	38.6
Ireland	50.1	40.1
Italy	46.9	36.7
Latvia	53.3	33.7
Lithuania	53.5	31.0
Luxembourg	41.8	36.0
Malta	45.1	37.5
Netherlands	49.5	42.1
Norway	54.7	44.7
Poland	47.6	33.9
Portugal	48.4	34.4
Romania	46.4	31.9
Slovakia	50.9	34.4
Slovenia	49.7	37.5
Spain	46.6	31.6
Sweden	47.6	38.2
Switzerland	44.3	34.6
United Kingdom	48.3	40.3
EU-27	48.0	36.0

Notes: All cancers excluding non-melanoma skin cancer. Source: IARC (52).

Age-standardized incidence rates

Age-standardized incidence rates for men and women are shown in Figure A1 and Figure A2. These rates take into account the different population sizes and age structures of the populations, but do not control for other important factors such as the underlying development of risk factors and screening. For instance, countries with more screening programs (e.g., for cervical cancer, breast cancer, colorectal cancer, prostate cancer, or lung cancer) or with higher participation rates in these programs might record higher incidence rates than other countries, because more cancer cases can be detected. In the same manner, an increase in incidence rates over time within a country might reflect higher screening activities leading to the detection of more cancer cases rather than a true increase in the number of new cases.

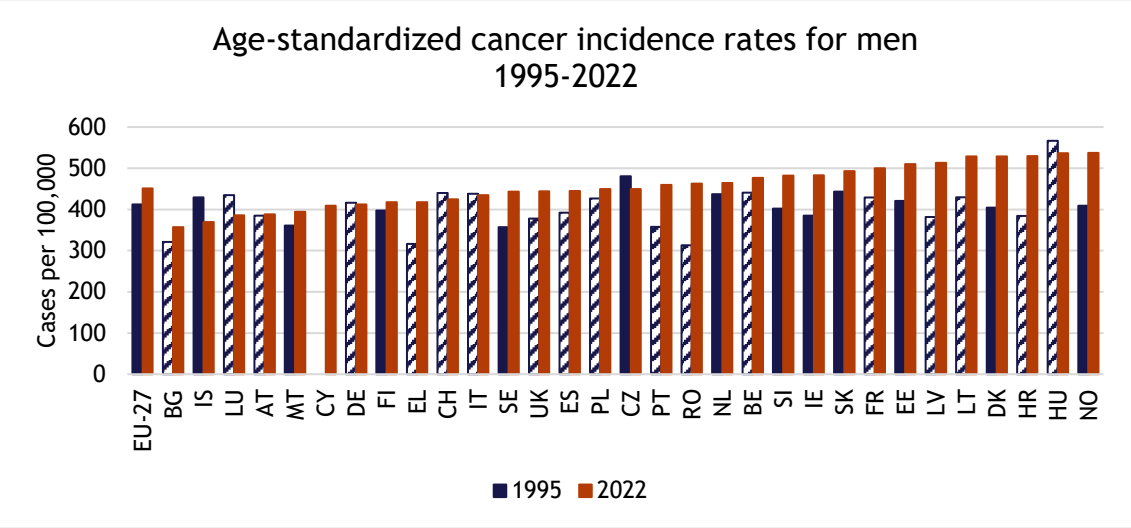

Figure A1: Estimated age-standardized cancer incidence rates (Old European standard) in men per 100,000 inhabitants, 1995-2022.

Notes: see notes for Figure 9. Source: IARC (5, 80).

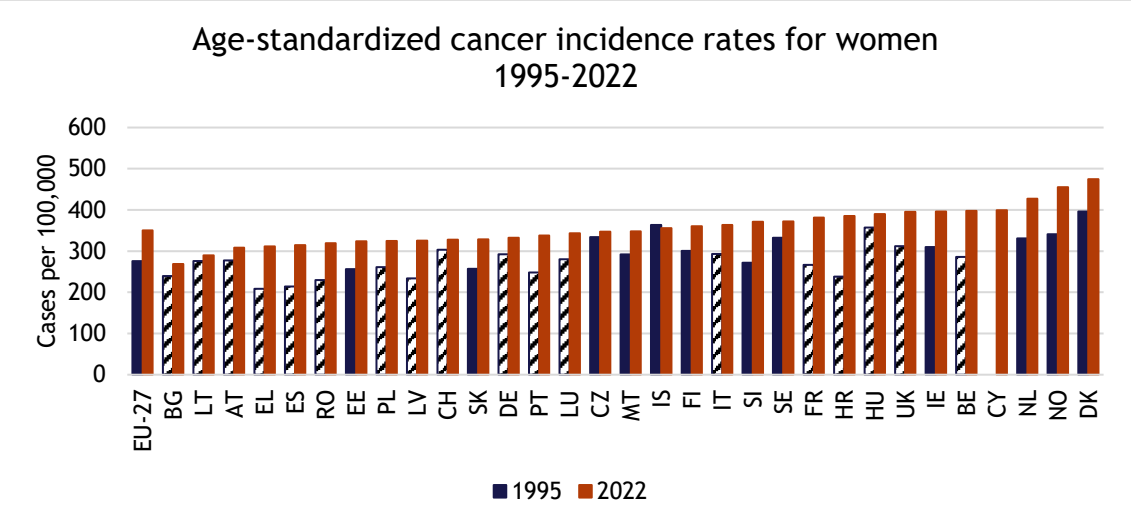

Figure A2: Estimated age-standardized cancer incidence rates (Old European standard) in women per 100,000 inhabitants, 1995-2022.

Notes: see notes for Figure 9. Source: IARC (5, 80).

Age-standardized mortality rates

Age-standardized mortality rates for men and women are shown in Figure A3 and Figure A4. These rates take into account different population sizes and age structures of the populations, but do not control for other important factors such as screening intensity and effectiveness of treatment.

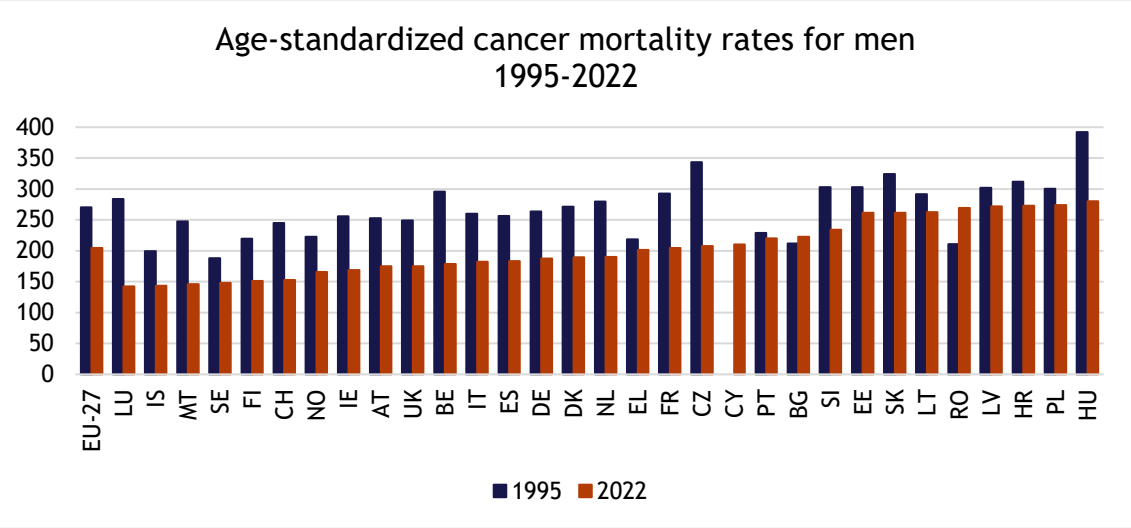

Figure A3: Estimated age-standardized cancer mortality rates (Old European standard) in men per 100,000 inhabitants, 1995-2022.

Notes: see notes for Figure 9. Source: IARC (5, 80).

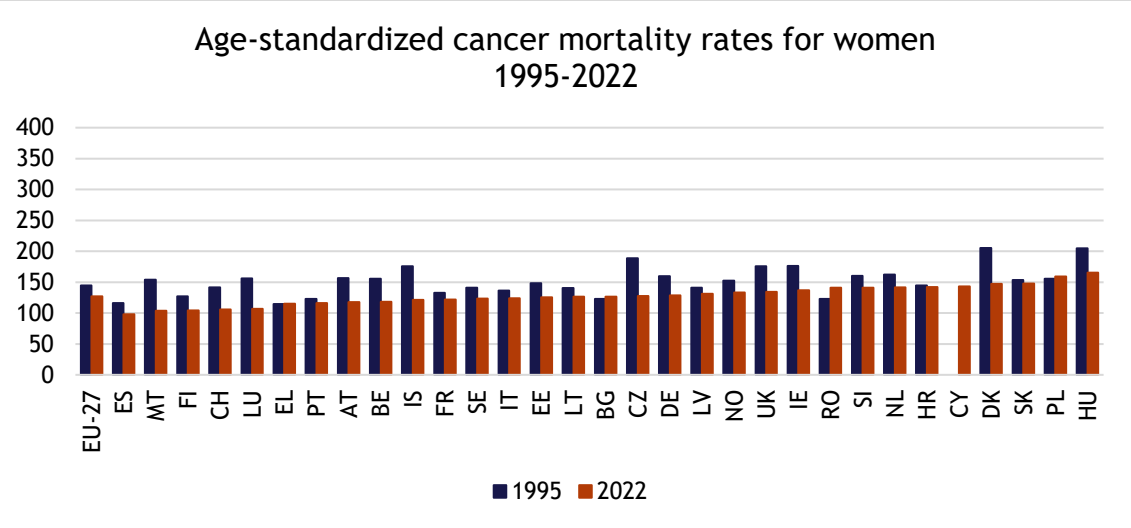

Figure A4: Estimated age-standardized cancer mortality rates (Old European standard) in women per 100,000 inhabitants, 1995-2022.

Notes: see notes for Figure 9. Source: IARC (5, 80).

B - Economic burden

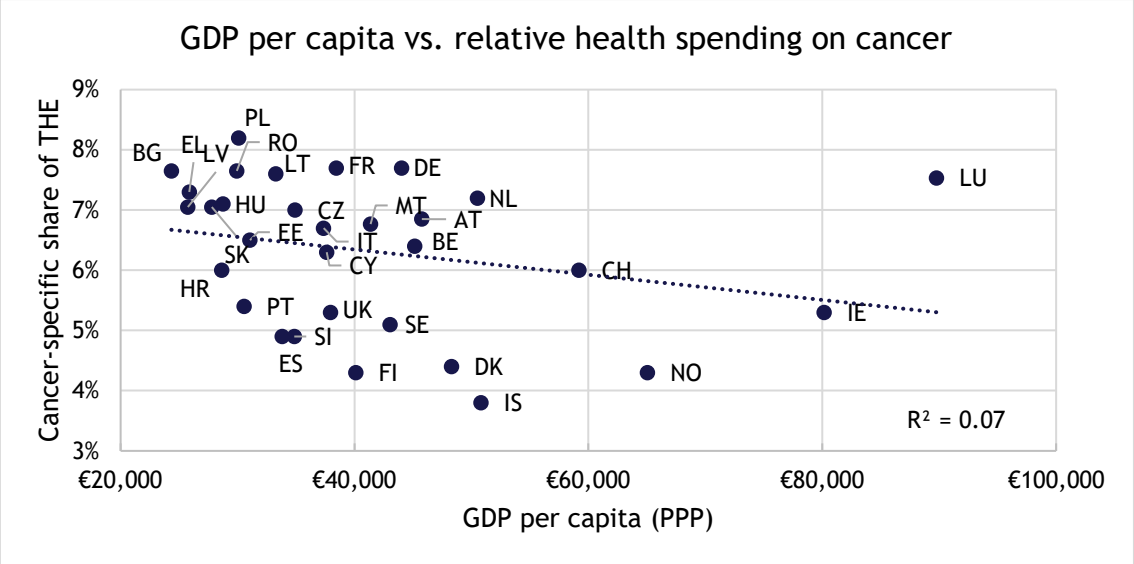

Figure B1: Country-level correlation of GDP per capita with cancer-specific share of total health expenditure (THE) in 2023.

Notes: PPP = purchasing power parity. Source: Cancer-specific shares based on own estimations, and GDP from Eurostat and ONS (114).

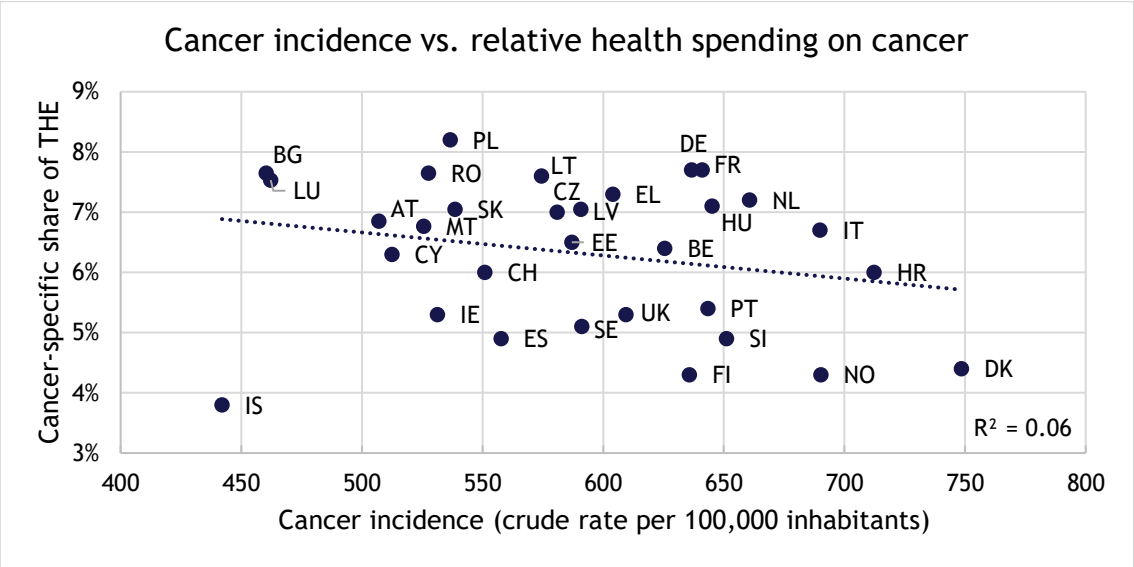

Figure B2: Country-level correlation of cancer incidence (crude rate per 100,000) in 2022 with cancer-specific share of total health expenditure (THE) in 2023.

Source: Cancer-specific shares based on own estimations, and cancer incidence from IARC (52).

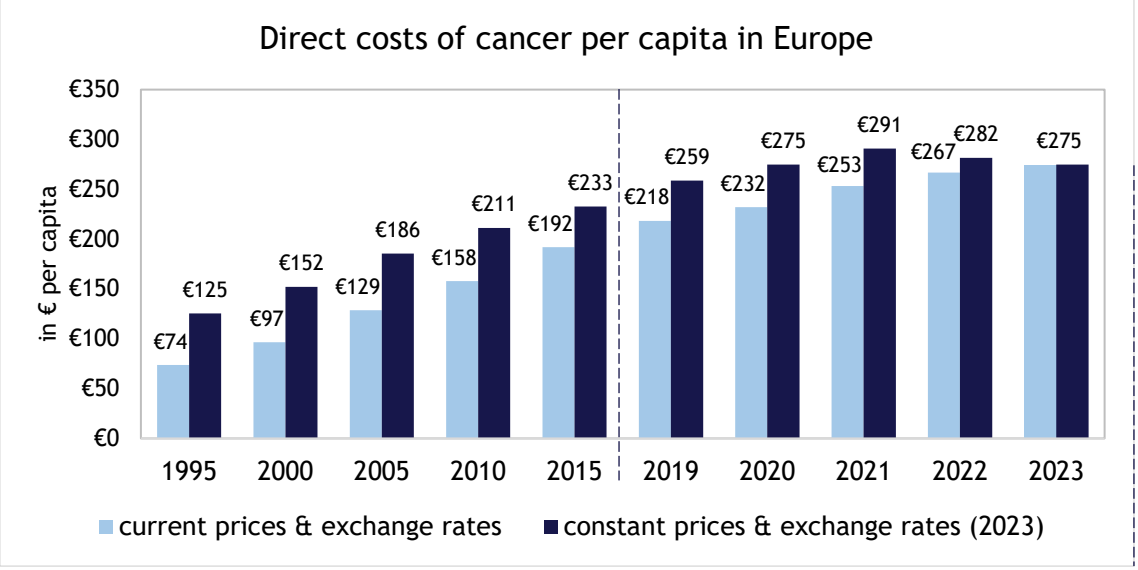

Figure B3: Direct costs of cancer per capita in Europe (in €), 1995-2023.

Notes and source: see Figure 25.

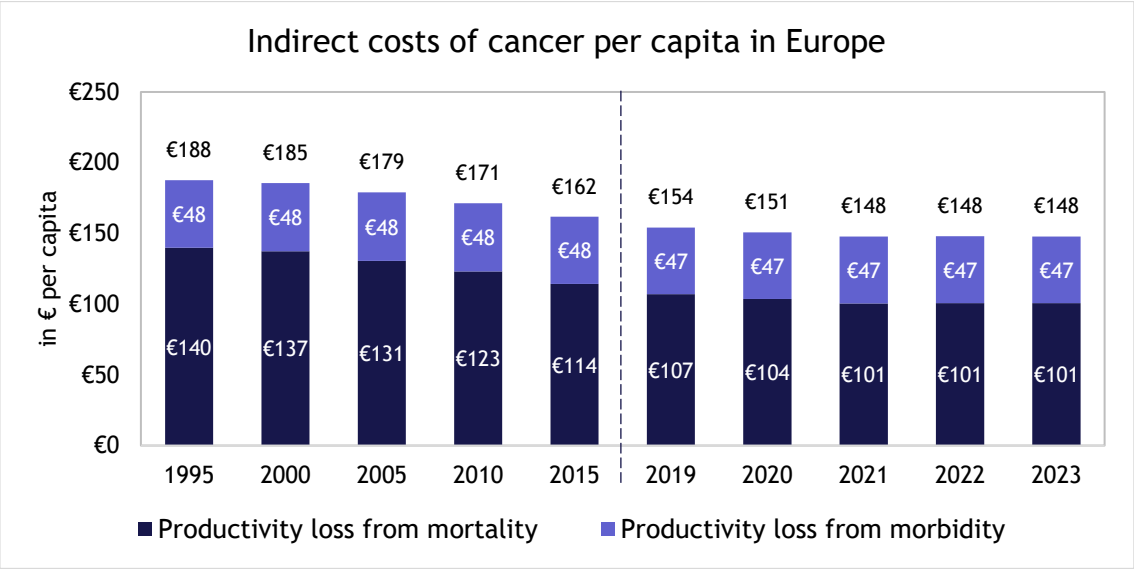

Figure B4: Indirect costs of cancer per capita in Europe (in €), 1995-2023.

Notes and sources: see Figure 29.

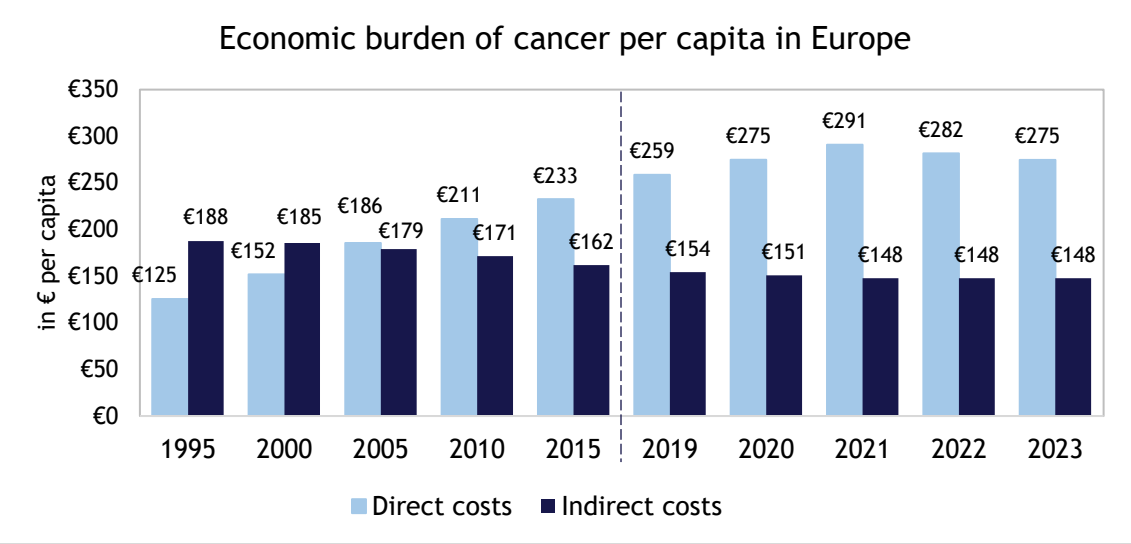

Figure B5: Economic burden of cancer per capita in Europe (in €; 2023 prices & exchange rates), 1995-2023.

Notes: see Figure 31.

C - Cancer medicines

List of cancer medicines

Data on approvals of new medicines by the EMA were sourced from the Union Register of medicinal products (497). Additional characteristics of the medicines were also collected from this database. Medicines with approval by the European Commission between January 1, 1995 and December 31, 2024 were included.

Table C1: List of centrally approved cancer medicines by the EMA, 1995-2024

Approval year	Chemical name	Cancer type	Orphan status	Medicine class	Monoclonal antibody	Route of administration	Solid tumors vs hematology
1995	docetaxel	breast	No	Chemo	No	IV	solid
1996	toremifene	breast	No	Hormone	No	Oral	solid
1996	topotecan	ovary	No	Chemo	No	IV, Oral	solid
1998	rituximab	lymphoma	No	Targeted	Yes	IV	hema
1999	temozolomide	brain CNS	No	Chemo	No	IV, Oral	solid
2000	trastuzumab	breast	No	Targeted	Yes	IV, SC	solid
2000	alitretinoin*	Kaposi's sarcoma	No	Chemo	No	Topical	solid
2001	capecitabine	colorectum	No	Chemo	No	Oral	solid
2001	bexarotene	lymphoma	No	Chemo	No	Oral	hema
2001	alemtuzumab*	leukemia	No	Targeted	Yes	IV	hema
2001	temoporfin	head & neck	No	Chemo	No	IV	solid
2001	imatinib	leukemia	No	Targeted	No	Oral	hema
2002	arsenic trioxide	leukemia	Yes	Chemo	No	IV	hema
2003	celecoxib*	colorectum	No	Targeted	No	Oral	solid
2004	ibritumomab tiuxetan*	lymphoma	No	Radio	Yes	IV	hema
2004	fulvestrant	breast	No	Hormone	No	IM	solid
2004	bortezomib	multiple myeloma	No	Targeted	No	IV, SC	hema
2004	mitotane	adrenal glands	Yes	Chemo	No	Oral	solid
2004	cetuximab	colorectum	No	Targeted	Yes	IV	solid
2004	pemetrexed	lung	No	Chemo	No	IV	solid
2005	bevacizumab	colorectum	No	Targeted	Yes	IV	solid
2005	erlotinib	lung	No	Targeted	No	Oral	solid
2006	clofarabine	leukemia	No	Chemo	No	IV	hema
2006	sorafenib	kidney	Yes	Targeted	No	Oral	solid
2006	sunitinib	GIST	No	Targeted	No	Oral	solid
2006	dasatinib	leukemia	No	Targeted	No	Oral	hema
2007	lenalidomide	multiple myeloma	Yes	Targeted	No	Oral	hema
2007	nelarabine	leukemia	Yes	Chemo	No	IV	hema
2007	5-aminolevulinic acid hydrochloride	brain CNS	Yes	Chemo	No	Oral, Topical	solid
2007	trabectedin	sarcoma	Yes	Chemo	No	IV	solid
2007	nilotinib	leukemia	Yes	Targeted	No	Oral	hema
2007	temsirolimus	kidney	Yes	Targeted	No	IV	solid
2007	panitumumab	colorectum	No	Targeted	Yes	IV	solid
2008	thalidomide	multiple myeloma	Yes	Targeted	No	Oral	hema
2008	lapatinib	breast	No	Targeted	No	Oral	solid
2008	azacitidine	leukemia	No	Chemo	No	IV, SC	hema
2009	degarelix	prostate	No	Hormone	No	SC	solid

App-roval year	Chemical name	Cancer type	Or-phan status	Medicine class	Mono-clonal antibody	Route of admin-istration	Solid tumors vs hematology
2009	catumaxomab*	cancer-caused ascites	No	Targeted	Yes	IP injection	solid
2009	gefitinib	lung	No	Targeted	No	Oral	solid
2009	everolimus	kidney	No	Targeted	No	Oral	solid
2009	vinflunine	urothelial	No	Chemo	No	IV	solid
2010	ofatumumab*	leukemia	Yes	Targeted	Yes	IV	hema
2010	pazopanib	kidney	No	Targeted	No	Oral	solid
2011	tegafur / gimeracil / oteracil	stomach	No	Chemo	No	Oral	solid
2011	cabazitaxel	prostate	No	Chemo	No	IV	solid
2011	eribulin	breast	No	Chemo	No	IV	solid
2011	ipilimumab	melanoma	No	Immuno (CPI)	Yes	IV	solid
2011	abiraterone	prostate	No	Hormone	No	Oral	solid
2012	vandetanib	thyroid	No	Targeted	No	Oral	solid
2012	vemurafenib	melanoma	No	Targeted	No	Oral	solid
2012	pixantrone	lymphoma	No	Chemo	No	IV	hema
2012	ruxolitinib	myelofibrosis	No	Targeted	No	Oral, Topical	hema
2012	axitinib	kidney	No	Targeted	No	Oral	solid
2012	decitabine	leukemia	Yes	Chemo	No	IV	hema
2012	crizotinib	lung	No	Targeted	No	Oral	solid
2012	brentuximab vedotin	lymphoma	Yes	Targeted (ADC)	Yes	IV	hema
2013	aflibercept	colorectum	No	Targeted	No	IV	solid
2013	pertuzumab	breast	No	Targeted	Yes	IV	solid
2013	bosutinib	leukemia	No	Targeted	No	Oral	hema
2013	enzalutamide	prostate	No	Hormone	No	Oral	solid
2013	ponatinib	leukemia	Yes	Targeted	No	Oral	hema
2013	vismodegib	skin (basal-cell)	No	Targeted	No	Oral	solid
2013	pomalidomide	multiple myeloma	Yes	Targeted	No	Oral	hema
2013	dabrafenib	melanoma	No	Targeted	No	Oral	solid
2013	regorafenib	colorectum	No	Targeted	No	Oral	solid
2013	sipuleucel-T*	prostate	No	Immuno (vaccine)	No	IV	solid
2013	afatinib	lung	No	Targeted	No	Oral	solid
2013	radium Ra223 dichloride	prostate	No	Radio	No	IV	solid
2013	trastuzumab emtansine	breast	No	Targeted (ADC)	Yes	IV	solid
2014	cabozantinib	thyroid	Yes	Targeted	No	Oral	solid
2014	siltuximab	Castleman disease	Yes	Targeted	Yes	IV	hema
2014	trametinib	melanoma	No	Targeted	No	Oral	solid
2014	obinutuzumab	leukemia	Yes	Targeted	Yes	IV	hema
2014	idelalisib	leukemia	No	Targeted	No	Oral	hema
2014	ibrutinib	lymphoma	Yes	Targeted	No	Oral	hema
2014	nintedanib	lung	No	Targeted	No	Oral	solid
2014	olaparib	ovary	No	Targeted	No	Oral	solid
2014	ramucirumab	stomach	No	Targeted	Yes	IV	solid
2015	ceritinib	lung	No	Targeted	No	Oral	solid
2015	lenvatinib	thyroid	No	Targeted	No	Oral	solid
2015	nivolumab	melanoma	No	Immuno (CPI)	Yes	IV	solid
2015	pembrolizumab	melanoma	No	Immuno (CPI)	Yes	IV	solid

App-roval year	Chemical name	Cancer type	Or-phan status	Medicine class	Mono-clonal antibody	Route of admin-istration	Solid tumors vs hematology
2015	dinutuximab*	neuroblastoma	No	Targeted	Yes	IV	solid
2015	sonidegib	skin (basal-cell)	No	Targeted	No	Oral	solid
2015	panobinostat	multiple myeloma	Yes	Targeted	No	Oral	hema
2015	carfilzomib	multiple myeloma	Yes	Targeted	No	IV	hema
2015	cobimetinib	melanoma	No	Targeted	No	Oral	solid
2015	blinatumomab	leukemia	Yes	Immuno (BiTE)	Yes	IV	hema
2015	talimogene laherparepvec	melanoma	No	Immuno (OVT)	No	Injection	solid
2016	pegaspargase	leukemia	No	Chemo	No	IM, IV	hema
2016	osimertinib	lung	No	Targeted	No	Oral	solid
2016	necitumumab*	lung	No	Targeted	Yes	IV	solid
2016	trifluridine / tipiracil	colorectum	No	Chemo	No	Oral	solid
2016	elotuzumab	multiple myeloma	No	Targeted	Yes	IV	hema
2016	daratumumab	multiple myeloma	Yes	Targeted	Yes	IV	hema
2016	olaratumab*	sarcoma	Yes	Targeted	Yes	IV	solid
2016	palbociclib	breast	No	Targeted	No	Oral	solid
2016	ixazomib	multiple myeloma	Yes	Targeted	No	Oral	hema
2016	venetoclax	leukemia	No	Targeted	No	Oral	hema
2017	alectinib	lung	No	Targeted	No	Oral	solid
2017	dinutuximab beta	neuroblastoma	Yes	Targeted	Yes	IV	solid
2017	inotuzumab ozogamicin	leukemia	Yes	Targeted (ADC)	Yes	IV	hema
2017	ribociclib	breast	No	Targeted	No	Oral	solid
2017	tivozanib	kidney	No	Targeted	No	Oral	solid
2017	avelumab	skin (Merkel cell)	Yes	Immuno (CPI)	Yes	IV	solid
2017	midostaurin	leukemia	Yes	Targeted	No	Oral	hema
2017	atezolizumab	urothelial	No	Immuno (CPI)	Yes	IV	solid
2017	lutetium (177Lu) oxodotreotide	neuroendocrine tumours	Yes	Radio	No	IV	solid
2017	padeliporfin	prostate	No	Chemo	No	IV	solid
2017	niraparib	ovary	Yes	Targeted	No	Oral	solid
2018	gemtuzumab ozogamicin	leukemia	Yes	Targeted (ADC)	Yes	IV	hema
2018	rucaparib	ovary	No	Targeted	No	Oral	solid
2018	tisagenlecleucel	leukemia	Yes	Immuno (CAR-T)	No	IV	hema
2018	axicabtagene ciloleucel	lymphoma	Yes	Immuno (CAR-T)	No	IV	hema
2018	neratinib	breast	No	Targeted	No	Oral	solid
2018	encorafenib	melanoma	No	Targeted	No	Oral	solid
2018	binimetinib	melanoma	No	Targeted	No	Oral	solid
2018	durvalumab	lung	No	Immuno (CPI)	Yes	IV	solid
2018	abemaciclib	breast	No	Targeted	No	Oral	solid
2018	brigatinib	lung	No	Targeted	No	Oral	solid
2018	mogamulizumab	Sezary syndrome	Yes	Targeted	Yes	IV	hema
2019	apalutamide	prostate	No	Targeted	No	Oral	solid
2019	dacomitinib	lung	No	Targeted	No	Oral	solid
2019	lorlatinib	lung	No	Targeted	No	Oral	solid

App-roval year	Chemical name	Cancer type	Or-phan status	Medicine class	Mono-clonal antibody	Route of admin-istration	Solid tumors vs hematology
2019	talazoparib	breast	No	Targeted	No	Oral	solid
2019	cemiplimab	skin (squamous cell)	No	Immuno (CPI)	Yes	IV	solid
2019	larotrectinib	solid tumors (NTRK)	No	Targeted	No	Oral	solid
2019	gilteritinib	leukemia	Yes	Targeted	No	Oral	hema
2020	polatuzumab vedotin	lymphoma	Yes	Targeted (ADC)	Yes	IV	hema
2020	darolutamide	prostate	No	Targeted	No	Oral	solid
2020	isatuximab	multiple myeloma	No	Targeted	No	IV	hema
2020	glasdegib	leukemia	Yes	Targeted	No	Oral	hema
2020	alpelisib	breast	No	Targeted	No	Oral	solid
2020	entrectinib	solid tumors (NTRK)	No	Targeted	No	Oral	solid
2020	belantamab mafodotin*	multiple myeloma	Yes	Targeted (ADC)	Yes	IV	hema
2020	avapritinib	GIST	Yes	Targeted	No	Oral	solid
2020	acalabrutinib	leukemia	No	Targeted	No	Oral	hema
2020	brexucabtagene autoleucel	lymphoma	Yes	Immuno (CAR-T)	No	IV	hema
2021	tagraxofusp	plasmacytoid dendritic cells	Yes	Targeted	No	IV	hema
2021	trastuzumab deruxtecan	breast	No	Targeted (ADC)	Yes	IV	solid
2021	fedratinib	myelofibrosis	Yes	Targeted	No	Oral	hema
2021	moxetumomab pasudotox*	leukemia	No	Targeted (ADC)	Yes	IV	hema
2021	selpercatinib	lung	No	Targeted	No	Oral	solid
2021	tucatinib	breast	No	Targeted	No	Oral	solid
2021	pemigatinib	bile ducts	Yes	Targeted	No	Oral	solid
2021	selinexor	multiple myeloma	No	Targeted	No	Oral	hema
2021	dostarlimab	endometrial	No	Immuno (CPI)	Yes	IV	solid
2021	duvelisib	leukemia	No	Targeted	No	Oral	hema
2021	idecabtagene vicleucel	multiple myeloma	Yes	Immuno (CAR-T)	No	IV	hema
2021	tafasitamab	lymphoma	Yes	Targeted	Yes	IV	hema
2021	pralsetinib	lung	No	Targeted	No	Oral	solid
2021	ripretinib	GIST	Yes	Targeted	No	Oral	solid
2021	sacituzumab govitecan	breast	No	Targeted (ADC)	Yes	IV	solid
2021	zanubrutinib	lymphoma	No	Targeted	No	Oral	hema
2021	amivantamab	lung	No	Targeted (BsAb)	Yes	IV	solid
2022	sotorasib	lung	No	Targeted	No	Oral	solid
2022	tepotinib	lung	No	Targeted	No	Oral	solid
2022	tebentafusp	uveal melanoma	Yes	Immuno (BiTE)	No	IV	solid
2022	lisocabtagene maraleucel	lymphoma	No	Immuno (CAR-T)	No	IV	hema
2022	enfortumab vedotin	urothelial	No	Targeted (ADC)	Yes	IV	solid
2022	relugolix	prostate	No	Hormone	No	Oral	solid
2022	ciltacabtagene autoleucel	multiple myeloma	Yes	Immuno (CAR-T)	No	IV	hema
2022	mosunetuzumab	lymphoma	Yes	Immuno (BiTE)	Yes	IV	hema
2022	capmatinib	lung	No	Targeted	No	Oral	solid

App-roval year	Chemical name	Cancer type	Or-phan status	Medicine class	Mono-clonal antibody	Route of admin-istration	Solid tumors vs hematology
2022	melphalan flufenamide	multiple myeloma	No	Targeted (PDC)	No	IV	hema
2022	teclistamab	multiple myeloma	No	Immuno (BiTE)	Yes	SC	hema
2022	asciminib	leukemia	Yes	Targeted	No	Oral	hema
2022	relatlimab/nivolumab	melanoma	No	Immuno (CPI)	Yes	IV	solid
2022	lutetium (177Lu) vipivotide tetraxetan	prostate	No	Radio	No	IV	solid
2022	tabelecleucel	lymphoproliferative disease	Yes	Immuno (allogeneic T-cell)	No	IV	hema
2022	loncastuximab tesirine	lymphoma	No	Targeted (ADC)	Yes	IV	hema
2023	tremelimumab	lung	No	Immuno (CPI)	Yes	IV	solid
2023	ivosidenib	leukemia	Yes	Targeted	No	Oral	hema
2023	futibatinib	bile ducts	No	Targeted	No	Oral	solid
2023	glofitamab	lymphoma	Yes	Immuno (BiTE)	Yes	IV	hema
2023	talquetamab	multiple myeloma	Yes	Immuno (BiTE)	Yes	SC	hema
2023	tislelizumab	esophagus	No	Immuno (CPI)	Yes	IV	solid
2023	elacestrant	breast	No	Hormone	No	Oral	solid
2023	cedazuridine, decitabine	leukemia	No	Chemo	No	Oral	hema
2023	epcoritamab	lymphoma	Yes	Immuno (BiTE)	Yes	SC	hema
2023	pirtobrutinib	lymphoma	No	Targeted	No	Oral	hema
2023	quizartinib	leukemia	No	Targeted	No	Oral	hema
2023	elranatamab	multiple myeloma	Yes	Immuno (BiTE)	Yes	SC	hema
2024	adagrasib	lung	No	Targeted	No	Oral	solid
2024	momelotinib	myelofibrosis	Yes	Targeted	No	Oral	hema
2024	retifanlimab	skin (Merkel cell)	Yes	Immuno (CPI)	Yes	IV	solid
2024	capivasertib	breast	No	Targeted	No	Oral	solid
2024	fruquintinib	colorectum	No	Targeted	No	Oral	solid
2024	sugemalimab	lung	No	Immuno (CPI)	Yes	IV	solid
2024	erdafitinib	urothelial	No	Targeted	No	Oral	solid
2024	odronextamab	lymphoma	Yes	Immuno (BiTE)	Yes	IV	hema
2024	toripalimab	head & neck	No	Immuno (CPI)	Yes	IV	solid
2024	zolbetuximab	stomach	Yes	Targeted	Yes	IV	solid
2024	mirvetuximab soravtansine	ovary	Yes	Targeted (ADC)	Yes	IV	solid

Notes: Medicines used with a therapeutic intent in cancer patients in the groups WHO ATC groups L01, L02, L03, L04, and V10 are included. Medicines with identical active substances have only been included at their first instance of marketing authorization. Medicines are listed chronologically according to the decision date by the European Commission. Chemo = chemotherapy; Hormone = hormone therapy; Targeted = targeted therapy; Immuno = immunotherapy; ADC = antibody-drug conjugate; CPI = checkpoint inhibitor; CAR-T = chimeric antigen receptor T-cell therapy; OVT = oncolytic virus therapy; BsAb = bispecific antibody; BiTE = bispecific T-cell engager; PDC = peptide-drug conjugate; Radio = radiopharmaceuticals; IV = intravenous; IM = intramuscular; SC = subcutaneous; Hema = hematologic malignancies; Solid = solid tumors. Lenalidomide, pomalidomide, and thalidomide are classified as targeted medicines, but they function as immunosuppressants. * Medicines marked with an asterisk were withdrawn from the market: alitretinoin in 2021, alemtuzumab in 2012, celecoxib in 2011, catumaxomab in 2017, ofatumumab in 2019, sipuleucel-T in 2015, dinutuximab in 2017, necitumumab in 2021, olaratumab in 2019, belantamab mafodotin in 2024, and moxetumomab pasudotox in 2021, while for ibritumomab tiuxetan the authorization lapsed in 2024. Medicines approved by regulatory agencies in Switzerland (Swissmedic) and the UK (MHRA) are not included in this table.

Data sources for medicine sales

The analysis presented in subsections 4.5 and 4.6 draws on several sources for medicine sales in value and volume. For most countries, data was acquired from IQVIA, which maintains a database called IQVIA MIDAS. For the Netherlands, data was acquired through IQVIA from Farminform. For Denmark, Signum Life Science provided sales data. For Estonia, Ravimiamet (Republic of Estonia Agency of Medicines) provided sales data. For Iceland, Frumtök (Icelandic Association of the Pharmaceutical Industry) provided sales data. No data could be acquired for Cyprus and Malta. Data for Greece and Luxembourg come from the IQVIA MIDAS database, but they lack sales in hospitals and are hence incomplete and were not used for most country-specific analyses.

The definition of "cancer medicines"[39] largely follows the definition of the therapeutic area "oncology" in the IQVIA MIDAS database, which relies on EphMRA (European Pharmaceutical Market Research Association) ATC codes. There is a great overlap between the EphMRA ATC codes and WHO ATC codes. Cancer medicines in the WHO ATC group L01 (antineoplastic agents) and L02 (endocrine therapy) were included along with four agents of group L04 (the immunosuppressants thalidomide, lenalidomide, pomalidomide, and siltuximab) and four agents of group VX10 (the therapeutic radiopharmaceuticals ibritumomab tiuxetan (90Y), radium (223Ra) dichloride, lutetium (177Lu) oxodotreotide, and lutetium (177Lu) vipivotide tetraxetan). The same definition was used to request and clean data for Denmark, Estonia, and Iceland.

Measurement of uptake in value

The sales data in all obtained sources are based on list prices (ex-manufacturer prices). These prices often do not reflect the actual final sales prices due to confidential rebates provided to public payers in most European health systems. As a result, relying on list prices leads to an overestimation of the costs associated with cancer medications. On the other hand, the data exclude any profit margins on medicines dispensed via retail, which can result in an underestimation of the actual costs of some cancer medicines.

The big advantage of measuring uptake of cancer medicines in value terms (euros) is that it enables aggregations, such as total spending on all cancer medicines or spending on medicines of a certain medicine class. It also enables comparisons of spending on cancer medicines versus other resources in cancer care. A limitation of this approach is that a common currency (euro) is needed, which means that sales figures in countries with other currencies make it necessary to define an exchange rate. The choice of the exchange rate, for instance based on current values or for a certain base year or based on PPP-adjusted values, will influence the level of sales and the relative position of a country in the sales ranking. In comparisons of sales over time in this report, all numbers were expressed in euros and inflation-adjusted (with the HICP) and exchange rate-adjusted unless otherwise noted. However, even in countries with a common currency (the euro area), prices of one and the same medicine can differ and higher sales in one country might simply reflect higher national (list) prices of a medicine rather than higher usage in volume terms.

[39] Note that the selection of medicines discussed does not encompass all medications used in the treatment course of cancer patients. Medications for managing pain and side effects of cancer treatments, such as antiemetics, were not included. However, these medicines are relatively inexpensive. Consequently, the exclusion of these medications results in only a minor underestimation of the costs of all medicines associated with cancer treatment.

Cancer medicine sales by country

Table C2: Cancer medicine sales - total (in million €; current prices; based on list prices leading to overestimation), 2014-2023

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
AT	506.9	609.1	724.7	841.9	936.6	1,107.4	1,292.0	1,446.2	1,588.0	1,776.2
BE	483.8	562.4	610.6	772.6	1,018.9	1,301.9	1,464.4	1,553.6	1,737.7	2,077.4
BG	126.8	142.5	158.1	201.8	221.7	266.6	340.9	403.7	455.0	573.8
HR	71.5	85.9	102.4	122.8	160.0	222.6	273.7	296.6	348.1	393.8
CZ	160.2	161.2	277.5	312.1	345.0	409.4	476.4	529.4	640.0	800.0
DK	287.9	316.6	367.9	460.1	545.0	596.8	701.4	701.5	739.8	792.5
EE	29.6	31.3	34.5	38.3	43.4	51.2	59.3	64.5	69.2	77.9
FI	218.1	233.8	260.1	275.3	331.2	394.7	422.7	481.1	468.1	510.5
FR	3,269.5	3,711.4	4,384.6	4,698.4	5,275.6	6,378.2	7,434.4	8,732.7	10,407	11,881
DE	4,666.5	5,081.6	5,820.4	6,572.8	7,407.6	8,672.5	9,933.7	10,748	11,260	12,249
EL*	45.3	46.5	44.4	43.6	43.8	44.2	47.0	49.9	48.4	44.5
HU	229.1	259.6	294.2	337.0	385.7	493.3	541.2	592.5	579.9	677.4
IS	9.5	11.2	13.5	15.9	20.8	22.4	26.6	32.5	35.2	38.5
IE	191.0	210.4	241.0	262.8	313.7	376.6	416.3	468.2	489.6	532.2
IT	2,513.1	2,806.6	3,188.1	3,760.4	4,508.4	5,303.5	6,102.9	6,973.7	7,993.1	9,175.8
LA	13.8	16.5	15.3	18.7	24.0	22.0	29.6	34.4	46.2	58.2
LT	23.2	31.2	36.8	48.7	55.9	73.1	105.9	137.1	162.4	177.5
LU*	5.6	5.9	6.0	6.3	7.0	7.4	8.2	9.1	10.0	9.7
NL	654.3	730.4	852.5	932.0	1,071.5	1,354.1	1,476.1	1,555.5	1,607.3	1,696.8
NO	161.5	176.8	214.2	324.2	362.4	404.8	449.7	549.2	640.9	657.6
PL	447.7	477.2	488.8	597.1	710.1	838.4	1,003.6	1,095.0	1,279.4	1,778.1
PT	226.2	251.7	284.6	339.3	399.7	464.4	501.5	566.6	627.5	726.5
RO	274.5	268.2	273.9	285.1	369.1	464.1	575.0	718.3	886.3	1,047.9
SK	147.5	154.0	173.1	159.3	170.0	193.7	210.7	219.2	235.3	277.0
SI	66.0	69.7	77.5	86.8	102.4	111.0	139.4	157.8	176.6	190.2
ES	1,741.5	1,869.0	2,250.4	2,733.0	3,198.5	3,788.9	4,559.8	5,296.0	5,692.1	6,358.3
SE	345.0	381.7	445.9	500.8	594.5	700.1	803.3	905.7	956.6	989.0
CH	480.4	574.8	658.5	751.7	803.7	943.4	1,095.4	1,179.9	1,353.7	1,496.2
UK	2,105.1	2,703.6	2,600.5	2,793.8	3,259.3	3,984.9	4,367.9	5,398.8	6,336.9	7,321.4
EU-27*	16,694	18,462	21,363	24,357	28,188	33,585	38,864	43,678	48,446	54,817
Europe	19,501	21,981	24,900	28,293	32,686	38,992	44,859	50,897	56,871	64,385

Notes: Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Ravimiamet for Estonia, Frumtök for Iceland, and Signum Life Science for Denmark. * Sales for Greece and Luxembourg only include retail sales and lack hospital sales, and they are excluded from the sum of the EU-27 sales.

Table C3: Cancer medicine sales - per capita (in €; current prices; based on list prices leading to overestimation), 2014-2023

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
AT	60	71	83	96	106	125	145	162	177	195
BE	43	50	54	68	89	114	127	134	150	177
BG	18	20	22	28	31	38	49	58	67	89
HR	17	20	24	30	39	55	67	73	90	102
CZ	15	15	26	30	33	38	45	50	61	74
DK	51	56	64	80	94	103	120	120	126	134
EE	22	24	26	29	33	39	45	49	52	57
FI	40	43	47	50	60	72	77	87	84	92
FR	49	56	66	70	79	95	110	129	153	174
DE	58	63	71	80	89	104	119	129	135	145
EL*	4.1	4.3	4.1	4.0	4.1	4.1	4.4	4.7	4.6	4.3
HU	23	26	30	34	39	50	55	61	60	71
IS	29	34	41	47	60	63	73	88	93	99
IE	41	45	51	55	65	77	84	94	97	101
IT	41	46	53	62	75	89	102	118	135	156
LV	6.9	8.3	7.8	9.6	12	11	16	18	25	31
LT	7.9	11	13	17	20	26	38	49	58	62
LU*	10	10	10	11	12	12	13	14	16	15
NL	39	43	50	55	62	78	85	89	91	95
NO	32	34	41	62	68	76	84	102	118	120
PL	12	13	13	16	19	22	26	30	35	48
PT	22	24	28	33	39	45	49	55	61	69
RO	14	13	14	15	19	24	30	37	47	55
SK	27	28	32	29	31	36	39	40	43	51
SI	32	34	38	42	50	53	67	75	84	90
ES	37	40	48	59	69	81	96	112	120	132
SE	36	39	45	50	59	68	78	87	92	94
CH	59	70	79	89	95	110	127	136	155	170
UK	33	42	40	42	49	60	65	81	95	109
EU-27*	39	43	49	56	65	77	89	101	112	126
Europe	38	42	48	54	62	74	85	97	108	122

Notes: Own calculations based on IQVIA MIDAS data and Farminform data for the Netherlands, Ravimiamet for Estonia, Frumtök for Iceland, and Signum Life Science for Denmark. * Sales for Greece and Luxembourg only include retail sales and lack hospital sales, and both countries are excluded in the calculation of the EU-27 per capita sales. Population data were sourced from Eurostat (54), and for the UK from the OECD (55) and the ONS (75).

Market share of medicines by group of countries

Table C4: Top ten medicines by market share (based on list prices) in Central and Eastern European countries.

2014		2019		2023	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Trastuzumab	10.9%	Nivolumab	7.4%	Pembrolizumab	14.8%
Bevacizumab	10.0%	Pembrolizumab	7.1%	Nivolumab	7.3%
Rituximab	9.6%	Bevacizumab	5.8%	Daratumumab	4.3%
Imatinib	7.6%	Trastuzumab	5.3%	Ibrutinib	4.2%
Sunitinib	4.4%	Ibrutinib	4.6%	Enzalutamide	4.1%
Bortezomib	3.9%	Lenalidomide	4.0%	Bevacizumab	2.9%
Nilotinib	3.0%	Rituximab	4.0%	Olaparib	2.6%
Dasatinib	2.8%	Abiraterone	3.1%	Atezolizumab	2.4%
Leuprorelin	2.7%	Enzalutamide	3.0%	Venetoclax	2.3%
Lenalidomide	2.3%	Pertuzumab	2.7%	Pertuzumab	2.2%
Total	57.1%	Total	47.0%	Total	47.2%

Notes: For EE, only retail data were included due to limited data availability.

Table C5: Top ten medicines by market share (based on list prices) in the Big Five countries.

2014		2019		2023	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Trastuzumab	8.6%	Pembrolizumab	7.3%	Pembrolizumab	14.6%
Rituximab	7.9%	Lenalidomide	6.3%	Daratumumab	6.4%
Bevacizumab	7.9%	Nivolumab	5.9%	Nivolumab	4.8%
Imatinib	6.0%	Trastuzumab	4.2%	Enzalutamide	3.6%
Lenalidomide	4.9%	Bevacizumab	3.9%	Ibrutinib	3.3%
Abiraterone	4.6%	Ibrutinib	3.9%	Atezolizumab	2.5%
Pemetrexed	3.4%	Rituximab	3.7%	Osimertinib	2.3%
Bortezomib	3.0%	Palbociclib	3.7%	Palbociclib	2.2%
Paclitaxel	2.9%	Abiraterone	3.4%	Lenalidomide	2.0%
Leuprorelin	2.6%	Daratumumab	3.4%	Apalutamide	2.0%
Total	51.7%	Total	45.8%	Total	43.7%

Table C6: Top ten medicines by market share (based on list prices) in Northern and Western European countries.

2014		2019		2023	
Medicine	Share of total sales	Medicine	Share of total sales	Medicine	Share of total sales
Trastuzumab	10.4%	Pembrolizumab	9.4%	Pembrolizumab	14.8%
Rituximab	8.9%	Lenalidomide	7.5%	Daratumumab	8.1%
Bevacizumab	7.9%	Nivolumab	6.0%	Nivolumab	4.8%
Imatinib	6.3%	Trastuzumab	4.9%	Enzalutamide	3.6%
Abiraterone	4.9%	Rituximab	4.5%	Ibrutinib	2.9%
Lenalidomide	4.9%	Enzalutamide	4.3%	Rituximab	2.7%
Bortezomib	3.9%	Bevacizumab	3.9%	Bevacizumab	2.5%
Pemetrexed	3.7%	Daratumumab	3.4%	Osimertinib	2.5%
Ipilimumab	2.5%	Ibrutinib	3.2%	Lenalidomide	2.3%
Leuprorelin	2.3%	Palbociclib	3.1%	Trastuzumab	2.2%
Total	55.7%	Total	50.1%	Total	46.4%

Notes: For EL and LU, only retail data were included due to limited data availability.

Measurement of uptake in volume

Full access to cancer medicines is attained when every patient that may benefit will receive the relevant medicine (492). The ideal data source to measure access would be patient-level data from country-wide clinical cancer registries. As such data either are not easily obtained or do not exist, country-level measures have to be used as a proxy for patient access to cancer medicines. This approach has been used in previous Comparator Reports (45-49). It is also the approach adopted in this report. Access to cancer medicines is equated with market uptake, i.e., total annual sales in volume of cancer medicines in a country.

Measuring the usage of cancer medicines in volume terms (e.g., in milligrams) eliminates the problem of varying medicine prices, rebates, and exchange rates between countries and over time. For the analysis of the uptake of a single medicine, sales can readily be expressed in milligrams (mg) of the active substance (except for CAR T-cell therapies). In this report, these sales were standardized by the number of incidence or mortality cases of a specific cancer type that the medicine is supposed to treat.

For the analysis of the uptake of multiple medicines, sales need to be standardized. A measure called the standard weekly dose (SWD) per patient – which is similar to the measure of defined daily dose (DDD) used by the WHO for many non-cancer medicines[40] – was calculated; see the next section. Annual sales in milligrams were divided by the SWD for every medicine to get the number of weekly doses sold. The weekly doses sold were then summed up across cancer medicines.

There are several factors that complicate the analysis of uptake in volume. First, national treatment guidelines might differ. Although the EMA provides a recommended dose for each medicine, variations in dosage and treatment duration might explain some of the differences in usage between countries. Second, stockpiling of medicines might occur. A certain portion of the initial sales of new products is often used to create inventory in the healthcare system, which leads to an overestimation of market uptake. Older products may experience decreases in inventory, and their market uptake may therefore be underestimated. Stockpiling distorts the actual usage data derived from sales figures, making it challenging to accurately assess how widely or quickly products are being adopted in the healthcare system.

In the analyses of single and multiple medicines, the number of milligrams or standard weekly doses were divided by the number of cancer patients in a country. This brings the sales closer to the actual need and demand for cancer care. The resulting measure of uptake is the number of milligrams or standard weekly doses sold per cancer patient. The number of cancer patients was defined in the following way. For most cancer types, the annual number of deaths (year 2022 with data from IARC) was used. This is because most newer medicines are initially used to treat advanced cases. In such a setting, treatment is directed toward a population that cannot be cured and will ultimately die from cancer. Incidence data (year 2022 with data from IARC) was used in specific cases for hematologic cancers (because these cancers do not follow the early-stage to late-stage progression typical of solid tumors and patients usually begin treatment immediately upon diagnosis) and breast cancer and immune checkpoint inhibitors (because many of the analyzed medicines are used with a curative intent in the early-stage setting in addition to the metastatic setting). Nevertheless, the standardization based on cancer incidence is sensitive to the extent of false-positive diagnoses and screening activities,

[40] DDD standardizes the dosage of medicines and thus enables an aggregation across medicines. However, the WHO does not provide DDD for virtually all cancer medicines (WHO ATC group L01).

as countries with more screening might have a higher share of early-stage cancers which require little or no treatment with medicines. Somewhat unreliable data on cancer incidence in some countries is another challenge.

Medicines included in the analysis of uptake in volume

For all analyzed medicines in section 4.6, the standard weekly dose (SWD) was calculated. The SWD is based on the recommended dose in milligram (mg) for a standard patient (75 kg body weight and body surface 1.9 m^2).

Table C7: SWD for the selected cancer medicines

Breast cancer		Gynecological cancers	
Abemaciclib	2,450	Olaparib	4,200
Palbociclib	656	Niraparib	1,867
Ribociclib	3,150	Rucaparib	8,400
Pertuzumab	140	Tumor-agnostic therapies	
Pertuzumab-trastuzumab	400		
Trastuzumab emtansine	90	Entrectinib	4,200
Trastuzumab deruxtecan	135	Larotrectinib	1,400
Sacituzumab govitecan	500	Immune checkpoint inhibitors	
Prostate cancer		Pembrolizumab	67
Abiraterone	7,000	Nivolumab	120
Enzalutamide	1,120	Ipilimumab	38
Apalutamide	1,680	Atezolizumab	413
Darolutamide	8,400	Durvalumab	375
Lung cancer		Avelumab	400
Osimertinib	560	Cemiplimab	117
Alectinib	8,400	Non-Hodgkin lymphoma	
Brigatinib	1,260	Ibrutinib	2,940
Lorlatinib	700	Brentuximab vedotin	45
Crizotinib	3,500	Polatuzumab vedotin	45
Selpercatinib	2,240	Zanubrutinib	2,240
Sotorasib	6,720	Tafasitamab	450
Gastrointestinal cancers		Glofitamab	10
Trifluridine / tipiracil	350	Leukemia	
Ramucirumab	300	Venetoclax	2,800
Regorafenib	840	Acalabrutinib	1,400
Pemigatinib	63	Obinutuzumab	250
Avapritinib	2,100	Midostaurin	350
Ripretinib	1,050	Gilteritinib	840
Melanoma		Bosutinib	3,150
Dabrafenib	2,100	Multiple myeloma	
Trametinib	14	Daratumumab	350
Encorafenib	3,150	Pomalidomide	21
Binimetinib	630	Carfilzomib	130
Vemurafenib	13,440	Ixazomib	3
Cobimetinib	315	Elotuzumab	375
Urinary tract cancers		Isatuximab	375
Axitinib	70		
Cabozantinib	420		
Lenvatinib	121		
Pazopanib	5,600		
Enfortumab vedotin	47		

Country ranking of uptake of newer cancer medicines

Table C8: Uptake of medicines relative to the highest-uptake country (HUC) and overall ranking

	Breast cancer	Prostate cancer	Lung cancer	Gastro-intestinal cancers	Melanoma	Urinary tract cancers	Gynecological cancers	Tumor agnostic therapies	Immune checkpoint inhibitors	Non-Hodgkin lymphoma	Leukemia	Multiple myeloma	Arithmetic mean	RANK
HUC	HR	FR	CH	LT	LT	FR	AT	AT	BE	LT	IE	FR	-	-
AT	84%	87%	88%	98%	64%	81%	100%	100%	95%	65%	99%	95%	88%	1
BE	80%	75%	63%	65%	56%	65%	58%	48%	100%	47%	59%	79%	66%	4
BG	73%	45%	41%	74%	77%	45%	44%	25%	60%	59%	69%	41%	54%	7
HR	100%	35%	21%	32%	36%	22%	26%	50%	42%	43%	52%	25%	40%	21
CZ	46%	42%	35%	26%	47%	43%	53%	67%	36%	27%	56%	34%	43%	18
DK	49%	71%	53%	14%	46%	54%	51%	33%	37%	17%	44%	69%	45%	16
EE	40%	28%	22%	7%	54%	65%	43%	8%	40%	29%	56%	26%	35%	25
FI	66%	76%	54%	41%	46%	77%	45%	73%	20%	19%	56%	33%	51%	13
FR	87%	100%	83%	46%	78%	100%	65%	13%	100%	38%	70%	100%	73%	3
DE	71%	68%	54%	59%	52%	63%	81%	60%	75%	45%	72%	62%	63%	5
HU	51%	31%	12%	48%	83%	37%	28%	37%	39%	44%	59%	24%	41%	20
IS	70%	47%	59%	17%	48%	43%	78%	0%	53%	20%	52%	48%	45%	17
IE	68%	95%	44%	27%	42%	65%	36%	31%	39%	36%	100%	51%	53%	9
IT	53%	50%	63%	48%	71%	54%	54%	36%	49%	37%	49%	59%	52%	12
LV	50%	24%	7%	26%	32%	41%	24%	0%	13%	28%	23%	3%	23%	27
LT	56%	26%	48%	100%	100%	68%	26%	2%	38%	100%	39%	25%	52%	11
NL	48%	42%	49%	27%	52%	21%	38%	24%	43%	22%	22%	76%	39%	22
NO	77%	64%	54%	14%	41%	66%	71%	58%	52%	21%	27%	41%	49%	14
PL	38%	16%	15%	21%	30%	25%	29%	14%	31%	27%	57%	24%	27%	26
PT	55%	37%	78%	20%	44%	38%	19%	19%	33%	23%	33%	33%	36%	23
RO	55%	24%	38%	25%	64%	31%	31%	0%	41%	75%	60%	55%	42%	19
SK	39%	45%	21%	19%	53%	53%	18%	19%	12%	67%	46%	29%	35%	24
SI	57%	44%	69%	49%	31%	47%	93%	70%	49%	44%	59%	39%	54%	8
ES	92%	63%	67%	28%	64%	31%	69%	0%	49%	56%	53%	57%	52%	10
SE	55%	69%	92%	24%	43%	56%	50%	70%	44%	29%	59%	95%	57%	6
CH	92%	78%	100%	55%	64%	77%	99%	50%	85%	43%	89%	86%	76%	2
UK	57%	48%	38%	21%	44%	51%	51%	58%	35%	27%	79%	40%	46%	15
EU-27	67%	60%	57%	43%	59%	56%	57%	32%	60%	42%	60%	62%	54%	-

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