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Original Research

The availability of essential cancer medication: An analysis of national formularies

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ABSTRACT

Objective: Compared to most other diseases, the total burden of common cancers is rapidly increasing in low- and middle-income countries (LMICs). The World Health Organization (WHO) publishes the Essential Medicines List, which provides guidance to countries in selecting which cancer medications should be prioritized for general public access. Countries commonly have formularies which are representative of the specific medications that the national government has prioritized for its populations.
Methods: National formularies were collected from 116 countries, and the quantification of essential cancer medication was computed using text-matching software. The proportion of essential cancer medications listed on national formularies (i.e. "concordance") was compared to per capita gross domestic product, per capita healthcare expenditures, the human development index, smoking prevalence, and the combined prevalence of overweight and obesity.
Results: Median concordance with cancer drugs among low- and middle-income countries (LMICs) was 42.71%. In bivariate comparisons, concordance was significantly associated with per capita GDP at PPP ($p = 0.005$), per capita health expenditures ($p = 0.050$), the human development index ($p < 0.001$), and the combined prevalence of overweight and obesity ($p = 0.006$). However, concordance was not associated with smoking prevalence ($p = 0.292$).
Conclusion: With national formularies analyzed for over 80% of all LMICs, this study found that most LMICs listed under half of cancer medications considered by the WHO to be essential. LMIC decision-making for policies related to cancer drug access may be heavily influenced by economic development, as well as by the high prevalence of certain cancer risk factors. The results from this study suggest that LMICs are generally ill-prepared to adequately provide essential treatment for their rapidly rising numbers of cancer patients.

1. Introduction

The predominant disease burden in developing countries is notably shifting from infectious diseases to non-communicable diseases, especially cancers and cardiovascular disease [1]. Specifically, low- and middle-income countries (LMICs) are consistently seeing the most marked increases in cancer incidence [1]. Unlike heart disease, treatment for the advanced stages of cancer requires complex interventions, often involving multiple pharmaceutical treatment regimens and use of other advanced therapeutics [2]. Hence, access to cancer medications is a critical factor in decreasing cancer mortality and improving survivability for populations globally [3].

As the United Nation's international public health specialized agency, the World Health Organization (WHO) in 1977 began publishing a list of medicines that should be considered essential components of what health systems provide their constituents [4]. The selection of medications for this "Essential Medicines List" (EML) is conducted through a process overseen by the WHO, in collaboration with leading experts, to recommend medicines based on disease prevalence, evidence of efficacy, evidence of safety, and

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comparative cost-effectiveness [5]. The most recent, 19th version of the EML was published in April 2015 and included a specific focus on cancer [6]. In this latest formulation, the WHO lists 48 cancer medications, which is a 50% increase over the 32 antineoplastic medications listed on the 18th EML.

However, despite its multilateral and multifaceted criteria, national governments are under no implicit legal requirement to provide access to cancer drugs listed on the EML. Instead, the EML serves as a guideline for sovereign states in deciding how to procure, finance and prioritize cancer drugs [7]. An indicator of whether the EML translates to national level pharmaceutical policy comes in the form of national drug formularies, which are generally published by individual governments and their health agencies. The impact of national formularies on patients' ability to access listed drugs may vary greatly between jurisdictions, depending on the extent of healthcare coverage, insurance schemes, resources, and financing, which varies country-to-country.

Though inclusion on a national formulary does not directly equate to availability of the drug domestically, it nevertheless indicates that the listed drug is recognized and prioritized as essential to its public health system. Therefore, in order to understand the degree to which essential cancer drugs are supported by national health policy, this study seeks to determine the agreement between national formularies and the WHO's global list for cancer medications. Specifically, this study primarily seeks to assess the variability in national "concordance" with cancer medications on the WHO's EML. We define the quantitative level of this agreement as "concordance," denoted as a percentage of the drugs listed on a national formulary that are also listed on the EML.

Though variations in national concordance may exist, little has been done to determine the specific macroeconomic factors that influence LMICs in making decisions about the selection of essential cancer medications. This stems from the dearth of knowledge about national dialogue regarding decisions that impact the inclusion of cancer drugs on medical formularies, including specifically how national governments negotiate with manufacturers through selection processes [8]. Therefore, once variations in concordance have been assessed, this study will compare these variations with country-level data on economic development. The results of this study can inform international and domestic policymakers on decisions related to national development that may influence concordance of national formularies with cancer medications on the EML.

2. Methods

We began this study by collating data from publicly available data sources, including the most recently updated EML [6]. The 19th global EML was obtained from the WHO's website [6]. We then tabulated characteristics of antineoplastic drugs, including sub-category, formulation, and indication.

All national formularies made available on the WHO's website [9] were included in this study. In the small number cases where the document provided by the WHO website clearly did not contain the full list of medicines, attempts were then made to obtain the full national formulary through national government webpages. Only full national formularies that used characters from the Roman alphabet were included. Out of 101 total national formularies with characters from the Roman alphabet, 63 were in English, 21 were in French, 15 were in Spanish, and 2 were in Portuguese.

The sole outcome measure in this study is the proportion of essential cancer medications on national formularies. In order to calculate this metric, the number of essential cancer medications appearing in a national formulary must be counted and then divided by 48, which is the total number of essential medications in the "Antineoplastics and Immunosuppresives" category listed on the latest EML. As the developing world is expected to experience a rapid increase in cancer burden over the next century [10], this study prioritized the assessment of concordance among LMICs, which are currently defined by the World Bank as countries having a gross national income (GNI) of less than $12,476 per capita, based on the Atlas method [11]. For this reason, all statistical analyses are restricted to LMICs. Nevertheless, as the WHO provided formularies for a small set of high-income countries (HICs), the calculation of cancer concordance for the national formularies of these HICs are included in Table 1.

To determine country-level concordance with the 48 cancer medications listed on the WHO's EML, QDA Miner, a software program for the analysis of textual data, was used to determine whether or not the document contained the EML medication name (i.e. the International Non-Proprietary Name) in any of the four languages in which national formularies were published. Wildcard symbols were used in situations when special characters might have been involved, and searches were not case sensitive. For example, the search for calcium folinate was stylized as follows: "calcium folinate" OR "folinic acid" OR "*cido fol*nico" OR "folinate de calcium" OR "acide folinique" OR "folinique de calcium" OR "folinico de c*lcio" OR "leucovorin" OR "leucovorina." In situations where the document did not provide machine-readable text (e.g., graphics embedded in Microsoft Word files), the documents were independently reviewed by the first author. Country-level rates of concordance were then depicted in a choropleth map, which was created using ArcGIS version 10.3.1 (Esri: Redlands, California).

Per capita gross domestic product (GDP) at purchasing power parity (PPP) and per capita health expenditures at PPP were obtained from the World Bank [12], and the human development index was obtained from the United Nations Development Programme (UNDP) [13]. As LMICs were the focus of this study, and this subset of countries may be particularly prone to issues deriving from financial scarcity, we selected indicators related to country-level economic development. As a common measure of country-level economic strength, per capita gross domestic product (GDP) at purchasing power parity (PPP) was deemed an appropriate selection for determining the relationship between wealth and cancer concordance [14]. Concordance was further compared to per capita healthcare expenditures at PPP in order to specifically explore whether concordance was significantly associated with investment in national health systems [15]. Finally, we compared concordance with the human development index (HDI), a broad measurement of human capability based on life expectancy, educational attainment, and per capita income [13].

Since differing levels of country-level wealth have broad impacts on the daily life of country residents [16], including employment choices and purchasing patterns, broad indicators for public health-related behaviors were chosen to elucidate the mechanism by which country-level wealth may impact concordance. We chose two covariates that broadly reflect public health-related behaviors: (1) the prevalence of tobacco consumption (among residents over age 14), and (2) the combined prevalence of overweight and obesity. These covariates are both widely considered to be major risk factors for many of the most highly-prevalent cancers and are broadly reflective of population-level habits affecting cancer risk [17]. These data were obtained from the World Health Organization [18].

Linear regression was used to quantify the association between concordance and national indicators for economic development and health-related behaviors. All statistical analyses were conducted in R version 3.2.3 (R Foundation for Statistical Computing: Vienna, Austria). Graphs showing trendlines were produced using JMP version 10 (SAS Institute: Cary, North Carolina).

Table 1
Concordance with the WHO's most recent listing of essential cancer medicines, by country.

Country	Concordance with Cancer EML
Afghanistan	6.25%
Algeria	25.00%
Angola	4.17%
Argentina	79.17%
Armenia	52.08%
Bahrain	87.50%
Bangladesh	31.25%
Barbados	70.83%
Belize	43.75%
Bhutan	18.75%
Bolivia	54.17%
Botswana	43.75%
Brazil	77.08%
Burkina Faso	25.00%
Burundi	16.67%
Cambodia	2.08%
Cameroon	37.50%
Cape Verde	77.08%
Central African Republic	25.00%
Chad	22.92%
Chile	58.33%
China	6.25%
Colombia	2.08%
Congo, Democratic Republic of	33.33%
Congo, Republic of	52.08%
Cook Islands	16.67%
Cote d Ivoire	75.00%
Djibouti	8.33%
Dominican Republic	58.33%
Ecuador	72.92%
Egypt	33.33%
El Salvador	58.33%
Eritrea	41.67%
Ethiopia	29.17%
Fiji	47.92%
Gabon	22.92%
Georgia	50.00%
Ghana	52.08%
Guinea	8.33%
Guyana	27.08%
Haiti	14.58%
Honduras	83.33%
India	64.58%
Indonesia	50.00%
Iran	91.67%
Iraq	87.50%
Jamaica	56.25%
Jordan	79.17%
Kenya	54.17%
Kiribati	22.92%
Korea, Democratic Republic of	6.25%
Lebanon	66.67%
Lesotho	25.00%
Madagascar	31.25%
Malaysia	8.33%
Maldives	22.92%
Mali	54.17%
Malta	64.58%
Marshall Islands	12.50%
Mauritania	10.42%
Mexico	87.50%
Morocco	22.92%
Myanmar	70.83%
Namibia	58.33%
Nauru	14.58%
Nepal	58.33%
Nicaragua	52.08%
Nigeria	39.58%
Niue	8.33%
Oman	81.25%
Pakistan	50.00%
Palau	10.42%
Papua New Guinea	37.50%
Paraguay	47.92%
Peru	81.25%
Philippines	79.17%
Rwanda	22.92%
Senegal	37.50%
Seychelles	33.33%
Solomon Islands	37.50%
Somalia	6.25%
South African Republic	43.75%
Sri Lanka	79.17%
St Vincent and the Grenadines	50.00%
Sudan	66.67%
Syrian Arab Republic	81.25%
Tanzania	56.25%
Thailand	72.92%
Timor-Leste	16.67%
Togo	33.33%
Tonga	16.67%
Trinidad and Tobago	83.33%
Tunisia	58.33%
Tuvalu	27.08%
Uganda	29.17%
Uruguay	41.67%
Vanuatu	81.25%
Venezuela	62.50%
Yemen	14.58%
Zambia	62.50%
Zimbabwe	56.25%

3. Results

The WHO's 19th EML includes 48 antineoplastic drugs, which are then subcategorized, in a mutually exclusive manner, as either immunosuppressive, cytotoxic/adjuvant, or hormone/anti-hormone. These drugs were predominately cytotoxic/adjuvant (n = 38; 79%) rather than hormone/anti-hormone (n = 8; 17%) or immunosuppressive (n = 2; 4%). Formulation and indication information was also provided within the WHO's EML documentation [6]. Specifically, 16 drugs were classified as tablets, 5 as capsules, and 34 as injectables. Furthermore, 26 were classified for treatment of blood cancers and 28 for treatment of organ cancers. It should be noted that these indications are neither mutually exclusive nor exhaustive, as some drugs like allopurinol or cyclosporine are primarily used for treatment of complications associated with cancer treatment; and some drugs like cyclophosphamide or vincristine can be used to treat either a blood cancer or an organ cancer.

Of the 116 countries that provided national formularies to the WHO web repository [9], 101 were available in a language with characters from the Roman alphabet. The median concordance among LMICs was 42.71% (n = 92 LMICs; Mean = 42.35%; Minimum = 2.08%; Maximum = 91.67%; Standard Deviation = 24.99%; Fig. 1). Nine HICs provided formularies on the WHO web portal (Bahrain, Barbados, Chile, Malta, Nauru, Oman, Seychelles, Trinidad and Tobago, and Uruguay). Median concordance among HICs was much higher, at 64.58%.

Although no country was completely concordant with the WHO's list, Iran had the highest concordance (91.67%), and Colombia and Cambodia both had the lowest concordance (2.08%). We also assessed concordance of national formularies by the six WHO geographic office regions. This includes the regional offices for Africa (AFRO), the Americas (PAHO), the Eastern Mediterranean (EMRO), Europe (EURO), South-East Asia (SEARO), and the Western Pacific (WPRO). Among LMICs, we found that median concordance was highest in PAHO (57.29%; n = 18), followed by EMRO (54.57%; n = 14), EURO (51.04%; n = 2), SEARO (50.00%; n = 11), AFRO (35.42%; n = 32), and WPRO (16.67%; n = 15).

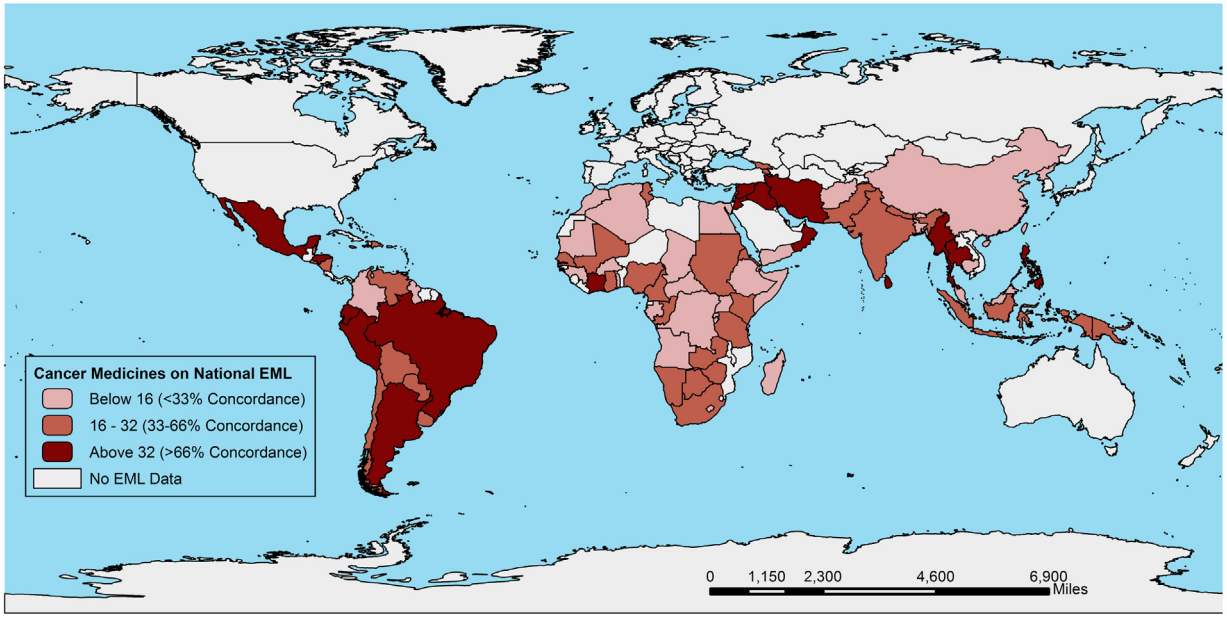

Fig. 1. World map showing countries by level of concordance with cancer medicines listed on the WHO Essential Medicines List.

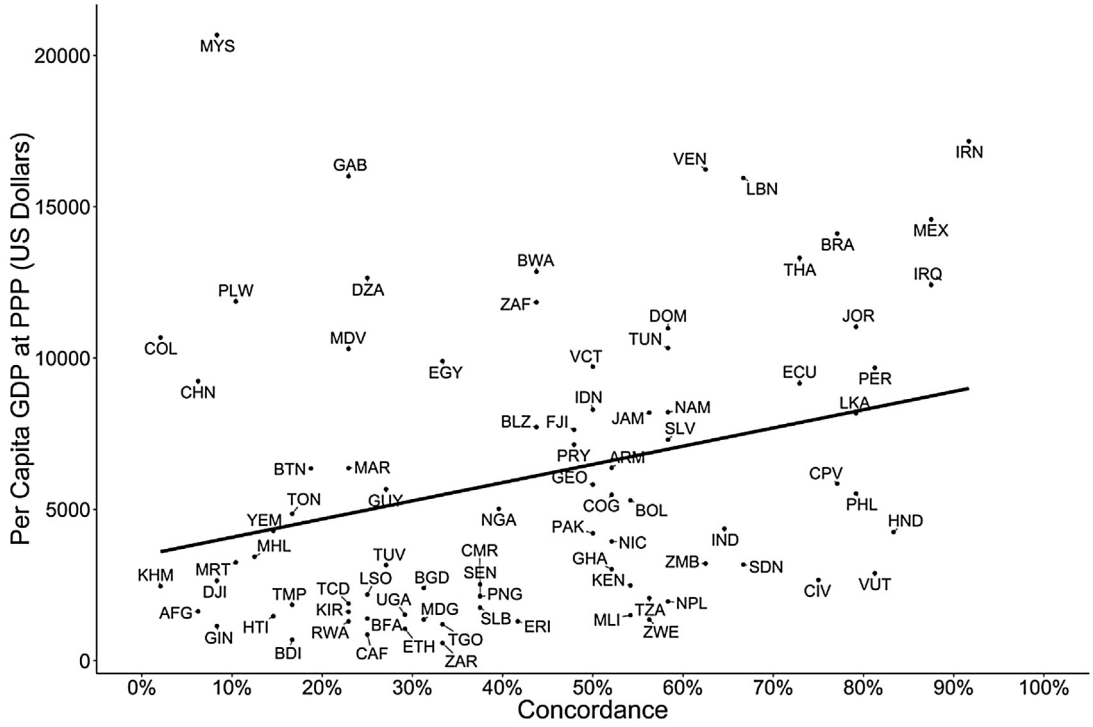

Fig. 2. Comparison of concordance with per capita GDP at PPP in US Dollars (n = 84 LMICs; p = 0.005; R^2 = 0.09).

Concordance was significantly positively associated with per capita GDP (p = 0.005; R^2 = 0.09; Fig. 2), indicating that wealthier countries were more likely to include a greater number of essential cancer medications. Concordance also exhibited a statistically significant association with per capita healthcare expenditures (p = 0.050; R^2 = 0.05), thereby suggesting that country-level wealth, as measured by GDP, is an indicator for investment into the national health system, which itself is significantly associated with concordance between national formularies and the global EML. Finally, concordance exhibited a close, statistically significant association with HDI (p < 0.001; R^2 = 0.14; Fig. 3).

As wealthier countries have more behavioral risk factors for highly prevalent cancers [16,19–21], we sought to assess whether the significant relationship between concordance and per capita GDP exists because wealthier countries have greater cancer risk. To test this hypothesis, we compared concordance to country-level combined rates of overweight and obesity, and we found a significant positive relationship (p = 0.006; R^2 = 0.09). We also tested this hypothesis by comparing concordance with smoking prevalence. In this case, we found a no relationship (p = 0.292; R^2 = 0.02).

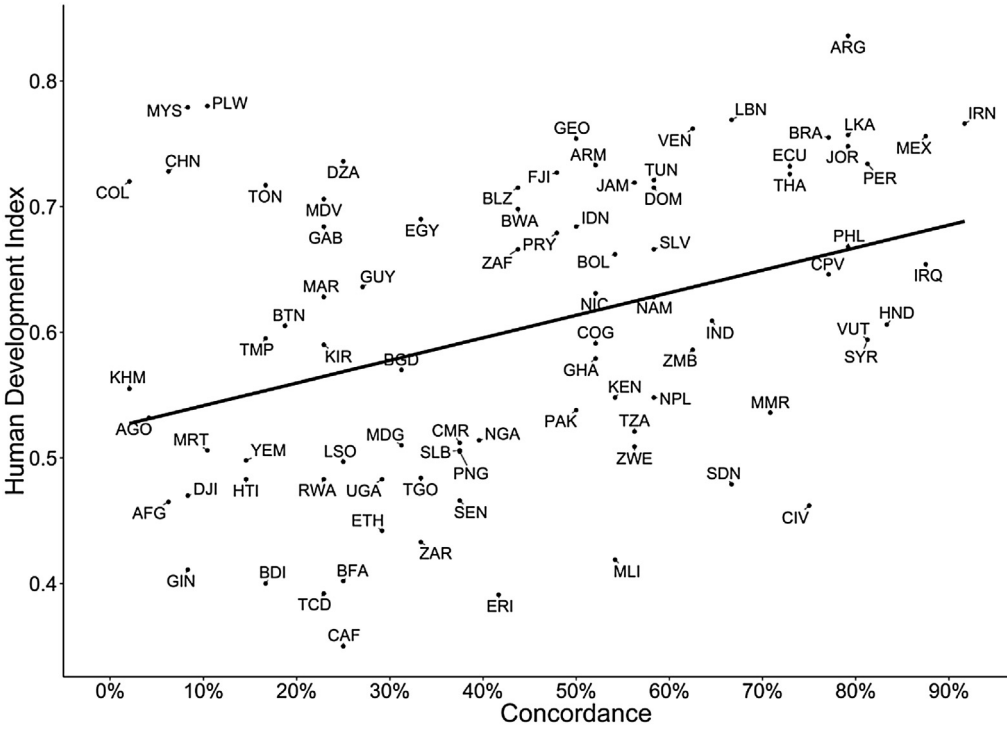

Fig. 3. Comparison of concordance with the human development index (n = 85 LMICs; $p < 0.001$; $R^2 = 0.14$).

4. Discussion

The sharp increase in the number of cancer medications listed on the 19th EML underscores the importance of preparing LMIC health systems to combat the rising threat of increasingly common cancers. The majority of antineoplastic drugs (79%) on the 19th EML were categorized as cytotoxic/adjuvant. Although the mechanisms of action for the listed cytotoxic drugs involve targeting different sub-cellular components, 20 (53%) of the drugs in the cytotoxic/adjuvant category were stated as indicated for treatment of at least 3 separate cancers. The preponderance of multiple-indication cytotoxic drugs on the 19th EML corresponds to the WHO's stated aim to support cost-efficacy [5], as this may provide guidance to countries for acquiring treatments for a greater number of cancers.

We found a significant association between concordance and several macroeconomic indicators of national development. This included a broad multi-faceted measure, the HDI. As the HDI is generally higher when life expectancy is higher, and there tends to be greater risk for cancer in those who have lived longer [22], the close relationship between concordance and the HDI may indicate that countries with already-high levels of cancer burden react to this challenge by listing a higher number of essential cancer medications on their formularies. Therefore, the HDI may capture a confluence of influential factors that prompt national governments to include more essential cancer drugs on their formularies.

Nevertheless, we found that concordance was not significantly associated with smoking prevalence, which itself bears an extremely close relationship with risk for lung cancer. Therefore, it may be that national governments are more receptive to listing more cancer drugs on formularies when the burden is high for specific types of cancer. Tobacco smoking exhibits especially close association with lung cancer [23], and it may be that high rates of lung cancer prompt policy initiatives advocating for smoking cessation or preventing uptake, and not policy initiatives revolving around drug procurement. Conversely, we found that concordance exhibited a statistically significant association with the combined prevalence of overweight and obesity. This globally-increasing risk factor, which may be considered by national governments to be less avoidable than tobacco consumption, may instead prompt policymakers to advocate for expanded cancer drug inclusion on national formularies [24].

Countries may look to historical data in guiding cancer policy, but may not take into account future projections when making these forms of health policy decisions. This is especially dangerous in the case of policies related to cancer drug access, as the cancer burden in LMICs is expected to rapidly worsen [10]. Furthermore, neglecting to institute adequate public health policy can be an important barrier toward preventing future national health emergencies [25]. In order to ensure adequate resources for providing sufficient standards of healthcare, it would be prudent for present policymaking to involve serious consideration of presently-available projections for future disease burden.

5. Conclusion

Exploring access variations allows for identification of decision-making factors related to policies that can impact access to essential medicines, as well as formulation of evidence-based policymaking to most effectively improve population health outcomes in response to the rise of cancer. This study builds upon and confirms prior analysis of the EML for cancer medicine inclusion [26]. This this study analyzed over 80% of LMICs in the world and found that no country's national formulary contained all the cancer medications recommended by the WHO's EML. Among LMICs assessed in this study, the median concordance was 42.71%, which means that most countries analyzed had national formularies that listed less than half the recommended cancer medications in the WHO's most recent update to the EML. Though previously recorded incidence rates and greater national wealth may encourage health ministries to invest in infrastructure related to non-communicable diseases, there is a dearth of information reported in the literature relating to possible reasons why one country would have more concordance

with the cancer section of the WHO's EML than another country. Therefore, much more research is necessary on this topic, as there are few actionable, evidence-based choices that are presently available to global health experts for promoting the availability of cancer medications through these policy-based methods.

6. Limitations

The main limitation of this research is the variability of national governments in updating their formularies. Furthermore, this study addresses national decisions to include certain quantities of essential cancer medications on national formularies, but it does not thoroughly explore the relative financial difficulty a health system may encounter when tasked with obtaining certain essential cancer medications.

Nonetheless, this study accessed national formularies directly from the WHO website at a single point in time, thereby providing a degree of control for the variability exhibited by countries in updating their formularies. Furthermore, this study uses concordance as a single metric that communicates the degree to which essential chemotherapy was found on national formularies. It therefore provides a clear snapshot of government support for a set of cancer medications vetted by a global health organization for efficacy, safety, and cost-effectiveness.

With the number of LMIC cancer cases expected to rapidly grow over the next twenty years, LMIC national governments should prioritize their support for policies that increase availability of essential chemotherapy. The listing of these drugs on national formularies may be one such way to promote availability in government healthcare facilities. However, the availability of a drug does not necessitate its affordability. A more in-depth exploration of prices for essential cancer drugs is conducted in a subsequent study.

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