Defining Essential Childhood Cancer Medicines to Inform Prioritization and Access: Results From an International, Cross-Sectional Survey

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PURPOSE Access to essential cancer medicines is a major determinant of childhood cancer outcomes globally. The degree to which pediatric oncologists deem medicines listed on WHO’s Model List of Essential Medicines for Children (EMLc) essential is unknown, as is the extent to which such medicines are accessible on the front lines of clinical care.

METHODS An electronic survey developed was distributed through the International Society of Pediatric Oncology mailing list to members from 87 countries. Respondents were asked to select 10 cancer medicines that would provide the greatest benefit to patients in their context; subsequent questions explored medicine availability and cost. Descriptive and bivariate statistics compared access to medicines between low- and lower-middle–income countries (LMICs), upper-middle–income countries (UMICs), and high-income countries (HICs).

RESULTS Among 159 respondents from 44 countries, 43 (27%) were from LMICs, 79 (50%) from UMICs, and 37 (23%) from HICs. The top five medicines were methotrexate (75%), vincristine (74%), doxorubicin (74%), cyclophosphamide (69%), and cytarabine (65%). Of the priority medicines identified, 87% (27 of 31) are represented on the 2021 EMLc and 77% (24 of 31) were common to the lists generated by LMIC, UMIC, and HIC respondents. The proportion of respondents indicating universal availability for each of the top medicines ranged from 9% to 46% for LMIC, 25% to 89% for UMIC, and 67% to 100% for HIC. Risk of catastrophic expenditure was more common in LMIC (8%-20%), compared with UMIC (0%-28%) and HIC (0%).

CONCLUSION Most medicines that oncologists deem essential for childhood cancer treatment are currently included on the EMLc. Barriers remain in access to these medicines, characterized by gaps in availability and risks of catastrophic expenditure for families that are most pronounced in low-income settings but evident across all income contexts.

JCO Global Oncol 8:e2200034. © 2022 by American Society of Clinical Oncology

INTRODUCTION Cancer is a leading global cause of noncommunicable disease mortality in children. The majority of this burden falls on low- and middle-income countries, where 80% of incident cases of childhood cancer occur. The significant gains in childhood cancer survival achieved in high-income countries in recent decades, resulting in cure rates exceeding 80%, have not been realized in most low- and middle-income countries, where an estimated 20%-30% of children with cancer are cured. These marked disparities spurred the launch of the WHO Global Initiative for Childhood Cancer (GICC) in 2018, which commits to improving the global survival rate for children with cancer to 60% by 2030. Access to essential cancer medicines is a key determinant of childhood cancer outcomes globally, as chemotherapy constitutes a critical component of curative treatment for many childhood malignancies. The WHO’s Model List of Essential Medicines (EML) provides the normative benchmark for the prioritization of medicines at a national level, particularly in low- and middle-income country health systems. The EML serves as a valuable tool for policymakers to undertake country-level selection of medicines to optimize universal health coverage. The Essential Medicines List for Children (EMLc) addresses the unique health circumstances and needs of children. Both the adult and child versions now incorporate cancer-specific recommendations, driven by the mounting epidemiologic...
Our Relevance
We evaluated the concordance of WHO’s Model List of Essential Medicines for Children (EMLc) cancer medicine inclusion with the priorities of treating clinicians and the relationship between inclusion and real-world availability and affordability internationally.

Knowledge Generated
Our findings demonstrate concordance between EMLc inclusion and frontline clinical priorities across income settings, affirming that most medicines deemed essential by pediatric oncologists worldwide are conventional cytotoxic agents currently on the EMLc. We show significant gradients in availability and affordability of essential cancer medicines for children across country income settings, including evidence of constrained availability and affordability in higher-income settings, implying challenges in access to essential childhood cancer medicines globally.

Relevance
Our findings underscore the urgent need for global and national policies to support access to essential cancer medicines as a key component of international efforts to improve childhood cancer outcomes through WHO’s Global Initiative on Childhood Cancer.

CONTEXT
Key Objective
We evaluated the concordance of WHO’s Model List of Essential Medicines for Children (EMLc) cancer medicine inclusion with the priorities of treating clinicians and the relationship between inclusion and real-world availability and affordability internationally.

METHODS
Study Population
This study was developed by investigators from a range of practice environments in low- and lower-middle-income countries (LMICs), upper-middle-income countries (UMICs), and high-income countries (HICs) and included members of the WHO Cancer Medicines Working Group and the Essential Medicines Working Group of the International Society of Paediatric Oncology (SIOP). All practicing physicians who deliver systemic anticancer therapy to children were eligible to participate in the survey; this included both formally trained and accredited pediatric oncologists and pediatricians who treat children with cancer. This study was run parallel to a study of cancer medicine priorities and access among adult oncologists.7

Survey Design and Distribution
An electronic questionnaire was developed using the Qualtrics survey platform. The survey was piloted and revised on the basis of feedback from study investigators and SIOP leadership. The final survey consisted of 29 questions and took approximately 8-10 min to complete (Data Supplement). The survey was only available in English, and respondents were not compensated for participation.

The anonymous survey captured information on demographics and clinical practice setting. The primary study question asked “Imagine your government has put you in charge of selecting pediatric anti-cancer medicines for the country. You are only allowed to select a maximum of 10 medicines that will be available to treat all paediatric cancers in your country. Which medicines would you recommend to the government to achieve the greatest benefit for the most patients?” The primary question was structured in this way to force participants to prioritize medicines on the basis of the magnitude of benefit, toxicity, and the absolute number of patients who may benefit. Respondents selected up to 10 medicines from a list of 164 cancer medicines derived from the Cancer Care Ontario Drug Formulary database, which included all medicines approved by Health Canada as of September 2020 and covered all medicines currently on the WHO EMLc.8

The second set of questions asked each physician to determine the ability of patients in their country to access each of their selected top 10 medicines in routine clinical practice. The questions were based on previous medicine access work by the European Society of Medical Oncology.9

The scale included four categories for medicine availability: (1) universally available (no significant out-of-pocket [OOP] expenses for > 90% of patients), (2) available with significant OOP expenses (mixed or partial reimbursement model and not universal health coverage, significant OOP for some patients), (3) available with high risk of catastrophic expenditure (significant OOP for > 50% of patients with a substantial risk of catastrophic health expenditure defined as “spending that absorbs more than 40% of total burden of noncommunicable diseases, including cancer, in many low- and middle-income countries.

However, the extent to which practicing pediatric oncologists deem EMLc-listed cancer medicines truly essential is largely unknown. It is also unknown to what extent essential childhood cancer medicines are accessible on the front lines of clinical care across different income and health system settings. To address these gaps in knowledge and inform global and national policy, we undertook the following study to understand (1) which medicines that pediatric oncologists worldwide deem most essential in the treatment of childhood cancers, (2) whether the EMLc reflects these priority medicines, and (3) the extent to which essential cancer medicines are available to pediatric patients in routine clinical care.
consumption, net of an allowance for food expenditures”), and (4) unavailable for other reasons (eg, procurement and regulatory).

The sampling frame for the survey was the SIOP membership list and aimed to capture responses from a diverse array of pediatric oncologists globally. The survey was opened and sent to SIOP members in 87 countries on November 9, 2020. One reminder e-mail was sent, and the survey was closed on December 14, 2020.

Statistical Analysis
Survey responses were directly downloaded into IBM SPSS (Windows 26.0, 2018) from Qualtrics. Participants were classified into three groups on the basis of World Bank income status of their country of practice: LMIC, UMIC, and HIC.10 Frequency tables were derived for rank order of medicines that respondents listed as most essential. Only medicines that received ≥ 5% of total responses were chosen as part of the global most essential medicines list. This ultimately corresponded to 31 medicines. The top 31 medicines from each income group were also selected to represent each income group’s priority medicines. Analysis on medicine availability was carried out for a subset of medicines that received at least 10 unique responses to the accessibility question, including 16 LMIC, 18 UMIC, and 15 HIC selections. Demographics and clinical practice setting of the three groups were compared with Pearson’s chi-square or the Fisher’s exact test for categorical data, and the one-way analysis of variance with Tukey’s post hoc tests for age, years in practice, and number of cancer types treated. A P value of < .05 was used as the cut point for statistical significance, and no additional adjustment for multiple comparisons was made.

RESULTS
Survey Distribution and Response
The survey was sent to 615 pediatric oncology practitioners from 87 countries via the SIOP listserv. Of 258 respondents who opened the survey link, 36 were excluded because they did not answer the primary study question (incomplete survey) and 63 respondents were excluded because of ineligibility (eg, trainee). The final study cohort included 159 respondents from 44 countries.

Characteristics of Study Participants
Among the 159 respondents, 43 (27%) were from LMICs, 79 (50%) from UMICs, and 37 (23%) from HICs (Table 1); 93% (148 of 159) were pediatric oncologists. Four LMIC and nine UMIC respondents did not complete the demographic portion, resulting in a sample size of 146 respondents (39 of 43 from LMICs, 70 of 79 from UMICs, and 37 of 37 from HICs) inclusive of demographics. Two thirds of respondents were female, and the mean age was 47 years. Half of the respondents worked in the public sector (51%, 75 of 146), 23% (33 of 146) worked in the private sector, and 26% (38 of 146) worked in both. Most respondents treated multiple cancer types, including lymphoma (84%, 123 of 146), leukemia (82%, 119 of 146), extracranial solid tumors (82%, 120 of 146), and brain tumors (76%, 111 of 146). The majority of respondents treated both children age < 15 years and adolescents (55%, 80 of 146).

Oncologists in HICs were more likely to be male than in LMICs or UMICs (P = .027). LMIC oncologists had been in practice for fewer years than HIC oncologists (mean 12 years vs 18 years; P = .027). HIC respondents were more likely to practice in a child and/or adolescent cancer center than LMIC and UMIC respondents (41% vs 26% vs 36%) and less likely to practice in a general hospital with pediatric services (8% vs 33% vs 39%; P = .004).

Which Essential Cancer Medicines Are Considered Most Essential?
The most frequently selected highest priority medicines by respondents are shown in Table 2. Medicines are reported in Table 2 if selected by ≥ 5% of respondents; this yielded 31 medicines. The top 31 medicines by frequency are shown for LMIC, UMIC, and HIC respondents for ease of comparison. Among the global list of 31 high-priority medicines, 90% (28 of 31) were cytotoxic agents and 10% (3 of 31) were targeted agents. Decade of first approval for the medicines by a stringent regulatory authority was as follows: 45% (14 of 31) were approved pre-1980s, 6% (2 of 31) in 1980s, 23% (7 of 31) in 1990s, 13% (4 of 31) in 2000s, and 13% (4 of 31) after 2010. The top 10 most frequently selected medicines were methotrexate (75%), vincristine (74%), doxorubicin (74%), cyclophosphamide (69%), cytarabine (65%), etoposide (59%), mercaptopurine (57%), carboplatin (47%), cisplatin (45%), and dactinomycin and L-asparaginase (both 40%; see Appendix Table A1 for the full rank order list).

Among the 31 highest priority medicines derived from the total sample, 87% (27 of 31) are represented on the 2019 WHO EMLc.5 Melphalan is on the WHO EML, but not the WHO EMLc. Three remaining medicines are not represented on the WHO EMLc or EML (temozolomide, Erwinia asparaginase, and blinatumomab). As shown in Figure 1, the most frequently selected highest priority medicines are considerably more likely to be listed on the EMLc compared with medicines selected by fewer respondents. Of the medicines chosen by at least 50%, 25%, 10%, 5%, and 1% of respondents, 100% (7 of 7), 100% (15 of 15), 90% (19 of 21), 87% (27 of 31), and 43% (35 of 81) are represented on the current EMLc, respectively.

There was close agreement between the lists generated by respondents from LMICs, UMICs, and HICs (Table 2): 77% (24 of 31) of medicines were common to all three top 31 lists. For the 7 of 31 medicines not common to all three lists, each medicine was selected by < 15% of the respondents in each category. The LMIC top 31 list contained only two medicines not currently on the EMLc (blinatumomab and...
| Respondent Characteristics | Total N = 159, No. (%) | LMICs n = 43, No. (%) | UMICs n = 79, No. (%) | HICs n = 37, No. (%) | P |
|----------------------------|------------------------|------------------------|------------------------|------------------------|---|
| Specialty                  |                        |                        |                        |                        |   |
| Pediatric oncologist       | 148 (93)               | 40 (93)                | 74 (94)                | 34 (93)                | 1.000 |
| Child cancer lead pediatrician | 4 (3)                | 1 (2)                  | 2 (3)                  | 1 (3)                  |   |
| Others**                   | 7 (4)                  | 2 (5)                  | 3 (4)                  | 3 (5)                  |   |
| Demographics               |                        |                        |                        |                        |   |
| Sex                        |                        |                        |                        |                        |   |
| Male                       | 56 (38)                | 12 (31)                | 23 (33)                | 21 (57)                | .028 |
| Female                     | 90 (62)                | 27 (69)                | 47 (67)                | 16 (43)                |   |
| Mean age (years)           | 47                     | 47                     | 45                     | 50                     | .039 |
| Mean years in practice     | 14                     | 12                     | 14                     | 18                     | .035 |
| Clinical practice          |                        |                        |                        |                        |   |
| Health system              |                        |                        |                        |                        |   |
| Public                     | 75 (51)                | 18 (46)                | 35 (50)                | 22 (60)                | .201 |
| Private                    | 33 (23)                | 11 (28)                | 12 (17)                | 10 (27)                |   |
| Both                       | 38 (26)                | 10 (26)                | 23 (33)                | 5 (14)                 |   |
| Location                   |                        |                        |                        |                        |   |
| Urban                      | 140 (96)               | 37 (95)                | 66 (94)                | 37 (100)               | .774 |
| Rural                      | 1 (1)                  | 0 (0)                  | 1 (1)                  | 0 (0)                  |   |
| Both                       | 5 (3)                  | 2 (5)                  | 3 (4)                  | 0 (0)                  |   |
| Types of cancer            |                        |                        |                        |                        |   |
| Brain                      | 111 (76)               | 32 (82)                | 50 (71)                | 29 (78)                | .428 |
| Leukemia                   | 119 (82)               | 39 (100)               | 54 (77)                | 26 (70)                | .001 |
| Lymphoma                   | 123 (84)               | 39 (100)               | 56 (80)                | 28 (84)                | .006 |
| Extracranial solid tumors  | 120 (82)               | 38 (97)                | 55 (79)                | 27 (73)                | .009 |
| Others                     | 28 (19)                | 6 (15)                 | 18 (26)                | 4 (11)                 | .138 |
| No. of above sites treated | Mean                   | 3.4                    | 4.0                    | 3.3                    | 3.1                    | .004 |
| Academic center            |                        |                        |                        |                        |   |
| Yes                        | 126 (86)               | 34 (87)                | 57 (81)                | 35 (95)                | .171 |
| No                         | 30 (14)                | 5 (13)                 | 13 (19)                | 2 (5)                  |   |
| Base of practice           |                        |                        |                        |                        |   |
| Cancer center              | 50 (34)                | 10 (26)                | 25 (36)                | 15 (41)                | .004 |
| General hospital           | 43 (30)                | 13 (33)                | 27 (39)                | 3 (8)                  |   |
| Pediatric hospital         | 30 (21)                | 8 (21)                 | 14 (20)                | 8 (22)                 |   |
| Combination                | 23 (16)                | 8 (21)                 | 4 (6)                  | 11 (30)                |   |
| Age of treated patients, years |                      |                        |                        |                        |   |
| Children < 15              | 62 (42)                | 19 (49)                | 38 (54)                | 5 (14)                 | < .001 |
| Children < 15 and adolescentsa | 80 (55)              | 18 (46)                | 31 (44)                | 31 (84)                |   |
| Children, adolescents and adults | 4 (3)                  | 2 (5)                  | 1 (1)                  | 1 (3)                  |   |

Abbreviations: BMT, bone marrow transplantation; HICs, high-income countries; LMICs, lower-middle-income countries; UMICs, upper-middle-income countries.

**Others included one each of intensivist, nurse practitioner, palliative care physician, hematologist, pediatric palliative care physician, pharmacist, and pediatric oncology/BMT physician.

**Thirteen (8%; four from LMICs and nine from UMICs) were missing much of these data since the entire survey was not completed.

**Only LMICs and HICs differed significantly (P = .030), Tukey's post hoc test.

**Only LMICs and HICs differed significantly (P = .027), Tukey's post hoc test.

**These were individual (select all that apply) items, and therefore, a P-value is provided for each.

†LMICs differed from UMICs (P = .026) and HICs (P = .005), Tukey's post hoc test.

‡Adolescents are defined as those between age 15 and 24 years.
TABLE 2. Most Frequently Selected Drugs by 159 International Pediatric Oncologists in Response to the Question “Imagine Your Government Has Put You in Charge of Selecting Pediatric Anti-Cancer Medicines for the Country. You Are Only Allowed to Select a Maximum of 10 Medicines That Will Be Available to Treat All Pediatric Cancers in Your Country. Which Drugs Would You Recommend to the Government to Achieve the Greatest Benefit for the Most Patients?”

| Total Sample (N = 159) | LMICs (n = 43) | UMICs (n = 79) | HICs (n = 37) |
|------------------------|----------------|----------------|---------------|
| Methotrexate           | 120 (75)       | 39 (91)        | 56 (71)       |
| Vincristine            | 118 (74)       | 36 (84)        | 53 (67)       |
| Doxorubicin            | 117 (74)       | 32 (74)        | 51 (65)       |
| Cyclophosphamide       | 110 (69)       | 32 (74)        | 48 (61)       |
| Cytarabine             | 103 (65)       | 31 (72)        | 45 (57)       |
| Etoposide              | 94 (59)        | 30 (70)        | 45 (57)       |
| Mercaptopurine         | 91 (57)        | 25 (58)        | 39 (49)       |
| Carboplatin            | 75 (47)        | 23 (53)        | 37 (47)       |
| Cisplatin              | 72 (45)        | 22 (51)        | 35 (44)       |
| Dactinomycin           | 63 (40)        | 19 (44)        | 33 (42)       |
| L-Asparaginase         | 63 (40)        | 18 (42)        | 26 (33)       |
| Ifosfamide             | 59 (37)        | 12 (28)        | 23 (29)       |
| Dexamethasone          | 49 (31)        | 12 (28)        | 23 (29)       |
| Pegaspargase           | 49 (31)        | 12 (28)        | 22 (28)       |
| Prednisone             | 39 (25)        | 11 (26)        | 15 (19)       |
| Daunorubicin           | 27 (17)        | 10 (23)        | 14 (18)       |
| Temozolomide           | 19 (12)        | 7 (16)         | 12 (16)       |
| Leucovorin             | 18 (11)        | 7 (16)         | 10 (13)       |
| Bleomycin              | 16 (10)        | 6 (14)         | 9 (11)        |
| Dacarbazine            | 16 (10)        | 4 (9)          | 9 (11)        |
| Erwinia asparaginase   | 16 (10)        | 3 (7)          | 11 (16)       |
| Imatinib               | 15 (9)         | 3 (7)          | 8 (10)        |
| Vinblastine            | 14 (9)         | 3 (7)          | 8 (10)        |
| Tretinoin (ATRA)       | 13 (8)         | 2 (5)          | 8 (10)        |
| Blinatumomab           | 10 (6)         | 2 (5)          | 8 (10)        |
| Rituximab              | 10 (6)         | 2 (5)          | 7 (9)         |
| Hydroxyurea            | 9 (6)          | 2 (5)          | 6 (8)         |
| Irinotecan             | 9 (6)          | 1 (2)          | 6 (8)         |
| Melphalan              | 8 (5)          | 1 (2)          | 6 (8)         |
| Mitoxantrone           | 8 (5)          | 1 (2)          | 6 (8)         |

**Abbreviations:** ATRA, all-trans retinoic acid; HICs, high-income countries; LMICs, lower-middle-income countries; UMICs, upper-middle-income countries.

*Medicines listed are those chosen by at least 5% of respondents in the total sample.

bMedicines are not included on the current WHO EMLc.

Access to Essential Medicines

The reported availability of all medicines with ≥ 10 responses registered is shown in Table 3. Availability varied substantially across economic settings. LMIC respondents reported a complete lack of medicine availability between 9% (doxorubicin, cytarabine, and etoposide) and 46% (pegaspargase) and indicated that access was associated with catastrophic expenditure between 8% (ifosfamide) and 20% (dexamethasone) of the time. Medicine nonavailability

melphalan, whereas the UMIC list contained six (temozolomide, Erwinia asparaginase, blinatumomab, melphalan, fludarabine, and topotecan), and the HIC list contained four (blinatumomab, Erwinia asparaginase, lomustine, and temozolomide). Melphalan and fludarabine are listed on the WHO EML for predominantly adult cancer indications, but are not included in the EMLc. Blinatumomab was the only non-EMLc medicine represented in the top 31 of all three income-stratified lists.
FIG 1. Association between rank order of all medicines identified by 159 oncologists globally as most essential and whether the drug is currently listed on the 2021 WHO EMLc. Medicines displayed in blue are currently listed on the EML; medicines in red represent medicines that are not. Only medicines that received at least 1% of the vote are included in this figure. The complete rank order list with medicine names can be found in Appendix Table A1. EML, List of Essential Medicines; EMLc, Essential List of Medicines for Children.

Access to medicines in UMICs appeared to be higher than that in LMICs, with a majority of respondents indicating universal availability for 16 of 18 analyzed medicines (pegaspargase and Erwinia asparaginase were the exceptions). The proportion of respondents indicating universal availability ranged from 12% for pegaspargase to 89% for both carboplatin and cyclophosphamide. The proportion of UMIC respondents indicating lack of availability for each medicine ranged from 0% for cisplatin, cyclophosphamide, and prednisone to 48% for pegaspargase and 50% for Erwinia asparaginase. The percentage of respondents indicating significant risk of catastrophic expenditure varied from 0% (multiple agents) to 24% for pegaspargase. All 16 top UMIC medicines were represented within the 18 top UMIC medicines. However, UMIC respondents reported universal availability less frequently than UMIC respondents and higher catastrophic expenditure more frequently, in each of the 16 matched pairs.

For the HIC group, there were 15 medicines with at least 10 responses in relation to access. A majority of respondents reported universal availability for all 15, ranging from 67% for pegaspargase to 100% for ifosfamide. No respondents indicated a risk of catastrophic expenditure for any of these medicines. A small proportion of respondents reported unavailability for 3 of 15 medicines: dactinomycin (11%), L-asparaginase (7%), and pegaspargase (8%). All 15 HIC medicines were also on the list for the top UMIC and LMIC medicines. Universal availability was reported by a higher proportion of HIC respondents than UMIC respondents in 11 of 15 direct comparisons, and a higher proportion of UMIC respondents indicated both catastrophic expenditure and nonavailability in 15 of 15 direct comparisons than HIC respondents. LMIC respondents reported lower universal availability than HIC in 15 of 15 direct comparisons, more catastrophic expenditure in 15 of 15 direct comparisons, and nonavailability in 12 of 15 comparisons, excluding three medicines where both groups reported zero nonavailability. Figure 2 compares the availability of the five highest priority medicines across respondent income settings.

**DISCUSSION**

Our study highlights several key findings related to the perceived priority and real-world availability of childhood cancer medicines, as reported by frontline clinicians from diverse health system settings internationally. First, there is substantial convergence between respondent priorities and existing EMLc listings for pediatric cancers. Respondent priorities coalesced around a core list of 31 medicines (composed of those deemed essential by at least 5% of respondents), the majority of which (87%) are already on the most updated version of the EMLc (2021). These findings affirm the relevance and resonance of current EMLc listings for frontline clinicians. Second, there was a fair degree of alignment between the priority medicines selected by clinicians from HICs, UMICs, and LMICs: 77% (24 of 31) of medicines were common to all three priority lists. Third, the majority (90%) of medicines on this priority list are traditional cytotoxic therapies licensed and in use for decades, rather than newer targeted agents or immunotherapies recently approved for use in humans: 74% of the medicines received US Food and Drug Administration regulatory approval before 2000, with nearly half (45%) approved before 1980. This reflects the impressive cure rates possible for many childhood cancers with regimens composed of generic cytotoxic medicines, provided that they are available and the capacities to administer them safely in combination are present.4,11 Most of these agents


**TABLE 3.** Access to the Most Frequently Selected Essential Medicines Identified by 159 International Pediatric Oncologists Stratified by World Bank Economic Classification (subset with at least 10 unique responses)

| Medicine            | Universally Available | Significant OOP Expenses | Risk of Catastrophic Expenditure | Not Available |
|---------------------|-----------------------|---------------------------|----------------------------------|---------------|
| **Top medicines in LMICs** |                       |                           |                                  |               |
| Vincristine         | 22 (56)               | 9 (23)                    | 4 (10)                           | 4 (10)        |
| Methotrexate        | 15 (42)               | 9 (25)                    | 4 (11)                           | 8 (22)        |
| Doxorubicin         | 15 (47)               | 10 (31)                   | 4 (13)                           | 3 (9)         |
| Cytarabine          | 16 (50)               | 10 (31)                   | 3 (9)                            | 3 (9)         |
| Mercaptopurine      | 13 (42)               | 6 (19)                    | 4 (13)                           | 8 (26)        |
| Cyclophosphamide    | 14 (47)               | 7 (23)                    | 5 (17)                           | 4 (13)        |
| L-Asparaginase      | 9 (36)                | 6 (24)                    | 4 (16)                           | 6 (24)        |
| Daunorubicin        | 6 (26)                | 7 (30)                    | 3 (13)                           | 7 (30)        |
| Etoposide           | 11 (50)               | 6 (27)                    | 3 (14)                           | 2 (9)         |
| Cisplatin           | 10 (53)               | 6 (32)                    | 3 (16)                           | 0 (0)         |
| Carboplatin         | 8 (44)                | 4 (22)                    | 2 (11)                           | 4 (22)        |
| Ifosfamide          | 8 (67)                | 1 (8)                     | 1 (8)                            | 2 (17)        |
| Prednisone          | 6 (50)                | 4 (33)                    | 2 (17)                           | 0 (0)         |
| Daunorubicin        | 5 (42)                | 2 (17)                    | 2 (17)                           | 3 (25)        |
| Pegaspargase        | 3 (27)                | 1 (9)                     | 2 (18)                           | 5 (46)        |
| Dexamethasone       | 7 (70)                | 1 (10)                    | 2 (20)                           | 0 (0)         |
| **TOP medicines in UMICs** |                       |                           |                                  |               |
| Doxorubicin         | 43 (83)               | 4 (8)                     | 1 (2)                            | 4 (8)         |
| Methotrexate        | 43 (86)               | 6 (12)                    | 0 (0)                            | 1 (2)         |
| Vincristine         | 39 (78)               | 7 (14)                    | 0 (0)                            | 4 (8)         |
| Cyclophosphamide    | 42 (89)               | 5 (11)                    | 0 (0)                            | 0 (0)         |
| Cytarabine          | 31 (74)               | 1 (2)                     | 1 (2)                            | 9 (21)        |
| Etoposide           | 32 (74)               | 2 (5)                     | 0 (0)                            | 9 (21)        |
| Carboplatin         | 33 (89)               | 3 (8)                     | 0 (0)                            | 1 (3)         |
| Ifosfamide          | 29 (85)               | 2 (6)                     | 2 (6)                            | 1 (3)         |
| Cisplatin           | 28 (85)               | 5 (15)                    | 0 (0)                            | 0 (0)         |
| Mercaptopurine      | 27 (82)               | 5 (15)                    | 0 (0)                            | 1 (3)         |
| Pegaspargase        | 3 (12)                | 4 (16)                    | 6 (24)                           | 12 (48)       |
| L-Asparaginase      | 15 (65)               | 4 (17)                    | 1 (4)                            | 3 (13)        |
| Dexamethasone       | 20 (87)               | 2 (9)                     | 0 (0)                            | 1 (4)         |
| Daunorubicin        | 12 (60)               | 3 (15)                    | 1 (5)                            | 4 (20)        |
| Temozolomide        | 9 (60)                | 5 (33)                    | 0 (0)                            | 1 (7)         |
| Prednisone          | 12 (86)               | 1 (7)                     | 1 (7)                            | 0 (0)         |
| Erwinia asparaginase| 3 (25)                | 1 (8)                     | 2 (17)                           | 6 (50)        |
| Daunorubicin        | 8 (80)                | 0 (0)                     | 1 (10)                           | 1 (10)        |
| **Top medicines in HICs** |                       |                           |                                  |               |
| Cyclophosphamide    | 28 (88)               | 4 (13)                    | 0 (0)                            | 0 (0)         |
| Methotrexate        | 27 (87)               | 4 (13)                    | 0 (0)                            | 0 (0)         |
| Doxorubicin         | 28 (97)               | 1 (3)                     | 0 (0)                            | 0 (0)         |
| Vincristine         | 24 (86)               | 4 (14)                    | 0 (0)                            | 0 (0)         |
| Etoposide           | 24 (89)               | 3 (11)                    | 0 (0)                            | 0 (0)         |

(Continued on following page)
are indicated in combination therapies that form standards of care across a broad range of childhood cancers. An important corollary is that there is some mutual dependence among these agents in the treatment of childhood cancers: they are most essential in combination, rather than singly. In recognition of this fact, the process for establishing and updating EMLc cancer and supportive care medicines has used a disease-specific listing approach, justifying inclusion of individual agents in relation to their use in multiagent regimens to treat specific cancers. Fourth, within LMICs and UMICs, there are major barriers to accessing these priority medicines. We identify a subset of perceived essential childhood cancer medicines not currently captured by the EMLc, providing consideration for additions to subsequent iterations of the list. This subset includes temozolomide, Erwinia

### TABLE 3. Access to the Most Frequently Selected Essential Medicines Identified by 159 International Pediatric Oncologists Stratified by World Bank Economic Classification (subset with at least 10 unique responses) (Continued)

| Medicine       | Universally Availablea | Significant OOP Expensesb | Risk of Catastrophic Expenditurec | Not Available |
|----------------|------------------------|---------------------------|----------------------------------|---------------|
| Mercaptopurine | 23 (85)                | 4 (15)                    | 0 (0)                            | 0 (0)         |
| Cytarabine     | 22 (85)                | 4 (15)                    | 0 (0)                            | 0 (0)         |
| Carboplatin    | 15 (83)                | 3 (17)                    | 0 (0)                            | 0 (0)         |
| Cisplatin      | 15 (83)                | 3 (17)                    | 0 (0)                            | 0 (0)         |
| Dactinomycin   | 14 (78)                | 2 (11)                    | 0 (0)                            | 2 (11)        |
| Dexamethasone  | 13 (81)                | 3 (19)                    | 0 (0)                            | 0 (0)         |
| l-Asparaginase | 13 (87)                | 1 (7)                     | 0 (0)                            | 1 (7)         |
| Prednisone     | 12 (92)                | 1 (8)                     | 0 (0)                            | 0 (0)         |
| Pegaspargase   | 8 (67)                 | 3 (25)                    | 0 (0)                            | 1 (8)         |
| Ifosfamide     | 10 (100)               | 0 (0)                     | 0 (0)                            | 0 (0)         |

NOTE. Values represent No. and percent of the number who responded. Responses may not equal the number who selected the drug in Table 2 since some respondents (four from LMICs and nine from UMICs) made their drug selections and exited the survey. 
Abbreviations: HICs, high-income countries; LMICs, lower-middle–income countries; OOP, out-of-pocket; UMICs, upper-middle–income countries.

aAvailable for all patients with no significant OOP expenses for more than 90% of patients (ie, universal health care coverage).
bAvailable for all patients with significant OOP expenses for some patients, on the basis of the health insurance schemes (mixed model, not universal health care coverage).
cNo universal health care coverage, substantial risk of catastrophic health expenditure. Catastrophic expenditure is defined as expenditure that absorbs more than 40% of total consumption, net of an allowance for food expenditures.

![FIG 2. Availability of the top five highest priority pediatric cancer medicines identified by 159 international pediatric oncologists according to the World Bank Income level of respondents. Each colored bar represents the proportion of respondents who indicated that each drug was universally available, available with significant expenditure, available with catastrophic expenditure for at least one third of patients, or not available at all for the majority of the population within their country. HICs, high-income countries; LMICs, lower-middle–income countries; UMICs, upper-middle–income countries.](image-url)
asparaginase, melphalan, topotecan, fludarabine, and blinatumomab. Among this diverse subset are cytotoxic therapies with potential relevance to an array of childhood cancers in various health system settings (temozolomide and topotecan); agents with unique, critical indications where effective alternatives are lacking (Erwinia asparaginase, in the context of hypersensitivity to L-asparaginase or pegaspargase); and specialized therapies, with innovative mechanisms of action and attendant high cost, conducive to administration in more advanced and well-resourced systems of care (blinatumomab) and with corollary implications for affordability. Continuous careful decision making that weighs the relative benefits and burdens of established and novel therapies will be needed to guide future iterations of the EMLc.

Our results reveal wide variability in availability across income settings, with concerning gaps across a range of essential medicines and substantial associated catastrophic expenditure. We document important, if expected, differences in medicine availability and catastrophic expenditure by country income level, in line with previous studies. Evidence of marked financial barriers in access to older, generic, and ostensibly cheap cytotoxic agents underscores critical issues with the affordability of childhood cancer treatment for most families in LMICs, where financial protection from catastrophic health expenditure is routinely limited. Importantly, however, notable gaps in the availability of essential medicines emerged in all income contexts, including HIC. Comparably, the risk of substantial OOP expenditure observed in UMICs and HICs is not trivial.

These findings suggest two key messages. First, the WHO EMLc reflects the medicines that matter most to clinicians treating children with cancer globally. Second, significant barriers in access to these medicines persist, including gaps in availability and patient-level financial constraints. Making lists of essential medicines is necessary but not sufficient: country-level policies that attend to these barriers are required to turn normative priorities into real-world access.

A few limitations of our study are worth noting. The overall response rate to our survey invitation through the SIOP listserv was low. This might have been due, in part, to the fact that the survey was only administered in English, limiting responses from a diverse international cohort of potential respondents. A conceptual limitation was the inherent tension in an exercise that asked participants to rank individual agents in terms of relative priority for childhood cancer care, in the context of an approach to treatment that naturally uses such agents in combination. Perhaps most importantly, our results reflect respondent perceptions rather than objective data on availability, affordability, and utilization at institutional or country levels.

To our knowledge, our study is the first to evaluate both the concordance of WHO EMLc cancer medicine inclusion with the priorities of treating clinicians and the relationship between such inclusion and the real-world availability and affordability of these medicines internationally. These findings have significant implications for future research and policy on childhood cancer medicines and health system financing. Country-specific studies—including in-depth prospective analyses of availability, utilization, and cost/affordability—are an important next step to develop policies that reflect the nuances of real-world access. Tailoring national formularies to local needs and pharmaceutical policies to on-the-ground realities will require understanding the political, social, economic, and health system dynamics in a given jurisdiction. Such efforts have begun; these studies demonstrate both access barriers common to adult cancer medicines and unique to childhood cancer populations. Ongoing expansion of this research to a broader range of countries and regions representing different health system organizations and macroeconomic realities is essential to developing impactful global and national policies to improve medicines access for children with cancer.

In policy terms, medicines deemed essential by WHO are more likely to be included on national medicines lists in all income settings. Our data confirm the relevance and value of EMLc-listed cancer medicines to frontline clinicians in a wide array of countries. Only a minority of oncologists reported universal availability in LMICs, despite the predominance of generic cytotoxic medicines in the prioritized list, and the related risks of catastrophic expenditure were substantial. These findings point to significant barriers in access to childhood cancer medicines related to health system capacities and market dynamics. Processes to update national medicines lists in many countries to reflect evolving WHO EMLc inclusion are variable across countries, resulting in outmoded lists in many contexts. Challenges with efficient procurement and supply management, fair pricing, quality assurance, and public health system financing routinely affect cancer medicine access for children. Fragmented markets, failed tenders, erratic stocks, production bottlenecks in the context of sole-source provision, fragile supply chains, and price inflation all constitute recurrent, fundamental challenges in access to quality-assured cancer medicines. Many health care systems lack mechanisms to assess the value of new and existing medicines, such as health technology assessment, that would facilitate medicine policy priority setting and context-sensitive pricing negotiations.

Although mechanisms exist to address some of these challenges, they are inconsistently applied in LMIC settings, because of competing political priorities, resource constraints, or limitations in health system capacities. Strategies including evidence-based forecasting of need and cost, pooled procurement, international reference pricing with appropriate comparator markets, competitive...
tendering from quality-assured suppliers, innovative financing mechanisms, and ring-fenced inventory for pediatric use may contribute to sustained supply of cancer medicines for children.\textsuperscript{4,15-17} The recent establishment of a Global Platform for Access to Childhood Cancer Medicines, through joint efforts by St Jude Children’s Research Hospital and the WHO, constitutes a landmark development in global policy on cancer medicines for children. In addition to galvanizing attention and funding for this critical global health issue, it has the potential to strengthen mechanisms for forecasting and bulk procurement of quality-assured medicines at competitive prices to enhance access for children with cancer internationally.

Our findings underscore the urgent need for global and national policies to support access to essential cancer medicines as a key component of international efforts to improve childhood cancer outcomes through WHO’s GICC.

However, access to essential medicines represents only one component of comprehensive efforts to improve childhood cancer outcomes globally. The narrow therapeutic indices of most cytotoxic therapies used in the treatment of childhood cancers, the need for pediatric-specific expertise to minimize treatment-related morbidity and mortality, and the requirement for robust surgical and radiotherapeutic capacities as critical treatment modalities for many pediatric malignancies all constitute critical factors in efforts to improve childhood cancer outcomes across a broad range of health systems.\textsuperscript{25} Neither EMLc inclusion alone nor even real-world access to EMLc-listed medicines will suffice; concerted efforts to reach GICC targets for global survival outcomes must acknowledge and incorporate the wider health system reforms required to realize the potential benefits of enhanced essential medicines access.

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The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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REFERENCES

1. Ward ZJ, Yeh JM, Bhakta N, et al: Estimating the total incidence of global childhood cancer: A simulation-based analysis. Lancet Oncol 20:483-493, 2019
2. Rodriguez-Galindo C, Friedrich P, Alcasabas P, et al: Toward the cure of all children with cancer through collaborative efforts: Paediatric oncology as a global challenge. J Clin Oncol 33:3065, 2015
3. World Health Organization: Global Initiative for Childhood Cancer. https://www.who.int/cancer/childhood-cancer/en
4. Denburg A, Arora B, Arora RS, et al: Access to essential medicines for children with cancer: A joint SIOP-CCI position statement. Lancet Oncol 18:20-22, 2017
5. World Health Organization: The Selection and Use of Essential Medicines: Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (Including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva, World Health Organization, 2019
6. World Health Organization: Model List of Essential Medicines for Children – 8th List. Geneva, World Health Organization, 2021 (WHO/MHP/HPS/EML/2021.03)
7. Fundytus A, Sengar M, Lombe D, et al: Access to cancer medicines deemed essential by oncologists in 82 countries: An international, cross-sectional survey. Lancet Oncol 22:1367-1377, 2021
8. Cancer Care Ontario: Drugs, 2021. https://www.cancercareontario.ca/en/drugformulary/drugs
9. Cherny N, Sullivan R, Torode J, et al: ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Ann Oncol 27:1423-1443, 2016
10. The World Bank: World Bank Country and Lending Group, 2021
11. Shulman L, Wagner CM, Barr R, et al: Proposing essential medicines to treat cancer: Methodologies, processes, and outcomes. J Clin Oncol 34:69-75, 2016
12. Cohen P, Friedrich P, Lam C, et al: Global access to essential medicines for childhood cancer: A cross-sectional survey. J Glob Oncol 4:1-11, 2018
13. Robertson J, Barr R, Shulman L, et al: Essential medicines for cancer: WHO recommendations and national priorities. Bull WHO 94:735-742, 2016
14. Marts YM, lwamoto K, Barr RD, et al: Shortages and price variability of essential cytotoxic medicines for treating children with cancers. BMJ Glob Health 5:e003282, 2020
15. Boaeng R, Renner L, Petricca K, et al: Health system determinants of access to essential medicines for children with cancer in Ghana. BMJ Glob Health 5:e002906, 2020
16. Tang B, Bodkin C, Gupta S, et al: Access to WHO essential medicines for childhood cancer care in Trinidad and Tobago: A health system analysis of barriers and enablers. JCO Glob Oncol 6:67-79, 2020
17. Boaeng R, Petricca K, Tang B, et al: Determinants of childhood cancer drug access in health system context: A comparative mixed-methods study of four English-speaking Caribbean countries. Lancet Global Health 9:e1314-e1324, 2021
18. Denburg AE, Cuadrado C, Alexis C, et al: Improving childhood cancer care in Latin America and the Caribbean: A PAHO Childhood Cancer Working Group position statement. Lancet Oncol 18:709-711, 2017
19. Arney L, Yadav P: Improving Procurement Practices in Developing Country Health Programs. Ann Arbor, William Davidson Institute, University of Michigan, 2014
20. Oluka PN, Saemnoga F, Kambaza S: Tackling supply chain bottlenecks of essential drugs: A case of Uganda local government health units. 4th International Public Procurement Conference, Seoul, South Korea, August 26-28, 2010, pp 26-28
21. Magdzire BP, Ward K, Leng HM, et al: Inefficient procurement processes undermine access to medicines in the Western Cape Province of South Africa. S Afr Med J 107:581-584, 2017
22. Martei YM, Chiyapo S, Grover S, et al: Availability of WHO essential medicines for cancer treatment in Botswana. J Glob Oncol 4:1-8, 2018
23. World Health Organization: Pricing of Cancer Medicines and Its IMPACTS. Geneva, World Health Organization, 2018
24. Denburg AE, Ramirez A, Pavuluri S, et al: Childhood cancer in health system context: Determinants of political priority and pathways to scale-up in five nations. PLoS One 14:e0221292, 2019
25. Atun R, Bhakta N, Denburg A, et al: Sustainable care for children with cancer: A Lancet Oncology Commission. Lancet Oncol 21:e185-224, 2020
## APPENDIX

**TABLE A1.** The Complete Rank Order List of Medicine Names, Frequencies, and Percentages

| Medication Name | No. of Times Selected (denominator 159) | Percent |
|-----------------|----------------------------------------|---------|
| Methotrexate    | 120                                     | 75.5    |
| Vinccristine    | 118                                     | 74.2    |
| Doxorubicin     | 117                                     | 73.6    |
| Cyclophosphamide| 110                                     | 69.2    |
| Cytarabine      | 103                                     | 64.8    |
| Etoposide       | 94                                      | 59.1    |
| Mercaptopurine  | 91                                      | 57.2    |
| Carboplatin     | 75                                      | 47.2    |
| Cisplatin       | 72                                      | 45.3    |
| Dactinomycin    | 63                                      | 39.6    |
| L-Asparaginase  | 63                                      | 39.6    |
| Ifosfamide      | 59                                      | 37.1    |
| Dexamethasone   | 49                                      | 30.8    |
| Pegaspargase    | 49                                      | 30.8    |
| Prednisone      | 39                                      | 24.5    |
| Danorubicin     | 27                                      | 17.0    |
| Temozolomide    | 19                                      | 11.9    |
| Leucovorin      | 18                                      | 11.3    |
| Bleomycin       | 16                                      | 10.1    |
| Dacarbazine     | 16                                      | 10.1    |
| Erwinia asparaginase | 16                                      | 10.1    |
| Imatinib        | 15                                      | 9.4     |
| Vinblastine     | 14                                      | 8.8     |
| Tretinoin (ATRA)| 13                                      | 8.2     |
| Blinatumomab    | 10                                      | 6.3     |
| Rituximab       | 10                                      | 6.3     |
| Hydroxyurea     | 9                                       | 5.7     |
| Irinotecan      | 9                                       | 5.7     |
| Melphalan       | 9                                       | 5.7     |
| Arsenic trioxide| 8                                       | 5.0     |
| Mitoxantrone    | 8                                       | 5.0     |
| Fludarabine     | 7                                       | 4.4     |
| Pegylated liposomal doxorubicin | 7 | 4.4 |
| Thioguanine     | 7                                       | 4.4     |
| Topotecan       | 7                                       | 4.4     |
| Dasatinib       | 6                                       | 3.8     |
| Idarubicin      | 6                                       | 3.8     |
| Brentuximab vedotin | 5 | 3.1 |
| Gemcitabine     | 5                                       | 3.1     |

(Continued in next column)

| Medication Name | No. of Times Selected (denominator 159) | Percent |
|-----------------|----------------------------------------|---------|
| Lomustine       | 5                                       | 3.1     |
| Busulfan        | 4                                       | 2.5     |
| Inotuzumab ozogamicin | 4 | 2.5 |
| Nivolumab       | 4                                       | 2.5     |
| Procarbazine    | 4                                       | 2.5     |
| Carmustine      | 3                                       | 1.9     |
| Midostaurin     | 3                                       | 1.9     |
| Pazopanib       | 3                                       | 1.9     |
| Sorafenib       | 3                                       | 1.9     |
| Alemtuzumab     | 2                                       | 1.3     |
| Azacitidine     | 2                                       | 1.3     |
| Bevacizumab     | 2                                       | 1.3     |
| Cladribine      | 2                                       | 1.3     |
| Dinutuximab     | 2                                       | 1.3     |
| Docetaxel       | 2                                       | 1.3     |
| Lorlatinib      | 2                                       | 1.3     |
| Megestrol acetate| 2 | 1.3 |
| Nelarabine      | 2                                       | 1.3     |
| Abemaciclib     | 1                                       | 0.6     |
| Bortezomib      | 1                                       | 0.6     |
| Brigatinib      | 1                                       | 0.6     |
| Chlorambucil    | 1                                       | 0.6     |
| Crizotinib      | 1                                       | 0.6     |
| Dabrafenib      | 1                                       | 0.6     |
| Decitabine      | 1                                       | 0.6     |
| Denosumab       | 1                                       | 0.6     |
| Epirubicin      | 1                                       | 0.6     |
| Everolimus      | 1                                       | 0.6     |
| Fluorouracil (5-fluorouracil) | 1 | 0.6 |
| Nilotinib       | 1                                       | 0.6     |
| Others (rasburicase) | 1 | 0.6 |
| Oxaliplatin     | 1                                       | 0.6     |
| Pamidronate     | 1                                       | 0.6     |
| Pembrolizumab   | 1                                       | 0.6     |
| Ponatinib       | 1                                       | 0.6     |
| Ruxolitinib     | 1                                       | 0.6     |
| Talazoparib     | 1                                       | 0.6     |
| Temsirolimus    | 1                                       | 0.6     |
| Trametinib      | 1                                       | 0.6     |
| Trastuzumab     | 1                                       | 0.6     |
| Vinorelbine     | 1                                       | 0.6     |
| Vorinostat      | 1                                       | 0.6     |

(Continued in next column)