CANCER PREVENTION AND CONTROL

Harmonization of the Essentials: Matching Diagnostics to Treatments for Global Oncology

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Although cancer incidence and mortality are increasing worldwide regardless of economic development levels,[1] the heaviest burden of this escalation is borne by low- and middle-income countries (LMICs).[2] Approximately three quarters of deaths from cancer occur in LMICs.[3] The rapid rise of cancer in LMICs has created an untenable strain on already overtaxed systems, leaving many patients without adequate care. LMICs have finite resources and thus must invest in areas in which maximum health gains can be made.

To realize health equity in cancer, the importance of the diagnostic laboratory cannot be overstated.[6] As recently as 2017, only one quarter of LMICs reported having pathology services available in the public sector.[3-5] Being unable to access pathology services results in delayed and incomplete diagnoses, inappropriate treatment decisions, and worsened prognoses, which ultimately result in higher mortality rates.[7] Although patients with cancer in LMICs may benefit from long-established effective treatments as well as new and targeted treatment protocols, accurate diagnoses are necessary to assign the correct treatment protocol in the first place.[8] It is vital then, that resource-restricted governments prioritize diagnostic services at the policy and health system level, proportionate to their prioritization of treatment services.[9]

The List of Essential Medicines (EML), List of Essential In Vitro Diagnostics (EDL), and List of Priority Medical Devices for Cancer Management, published by the World Health Organization (WHO), were created as pragmatic guides for the strategic procurement of medicines and diagnostics to be used in resource-constrained settings and by middle- and high-income countries.[3-5] The lists include medicines, diagnostics, and equipment that should be widely available and affordable throughout a country's health care system.[3-5] Pharmaceuticals alone represent the second largest public expenditure in health care systems,[3-5] so these lists serve as a vital tool for resource-constrained health care systems, ensuring that they receive the best value possible for their patients within the available budgetary resources. For the lists to be effective in advancing cancer care, they must be used in combination with each other and must reflect harmonization across the cancer spectrum. As evidenced by global efforts to combat infectious diseases such as tuberculosis and malaria, attempts to curb disease burden are impossible without pathology services to guide decisions regarding therapy.[10] Policy makers, when procuring therapeutic drugs, must also reference the EDL and the List of Priority Medical Devices for Cancer Management to ensure that their health care facilities are appropriately outfitted with the infrastructure and reagents necessary for accurate treatment planning for the procured drugs.[10]

To move toward this harmonization, the 2019 EML was matched to the existing EDL and updated by pathology experts to provide the full details of diagnostic tools needed to effectively use these treatments. Construction of this table was completed using a stepwise approach. First, the EML was reviewed and listed cancer diagnoses were extracted. Second, all agents from the EML that treat those specific cancers were collected by cancer type. Third, for each cancer type, a category of diagnostics required for initial definitive diagnosis was assigned and the cancers were sorted according to category. Finally, the specific details of making a complete diagnosis to indicate a specific treatment were inserted (D.A.M. Jr), checked by experts (E.A.M., J.E.B., J.L.K.), and rechecked by secondary experts (H.M.R., R.G.). Finally, oncologists (Y.M.M., T.F., L.N.S.) reviewed the list of medicines to modify tumor categories that could be treated with the existing list of medications.

Table 1 presents an aggregation of key information from the three Essential Lists. It provides a strategic roadmap for procuring cancer drugs based on available pathology services, and inversely acts as a roadmap for procuring reagents and equipment on the basis of available therapeutics. The table also highlights possible additional indications that a health care institution may be capable of identifying and treating based on what is already available. By combining the three Essential Lists into a single streamlined source, policymakers can use it while considering the entire care pathway when making procurement decisions for patients with cancer to ensure that each purchased component functions within an effective, cohesive system.

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TABLE 1. The Combined Essential Diagnostics List, Essential Medicines List, and Essential Equipment for Cancer Management Table, With Required Diagnostic Category, Cancer Types, Essential Medicine List Components, and the Specifics of Diagnosis

Diagnostics Required for Specific Cancer Type	Essential Medicines	Specifics of Diagnosis
Histology		
Cervical cancer	Carboplatin, cisplatin, paclitaxel	Standard histologic parameters
Colon cancer	Calcium folinate, capecitabine, fluorouracil, irinotecan, oxaliplatin	Standard histologic parameters
Gestational trophoblastic neoplasia	Calcium folinate, cyclophosphamide, dactinomycin, etoposide, methotrexate, vincristine	Standard histologic parameters
Head and neck cancer	Cisplatin	Standard histologic parameters
Non–small-cell lung cancer	Carboplatin, cisplatin, etoposide, gemcitabine, paclitaxel, vinorelbine, erlotinib	Standard histologic parameters, molecular testing for *EGRF* mutation for erlotinib treatment
Osteosarcoma	Calcium folinate, carboplatin, cisplatin, doxorubicin, ifosfamide, methotrexate, mesna	Standard histologic parameters
Rectal cancer	Calcium folinate, capecitabine, fluorouracil	Standard histologic parameters
Retinoblastoma	Carboplatin, etoposide, vincristine	Standard histologic parameters
Histology with or without IHC		
Epithelial ovarian cancer	Carboplatin, gemcitabine, paclitaxel	Standard histologic parameters; IHC may be required for challenging cases
Kaposi sarcoma	Bleomycin, doxorubicin, paclitaxel, vinblastine, vincristine	Standard histologic parameters; IHC may be required for challenging cases
Nephroblastoma	Dactinomycin, doxorubicin, vincristine	Standard histologic parameters; Wt-1 required for metastatic cases or monophasic cases
Ovarian germ cell tumor	Bleomycin, cisplatin, etoposide, ifosfamide, paclitaxel, vinblastine, mesna	Standard histologic parameters; IHC may be required for challenging cases
Prostate cancer	Docetaxel, abiraterone, bicalutamide, leuprorelin, prednisolone	Standard histologic parameters; IHC may be required for challenging cases
Rhabdomyosarcoma	Cyclophosphamide, dactinomycin, ifosfamide, vincristine, mesna	Standard histologic parameters, myogenin required for primitive, poorly differentiated tumors
Testicular germ cell tumor	Bleomycin, cisplatin, etoposide, ifosfamide, vinblastine, mesna	Standard histologic parameters; IHC required to precisely assess components (HCG for syncytiotrophoblast, CD30 for embryonal carcinoma, Oct 3/4 or CD117 for seminoma; classify as seminomatous *v* nonseminomatous GCT)
Histology with or without IHC with or without molecular testing		
Melanoma	Nivolumab, pembrolizumab	Standard histologic parameters; IHC may be required for challenging cases; BRAF testing
Histology with or without ISH		
Nasopharyngeal carcinoma	Carboplatin, cisplatin, fluorouracil, paclitaxel	Standard histology that can be confirmed by ISH for Epstein-Barr virus
Histology plus IHC		
Breast cancer	Capecitabine, carboplatin, cyclophosphamide, docetaxel, doxorubicin, fluorouracil, methotrexate, paclitaxel, vinorelbine, trastuzumab, anastrozole, leuprorelin, tamoxifen	Standard histologic parameters, estrogen receptor/progesterone receptor (IHC) required for hormonal therapy; HER2 (IHC) required for trastuzamab, aromatase resistance testing
Burkitt lymphoma	Calcium folinate, cyclophosphamide, cytarabine, doxorubicin, etoposide, vincristine, prednisolone	Standard histologic parameters (tingible body macrophages, frequent mitoses, monotonous cytology) plus IHC for characterization; $CD20^+$, $CD10^+$, BCL2-negative, Ki67 essentially 100%
Diffuse large B-cell lymphoma	Cyclophosphamide, doxorubicin, vincristine, rituximab, prednisolone	Standard histologic parameters (diffuse sheets of large cells) plus IHC for characterization; CD20 required for rituximab
Follicular lymphoma	Bendamustine, cyclophosphamide, doxorubicin, vincristine, rituximab, prednisolone	Standard histologic parameters (vary by grade) plus IHC for characterization; CD20 required for rituximab; $CD20^+$, $CD10^+$, BCL2-positive

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TABLE 1. The Combined Essential Diagnostics List, Essential Medicines List, and Essential Equipment for Cancer Management Table, With Required Diagnostic Category, Cancer Types, Essential Medicine List Components, and the Specifics of Diagnosis (Continued)

Diagnostics Required for Specific Cancer Type	Essential Medicines	Specifics of Diagnosis
Gastrointestinal stromal tumor	Imatinib	Standard histologic parameters plus IHC for characterization, c-kit for imatinib treatment
Hodgkin lymphoma	Bleomycin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, procarbazine, vinblastine, vincristine, prednisolone	Standard histologic parameters plus IHC for characterization; CD30^{+}, CD15^{+}, CD15^{-}, CD20^{+}, CD20^{-}, PAX5-positive (weak), CD45^{-}
Multiple myeloma	Cyclophosphamide, doxorubicin, melphalan, bortezomib, thalidomide, lenalidomide, dexamethasone, prednisolone	Standard histologic parameters plus FC or IHC for characterization; CD138^{+}, CD38^{+}, immunoglobulin light chain restricted; Epstein-Barr virus–negative (helpful for excluding plasmablastic lymphoma in immunocompromised setting)
Morphology review plus immunophenotype (FC or IHC) with or without molecular testing or cytogenetics testing		
Acute lymphoblastic leukemia	Asparaginase, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, etoposide, mercaptopurine, methotrexate, pegaspargase, tioguanine, vincristine, dexamethasone, hydrocortisone, methylprednisolone, prednisolone	Peripheral blood smear or bone marrow aspirate review for evaluation of cytologic features (blasts); B cell (FC or IHC): TdT-positive, CD19^{+}, cCD79a^{+}, cCD22^{+}, often CD10^{+}; T-cell (FC or IHC): TdT-positive; cCD3^{+}
Acute myeloid leukemia	Cytarabine, daunorubicin	Peripheral blood smear or bone marrow aspirate review for evaluation of cytologic features (blasts more than 20% of nucleated cells for most subtypes); highly variable immunophenotype by FC; often CD45^{dim}, CD34^{+}, MPO^{+}
Acute promyelocytic leukemia	Arsenic trioxide, cytarabine, daunorubicin, mercaptopurine, methotrexate, realgar-Indigo naturalis formulation, all-trans retinoic acid	Peripheral blood smear or bone marrow aspirate review for evaluation of cytologic features (bundles of Auer rods); expected immunophenotype (FC): HLA-DR^{-}, CD34^{-}, CD33^{bright}; must confirm presence of t(15;17) by RT-PCR or confirm karyotype by FISH
Chronic lymphocytic leukemia	Bendamustine, chlorambucil, cyclophosphamide, fludarabine, rituximab, prednisolone	Review of peripheral blood smear, bone marrow aspirate or tissue for evaluation of morphologic features (small cells, clumped chromatin, proliferation centers); CD20^{+} (required for rituximab treatment), CD5^{+}, CD23^{+}, CD10^{-}, immunoglobulin light chain restricted by FC; CD20 and light chain are dim by FC; cyclin D1–negative by IHC, or no t(11;14) by karyotype or FISH
Histology plus IHC plus molecular testing		
Ewing sarcoma	Cyclophosphamide, doxorubicin, etoposide, ifosfamide, vincristine, mesna	Standard histologic parameters plus IHC plus translocation analysis
Peripheral blood smear plus molecular testing		
Chronic myeloid leukemia	Hydroxycarbamide, dasatinib, imatinib, nilotinib	Review of peripheral blood smear or bone marrow aspirate for evaluation of cytologic features (myeloid hyperplasia and left shift, increased basophils, small hypolobated megakaryocytes in bone marrow, blasts greater than 20% indicate a blast crisis [may be acute myeloid leukemia or acute lymphoblastic leukemia blasts]); must confirm presence of t(9;22) or BCR-ABL1 by RT-PCR or karyotype by FISH. Molecular sequencing can evaluate for imatinib resistance (not widely available, clinical protocol subjugates diagnostics)

Abbreviations: FC, flow cytometry; FISH, fluorescence in situ hybridization; GCT, germ cell tumor; HCG human chorionic gonadotropin; IHC, immunohistochemistry; ISH, in situ hybridization; MPO, myeloperoxidase; Oct 3/4, octamer binding transcription factor; RT-PCR, reverse transcriptase polymerase chain reaction; TdT, terminal deoxynucleotidyl transferase (TdT); Wt-1, Wilms tumor–1.

A review by oncology experts of the complete list of essential medicines in the published list reveals that additional tumor types that are not currently listed can also be treated, including gastric, esophageal, anal, pancreatic, hepatocellular, urothelial, small cell, and renal cell carcinomas, cholangiocarcinoma, and some soft-tissue sarcomas. In addition, there are rare cancers that can be treated with some of the listed agents; referring to the US Food and Drug Administration approval lists by cancer type can identify the correct match for diagnosis and treatment along with appropriate protocols. In consideration of these unlisted tumors, additional diagnostic tools should be made available, including immunohistochemical (IHC) stains for parsing a differential diagnosis (depending upon the population epidemiology) and therapeutic IHC stains for immuno-oncology agents. It is important to note, for example, that pembrolizumab is mentioned as a first-line therapy option for metastatic or unresectable melanoma but is, in fact, a second-line therapy for patients with any unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumor who have no alternative standard therapy.

It is crucial that the Essential Lists be updated and expanded in a coordinated fashion to ensure that the information presented in each list is complimentary and in sync with the other lists. Otherwise, the effectiveness of the Essential Lists might be called into question, because functioning cancer care requires access to reagents, complex equipment, and medicines in combination.[11] The WHO should incorporate and disseminate this table—with vetting by a wider audience of experts including LMIC participants—as an additional resource for LMICs that need to make procurement decisions to ensure that all necessary components are being considered. Proper use of the Essential Lists and corresponding table will deliver improved patient outcomes without wasting limited budgetary resources. Ultimately, the coordinated use of diagnostics and therapeutics will give patients the best chances for survival, whereas a lack of matched diagnostics and therapeutics will expose patients to the toxicities of inappropriate treatment without a chance for benefit.

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