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# 3.4.6 Drug utilization research in the area of cancer drugs

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**Key points**

- Cancer is a leading cause of morbidity and mortality world-wide. Its wide-ranging impacts on both patients and healthcare systems underpin the rapid development of new therapeutic alternatives for the treatment of cancer.
- Evaluating aspects of systemic anti-cancer therapy (SACT) may offer important insights into routine care; this is particularly relevant in cancer since clinical trials – upon which cancer drugs are being approved for use – do not necessarily reflect clinical practice.
- Questions of clinical relevance may focus on when, where, how, and for/by whom drugs are used in clinical practice, and whether this is in line with expectations based on cancer epidemiology, forecasting, and clinical guidelines. Furthermore, considering the substantial costs involved in cancer care, health economic studies as well as assessing potential inequities in access to cancer treatment are of interest.
- However, the large variety of available treatment options and diverse combination/sequencing regimens of different cancer medicines complicate the conduct of drug utilization studies in this area.
- This is further exacerbated by a lack of structured data and methodological challenges; for instance, using defined daily doses (DDDs) as a measure of drug use is not always appropriate since many drugs used in cancer do not have DDDs assigned.

**Key words**: Cancer, systemic anti-cancer treatment, SACT, chemotherapy, targeted treatment, immunotherapy

# Introduction

## Cancer epidemiology

Cancer is the second leading cause of death worldwide after cardiovascular diseases, in 2020 attributing to nearly 10 million deaths or approximately one out of six deaths overall (1). In Europe alone, 4.3 million new cases were diagnosed in 2020 with 1.9 million recorded deaths. Age-standardized incidence and mortality, and the relationship between them, varies across regions due to a complex set of factors, including exposure to carcinogens through environment or lifestyle and the capacity for screening, diagnosis, and treatment in the respective healthcare setting, see Figure 1. Even though cancer incidence and mortality increase with age there are still approximately 400,000 children diagnosed with cancer world-wide every year (1).

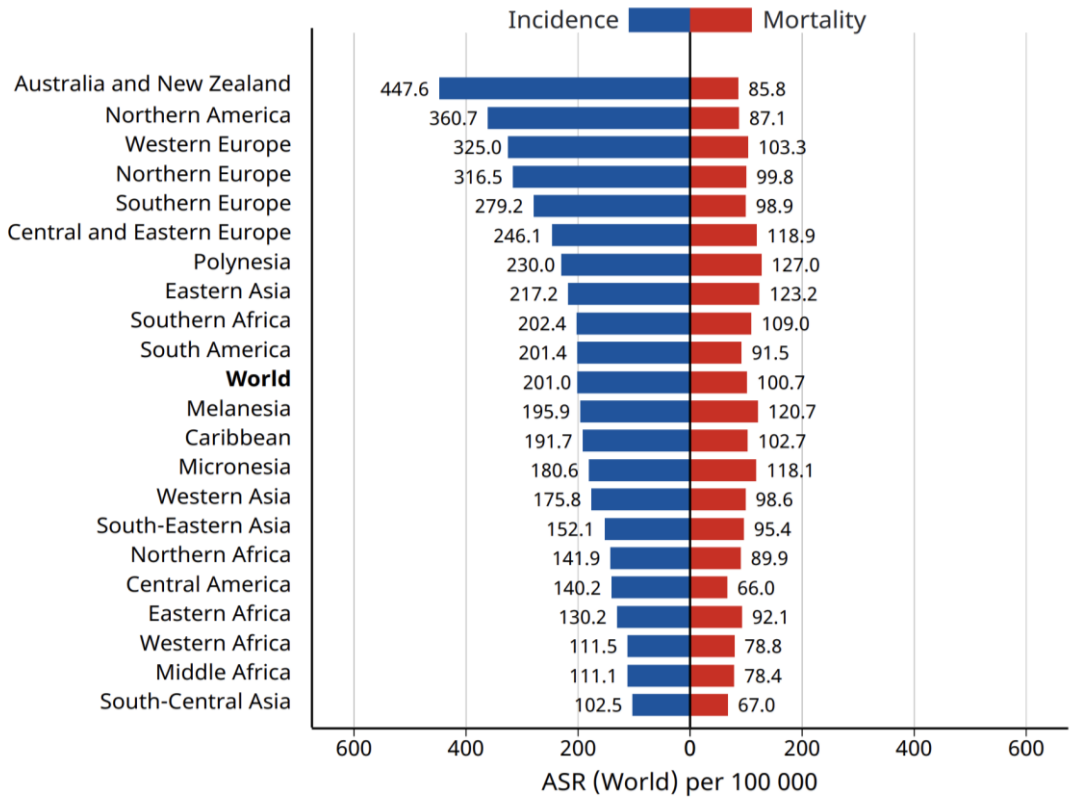



*Figure 1: Age standardised incidence and mortality rates (ASR) in 2020 globally, all cancers. Source: International Agency for Research on Cancer / World Health Organisation (1)*

Cancer is, however, not a single disease; characterized by uncontrolled cell growth, it can start anywhere in the human body and may spread to other parts. Our understanding of cancer and, consequently, the potential targets for treatment have changed considerably based on the mapping of the human genome (**2**). Several common types of solid cancers

such as breast, cervical, oral, colorectal, and testicular cancer as well as different types of haematological cancers including leukaemia and lymphoma in children can now be controlled when detected early and treated according to best practices. For instance, an estimated 90 – 98% of patients with early stage breast cancer – often identified through routine screening – survive at least 5 year after diagnosis (3). In the UK, around 72% of children diagnosed with any cancer survive for 20 years or more (4); long-term survival rates for children following a diagnosis of lymphoblastic lymphoma exceed 80% with intensive treatment, and are above 90% if the cancer is at an early stage (5). Although cancer may not necessarily be curable some types have become manageable, with treatment options available to slow disease progression, ease symptoms, and prolong life.

The World Health Organization (WHO) has estimated that 30–50% of cancers can be prevented by avoiding risk factors – such as smoking, alcohol consumption, or obesity – and implementing existing evidence-based prevention strategies (**6**). Furthermore, approximately 13% of cancers diagnosed in 2018 globally can be attributed to infections, such as H. pylori, human papillomavirus (HPV), hepatitis B or C virus, or Epstein-Barr virus. This has led to new therapeutic options for preventing cancer through immunization.

### Cancer drugs

The world-wide impact of cancer on life expectancy, quality of life and need for healthcare interventions together explain the research interest and rapid development of new therapeutic alternatives for the treatment of cancer. After the introduction of the first cytotoxic agents nitrogen mustard and folic acid inhibitors (such as methotrexate) in the late 1940s and early 1950s, the following decades saw the introduction of several other systemic anti-cancer treatment (SACT) options including hormone treatment in the 1970s, molecularly targeted therapy from the mid-1990s onwards, and modern immunotherapy since the early 2010s (**7**); see Table 1 for further details.

While cytotoxic agents (commonly referred to as chemotherapy) act through interfering with cell division, thus killing primarily rapidly dividing cells, hormone treatment acts through disrupting hormone-dependent tumour growth with the possibility of a more targeted effect. Molecularly targeted therapy inhibits growth of cancer cells by interfering with specific functions needed for carcinogenesis and tumour growth. In contrast, immune

checkpoint inhibitors (ICIs) block proteins (so-called checkpoints) from interacting with T-cells, therefore increasing the body's immune response towards cancer cells (**7**).

Most recently, with the advent of modern diagnostics and based on an increasing and evolving understanding of the genetic aspects of cancer, the concept of precision medicine has been introduced in cancer treatment. Using specific information on a patient's tumour through gene mapping, individualized treatment plans may facilitate optimal treatment outcomes by selecting SACT options most likely to be effective in the given situation; an early example of this is the use of trastuzumab in HER2-positive metastatic breast cancer (**8**). An even more advanced approach to cancer treatment is gene-therapy, which has become available to treat some forms of leukaemia in children and lymphoma in adults. In chimeric antigen receptor (CAR) T-cell therapy, T-cells are modified to recognise and target a specific protein on cancer cells (9).

*Table 1: Examples for the main types of systemic anti-cancer treatment (SACT) currently in use (9)*

| **Category** | | **Examples** |
|---|---|---|
| Chemotherapy | | Some of the most widely used chemotherapy drugs include:<br>• **5-fluorouracil (5-FU)**: breast cancer, head & neck cancers, colon cancer, skin cancer<br>• **carboplatin/cisplatin**: e.g., in gynaecological cancers, head and neck cancers, testicular cancer, small cell lung cancer<br>• **doxorubicin**: e.g., cancers of the breast, ovary, bladder, thyroid; Hodgkin lymphoma |
| Hormone therapy | | • **tamoxifen** targeting hormone receptors in breast cancer (10)<br>• **leuprorelin** (LH blocker) in breast and prostate cancer<br>• **abiraterone**/enzalutamide in prostate cancer |
| Targeted therapy | Monoclonal antibodies | • **trastuzumab** in breast and stomach cancer (11)<br>• **rituximab** in non-Hodgkin or follicular lymphoma |
| | Growth inhibitors | • **imatinib** (tyrosine kinase inhibitor) in chronic myelogenous leukaemia (12)<br>• **everolimus** (kinase inhibitor) for brain cancer, advanced kidney cancer<br>• vemurafenib (BRAF inhibitor) for advanced melanoma<br>• trametinib (MEK inhibitor) for advanced non-small cell lung cancer (NSCLC) |
| | Anti-angiogenesis | • **thalidomide** in multiple myeloma<br>• aflibercept (VEGF inhibitor) in metastatic colorectal cancer |

| | | |
|---|---|---|
| | (blocks blood vessel growth) | |
| | DNA repair pathway | • olaparib (PARP inhibitor) in gynaecological cancers |
| Immunotherapy | | ipilimumab and/or **nivolumab** targeting the CTLA-4 receptor and PD-1 receptor, respectively, in malignant melanomas (13) |

Drugs highlighted in bold are included in the World Health Organisation (WHO) Essential Medicines List (EML). Approved indications for drugs may differ between countries.

5-FU – 5-fluorouracil; BRAF – B-raf protooncogene; CTLA-4 – cytotoxic T-lymphocyte associated antigen 4; HERs – human epidermal growth factor receptor 2; LH – luteinizing hormone; NSCLC – non-small cell lung cancer; PARP – poly-ADP ribose polymerase; PD-1 – programmed death cell protein 1; VEGF – vascular endothelial growth factor

## Trends in approval of cancer drugs

In Europe most cancer drugs are authorized by the European Medicines Agency (EMA) through centralised marketing authorisation applications (MAA) (14). There are several important aspects of marketing authorizations relevant to cancer drugs such as:

- *conditional marketing authorization* for drugs that address unmet medical needs
- *accelerated assessment* for therapeutic innovations with a major interest for public health, which reduces the timeframe for the Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorisation application
- *orphan designation* to facilitate the development and authorisation of medicines for rare diseases (15)
- *exceptional circumstances* if the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical
- *additional monitoring* to enhance reporting of suspected adverse drug reactions for medicines for which the clinical evidence base is less well developed (16)

The number of cancer medicines approved by the EMA has increased significantly from less than five annually in the period 1995 – 2000 to more than 10 every year since 2013 (**17**). The majority of newly approved drugs are now targeted therapy or immunotherapy, see Figure 2 (**18**).

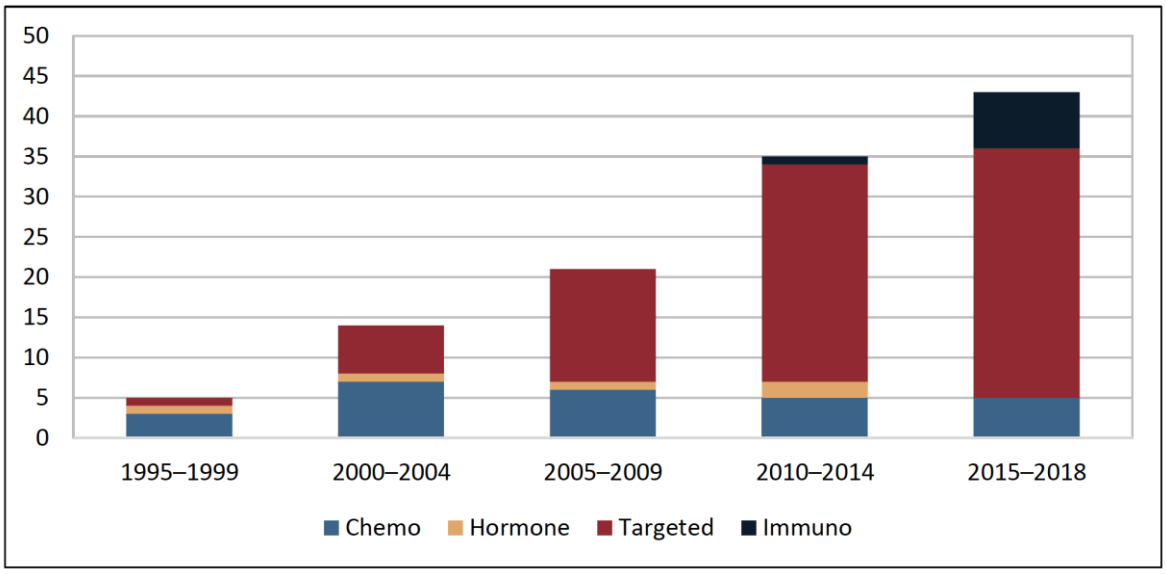
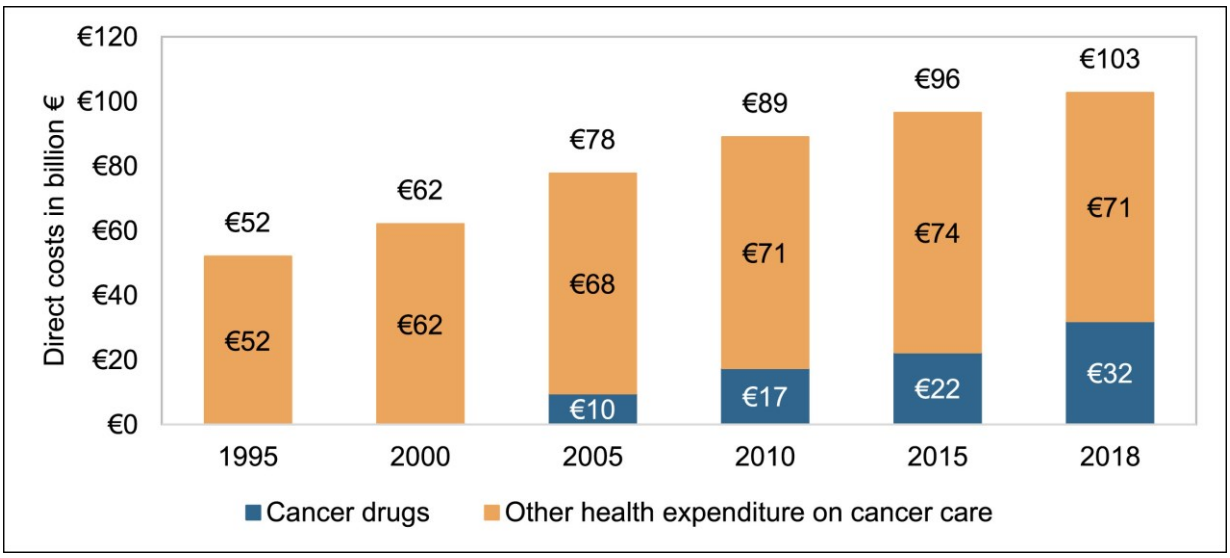



*Figure 2: Number of European Medicines Agency approved cancer medicines per type, 1995 – 2018. Reproduced from (**18**)*

In 2018 the total cost of cancer care in Europe was estimated at €199 billion, with nearly equally large costs within and outside the health-care system (**19**). This included direct costs including cancer drugs (see Figure 3) and informal care costs and indirect costs from a societal perspective. In 2018 the indirect costs of cancer through productivity loss from morbidity was €20 billion, while the productivity loss from premature mortality was €31 billion for men and €19 billion for women and decreased over time. However, the total costs of cancer differed greatly between countries.




Notes: Costs for 1995 and 2000 represent total direct costs, as it was not possible to separate costs because of lack of data on drugs. Cancer drug expenditure do not include confidential rebates, whose size might have increased over time. The 1995 estimates could only be adjusted for country-specific inflation between 1996 and 2018 due to lack of data.

*Figure 3: Direct costs of cancer in Europe in billion € (2018 prices and exchange rates), 1995 – 2018. Reproduced from (**19**)*

Considering the high costs associated with treatment, access to cancer medicines is a challenge in many countries – particularly, although not exclusively, in settings with limited resources. Drugs not included in the WHO model list of essential medicines tend to be approved for use in low- and middle-income countries only several years after they have become available in high income countries; and even when drugs obtain approval, they may not be available or accessible to patients (**20**).

## Methodological aspects

Studying utilization of cancer drugs introduces additional and severe challenges compared to many other therapeutic areas. The reasons are manifold. First and foremost, there exists a plethora of different pharmacological approaches for treating cancer, and SACT most commonly comprises more than one individual drug; with the type of combination treatment (and its sequence) being dependent on a number of factors, including type, location, and stage of cancer as well as other patient-related factors (such as patient fitness and existing co-morbidities). Furthermore, SACT might be combined with other treatment modalities such as surgery and radiotherapy, which may be given both as inpatient and outpatient care over time. This increases challenges with limited availability of structured data and may necessitate more complex data retrieval to capture relevant information over time and across settings. In addition, even though cancer in general is a common disease, there are many variants and often (very) small patient groups affected by any particular type of cancer. This has greatly influenced advances within precision medicine where treatments are tailored to specific situations or even individual patients; however, small populations for many cancer types and the potential variations in treatment make it difficult to study treatment effects and safety.

In clinical practice, treatments are often given across years as neo-adjuvant treatment (e.g. prior to surgery) (21), adjuvant treatment (i.e., with curative intent), and also as maintenance treatment not to be confused with palliative treatment (22). During the maintenance and palliative phases of cancer treatment, many patients may receive different SACTs over several years. Previously used drugs may also be used again later in case of disease progression.

For drug utilization research purposes, the classification in the ATC-system is one possible starting point for selection of appropriate groups and substances (**23**). However, to account for the large variation in the combination and/or sequence of the drugs being used (as well as different dosing schemes and routes of administration) the given treatment might in some cases be recorded as a defined regimen and not by the individual drugs given; this may be relevant for both treatment guidelines and IT systems used to manage treatment.

In addition to difficulties when assessing potential exposure to treatment, other important and challenging factors relate to the need to align the drug use to the type of cancer including grading (malignancy) and staging (size and spread), but also where in a treatment pathway – consisting of different drugs as monotherapy and/or combination therapy and combinations of other treatment options – a patient is being treated. This is further complicated by local adaptations of regimens and treatment pathways over time in routine clinical care. Since many of the newer cancer drugs are expensive, their use will also be heavily influenced by the degree of coverage by private or national health insurance.

### Defined daily dose in cancer drugs

The concept of defined daily doses, DDD, needs to be handled carefully for cancer drugs. In most cases there are no DDDs assigned, or they are assigned for indications outside oncology. The antineoplastic agents in L01 for instance, except for L01E protein kinase inhibitors, have no DDDs assigned due to their highly individualised use and wide dosage ranges (**23**). If using DDDs, be careful to check that the formally assigned DDDs are valid in a specific situation.

Amount in gram might be used in situations where only one substance is studied, or alternatively (and preferably) individual data describing number of patients or number of treatment cycles. Apart from circumventing the possible issue of incorrectly calculating the volume of cancer drugs used by applying potentially inappropriate DDDs as a unit of measurement, using the number of treatment cycles (either on an individual or an aggregate level, e.g., per patient, or by indication/per year) has the additional advantage of enabling the assessment of treatment duration and facilitating the evaluation of physicians' adherence to treatment guidelines or recommendations.

### Cost and expenditures

Due to the lack of robust ways of measuring the amount of SACT used and the importance placed on the expenditures on cancer drugs, international comparisons in particular tend to focus on total cost of the drugs instead of amount distributed, see also Chapter 2.12 (Measuring expenditure).

When comparing the cost for drugs between countries the exchange rates vary over time and do not illustrate price parity. Furthermore, the cost of drugs dispensed from pharmacies may or may not focus on the total cost or the reimbursement cost and may not include the cost of distributing and handling the drugs at pharmacies. For drugs administered at hospital or policlinics the cost of distribution and handling is most often not included in any statistics; moreover, volumes relate to distributed volume including waste, and not actually administered amount. Even more important to consider is the fact that local, regional, or even national procurement of drugs to hospitals and policlinics can reduce costs; information that is usually very difficult to obtain since agreements may be of a sensitive nature and, thus, not publicly available. In addition, different forms of risk-sharing/ managed-entry agreements in the field of oncology further complicate the situation (**24,25**). During the last years, due to high costs associated especially with advanced therapy medicinal products (ATMP) often for small patient groups (26), these new models have been implemented to cover escalating costs, often with confidential discount. This impedes using expenditures for trend analyses and comparisons between countries.

### Data sources

The lack of DDDs and the fact that cancer drugs are distributed both as drugs administered at hospitals or policlinics and as drugs prescribed and dispensed at pharmacies complicate drug utilization research. Add to that the need for knowledge about type of cancer, grade and stage, combination therapy and other treatment options such as radiotherapy and surgery and it is obvious that it is a daunting task to describe how cancer drugs are used and how their use has developed over time.

To perform relevant drug utilization studies, as well as for analytical studies of pharmacoepidemiology, real world data from national health data registries (such as cancer registry, inpatient registry etc.), quality registers and data from health records are most often needed (**27**). This also makes it possible to study patient-level data depending on

legislature. The European Network of Cancer Registries (ENCR), supported by the European Commission, promotes collaboration between cancer registries and defines data collection standards, including a standard dataset (28). If no electronic systems for prescribing, administering and/or dispensing SACT exist, manual data collection can be used, e.g., obtaining data from paper-based records; see also Chapter 2.8 (Primary data collection). This is, however, a considerably resource-intense task and severely limits the scope of any research study.

In addition to quantitative data, drug utilisation studies in cancer – similar to other areas of interest – may benefit from qualitative components; for instance, to evaluate patients' quality of life. Furthermore, in the absence of comprehensive, reliable quantitative data, a wide range of qualitative study designs may be used depending on research question and study aim; see also Chapter 2.2 (Qualitative studies).

## Drug utilisation research in cancer

Following successful completion of randomised controlled trials (RCTs) and subsequent approval through regulatory agencies, cancer drugs may be recommended for use in defined patient populations and incorporated into clinical treatment guidelines. Similar to other disease areas, drug utilisation studies in cancer may subsequently be conducted to address a number of issues (**29**). These include access/market uptake; physician adherence to guidelines; patient adherence to treatment; and effectiveness and safety in clinical practice.

The availability of (and access to) individual drugs, as well as their uptake within populations, depend on several factors such as existing resources, both financial and clinical; reimbursement systems and prescribing incentives; national disease priorities; and specific policies and guidelines. In addition, supply of certain drugs may be limited on occasion due to local, national, or international shortages for various reasons. Aggregate data on the overall volume and cost of cancer drugs used in a geographical area over time are of interest to health care systems and policy makers more broadly to allow forward planning and support appropriate use of limited resources. More detailed descriptions of drug use may be of interest to the clinical community to increase understanding of treatment in practice and facilitate benchmarking – i.e., comparing routine care across areas and health care providers to identify "best practice" and ensure quality of care (**30,31**).

Questions of clinical relevance may, for instance, focus on when, where, and for/by whom drugs are used in clinical practice, and whether this is in line with expectations based on cancer epidemiology, forecasting, and clinical guidelines. Studies may also be conducted to assess potential differences in treatment between different cancers, patient populations, or settings to identify factors potentially affecting the use of cancer drugs. Evaluating detailed aspects of treatment regimens (choice of drug, formulation, dose) and/or patients' treatment pathways (duration of treatment and sequencing of treatment options) may offer further important insights into routine care, information that may be useful to evaluate clinicians' adherence to treatment guidelines and, potentially, inform subsequent research.

Obtained data may also be relevant for other purposes such as Health Technology Assessments (HTA), the process by which regulators make reimbursement decisions. Similarly, assessing the safety and effectiveness of cancer drugs in clinical practice – as opposed to results obtained through RCTs – is crucial to understand what does or does not work in specific populations, enabling the addressing of existing uncertainties and thereby facilitating informed decision making.

This is particularly relevant for two main reasons: first, cancer RCTs – similar to those conducted in other disease areas – commonly have very stringent eligibility criteria, resulting in trial populations that frequently differ considerably from populations eventually being treated with the drug in question (32–34). Secondly, treatment efficacy may be difficult to interpret as trial results are not necessarily expressed as hard endpoints (overall or landmark survival). They may instead comprise proxies such as progression-free survival, owing to the relatively short follow-up period of many trials (**35**). In addition, RCTs may be too short in duration (or with too small a sample size) to provide reliable estimates of anything other than the most common and frequent treatment side effects.

Additional topics such as patient adherence to cancer treatment; the impact of cancer drugs on patients' quality of life; and the cost-effectiveness of new drugs are also of interest to a wide range of stakeholders. These can be tackled using various study designs and methods – including qualitative and mixed-methods research. With increasing numbers of patients being treated following a diagnosis of cancer, and for longer periods of time (including, e.g., neo-adjuvant and/or continuous maintenance treatment), patient-reported outcome measures (PROMs) in particular have come into focus more recently. PROMs are considered

to provide valuable input for cancer care, with initial recommendations advocating their routine inclusion in clinical practice (**36**). For instance, as part of the Scottish Cancer Medicines Outcomes Programme (CMOP), a mixed-methods study aimed to identify which quality of life-related aspects of cancer treatment are important to clinicians and patients (37). For an overview of examples, see Table 2.

*Table 2: Examples of drug utilisation research in the area of cancer*

| **Area of interest** | **Study aims** | **Examples** |
|---|---|---|
| Access/drug uptake (aggregate – population level) | Describe/summarise the use of new and/or established drugs in a given setting over a specific time period | Trends in cost and use of targeted treatments 2001 to 2011 (USA) (**38**) |
| | Evaluate whether uptake is in line with expectations | HPV administration trends adults 27-45 (USA) (39)<br>Vaccine coverage among adolescents (USA) (40) |
| | Compare the use of drugs over time and across regions | SACT at end of life 2015 vs 2019 (USA) (**41**) |
| | Evaluate the cost-effectiveness of cancer drugs in specific populations/indications | Health-care costs of abiraterone/enzalutamide prostate cancer (Scotland) (42)<br>Cost-effectiveness of ipilimumab/nivolumab in lung cancer (USA) (**43**) |
| Drug use in clinical practice (granular – individual level) | Describe patient populations (e.g., demographics, indications) | Abiraterone/enzalutamide in metastatic prostate cancer (Scotland) – trial eligibility (**44**) |
| | Describe treatment and treatment pathways (prescriber, setting; regimen/drug, form, dose; treatment duration, sequencing of drugs) | Opportunities and challenges using record linkage (Scotland) (**27**)<br>Use of Olaparib in ovarian cancer (Sweden) (45) |
| | Assess clinicians' adherence to guidelines (e.g., indication) | Adjuvant treatment in breast cancer (Malaysia) (**46**) |

| | | |
|---|---|---|
| | | Guideline adherence oncology (Australia) (**47**) |
| | Assess patients' adherence to drug (e.g., oral doses to be taken at home) | Predictors for adherence to oral anti-cancer medication (USA) (**48**) |
| | Analyse factors influencing the use of specific drugs | Trastuzumab biosimilars in China (**49**) |
| Treatment outcomes (granular – individual level) | Evaluate the safety of cancer drugs in clinical practice (including long-term effects and rare adverse events) | Trastuzumab in breast cancer – switching to biosimilars (**50**)<br>Ipilimumab/nivolumab in renal cell cancer (Canada) (51) |
| | Evaluate the (comparative) effectiveness of cancer drugs in clinical practice | Abiraterone/enzalutamide in metastatic prostate cancer (Scotland) (**44**) |
| | Investigate the effect of cancer drugs on patients' quality of life | Chemotherapy (India) (**52**)<br>Tamoxifen (The Netherlands) (53) |
| Other | Assess stakeholder opinions | Patient preference lung cancer (Belgium and Italy) (**54**)<br>Oncologist perception of treatment access (Norway) (**55**) |

## Future trends

Conducting drug utilization research in the area of cancer is challenging, not least due to the complexities inherent in cancer treatment. While the development of patient-centred, individually tailored treatment options and the introduction of ATMP such as CAR-T cell therapy opens up new challenges, this also presents renewed opportunities where drug utilisation research could play a role. The drive towards implementing electronic systems for prescribing, dispensing, and/or administering medicines – including SACT – can offer enhanced access to high-quality, patient-level data which in turn may support research activities; nevertheless, close collaboration with clinicians and other stakeholders is strongly recommended to facilitate appropriate use of methods and data, and support interpretation of findings.

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