Enhancing Global Access to Cancer Medicines

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Abstract: Globally, cancer is the second leading cause of death, with numbers greatly exceeding those for human immunodeficiency virus/acquired immunodeficiency syndrome, tuberculosis, and malaria combined. Limited access to timely diagnosis, to affordable, effective treatment, and to high-quality care are just some of the factors that lead to disparities in cancer survival between countries and within countries. In this article, the authors consider various factors that prevent access to cancer medicines (particularly access to essential cancer medicines). Even if an essential cancer medicine is included on a national medicines list, cost might preclude its use, it might be prescribed or used inappropriately, weak infrastructure might prevent it being accessed by those who could benefit, or quality might not be guaranteed. Potential strategies to address the access problems are discussed, including universal health coverage for essential cancer medicines, fairer methods for pricing cancer medicines, reducing development costs, optimizing regulation, and improving reliability in the global supply chain. Optimizing schedules for cancer therapy could reduce not only costs, but also adverse events, and improve access. More and better biomarkers are required to target patients who are most likely to benefit from cancer medicines. The optimum use of cancer medicines depends on the effective delivery of several services allied to oncology (including laboratory, imaging, surgery, and radiotherapy). Investment is necessary in all aspects of cancer care, from these supportive services to technologies, and the training of health care workers and other staff. CA Cancer J Clin 2020;70:105-124. © 2020 American Cancer Society.

Keywords: antineoplastic agents, drug regulation, health services accessibility, immunomodulation, price, research design

Global Cancer Burden

Despite substantial treatment advances, cancer was the second leading cause of death globally (after cardiovascular disease) in 2017.1 Deaths caused by cancer (17%) far exceeded those caused by communicable diseases such as human immunodeficiency virus/acquired immunodeficiency syndrome (1.7%), tuberculosis (2.1%), or malaria (1.1%). Between 2007 and 2017, deaths from cancer increased by 25.4% (from 7.62 to 9.56 million).

In 2018, GLOBOCAN estimated that 18.1 million people were diagnosed with cancer, and 9.6 million people died from cancer worldwide.2,3 About 4% of these new cancer cases occurred in low development index countries, 16% occurred in medium development index countries, and the remainder occurred in high or very high development index countries.3 Approximately 5% of the cancer deaths occurred in low development index countries, 20% occurred in medium development index countries, and the remainder occurred in high or very high development index countries. The absence of high-quality cancer registries for approximately 85% of the world’s population, particularly in low-income and middle-income countries, affects the robustness of these estimates.3 Nearly 50% of cancer cases and 60% of
cancer deaths occurred in Asia (home to 60% of the world’s population), but only 6.5% of people in this region are covered by registries. Cancer ranks as the first or second cause of premature death in almost 100 (of 185) countries. Globally, in 2018, 1 in 5 men and 1 in 6 women developed cancer, and 1 in 8 men and 1 in 10 women died from it. The 4 leading causes of cancer death worldwide are malignancies of the lung, colorectum, stomach, and liver. Incidence rates for cancer overall and for individual cancer types vary by country and reflect population age distribution, differences in prevalence and distribution of the main risk factors for cancer (including the extent of a country’s economic development and associated social and lifestyle factors), and availability of screening and diagnostic services to detect cancer. In emerging economies, there is ongoing displacement of infection-related and poverty-related cancers (eg, cervix, stomach, and liver) by cancers that are frequent in developed countries (eg, colorectal).

For 37.5 million patients diagnosed with one of 18 cancers between 2000 and 2015 across 71 countries in the CONCORD program, the differences in 5-year survival between countries were wide. For instance, 5-year survival for lung cancer was approximately 33% in Japan but 4% in India. Five-year survival for breast cancer was 90% in the United States but 40% in South Africa. Because the quality and completeness of cancer registry data and follow-up varied between countries, this affected the comparability of survival estimates in CONCORD. Survival outcomes for many low-income and middle-income countries not covered by CONCORD are likely to have been worse.

Drilling deeper into country-specific cancer survival data may reveal racial, ethnic, or regional variation in cancer survival. For instance, African American individuals have the lowest survival rate of any racial or ethnic group in the United States for most cancers. The 5-year survival rate for breast cancer diagnosed during 2008 through 2014 was 81% among African American women compared with 91% among white women.

Advanced stage at presentation, limited access to timely diagnosis, and to affordable, effective treatment, and high-quality care are just some of the factors that lead to disparities in cancer survival between countries and within countries. Target 3.4 of the United Nations Sustainable Development Goals to reduce premature deaths from noncommunicable diseases by one-third by 2030 will not be achieved if measures are not taken to reduce disparities in access to cancer treatment and high-quality care.

We undertook this article to review global access to cancer medicines. The primary objectives were to assess the uptake of cancer medicines on the World Health Organization Model Lists of Essential Medicines, to review affordability and other key factors that affect access to cancer medicines (particularly access to essential cancer medicines), and to identify solutions that could address the access problems.
Essential Medicines for Cancer

Access to cancer medicines is a major challenge particularly in resource-poor settings and emerging economies. The World Health Organization produces Model Lists of Essential Medicines to help these countries select medicines for procurement and inclusion on their national essential medicines lists and, increasingly, on their national reimbursable medicines lists. Essential medicines are defined as “those that satisfy the priority health care needs of the population.” Given that cancer is the second leading cause of death globally, that the number of deaths from cancer is increasing, and that some cancers are highly responsive to therapy, there is a strong argument to consider certain anticancer drugs as essential medicines. For essential cancer medicines on the World Health Organization Model Lists of Essential Medicines, 2019, see who.int/medicines/publications/essentialmedicines/en/.6

The decision to assign a drug as an essential cancer medicine by an expert committee depends on the estimated magnitude of its benefit and relative toxicity for each indication compared with other therapeutic options, as well as its impact on monitoring, cost, diagnosis, and overall disease management.7 Cancer medicines are evaluated using the European Society for Medical Oncology Magnitude of Clinical Benefit Scale.8 On this scale, medicines with scores of 4 and 5 in the noncurative setting and ratings of A and B in the curative setting, with an additional overall survival of at least 4 to 6 months compared with the standard of care, can be considered for inclusion on the Model Lists of Essential Medicines.9

Inclusion of a medicine on the World Health Organization Model Lists of Essential Medicines recognizes the human rights to have these medicines available globally, stimulates entry of new manufacturers, rallies stakeholder support, and, over time, shapes market forces to improve affordability and access of even highly priced, patented medicines, as was the case for antiretroviral therapy.7

Access to Cancer Medicines

In an analysis of national medicines lists of 135 countries with a per-capita gross national income (see World Bank definitions) for 2015 <$25,000, only 10% of countries included all 25 essential cancer medicines from the World Health Organization Model Lists of Essential Medicines 2013, whereas only 37% included at least 20 essential cancer medicines.10 The median number of essential cancer medicines that appeared on national lists was 9 for the 28 low-income countries studied, 18 for 44 lower-middle-income countries, 19 for 42 upper-middle-income countries, and 20 for 18 high-income countries. With the introduction of the World Health Organization Model Lists of Essential Medicines 2015, 19% of all countries included trastuzumab, 37% included ≥1 aromatase inhibitor, 30% included imatinib, and 25% included rituximab. Almost 50% of countries included ≥1 granulocyte-colony-stimulating factor. However, these data do not provide information on access to essential cancer medicines in these countries. Even if an essential cancer medicine is included on a national medicines list, cost might preclude its use, it might be prescribed or used inappropriately, weak infrastructure might prevent it being accessed by those who could benefit, or quality might not be guaranteed. Conversely, essential cancer medicines that are not included on a national list might be available through other reimbursement models, donations, or specialized hospital lists.11 For these reasons, more sensitive indicators are required to measure access to essential medicines.12

A survey of 63 countries in Africa, Asia, Oceania, the Middle East, North America, Latin America, and the Caribbean found that the majority of essential cancer medicines on the World Health Organization Model Lists of Essential Medicines 2015 were included on national formularies; however, the cost was to be borne by the patient for 58% of essential cancer medicines in low-income countries, for 32% in lower-middle-income countries, for 1.8% in upper-middle–income countries, and for none in high-income countries.13 Disparities in cancer medicine access also existed between the wealthier countries of Western Europe and developing economies of Eastern Europe, although they were less profound for essential cancer medicines.14

Pharmaceutical companies had access initiatives for 57% of essential cancer medicines on the World Health Organization Model Lists of Essential Medicines 2017.15 They mainly involved pricing initiatives and, on average, applied to <5 priority countries.

Cancer medicines not on the World Health Organization Model Lists of Essential Medicines can remain unapproved for many years in low-income and middle-income countries.16 Although the rational selection of cancer medicines and the rational application of access requirements can deliver better value for money without compromising health outcomes, cost-containment measures in some countries have resulted in reduced or delayed access.8

Target 3.8 of the United Nations Sustainable Development Goals, “to achieve universal health coverage, including financial risk protection, access to quality essential health care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all” by 2030, will not be achieved unless measures are taken to improve access to essential cancer medicines.

Spiraling Cancer Medicine Prices

Global spending on cancer medicines and related supportive care increased from $96 billion in 2013 to $133 billion in 2017.17
TABLE 1. Definition of Terms Used to Describe Some Trading and Anticompetitive Business Practices

| TERM                      | DEFINITION                                                                 | EXAMPLE                                                                 |
|---------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Parallel trade (WHO 2018) | Suppliers outside of a manufacturer’s distribution system export a medicine from countries with low prices to those with higher prices without the manufacturer’s consent | Observed in the common internal EU market and is a cause of cancer medicines shortages in some countries with lower prices (eg, Eastern and Central European countries, Portugal, United Kingdom) |
| Pseudogeneric (WHO 2018)  | Usually marketed by the originator pharmaceutical company for their own branded medicine, but at a lower price It reduces the market share and discourages genuine generics from entering the market Overall savings to health systems may be diminished because competition is reduced and the prices of pseudogenerics may not be as low as genuine generics | Azacitadine                                                                 |
| Collusion (WHO 2018)      | Competing companies may engage in explicit or tacit agreement by either fixing the price or sharing the market | Attorneys General of 45 states and the District of Columbia in the United States have alleged collusion by 18 generic companies and subsidiaries for 15 medicines (including zoledronic acid) |
| Product hopping (WHO 2018) | To maintain market exclusivity, a patented medicine is reformulated to a product that offers little or no therapeutic advantage | Promotion of pegfilgrastim began before competing biosimilar products of filgrastim were launched |

The growth rate of cancer medicines expenditure greatly exceeds that of newly diagnosed cancer cases; during 2012 through 2016, cancer medicines expenditure per incident cancer case was about 2-fold to 8-fold higher than the overall per capita health expenditure.8 The global market for cancer medicines is estimated to reach up to $200 billion by 2022.17

High prices are a major factor preventing patients’ access to cancer medicines, even in high-income countries.8 As an example, although the combination of docetaxel, trastuzumab, and pertuzumab is highly effective for treating metastatic breast cancer, health economic analyses show that it is not cost-effective at a willingness-to-pay $100,000 per quality-adjusted life-year gained in the United States or £30,000 in the United Kingdom.18-20 If price rises are left unaddressed, an increasing number of highly effective regimens may be unaffordable.

Cancer medicine pricing varies considerably between countries and might not correlate with a country’s purchasing power.8 Despite comparable gross national incomes, essential cancer medicine prices were higher in Africa than in Latin America.21 There was up to a 92% difference in list prices for cancer medicines between 15 European countries and up to a 58% difference in actual prices paid.22 For 31 cancer medicines in 16 European countries, Australia, and New Zealand, the difference in list prices between the highest and lowest priced country ranged between 28% and 388%.23 This shows a lack of transparency in global cancer medicine pricing that might be exacerbated by the rise in confidential agreements on rebates and prices.8 Price differences between countries can lead to parallel trading (defined in Table 18,24) and cancer medicines shortages in some countries.24 An analysis of the top 10 selling cancer medicines in the United States and the United Kingdom found that US launch prices were 42% higher than in the United Kingdom.25 By 2015, their average annual price inflation was 8.8% in the United States but was restricted by price regulations to 0.33% in the United Kingdom. During 2005 through 2017 (mean, 8-year follow-up) in the United States, the mean cumulative cost increase (adjusted for general inflation) for 24 injectable cancer drugs was 19.1% (95% CI, 11%-27.2%).26 In the United States, the largest payer for health care (Medicare) is not allowed to negotiate prices, and so cancer medicine prices are driven by pharmaceutical companies to what the market will bear.27 US cancer medicine prices may have a global impact if they are used to benchmark prices elsewhere in the world.

In countries with universal health coverage, essential cancer medicines are available free of cost to patients through health insurance, social security schemes, or tax-based government provided health care.11,28 However, full costs are borne by patients in some countries (eg, India) potentially pushing them into poverty. Other countries provide intermediate assistance. In the absence of financial support from governments, a course of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for non-Hodgkin lymphoma would cost approximately 5.6 years of average annual wages in South Africa and 1.1 years of annual wages in the United States.8 The goal is for all essential cancer medicines to be accessible under universal health coverage by all who need them.28 Insured patients with cancer in high-income countries have reported financial hardship and treatment nonadherence because of high cancer medicine prices.8,29
Cancer medicines have generated income for originator companies far in excess of research and development costs for those medicines and financial incentives for future research and development.8,30 Prices do not take account of the public investment that may have contributed to research and development or of the human investment from clinical trial participation. Because developing new cancer medicines is risky, revenues should also cover costs for drugs that do not reach the market successfully. However, by the end of 2017, average income (in US dollars) from 99 cancer medicines for the originator companies was $14.50 (range, $3.30-$55.10) for every dollar spent on risk-adjusted research and development.31 Production costs of some cancer medicines are also relatively small in relation to their prices. The estimated generic production costs of 4 tyrosine kinase inhibitors was from 0.2% to 2.9% of their prices on the US market.32 Companies often set cancer medicine prices according to income expectations rather than on the value of cancer medicines, and high expenditure occurs on marketing and promotional activities.8 The price of lenalidomide was increased 3 times in 2017 without evidence of how its benefits had changed during that time.8

**Approaches to Decreasing Cancer Medicine Costs**

**Generics and Biosimilars**

The oncology biologic products that lost patents between 2016 and 2020 were estimated to account for $20 billion in global annual expenditure.33 Generics and biosimilars can help to improve the cost-effectiveness of cancer drugs and make them accessible to more patients.8 Table 28,33-39 summarizes the differences between generics and biosimilars.

Some changes to the reimbursement legislation for biosimilars are necessary in the United States to ensure that cost savings occur.33 Health care professionals and patients should be educated about the benefits of using generics and biosimilars.8,33 Price competition is optimized when many companies are competing to market generics.8 Prices must be balanced because prices that were too low have driven some manufacturers out of business and caused cancer medicine shortages.34 Anticompetitive business practices, such as the introduction of pseudogenics, collusion (price fixing or market sharing), product hopping, and delaying the entry of a generic or biosimilar, should be discouraged.8 Table 1 provides definitions of anticompetitive business practices.

High application costs and lengthy regulatory reviews may delay the time for biosimilars and generics to reach market.8 To improve access, regulatory, prescribing, and dispensing requirements should be harmonized globally, particularly in relation to nomenclature, switching, and substitution. The World Health Organization has a pilot procedure for prequalification of trastuzumab and rituximab.40 Products that meet the World Health Organization’s standards are considered acceptable for procurement by United Nations and World Health Organization member states.

Poor manufacturing processes, quality control, storage, and regulatory enforcement have led to the production of substandard oncology generics in middle-income countries.37 There is particular concern for cancer medicines with a narrow therapeutic index. Because high-income countries depend on middle-income countries for some generic supplies, regulators from high-income countries are increasingly inspecting manufacturing sites in middle-income countries that supply them (eg, the US Food and Drug Administration [FDA] in India). Such collaborations should be used to improve the training and education of regulators in low-income and middle-income countries so that their benefits can extend to all pharmaceutical manufacturing sites in those countries.

Because of the lack of patent laws, intended copies of biologics had been produced in some middle-income countries before biosimilars for these were introduced in high-income countries (eg, rituximab in Latin America).41 The intended copies may not meet the current regulatory standards for biosimilars and should be re-evaluated.

**Fairer Prices for Cancer Medicines**

Without a proper value assessment, there is a risk of wasting money on cancer medicines that provide minimal or no benefit, as happened with the old version of the Cancer Drugs Fund in England (Table 3 explains the changes that have happened to this fund over time).42 Reducing prices of cancer medicines would improve their affordability, increase their accessibility, and increase sales volumes. It would also allow other cancer medicines to be considered for inclusion on the World Health Organization Model Lists of Essential Medicines. Table 4 describes some methods to help reduce cancer medicine prices.8,24,28,30,42-52

Although a combination of these methods can continue to be used, recent publications suggest that further change is required.28,30 Building on the work of others, we propose that an international body comprising representatives from the pricing authorities of all countries is convened.8,28,30 Among its aims would be to reduce cancer medicine prices to levels affordable by health care systems and manufacturers globally. For each cancer medicine, it could mandate pharmaceutical companies to provide the cost of research and development (including a breakdown of company, public, and philanthropic investment), ingredients, labor, manufacturing, regulation, storage, and distribution and to justify any costs that may differ between countries. These costs could be used in high-quality health technology assessments to assess the cancer medicine’s cost-effectiveness at various prices and incremental cost-effectiveness ratios per quality-adjusted life-year. The environmental impact of a cancer medicine
TABLE 2. Main Differences Between Generics and Biosimilars

| AREA                        | GENERIC                                                                 | BIOSIMILAR                                                                 |
|-----------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Definition                  | FDA definition: “a medication created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality, and performance characteristics” (FDA 2018)
                      | A biologic product that is not chemically identical but is highly similar to an approved biological product (eg, in terms of purity, chemical identity, structure, bioactivity, pharmacodynamics, pharmacokinetics) with no clinically meaningful differences in efficacy and safety (Lyman 2018)
                      | Biosimilars do not meet generic definition because slight variation in the manufacturing process can alter the biosimilar and potentially lead to small differences in immunogenicity and adverse events |
| Development                 | Approval based on pharmaceutical equivalence and human bioequivalence to the branded drug (Lyman 2018)
                      | Development more complex and expensive than for generics (eg, analytical studies required to characterize protein structure and function; the manufacturing process is assessed for differences that may affect safety and efficacy compared with the originator; residual uncertainty must be addressed through preclinical studies and alterations in manufacturing; clinical confirmation of biosimilarity requires pharmacokinetic, pharmacodynamic, immunogenicity, and toxicity studies; a comparative dose-ranging, efficacy, and safety clinical trial may also be required) (Lyman 2018, Renwick 2016)
| Availability                | Usually widely available in countries that do not have patent restrictions for drug (eg, cisplatin, docetaxel, imatinib) |
                      | Trastuzumab, rituximab, bevacizumab, filgrastim, pegfilgrastim, epoetin α, and others expected (Lyman 2018) |
| Impact on prices            | In Europe and the United States, a generic will enter the market usually priced at 70%-80% of the originator price and further price reductions occur over time, taking the price to as low as 20% of the originator price (WHO 2018)
                      | Biosimilar list prices are 70%-85% of the originator price (Renwick 2016); biosimilars have not yet reduced costs to the extent seen with generics because biosimilar development is more costly and takes longer than for generics |
| Interchangeability          | Can be interchanged with their reference products because they are identical (Renwick 2016)
                      | Cannot be assumed to be interchangeable with its reference product unless data show that, if given more than once, switching between products causes no greater safety or efficacy risk than continuous treatment with reference product (Lyman 2018)
                      | Interchangeability would allow biosimilar to compete with the reference product on the basis of price alone (Renwick 2016)
                      | The FDA has an interchangeability designation but, to date, no biosimilar has been approved as fully interchangeable in the United States (Lyman 2018)
                      | Interchangeability trials are conducted rarely by manufacturers because of cost, time, and regulatory uncertainty over how to show interchangeability (Renwick 2016); financial incentives may encourage such trials |
| Switching policies          | Policies vary between countries; many promote switching (Yang 2016)
                      | Policies on automatic substitution of a biosimilar at the point of dispensing vary between countries (Renwick 2016); some prohibit the practice while some allow substitution for treatment-naive patients |
                      | In the absence of interchangeability evidence, policies for switching to a biosimilar vary between countries (Renwick 2016)
                      | Some countries (eg, Netherlands) advise prescribers against switching to a biosimilar, particularly when a patient is responding well to the reference product, and to reserve the biosimilar for treatment-naive patients; this restricts the market potential of the biosimilar and potential savings to health systems |
                      | Some countries (eg, the United Kingdom) leave the decision to switch at the discretion of the prescriber with patient’s response monitored closely |
                      | Where a biosimilar is purchased under pooled procurement agreements, local policies should be in place to guide switching |
                      | Real-world data could be collected on the outcomes of patients who have been switched, particularly as the real-world switching scenario may become more complex as more biosimilars are approved (Lyman 2018)
| Substitution policies at the point of dispensing | Policies vary between countries. Many promote substitution at the point of dispensing (Yang 2016); in the United States and Canada, pharmacists inform patients when switching and patients inform prescribers of the change (Yang 2016)
                      | Policies on automatic substitution of a biosimilar at the point of dispensing vary between countries (Renwick 2016); some prohibit the practice while some allow substitution for treatment-naive patients |
| Nomenclature                | International nonproprietary name used |
                      | To ensure the correct biosimilar is prescribed and dispensed for a specific biologic drug, the FDA uses the same international nonproprietary name for biosimilars plus a manufacturer-specific suffix; taken together, the nonproprietary name and suffix produce a proper name (FDA 2017) |
should also be considered. Alternative ways of funding research and development, incentivizing future research and development, and agreement on acceptable profit margins could also be discussed. Some suggest that patents on cancer medicines could even be abolished so that several manufacturers could enter the international market. Further price negotiations could occur at the country and regional levels. In the United States, legislation should be introduced to allow payers of health care (eg, Medicare) to negotiate cancer medicine prices. Details of prices paid by countries could be recorded on an international database and used to adjust an international reference price for each cancer medicine. Prices should be monitored regularly to ensure they reflect changes in market conditions (eg, introduction of a new class of cancer medicine). In the interests of transparency, details about discounts and rebates should not remain confidential. Countries should also share any new evidence gathered from managed entry agreements for cancer medicines.

Potential barriers to such collaboration may include a reluctance to change, the possibility of bias in the cost data provided by pharmaceutical companies, countries in which the economies depend on pharmaceutical companies may want to protect the commercial interests of those companies, trade wars between countries do not produce a climate conducive for collaboration, and low-income and middle-income countries may not have the capacity to participate or may have inadequate data on cancer medicine prices in their countries. As an initial step, we will discuss our findings and proposal with associations of the pharmaceutical industry and the pricing authorities in our own countries. If this generates sufficient interest, we will extend our discussions more widely, for instance, to the European Union, the United Nations, the Commonwealth, and the G20.

**Optimizing Schedules for Cancer Therapy**

If justified by data, using cancer medicines at lower, less frequent doses for shorter durations would reduce costs and adverse events and would improve access. However, the optimal schedule is not always clear.

For instance, the optimum, cost-effective doses have not been determined for many approved immune checkpoint inhibitors. Although flat dosing is feasible for immune checkpoint inhibitors because there is no clear relationship between dose response or dose toxicity, weight-based doses continue to be approved for some. While treatment with ipilimumab is usually limited to 4 doses, the optimal treatment duration for other immune checkpoint inhibitors is not defined. In the absence of a complete response, many patients are continued on therapy indefinitely, with significant cost implications.
| METHOD                          | COMMENTS                                                                                                                                                                                                 |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reduce drug wastage            | CMs should be produced at pack sizes or dosages that do not result in drug wastage (WHO 2018)                                                                                                             |
| Cost-based pricing             | Prices set according to direct costs of ingredients, labor, R&D, manufacturing, regulation, marketing, sales, storage, distribution, and include an acceptable level of profit (WHO 2018) |
|                                | Not widely used because of difficulties in obtaining information required to determine prices                                                                                                          |
| Enforced price caps            | Prevents a CM price increasing over a specified time (eg, used for single branded CMs in India) (WHO 2018)                                                                                               |
| Tiered pricing                 | Allows progressive reduction in price over time (WHO 2018)                                                                                                                                             |
| External reference pricing     | Prices set according to prices in comparable countries (eg, Europe, Africa)                                                                                                                             |
|                                | Motivates pharmaceutical companies to keep list prices high, so can be inflationary (WHO 2018)                                                                                                           |
|                                | Differences between list prices and actual prices paid reduces effectiveness of method                                                                                                                |
|                                | LMICs have used prices from countries with wide-ranging national incomes (WHO 2018)                                                                                                               |
| Internal reference pricing     | Prices set according to benchmark prices within a country for comparable medicines (eg, in Australia, the price of nilotinib is benchmarked against that of imatinib) (WHO 2018) |
| Pooled procurement             | Multiple payers within a country or across different countries can use their collective bargaining power to negotiate price reductions with suppliers (WHO 2018) |
|                                | Pooled procurement has improved purchasing power nationally (eg, Thailand) and internationally (eg, Pan American Health Organization Strategic Fund) and helped to reduce actual CM prices in these regions (WHO 2018, Sruamsiri 2016) |
|                                | For it to work successfully across multiple jurisdictions, some alignment in legal, regulatory, and other policies is necessary (eg, product registration, manufacturing, quality assurance, patent laws), and transparency in the pricing market for CMs is necessary (Wirtz 2017, Martei 2018) |
|                                | Procurement that relies only on one manufacturer risks encountering medicines shortages if that company experiences manufacturing problems; agreements should specify the contract period and require the company to provide advance notification of any impending supply problems |
|                                | Advance purchase commitments could be made to guarantee supply and prevent shortages (The Economist Intelligence Unit 2017)                                                                               |
| Differential pricing           | Prices set according to various factors, including a country’s cancer burden, health system design, existing health expenditure, and wealth (measured by gross domestic product or GNI per capita) (WHO 2018) |
| according to a country’s       | For it to be effective, it must take into account income inequality within a country and a government’s capacity to invest more in health                                                                  |
| ability to pay                 | Price differences between countries can lead to parallel trading and CM shortages in some countries                                                                                                     |
| Local formularies              | Guide health care professionals to select cost-effective CMs procured locally; national formularies can help facilitate preparation of local formularies                                                                 |
| Biosimilars and generics       | See Table 2                                                                                                                                                                                               |
| Value-based pricing            | HTAs conducted to determine the societal value of reimbursing a CM                                                                                                                                          |
|                                | Consider efficacy, toxicity, quality-of-life, economic, and financial impact of CM, often in context of disease prevalence, medical need, and established alternative treatments, as well as access and targeting patients most likely to benefit |
|                                | HTAs can be used to negotiate price reductions; a Thai HTA found that oxaliplatin was cost-effective only as part of FOLFOX chemotherapy if its price was reduced by at least 40%; a 70% price reduction was negotiated, saving the health system $4.75 million (Wirtz 2017) |
|                                | Reliability of value-based pricing varies because there is variation in the robustness of assessments between countries, incomplete evidence to perform assessments, inappropriate use of comparators, and differences in value perception between patients, decision makers, and pharmaceutical companies (WHO 2018); there is also duplication of effort between countries; countries with similar wealth, health care priorities, societal values, and CM prices should collaborate where possible to avoid such duplication |
|                                | LMICs could use HTAs produced by HICs, but the maximum, acceptable incremental cost-effectiveness ratio per quality-adjusted life-year for a CM may differ between countries |
|                                | Although 12 mo of adjuvant trastuzumab was cost-effective in some countries, it was not cost-effective in 7 Latin American countries; its price would have to decrease by 70%-95% to become cost-effective in this region (Pichon-Riviere 2015) |
|                                | LMICs may lack expertise and resources to conduct HTAs                                                                                                                                                     |
|                                | ASCO and ESMO have tools that can be used by clinicians to assess the value or clinical benefit, respectively, of a CM while awaiting HTA (Schnipper 2016, Cherny 2017)                                           |
The addition of adjuvant trastuzumab for 1 year to standard chemotherapy is licensed for human epidermal growth factor receptor 2 (HER2)-positive, early breast cancer and has brought significant improvements in disease-free survival and overall survival.\(^{54-62}\) The choice to use trastuzumab for 1 year in the initial pivotal trials was arbitrary.\(^{63}\) It is possible that an even shorter trastuzumab duration could be as effective as 1 year, at lower cost and cardiac toxicity, and better convenience. Some support for a shorter treatment duration was provided by a small trial, in which 9 weeks of trastuzumab showed a benefit similar to that from 1 year of trastuzumab when given with standard chemotherapy.\(^{54,65}\) Several other trials failed to show noninferiority of the shorter trastuzumab duration (9 weeks or 6 months).\(^{56-68}\)

The larger, phase 3 PHARE (Protocol for Herceptin as Adjuvant Therapy With Reduced Exposure) and PERSEPHONE (6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer) trials in HER2-positive, early breast cancer had similar designs and assessed the same clinical endpoints.\(^{69,70}\) The final PHARE analysis, with a median follow-up of 7.5 years, failed to show that 6 months of trastuzumab was noninferior to 12 months of trastuzumab; the frequency of cardiac events was lower in the 6-month arm. In contrast, PERSEPHONE, with a median follow-up of 5.4 years, found that 6 months of trastuzumab was noninferior to 12 months of trastuzumab with less cardiotoxicity and less severe adverse events. The hazard ratios and confidence intervals for the 2 trials were similar, but the prespecified noninferiority margins chosen were different (PERSEPHONE: noninferiority margin, <3%; hazard ratio, 1.28; PHARE: noninferiority margin, 2%; hazard ratio, 1.15). This difference explains the discordant conclusions between the 2 studies and brings into question the feasibility of using noninferiority margins in oncology trials in which survival is the primary outcome. Although noninferiority margins should take account of the treatment effect

### TABLE 4. Continued

| METHOD                                      | COMMENTS                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Managed entry agreements (risk-sharing agreements) | Specify conditions (eg, price, volume prescribed, health outcomes) for reimbursing a CM with uncertain cost-effectiveness (WHO 2018\(^8\))                                                                                                                                                                                                 |
observed in historical trials, selecting an acceptable margin can be somewhat subjective. Problems could be reduced by obtaining international agreement on noninferiority margins to use in oncology trials of the same type before they are begun.

Trastuzumab with nonanthracycline-based chemotherapy is associated with less cardiac events than trastuzumab with anthracycline-based chemotherapy. However, only approximately 10% of patients in the PERSEPHONE and PHARE trials received nonanthracycline-based chemotherapy; these numbers were too small to address the noninferiority of 6 months trastuzumab in this group.

According to the hazard ratios for PHARE and PERSEPHONE, the difference in benefit for 12 versus 6 months of trastuzumab treatment is likely to be small. Therefore, it is reasonable to consider 6 months of trastuzumab for some patients with HER2 positive, early breast cancer when resources are a problem, especially in those with small tumor loads.

During preclinical and clinical development of a cancer drug, greater attention should be given to identifying the most effective, as well as the safest, schedule.

Another way to reduce the cost and time burden on patients and health systems is by using more convenient cancer medicine formulations, particularly in low-income and middle-income countries where patients may have to travel long distances to receive an intravenous infusion. The availability of subcutaneous trastuzumab (Herceptin; Genentech) allows the possibility of administration by local health care professionals or patients themselves. However, the clinical trials to support noninferiority of subcutaneous versus intravenous trastuzumab were not published until 2012 and 2013. Biosimilars of subcutaneous trastuzumab are currently unavailable because this remains under patent.

Reformulation of a cancer medicine should not be seen only as a strategy to extend patent protection later in the development pathway; rather, the most patient-friendly formulations of a cancer medicine should be investigated from the onset of clinical development.

### Biomarkers

The central role of oncogenes in cancer provides the foundation for developing personalized therapy and allows treatment and resources to be targeted to patients most likely to benefit. Table 5 describes different types of biomarkers used to target cancer medicines.

### Optimizing Cancer Medicine Research

In 2017, there were twice as many clinical trials registered for cancer medicines than in the next 4 highest therapeutic categories. In immuno-oncology alone, there were 940 drugs in clinical development, 1064 drugs in preclinical development, and 3042 trials targeting the enrollment of 57,706 patients (including 469 combination trials only involving programmed death-1 receptor/programmed death-1 receptor ligand–1 inhibitors). Although these trials might lead to some breakthroughs, the field is fragmented and uncoordinated, with inefficiencies because of duplication of research and pursuit of marginal indications with clinically less significant health outcomes. Research and development incentives and regulatory flexibility might also favor initial application for orphan rather than for commoner indications.
Pharmaceutical companies are not typically interested in sponsoring trials for neglected cancers (eg, liver, brain) or for investigating de-escalation of established cancer medicines that are no longer under patent.\textsuperscript{79} PHARE (described above) was funded by the French National Cancer Institute, whereas the International Duration of Evaluation of Adjuvant Therapy (IDEA) analysis of colon cancer was funded by various noncommercial grants.\textsuperscript{69,80}

Although participation in commercial clinical trials provides middle-income countries access to biomarkers and to standard and investigational drugs, which might not otherwise be available, the trials might not always address the health priorities of these countries, and access might stop on trial completion.

Conversely, if governments funded large trials comparing standard schedules with schedules that included less drug (lower doses, shorter durations), this might provide double benefit: generating data that could support future use of shorter schedules while using significantly less drug during the study than the same patients would have received on standard schedules, especially with 1:2 randomization designs. Clearly, such trials must be scientifically justified. There is always a trade-off between efficacy and quality of life, especially for cancer drug trials in advanced disease; less intense drug schedules might be justified by reducing side effects, even if efficacy is no better or is slightly lower. Government funding for such trials may be lacking in resource-poor settings, however.

Another way of reducing cancer medicine prices is to lower cancer drug development costs. Table 6 outlines some strategies to increase clinical trial efficiency.\textsuperscript{53,74,79,81-89}

An international body representing the governments of all countries and working in partnership with academic research groups, cancer clinical trial networks (eg, the National Cancer Institute, the Institute of Cancer Research, the European Society for Medical Oncology, the American Society of Clinical Oncology), the World Health Organization, the pharmaceutical industry, not-for-profit organizations, and patient advocate groups could be responsible for setting the global research priorities for developing cancer medicines. It is not a responsibility that should be fragmented or left to one sector alone. Such a body could ensure that research priorities are driven by health needs rather than commercial potential, that limited resources are used efficiently, and that new cancer medicines are affordable and accessible by all who need them. It could identify the best ways to fund and incentivize research and development, monitor performance, and avoid duplication of work. To reduce the cost and effort involved in conducting clinical trials, it could harmonize the international legal, ethical, and financial regulations covering trials (eg, data protection laws on clinical trials to allow smoother transfer of patient-level data; it could work with the International Conference on Harmonization to ensure that international good clinical practice guidance is adopted by all countries without the need to revert to local guidance).

Potential barriers to such collaboration may include a reluctance to change, reluctance to abandon local regulations in favor of international regulations, reluctance to share decision making, competition between researchers in different countries, competition between pharmaceutical companies working in the same therapeutic area, the commercial interests of those companies, and low-income and middle-income countries may not have the capacity to participate.

**Real-World Evidence**

Real-world data, gathered during normal clinical care, relate to patient health status (eg, physiologic parameters, survival, tumor response rate, adverse events) or health care delivery parameters.\textsuperscript{90,91} Sources include electronic health records, patient registries, digital devices, and insurance claims. The strength of real-world evidence depends on the methodology used and the reliability and relevance of the data.\textsuperscript{90}

Real-world evidence is used in prospective and retrospective observational studies to generate hypotheses for further investigation (eg, cancer medicine safety and efficacy in patients excluded from randomized clinical trials) or to provide supportive evidence.\textsuperscript{90,92} Confounders can bias results, especially if they are not accounted for by statistical adjustments.\textsuperscript{93}

Pragmatic trials with planned interventions, with or without randomization, can be conducted in real-world settings (eg, PERSEPHONE).\textsuperscript{91} Real-world evidence could confirm the clinical benefit of cancer medicines that have undergone accelerated approval.\textsuperscript{90,92} Hybrid trials can be designed to incorporate traditional and pragmatic elements.\textsuperscript{90}

Although real-world evidence is widely used to evaluate cancer medicine safety, it has been used in limited instances to support efficacy in registration submissions.\textsuperscript{90} Blinatumomab was approved for the treatment of Philadelphia chromosome-negative acute lymphoblastic leukemia based on the rate and duration of complete remission in a single-arm trial in 185 patients compared with historical data (extracted from >2000 patient records) for 694 control patients.

Real-world data are also used in health economic analyses. Cancer registry incidence data and outcomes data linked to Medicare claims were used to show rituximab’s cost-effectiveness for chronic lymphocytic leukemia and certain lymphomas in the United States.\textsuperscript{94}

**Optimizing Cancer Medicine Regulation**

The mean time from cancer medicine application at the FDA to submission at the European Medicines Agency or Health...
### TABLE 6. Strategies to Increase Efficiency of Cancer Drug Clinical Trials

| STRATEGY | COMMENTS | EXAMPLES |
|----------|----------|----------|
| **For implementation by sponsors and investigators** | | |
| Use adaptable, flexible trial designs to reduce cancer drug development time | With traditional designs, cancer drug development from first-in-human studies to regulatory approval can take ≥10 y (Cescon & Siu 2017<sup>81</sup>) | KEYNOTE-001 started as a dose-escalation study of pembrolizumab in advanced solid tumors; over time, its design was adapted to take account of the emerging data from the trial; several expansion cohorts were added to investigate doses and schedules for melanoma and NSCLC, culminating in the enrolment of >1200 patients and accelerated regulatory approval (Kang 2017<sup>83</sup>) |
| | Recent changes in trial designs have helped to reduce development times to 3-4 y, as demonstrated for pembrolizumab and crizotinib (Cescon & Siu 2017<sup>81</sup>, Kazandjian 2014<sup>82</sup>) | The data identified PD-L1 expression as a predictive biomarker for patients with NSCLC who were most likely to benefit from pembrolizumab and allowed the targeting of pembrolizumab to patients whose NSCLC tumors expressed PD-L1 with a ≥50% tumor proportion score |
| | The new designs increase protocol complexity and require multiple protocol amendments, which have the potential to cause adherence problems at clinical sites | |
| **Use umbrella trials or basket trials to answer multiple questions in a single trial** | May require collaboration between multiple drug developers | Lung Cancer Master Protocol (NCT02154490) is an umbrella trial |
| | May eliminate the need for a control arm in genomic-based trials that are used to identify patients who are most likely to benefit from molecularly targeted cancer drugs | During a phase 1 basket trial of crizotinib across different types of solid tumors, a response was observed in 2 patients with ALK-positive NSCLC (Kazandjian 2014<sup>82</sup>); subsequently, the protocol was amended to include an expansion cohort of patients with ALK-positive NSCLC; after positive objective responses in these patients, 2 further trials were conducted to confirm these results and seek regulatory approval |
| | Umbrella trials can be used to evaluate multiple classes of drugs in patients with specific tumor mutations (Sharpless & Doroshow 2019<sup>79</sup>) | Basket trials can be used to investigate a cancer drug or a drug combination targeting a specific molecular aberration across many different cancer types; especially useful to study rare cancer types |
| | Basket trials can be used to investigate a cancer drug or a drug combination targeting a specific molecular aberration across many different cancer types; especially useful to study rare cancer types | |
| **Share a single, common control group between several clinical trials for the same indication** | Requires collaboration between multiple drug developers working to a standard clinical trial protocol | Being implemented in antibiotic trials |
| | Reduces duplication of effort in recruiting control group | |
| **Nonrandomized trials using historical controls** | Reduces the cost of each trial and increases the number of patients available to take part in other trials | |
| **Biomarker-driven patient selection** | Might be justified in some patient populations | Most women with stage I HER2-positive BC would not have been eligible for pivotal trials with adjuvant trastuzumab; however, accumulating evidence from retrospective studies has been supportive of its use, so patients would be unlikely to enroll in a study with a no-trastuzumab arm; therefore, Tolaney et al studied a relatively nontoxic regimen of adjuvant paclitaxel and trastuzumab in an uncontrolled, single-group study of 406 women and showed a 3-y rate of invasive-disease free survival of 98.7% (Tolaney 2015<sup>84</sup>) |
| | If treatment benefit is clearly limited to the biomarker-positive group, then either enroll only biomarker-positive patients or enrich enrollment with such patients | FDA approved pembrolizumab for the treatment of adults and children with unresectable, previously treated, MSI-H or dMMR solid tumors regardless of tumor type or site (Lemery 2017<sup>85</sup>) |
| | | The approval was based on data from 149 patients with unresectable or metastatic, MSI-H or dMMR cancer (84% colorectal, 53% other tumors) across 5 trials; further trials are to be conducted to evaluate response and duration, and it is likely that these will select patients on the basis of MSI-H or dMMR biomarkers |
Canada was 12.9 months and 28.4 months, respectively.95 After regulatory approval by the European Medicines Agency or the FDA, it can take ≥1 year for a cancer medicine to be registered in low-income and middle-income countries.96 The process for registering cancer medicines in low-income and middle-income countries is complex, inefficient, and costly.96,97 Many regulators are unable to meet the regulatory standards outlined by the World Health Organization.28 The quality of regulatory training across low-income and middle-income countries is inconsistent and is being addressed by the World Health Organization.97 The World Health Organization estimates that 10.5% of medicines in low-income and middle-income countries are substandard and falsified.98 It defines a substandard medicine as an authorized medical product that fails to meet its quality standards or specifications.98,99 The World Health Organization defines a falsified medicine as a medical product that is deliberately or fraudulently

### Table 6. Continued

| STRATEGY                                      | COMMENTS                                                                 | EXAMPLES                                                                                                                                 |
|-----------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Identify a universal biomarker to determine PD–L1 expression | Currently, different PD-1/PD-L1 inhibitors require different methods for detection; this means that the oncologist must know which test to order or laboratory staff have to determine which test to perform, and the differences in scoring may cause problems in result interpretation (Osmani 201814) | Genomic analyses of biopsy samples from 4 patients with metastatic melanoma who relapsed after an initial objective response with pembrolizumab showed defects in interferon signaling and antigen presentation (Zaretsky 201696); early prioritization of these analyses would have allowed this important result to inform future development earlier |
| Identify and characterize exceptional responses during phase 1 clinical trial stage | Assists patient selection in future trials and informs further development |                                                                                                                                                                                                 |
| Extend DLT assessment for ICIs               | As the maximum tolerated dose is not reached for many ICIs, the typical 3 + 3 dose-escalation design with a DLT assessment is inadequate for guiding the optimum dose and schedule (Baik 201733, Garralda 201797) | To take account of late toxicities, future trial designs with ICIs should include longer overall follow-up and DLT periods of at least 6-8 wk before escalating to higher doses; PK/PD modelling should guide the selection of dose and regimen beginning early in preclinical development, fine-tuning them as additional data are obtained |
| Reduce the excessive documentation required at clinical sites | Allow direct transfer of data from the patient’s electronic medical record into research database (Stewart 201888) | Requires support from information technology specialists |
| Remove excessive restrictions on eligibility criteria in clinical trials | Use more pragmatic eligibility criteria to improve the speed of patient enrollment (Stewart 201888) | Interrogation of data could help to answer the questions that have remained unanswered for some time (eg, in conjunction with nonanthracycline-based chemotherapy, which women with early BC can be treated with 6 mo trastuzumab instead of 12 months trastuzumab?) |
| Global agreement required for implementation | Set up one global database for depositing the raw data, clinical trial protocols, and statistical analysis plans from all completed clinical trials on cancer drugs and biomarkers | Interrogation of data could help to answer the questions that have remained unanswered for some time (eg, in conjunction with nonanthracycline-based chemotherapy, which women with early BC can be treated with 6 mo trastuzumab instead of 12 months trastuzumab?) |
|                                      | Accessible to all those involved in cancer research, and standards should be set for data sharing (Eichler 201689) | Interrogation of data could help to answer the questions that have remained unanswered for some time (eg, in conjunction with nonanthracycline-based chemotherapy, which women with early BC can be treated with 6 mo trastuzumab instead of 12 months trastuzumab?) |
|                                      | Could be used to create historical controls for some new trials to allow fewer patients to be enrolled (Sharpless & Doroshow 201997); confounding and bias will have to be minimized | Historical controls could be useful in the study of rare tumors where randomization is not feasible; historical controls could also be used where patients are unlikely to enroll in a control arm because of the accumulating clinical evidence against it |
|                                      | Improves transparency |                                                                                                                                                                                                 |
|                                      | Standardizing methods for imaging and interpretation criteria and classical clinical endpoints (eg, disease-free survival) would allow easier comparison of results between trials |                                                                                                                                                                                                 |

Abbreviations: ALK, anaplastic lymphoma kinase; BC, breast cancer; DLT, dose-limiting toxicity; dMMR, mismatch-repair-deficient; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; ICIs, immune checkpoint inhibitors; KEYNOTE-001, Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non–Small-Cell Lung Carcinoma (clinicaltrials.gov identifier NCT01295827); MSI-H, microsatellite-instability-high; NSCLC, non–small–cell lung cancer; PD, pharmacodynamic; PD-1, programmed death-1 receptor; PD–L1, programmed death-1 receptor ligand-1; PK, pharmacokinetic.
Access to Cancer Medicines

Concurrent Support to Optimize the Use of Cancer Medicines

The optimum use of cancer medicines depends on the effective delivery of several services allied to medical oncology (including laboratory, imaging, surgery, and radiotherapy). It requires investment in these services as well as in technologies and trained health care workers able to provide good quality care.

Oncology-Related Laboratory Services

High-quality pathology services are crucial for almost any cancer diagnosis. For instance, immunohistochemistry is required to identify the hormone receptor and HER2 status of breast cancer to guide treatment choice. Molecular diagnostic facilities are required to target or monitor chronic myeloid leukemia treatment with imatinib, or epidermal growth factor (EGFR) tyrosine kinase-mutated non–small-cell lung cancer with erlotinib. To ensure that the right patients benefit from such essential cancer medicines, access to basic and advanced molecular diagnostic facilities must be considered alongside their procurement.

However, pathology services are inadequate in many settings with limited resources. In low-income countries, such as some parts of Africa, only one pathologist may serve millions of people. In middle-income countries, biomarker testing for lung cancer tends to be confined to large hospitals in a few large cities (for instance, testing for EGFR mutations is provided in only 6 centers in Thailand, 1 center in Myanmar, and 2 centers in Vietnam). Some testing is outsourced to high–income countries, but it can be costly, with long turnaround times.

In many middle–income countries (including Latin America, South East Europe, Egypt, and South East Asia), pharmaceutical companies provide financial and technical support to optimize the use of cancer medicines. However, these services are often limited and do not provide the same level of quality as in high–income countries.

We propose that one global regulatory body for cancer medicines should be convened with regulatory experts from all countries. The full expertise of stringent regulatory authorities and the World Health Organization should be used. It could set global regulations on cancer medicines, monitor a pharmaceutical company’s drug development program, assess new cancer medicines for global registration, monitor the safety and efficacy of all cancer medicines globally, regularly review global product labels against the latest clinical evidence, and withdraw cancer medicines that no longer have a positive benefit–risk profile. It could allow cancer medicines to be registered in multiple countries simultaneously. It could free resources for countries to better enforce regulatory legislation in their jurisdictions, inspect manufacturing sites, and conduct postmarketing pharmacovigilance, postmarketing quality surveillance, and supply chain security; data from these activities could be shared with the global regulator.

Regulatory harmonization or mutual recognition could reduce duplication of effort, cost, and approval times. Regulation is being harmonized regionally across groups of countries (eg, African Medicines Regulatory Harmonization). There is scope to improve collaboration and sharing of data between regions. The FDA and the European Medicines Agency share information on applications with each other, and inspectorate reports are mutually recognized between the regulators of many high–income countries. Some countries (eg, Mexico) require only abbreviated marketing applications when products have already been approved by a stringent regulatory authority. The World Health Organization Collaborative Registration Procedure supports registration in low–income and middle–income countries. The World Health Organization could prequalify more cancer medicines.

No single regulator can guarantee medicines safety in its country because manufacturing and supply chains are globalized and increasingly depend on the safety and quality systems in other countries. Strengthening regulatory systems in low–income and middle–income countries will improve reliability in the global network.
support for biomarker testing related to their cancer medicines. For instance, AstraZeneca’s patient support program sponsors the EGFR test in Egypt, but it is only used by patients who have health insurance. The availability of such testing depends on global market decisions made by the companies and may not be sustainable in the long term. The benefit of such support is often restricted to some patients, and it may create conflict-of-interest issues for clinicians. In addition, it may reduce the impetus to implement local testing if the companies outsource the testing to laboratories in high-income countries.

Barriers to biomarker testing include economic factors, lack of technical expertise, lack of strategic planning to address the infrastructural barriers, and insufficient laboratory quality standards and accreditation. These barriers are seen across many low-income and middle-income countries, and greater collaboration would help to resolve them. A recent series in The Lancet discussed possible solutions to these barriers, such as establishing robust supply chains for laboratory consumables, training biomedical engineers to maintain equipment, creating free open-sourced laboratory information systems, and establishing national or external accreditation programs for laboratories.

Centralized biomarker testing (within a country or groups of countries) can provide consistent results and reduce costs. Good communication and connectivity between the referring clinic and the central laboratory is important. Central laboratories can also serve as hubs for training and research, as happened between Ghana and Norway.

Imaging, Surgical, and Radiotherapy Services
Access to safe and effective imaging, surgical, and radiotherapy services is important for most cancers. For instance, surgery ensures that (neo)adjuvant chemotherapy regimens for early stage breast or colon cancer will be curative rather than palliative, and access to radiotherapy is necessary for curative treatment of stage IIB cervical cancer with cisplatin.

Follow-up care for cancer survivors and palliative care
Coordination between generalists and oncology specialists is required to provide follow-up care for cancer survivors. This includes monitoring and managing the late and chronic effects of cancer (eg, depression) and cancer treatment (eg, persistent pain after breast cancer surgery or cardiovascular disease with anthracyclines), as well as monitoring for cancer recurrence.

Expertise in palliative care and access to palliative interventions (including analgesics, adjuvant therapy, cancer chemotherapy, radiotherapy, and psychosocial support) are necessary to manage the symptoms of patients with terminal cancer.

Education, Infrastructure, and Equipment
Appropriate expertise, infrastructure, and equipment are necessary for storage, prescribing, preparation, and administration of cancer medicines and supportive therapies (eg, blood products, granulocyte-colony–stimulating factors) and for monitoring patients who receive them.

Access to oncology specialists can be challenging in low-income and middle-income countries because of inadequate numbers and location. Postgraduate courses in oncology could be provided through partnerships with specialists in low-income and middle-income countries and specialists in high-income countries. An alternative workforce of generalists (including physicians, nurses, and pharmacists) could be trained to provide basic cancer care (such as diagnosis, treatment, management of cancer medicine side effects, and palliative care) under the supervision of oncology specialists, as implemented in India and Rwanda.

Various locally appropriate methods can be used to deliver training and share expertise. Workforce planning should allow for expected increases in cancer incidence.

To improve outcomes, health care professionals should educate patients about their cancer and treatment while being sensitive to religious, cultural, and personal beliefs that could affect acceptance. We refer readers to the extensive literature that exists on educating health care professionals, patients, and the public.

Rational Use of Cancer Medicines
Inappropriate cancer medicine use can cause harm and waste resources. To optimize outcomes, evidence-based, economically wise practice must be emphasized throughout the cancer care process, from diagnosis and prescribing to dispensing and administration. Systems should be in place to identify and address problematic cancer medicine use (eg, tracking local and national cancer medicine use to forecast future use, purchase, and budgets and to prevent stock shortages that cause missed treatment).

Locally adapted cancer treatment guidelines that take account of available resources can help to improve affordability. For instance, the cost of diagnosing and treating a child with Hodgkin lymphoma was lower in Rwanda than in South Africa because radiotherapy and computed tomography scans were not standard components of care in Rwanda due to a lack of availability, chemotherapy costs were lower, and care was provided by generalists with support from volunteer US-based oncologists.

The National Comprehensive Cancer Network (NCCN) Framework for Resource Stratification defines appropriate pathways for management of some cancers based on available resources: basic, core, enhanced, and NCCN guidelines.

The NCCN Harmonized Guidelines are region-specific guidelines that low-income and middle-income countries...
Health care professionals should have access to unbiased, free information on cancer medicines and training. Checklists incorporating local treatment guidelines can be used to guide appropriate treatment. They could be paper-based or embedded into digital tools.

Digital Medicine
In 2016, 84% of the global population and 67% of the rural population had access to mobile broadband networks ≥3G. Such uptake could provide opportunities to improve access to cancer care in low-income and middle-income countries, but more research is necessary to show its cost-effectiveness.

Digital tools could be used to diagnose cancers (eg, smartphone microscope for histopathologic diagnosis of melanoma); prescribe an appropriate cancer medicine and check its authenticity; remind patients to take cancer medicines, attend clinic appointments, monitor their response to treatment, report adverse events, and seek advice from a health care professional; and to maintain cancer registries. They could reduce the number of journeys a patient makes from remote locations to cancer centers. They could be used to share expertise between health care professionals in different parts of a country or between different countries either at the point of care (eg, to aid diagnosis, guide surgery) or as part of training programs. In China, a telepathology service for cancer diagnosis linked 20 consultation centers with 80 national experts. In Australia and India, rural-based generalist physicians and nurses provided cancer care (including chemotherapy) under the supervision of oncology specialists based in tertiary cancer centers via teleconferencing, electronic health records, or WhatsApp. Ideally, communication technology that protects confidentiality of medical information is preferred to general social media technology.

Low-income and middle-income countries are shifting their focus to nationally owned digital programs integrated within health care systems to provide measurable, long-term impact. Table 7 describes factors to consider when implementing such programs.

### Funding and Partnerships
Currently, little development assistance is provided for controlling cancer. Many low-income and middle-income countries, particularly upper-middle countries, need to fund their public health systems to provide quality, multidisciplinary cancer care. National cancer control programs will be crucial. However, allocation of funds to cancer should not divert resources away from other diseases.

Given that global deaths from cancer far exceed those for human immunodeficiency virus/acquired immunodeficiency syndrome, tuberculosis, and malaria, there is a case for raising a Global Fund for cancer similar to funds for these 3 infections. It has been suggested that the Global Fund could cover universal health coverage (specifically, health workers, health information, governance, and accountability). Funding for universal health coverage and cancer could be mutually beneficial. Synergy between oncology and other services should also be considered. For instance, funding for laboratory and imaging infrastructure in oncology could benefit patients with other diseases. Because patients who receive cytotoxic chemotherapy are susceptible to infections, there could be synergy with infrastructure for the diagnosis and management of some infectious diseases.

Funding initiatives should be provided in a way that meets national health system objectives and builds an infrastructure for sustained cancer management. Cross-sector partnerships between local stakeholders (including government agencies, health care professionals, patients), pharmaceutical companies, other private providers, and not-for-profit organizations are necessary.

### Conclusion
Various strategies can be implemented to enhance access to cancer medicines, from reducing development costs and improving reliability in the global supply chain to improving affordability. We have reviewed these potential strategies
to stimulate debate on the best ways forward; if successful, these could also be applied to other therapy areas. Some of these strategies can be implemented immediately. For instance, sponsors and investigators could consider strategies to increase the efficiency of cancer drug clinical trials while designing those trials. Countries that are introducing national cancer control programs could consider various factors, including the concurrent support that will be required to optimize the use of cancer medicines, universal health coverage, other funding initiatives, and the establishment of digital health programs. All countries could review their price regulation policies for cancer medicines and assess whether further change is necessary. All pharmaceutical companies in the oncology market could take the initiative to make cancer medicine prices fairer and more transparent. Other strategies (eg, the creation of a global regulatory body, convening an international body to reduce cancer medicine prices to levels affordable by health care systems and manufacturers, or harmonizing the international legal, ethical, and financial regulations for clinical trials) will take longer to implement because they depend on international cooperation between all stakeholders willing to make the changes.

Without timely, coordinated, global intervention, patients with treatable cancers will continue to die. A truly successful cancer medicine will be one that is safe, effective, and accessed and used appropriately by all those who need it anywhere in the world. ■

Acknowledgement: The authors would like to thank Sunil P. Verma, MD, for his contribution and review of this work.

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