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Cancer medicines on the WHO Model List of Essential Medicines: processes, challenges, and a way forward

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The selection of cancer medicines for national procurement requires deliberate evaluation of population benefit, budget impact, sustainability, and health system capacity. However, this process is complicated by numerous challenges, including the large volume and rapid pace of newly developed therapies offering marginal gains at prohibitively high prices. The WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) have undergone a series of evidence-based updates to ensure recommended cancer medicines offer meaningful clinical benefit. This Health Policy paper describes how cancer medicines are listed on the EML and EMLc, including two updated WHO processes: (1) the formation of the Cancer Medicines Working Group, and (2) additional selection principles for recommending cancer medicines, including a minimum overall survival benefit of 4–6 months with improvement to quality of life compared with standard treatment. These updates, along with proposals to include formal price considerations, additional selection criteria, and multisectoral collaboration (eg, voluntary licensing) promote procurement of high-value essential cancer medicines on national formularies in the context of supporting sustainable health systems to achieve universal health coverage.

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Introduction

Cancer is a major public health problem accounting for approximately 10 million deaths worldwide in 2020.[1] By 2030, it is estimated that the annual number of new cancer cases globally will increase to 21·6 million and that the number of cancer-related deaths will increase to 16·5 million annually.[1] The greatest burden is in low-income and middle-income countries (LMICs), where more than two-thirds of global cancer cases and deaths occur—an estimate expected to increase over the next decade.[1]

Medicines are an important part of cancer treatment for both curative and non-curative intent, in addition to the primary treatments of surgery and radiotherapy. Despite substantial therapeutic advances in some cancers over the past few decades, many LMICs do not have appropriate infrastructure and consistent access to cancer medicines, including conventional cytotoxic agents, which has contributed to worse survival outcomes for patients in these countries compared with patients in high-income countries.[2]

In 1977, WHO established the WHO Model List of Essential Medicines (EML), complemented since 2007 by the Model List of Essential Medicines for Children (EMLc), to aid countries and regional authorities in selecting effective, safe, and ideally cost-effective medicines for national essential medicines lists (NEMLs).[3] The WHO EML and EMLc provide national and subnational policy makers with evidence-based guidance to optimise country-level priority setting for high-value medicines. The aim is to assist countries in establishing national formularies that meet the priority health-care needs of the population—a crucial element in defining a medicine as essential.[3] However, selection and procurement of cancer medicines has become increasingly difficult as therapeutics often come to market with marginal survival benefits, unknown effects on quality of life, and prohibitively high prices.[4] To achieve the vision for universal health coverage outlined in UN Sustainable Development Goal 3.8,[5] countries need to invest resources in high-value care to maximise health outcomes. However, substantial differences exist among the NEMLs of individual countries and the WHO EMLs that cannot be explained by country-level variations, such as differences in epidemiology, resources, and competing disease burden.[6] This finding suggests that resources are probably spent on low-value care, diverting finite health system resources away from other, more effective treatments.

Given contemporary challenges in procurement, accessibility, affordability, and delivery of cancer treatment, important updates to WHO EML processes have been implemented for cancer medicines. LMICs increasingly rely on the WHO EMLs owing to insufficient health budget allocation and regulatory capacity to independently review efficacy and safety evidence of new medicines for country reimbursement. Patients with cancer in these countries easily incur catastrophic expenditure owing to a scarcity of government insurance schemes and availability of medicines as out-of-pocket expenses.[2] Therefore, to support countries in procuring high-value cancer medicines, the context and reasoning for updates to EML processes ought to be disseminated to a global audience. The aim of this Health Policy paper is to provide a summary of these updates, including the formation of the Cancer Medicines Working Group (CMWG), adoption of additional selection principles, and a vision for a way forward. The commitment of WHO is to advance an evidence-based and transparent process as part of the mandate to support countries to increase high-value care and ensure cancer medicines listed on NEMLs deliver substantial benefit to populations, in terms of disease coverage, clinical impact, and value.

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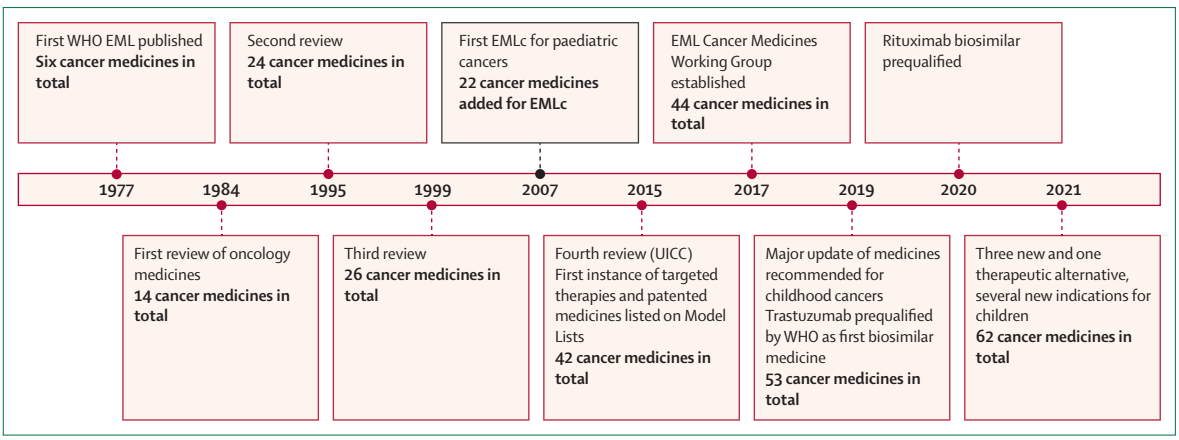

Figure 1: **Timeline of activities to recommend cancer medicines on the WHO EML**
EML=Model List of Essential Medicines. EMLc=Model List of Essential Medicines for Children. UICC=Union for International Cancer Control.

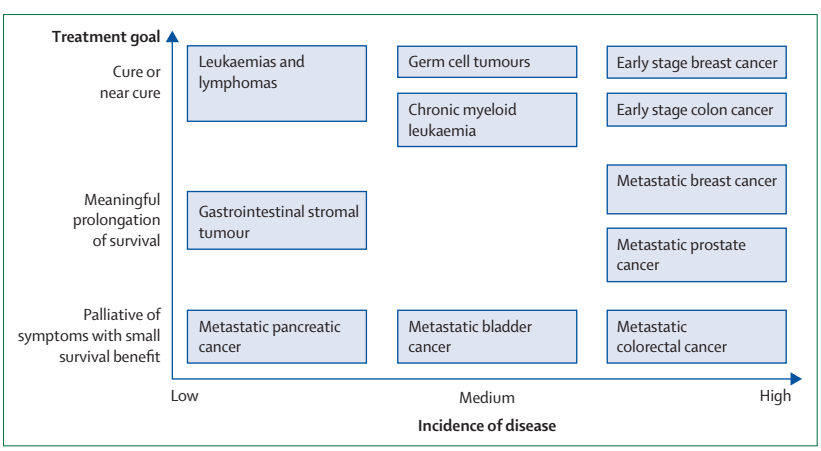

Figure 2: **Prioritisation of cancers for the WHO EML based on treatment goal and incidence of disease**
Adapted from slides presented at the 2015 Open Session of the 20th WHO Expert Committee Meeting on the Selection and Use of Essential Medicines, with permission from G de Lima Lopes, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA. EML=Model List of Essential Medicines.

The process for prioritising cancer indications and medicines on the WHO EML and EMLc

Since 1977, cancer medicines on the WHO EMLs have undergone four comprehensive reviews (figure 1). In 2015, WHO commissioned a review and update of all cancer medicines to respond to priority adult and paediatric malignancies.[7] More than 90 global experts convened to develop 29 disease-based applications for consideration by the WHO Expert Committee on Selection and Use of Essential Medicines (WHO Expert Committee). The review followed a disease-based approach, prioritising cancers on the basis of disease burden and effect of available medicines. For example, breast cancer was prioritised because of high global incidence and substantial effect of available medicines. Chronic myeloid leukaemia and diffuse large B-cell lymphoma were also considered high priorities, despite low incidence, because existing medicines have a substantial effect on survival outcomes. Diseases that were considered a lower priority had low incidence and had therapies without substantial effect or with added toxicities (figure 2).[7]

The 2015 update of the WHO EML was the first instance in which patented cancer medicines were listed as essential medicines (figure 1). Furthermore, the 2015 update included high-priced targeted therapies, such as trastuzumab for HER2-positive breast cancer, rituximab for follicular and diffuse large B-cell lymphoma and chronic lymphocytic leukaemia, and imatinib for chronic myeloid leukaemia. These medicines were added due to meaningful improvements in overall survival compared with the existing standard of care. This choice reflects the WHO EML selection principle that high prices should not deter inclusion if a medicine offers substantial benefits to patients (while fulfilling other criteria for essential medicines). In 2001, this criterion was formally endorsed to include expensive but highly effective antiretroviral medicines for HIV on the WHO EML, with the goal of increasing access and stimulating competition to lower prices, particularly in LMICs.

Challenges in selecting priority cancer medicines for the WHO EML and EMLc

The selection of essential cancer medicines is challenging for several reasons, including the increasing number of therapeutic options, rapid pace of innovation, limitations in clinical trials that introduce uncertainties about efficacy and safety estimates, and high prices. The evolving landscape of clinical trial design and accelerated approvals based on early phase trials, increasing use of surrogate endpoints, as well as other methodological choices has affected the reliability of and confidence in clinical data.[8] Indeed, these challenges have translated into marginal survival gains for many newly approved cancer medicines across countries, jeopardising the sustainability of publicly funded health-care systems. In 2017–21, the US Food and Drug Administration

issued 161 new approvals of therapeutic agents for adult patients with solid tumours. However, less than a third (57 [27%]) of newly approved medicines were supported by evidence of overall survival benefit.[9] Approvals of medicines to treat haematological malignancies seem to have similar problems, with most medicines tested in studies with single-arm designs and a scarcity of confirmatory trials.[10] In addition, trials are generally not conducted in low-income countries. As a result, the generalisability of efficacy, safety, and dosage is often limited. Furthermore, the current fragmentation of the decision making ecosystem often cannot identify high-value medicines effectively.[11] Policy makers, the public, and other stakeholders often have a partial understanding of these challenges and advocate for increased access to medicines despite substantial uncertainty about the magnitude of benefit (if any) associated with these medicines.

Development of the CMWG and principles for selecting cancer medicines

The WHO recommendations for essential medicines are made with numerous principles for selection, such as disease burden, public health relevance, clinical effectiveness and safety, and cost-effectiveness (panel). However, contemporary challenges in oncology necessitate additional selection principles. In 2017, the WHO Expert Committee recommended the establishment of the CMWG. Although the recommendation of cancer medicines for inclusion in the WHO EMLs is the mandate of the WHO Expert Committee (and not the CMWG), the CMWG was established to provide independent evaluation on scientific, technical, and strategic aspects of cancer medicines for potential inclusion on the WHO EMLs. Secondary aims for the CMWG were to review tools and thresholds to define clinical relevance, including additional selection principles specifically for cancer medicines. To ensure a diversity of perspectives, the CMWG consisted of experts from oncology and health policy across six WHO regions (Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific). Given the barriers to country access, representation from LMICs was an important element for membership. In the years following its formation, the CMWG engaged in a series of discussions about how to prioritise cancer medicines for the WHO EMLs.[12] These discussions culminated in two recommendations to the WHO Expert Committee: (1) the use of the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) and (2) the use of an overall survival threshold (figure 3).

The ESMO-MCBS

The WHO Expert Committee formally endorsed the CMWG recommendation to use the ESMO-MCBS[13] as a screening tool to identify high-value cancer medicines that have therapeutic value sufficient to be considered for inclusion on the WHO EMLs and to inform minimum thresholds for overall survival benefit. To be eligible for possible inclusion on the WHO EMLs, medicines for solid tumours must have an ESMO-MCBS score of A or B in the curative setting or 4 or 5 in the non-curative setting (indicating high or substantial benefit) as opposed to scores of C or 1, 2, and 3 (indicating low benefit). Applications submitted for cancer medicines undergo review by the CMWG for advice to the WHO Expert Committee. The ESMO-MCBS was chosen because it considers a variety of additional factors beyond survival, such as quality of life and treatment toxicities, which are important dimensions that align well with the decision-making process of the WHO Expert Committee.[13] While acknowledging the role of the ESMO-MCBS as a screening tool, it should be noted that only a few medicines receiving a high score on the ESMO-MCBS are then recommended as essential medicines by WHO.

A minimum threshold for overall survival

The second adopted recommendation was a minimum overall survival benefit threshold of 4–6 months compared with standard therapy as a prerequisite for inclusion of first-line cancer medicines on the WHO EMLs. A range was preferred over a fixed value given the variability associated with trial effect sizes, translation to real-world populations, and prognoses of different cancers. The threshold is also interpreted with consideration of natural history and stage of disease, because an overall survival benefit of 4–6 months might

***Panel*: Principles for the selection of essential medicines (adopted in 2001) and principles specific to cancer medicines (adopted in 2019)**

Selection of essential medicines

- Public health relevance
- Review of benefits including clinical evidence, a summary of available data, and a summary of available estimates of comparative effectiveness
- Review of harms and toxicity estimates of total patient exposures, description of adverse events and estimates of their frequency, a summary of available data, a summary of comparative safety against comparators, and identification of variations in safety that might relate to health systems and patient factors
- Summary of available data on comparative cost and cost-effectiveness of the medicine (within the same therapeutic class)
- Summary of regulatory status and market availability of the medicine

Selection of cancer medicines

- Adoption of the European Society of Medical Oncology Magnitude of Clinical Benefit Scale as a screening tool to identify cancer treatments that have potential therapeutic value (score of A or B in the curative setting and of 4 or 5 in the non-curative setting) that warrant full evaluation for listing on the WHO Model List of Essential Medicines (EML)
- Adoption of a threshold for benefit of at least 4–6 months overall survival gain for medicines or regimens to be considered as candidates for inclusion on the WHO EML without detriment in quality of life

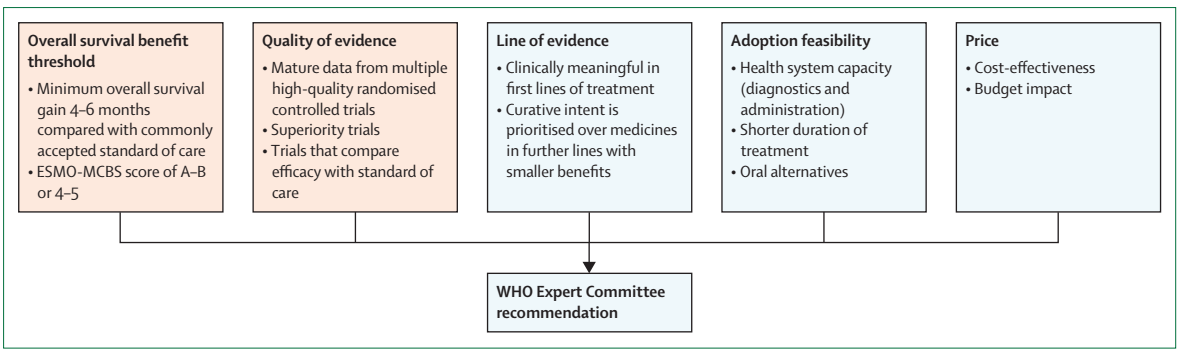

Figure 3: **Adopted and proposed principles to prioritise cancer medicines for inclusion on the WHO EMLs**
The orange pillars are formally adopted by the WHO Expert Committee and the blue pillars are proposed principles under discussion. Price (cost-effectiveness data) is considered by the WHO Expert Committee when evaluating medicines with therapeutic equivalents on the WHO EMLs. EML=Model List of Essential Medicines. ESMO=European Society of Medical Oncology. MCBS=Magnitude of Clinical Benefit Scale.

be difficult if not impossible to achieve in some malignancies. Several arguments support the use of this threshold. First, the longer the overall survival benefit (ie, several months versus a few weeks), the more likely it is that it might translate into meaningful real-world benefit. Outcomes in clinical practice are often inferior to those reported in experimental trials.[14] For this reason, both the American Society of Clinical Oncology and ESMO have endorsed gains of 3 months for overall survival benefit as meaningful.[13,15] Second, any therapy, particularly for the treatment of cancer, is invariably associated with toxicities that might offset clinical benefits. Therefore, a consistent interval for the magnitude of benefit of at least 4–6 months increases the confidence of a net benefit to harm ratio. Third, establishing a reference interval supports national reimbursement authorities to prioritise clinically meaningful cancer medicines by providing a clear threshold for public coverage, which might also be used as a basis for health technology assessment and in national clinical practice guidelines.[11]

The emphasis on the magnitude of benefit and overall survival endpoint is supported by many examples of regulatory approvals based on uncertain data and surrogate measures that did not translate into long-term benefits for patients.[16] Although the conditional approval of new medicines and subsequent withdrawal might be aligned with the aim of regulatory bodies—where early access to promising medicines for severe diseases might justify some degree of uncertainty about clinical efficacy[10]—this practice fundamentally differs from the purpose of the WHO EMLs to confidently recommend medicines with established evidence showing clinically meaningful benefit. Therefore, overall survival data must be consistent across multiple high-quality clinical trials comparing the proposed medicine against current standard of care. The conservative and parsimonious approach of WHO ensures medicines withdrawn from the market are never formally evaluated, sparing millions of patients from ineffective therapeutics with possible toxicities and saving billions of dollars of health expenditure. For example, in the 2000s, bevacizumab received regulatory approval in most countries for several types of malignancies. However, updated evidence suggested bevacizumab offered marginal or no overall survival or disease-free survival gains, including for colorectal and breast cancers for which bevacizumab had been widely adopted.[17] Bevacizumab is listed as an essential medicine solely for treatment of age-related macular degeneration, as it decreases the progression of vision loss.[18] In fact, the WHO decision to wait for confirmatory oncology data meant the medicine was never formally recommended for cancer indications. This strategy is aligned with the WHO mission to focus on high-priority health services without imposing financial hardship on countries due to health-related spending.

Factors that might influence the overall survival threshold for inclusion in the WHO EMLs

Although overall survival and quality of life are the most meaningful outcomes for patients, medicines with a substantial effect on progression and disease-free survival could also be considered if overall survival benefit is anticipated. For instance, in 2019, epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors had not shown a 4–6-month overall survival benefit over platinum-based chemotherapy in EGFR mutation-positive advanced non-small-cell lung cancer. However, the use of erlotinib (with therapeutic alternatives afatinib and gefitinib) was associated with similar survival benefits to platinum-based chemotherapy, and its use was associated with superior quality of life (oral administration versus intravenous chemotherapy administration, which meant less usage of scarce hospital resources), decreased severe toxicities, and availability of generic versions. Together, these factors supported the inclusion of EGFR tyrosine-kinase inhibitors on the WHO EML. By contrast, in 2021, despite promising preliminary results based on surrogate outcomes, zanubrutinib for chronic lymphocytic leukaemia was not recommended due to an absence

of mature data compounded by high budget impact compared with available treatment options.

Additional principles under discussion by the WHO Expert Committee

Although prioritising cancer medicines with a minimum of 4–6 months overall survival benefit identifies effective treatments, recommending medicines on the basis of this principle alone does not guarantee access at the country level. Indeed, to achieve universal health coverage, several barriers need to be addressed to ensure sustainable and durable population health impact through better access to essential cancer care. The following sections elaborate on additional criteria under discussion to ensure medicines recommended for inclusion on the WHO EMLs are feasible for country adoption.

Disease stage and line of therapy

Medicines used with curative intent and those effective in the first-line treatment of advanced cancers have clinically meaningful benefits and are therefore prioritised over medicines in later lines of therapy. Indeed, second-line medicines tend to have greater toxicities and require more supportive care than first-line therapies. Although the WHO EML also includes medicines used in subsequent lines of treatment, analyses of contemporary clinical trials show the effectiveness of cancer medicines tends to decrease in advanced stages of disease after subsequent lines of treatment, unless salvage therapies can be used after disease progression.[8,19] Therefore, medicines that are effective in the early stage or first line of treatment tend to offer better value to improve health outcomes. For example, long-term effects can be seen in patients treated with imatinib, the first oral targeted therapy recommended by WHO for the first-line treatment of chronic myeloid leukaemia.[20] Thereafter, in 2017, dasatinib and nilotinib were included in the WHO EML given their value as second-line treatments for a substantial proportion of patients who do not benefit from or are intolerant to standard-dose imatinib. Dasatinib and nilotinib showed high response rates, and have shown improvements in progression-free and overall survival compared with imatinib.[21] However, an argument against favouring first-line treatments is that most patients with cancer in LMICs are diagnosed in advanced stages of disease, because early detection programmes and access to care are limited. Preferentially endorsing available treatments focused on curative settings might exclude a substantial fraction of patients from effective options, in turn threatening equity for patients in LMICs.

Health system feasibility

Feasibility is the extent to which a new medicine can be successfully implemented within a given setting. Since the Alma Ata Declaration of 1978, WHO has promoted health-care interventions at a community level to attain the goal of Health for All.[22] However, most interventions with tangible results target acute, episodic illnesses, with medicines easily administered in ambulatory care facilities. Cancer care is often positioned at the opposite end of a spectrum, with primary health care at the antipode, characterised by high-cost interventions administered by highly specialised health professionals in tertiary care facilities. Therefore, cancer medicines with low barriers to implementation in terms of diagnostic infrastructure, health-care worker training, resources for the management of side-effects, and monitoring capabilities are preferred. For example, tamoxifen for treatment of early breast cancer can be taken orally, with low-intensity monitoring and less severe side-effects.[23] For these reasons, tamoxifen is included as an essential medicine on the WHO EML for this indication. By contrast, other cancer medicines require highly accurate diagnostic technology limited to sophisticated laboratories that are often only available in large metropolitan centres, or intense monitoring to control toxicities. Health authorities ought to develop a strategic model for managing the introduction of innovative cancer therapies into their health-care systems and for avoiding serious discrepancies in access. Some countries that launched innovative medicines as part of the services provided to their populations then preferred to withdraw them from reimbursement lists or restrict access as high medicine prices increased out-of-pocket costs for patients, and governments incurred large budget impacts to country health services.

A note about increasing prices

The price of medicines has been a specific concern of WHO member states since the concept of national medicine policies and essential medicines was first introduced in 1975,[24] and remains a concern more than 40 years later. Despite the curative potential of other treatment modalities in some cancers, such as surgery or radiotherapy, countries spend more resources on pharmacological therapies.[25] Low-income countries are disproportionately disadvantaged because 50% of their health-care financing is borne from out-of-pocket expenses, compared with 30% in middle-income countries, and 14% in high-income countries.[25]

The WHO Expert Committee has considered the potential strain on health systems by recommending highly effective yet highly priced medicines as part of universal health coverage benefits packages. Because medicine prices are negotiated and reimbursed at the country level, prices vary between nations. Although it is not possible to review country-level budget impact in the evaluation of medicines for the WHO EMLs, including highly priced medicines can expose individuals and health systems to substantial financial consequences. For these reasons, the 2021 WHO Expert Committee recommended the formation of a price working group[26]

dedicated to identifying polices and rules to make highly priced medicines more affordable. While discussions are ongoing within this pricing stream, possible solutions might include identifying cost-effectiveness thresholds (ie, a minimum incremental cost-effectiveness ratio to assess the cost per life-year gained), enabling better value procurement through tendering and competition, establishing transparency with global reference prices, and expanding the use of voluntary licences to cancer medicines.

A way forward

The adoption of a list of essential medicines is only a first step. Governments should continuously reassess NEMLs to ensure a high return on investment. Unfortunately, this activity is challenging for anticancer medicines because of their use in hospitals, which are often missed in national audits. NEML reassessment should include transparent volume data and purchasing prices to measure investments and progress towards universal health coverage. The rapidly expanding number of therapeutics against cancer with marginal benefits and high prices constrains national health systems and jeopardises any vision for universal health coverage, as outlined in UN Sustainable Development Goal 3.8.[5] Furthermore, multisectoral collaboration is required with WHO member states, pharmaceutical companies, regulatory bodies, and other stakeholders to increase access to effective but high-priced essential medicines. Use of voluntary licences to manufacture generic, high-quality medicines in LMICs must be rapidly escalated. It is intolerable that not a single cancer medicine is included in international voluntary licensing and patent pooling programmes. An essential component of governance should be to convene countries to understand challenges for accessing essential cancer medicines and the impact of policies to lower the price of cancer medicines. Problems related to poor accessibility to the best therapeutics are intricately linked to the limited ability to promote actions such as price negotiations, value-aligned pricing strategies, patent pools, and identification of generic and biosimilar alternatives, as referenced in the World Health Assembly Resolution 70.12 in 2017.[27] Countries able to offer numerous essential medicines while facing resource constraints, such as Botswana, whose NEML has an 80·5% alignment for cancer medicines with the WHO EML,[28] would be in a strong position to inform WHO EML processes for prioritisation of highly priced medicines.

Selecting medicines for NEMLs is an important component of improving cancer outcomes. Even now, access to basic cancer medicines, such as conventional chemotherapies, remains a challenge in many countries.[2] Given these barriers, the WHO Expert Committee, with support from the CMWG, has updated processes to ensure only high-value medicines are recommended on the WHO EMLs. The endorsements of a minimum threshold for overall survival gain, use of the ESMO-MCBS tool, and concurrent proposals to include formal price considerations and additional selection principles, ensure cancer medicines recommended for inclusion on the WHO EMLs offer maximum overall survival benefit and are sensitive to associated health system impacts.

Contributors

All authors participated in the development of the report, including conception, provision of data and references, writing of the manuscript, and approval of the final version. KJ and LM wrote the first complete draft, which was improved and revised by all authors.

Declaration of interests

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