Penn Medicine

World Health Organization: Essential Medicines and Devices for Cancer:

Principles, Methodologies, and Outcomes

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Partners In Health

the cure is within

ABRAMSON CANCER CENTER

The WHO Process

Essential Medicines List for Cancer

2014-2015 Process completed

2016-2017 Process underway

Medical Devices for Cancer

2015-2016 Process underway

Relevance to Public Sector

- The purpose of the EML is to provide useful information to public sector officials on medicines that are essential to cancer care programs
- Drugs should be directly traceable to the type of cancer they are used to treat
- Dosing and scheduling information included in disease-based briefings for volume estimates to drive national purchasing
- Inclusion of medicines on the WHO EML may help pressure prices downward

UICC Task Team

In 2014 and 2016, the UICC responded to an invitation by the WHO to convene a task team charged with creating a new framework for evaluation of drugs for inclusion – Julie Torode

Core Task Team included representatives of UICC, Dana-Farber Cancer Institute, ESMO, ASCO, SIOP, US National Cancer Institute, NCCN International

Collaborations from the outset with the WHO was critical to this work, with special thanks to Dr Nicola Magrini

More than 90 international volunteers participated

Measurements of Benefit – Example 1

- **Incremental benefits above surgery alone – curable diseases**

Early-stage breast cancer – ER positive, HER2 negative, 4 positive axillary nodes

- Survival without surgery – **0%**
- Surgery alone – **60%** long-term survival
- Surgery + tamoxifen – **80%** long-term survival
- Surgery + tam + chemo – **85%** long-term survival

Measurements of Benefit – Example 2

Incremental benefits with specific regimens without surgical benefit – curable diseases

Diffuse Large B-Cell lymphoma

- Survival without medicines – **0%**
- Survival with CHOP – **55%**
- Survival with R-CHOP – **70%**

Measurements of Benefit – Example 3

Incremental benefits with medicines for incurable diseases

***Non-small cell lung cancer - metastatic*;**

Median survival

- Without chemotherapy – **6 months**
- With chemotherapy regimen A – **10 months**

- Role of genomics and targeted therapies?
  - Median survival in some cases 20+ months
  - You need to be able to test for mutations, and have available appropriate targeted therapies
- Role of immunotherapy?

Disease-based Briefings Included:

- Executive summary
- Public health relevance
- Requirements for diagnosis, treatment, and monitoring
- Overview of regimens
- Review of benefits and harms (including systematic reviews)
- Recommended additions proposed to the EML

Process and Analysis

Applications prepared for

- 22 adult cancers determined to be high priority
- 7 pediatric cancers determined to be high priority

- **Written by one person/group and reviewed by at least 2 others**

- **Central committee synthesized documents**

ADULT CANCERS		PEDIATRIC CANCERS
AML and APL (adult+ped)	GTN	ALL
CLL	Head and neck cancer	Burkitt lymphoma
CML	Hodgkin lymphoma (adult+ped)	Ewing sarcoma
DLBCL	Kaposi sarcoma	Hodgkin lymphoma
Early stage breast cancer	Metastatic breast cancer	Osteosarcoma
Early stage cervical cancer	Metastatic colorectal cancer	Retinoblastoma
Early stage colon cancer	Metastatic prostate cancer	Rabdomyosarcoma
Early stage rectal cancer	Nasopharyngeal cancer	Wilms tumor
Epithelial ovarian cancer	Non-small cell lung cancer	
Follicular lymphoma	Ovarian germ cell tumors (adult+ped.)	
GIST	Testicular germ cell tumors (adult+ped)	

Old List – 30 Drugs

ADULTS -- 18th edition (April 2013) -- Rev. Oct.2013 - English

Section 8.2 Cytotoxics and adjuvant medicines

Complementary List

allopurinol [c]	*Tablet: 100 mg; 300 mg.*
asparaginase	*Powder for injection: 10 000 IU in vial.*
bleomycin	*Powder for injection: 15 mg (as sulfate) in vial.*
calcium folinate	*Injection: 3 mg/ml in 10-ml ampoule.Tablet: 15 mg.*
□ *carboplatin*	*Injection: 50 mg/5 ml; 150 mg/15 ml; 450 mg/45 ml;*
chlorambucil	*Tablet: 2 mg.*
cyclophosphamide	*Powder for injection: 500 mg in vial. Tablet: 25 mg.*
cytarabine	*Powder for injection: 100 mg in vial.*
dacarbazine	*Powder for injection: 100 mg in vial*

2014 Proposed List – 52 drugs

An excerpt from our application

Bleomycin	Testicular germ cell tumor, Ovarian germ cell tumor, Hodgkin lymphoma, Kaposi sarcoma
Calcium folinate	Early stage colon cancer, Early stage rectal cancer, Gestational trophoblastic neoplasia, Metastatic colorectal cancer
Capecitabine*	Early stage colon cancer, Early stage rectal cancer, Metastatic colorectal cancer, Metastatic breast cancer
Carboplatin	Epithelial ovarian cancer, Early stage breast cancer, Metastatic breast cancer, Nasopharyngeal cancer, Non-small cell lung cancer, Ovarian germ cell tumor, Osteosarcoma, Retinoblastoma
Chlorambucil	Chronic lymphocytic leukemia
Cisplatin*	Epithelial ovarian cancer, Early stage cervical cancer, Head and neck cancer, Testicular germ cell tumor, Ovarian germ cell tumor, Nasopharyngeal cancer, Non-small cell lung cancer, Osteosarcoma
Cyclophosphamide	Chronic lymphocytic leukemia, Diffuse, large B-cell lymphoma, Early stage breast cancer, Metastatic breast cancer, Gestational trophoblastic neoplasia, Hodgkin lymphoma, Follicular lymphoma, Burkitt lymphoma, Rhabdomyosarcoma, Ewing sarcoma, Acute lymphoblastic leukemia
Cytarabine	Acute myelogenous leukemia, Acute promyelocytic leukemia, Acute lymphoblastic

WHO Approvals and Denials – May 2015

Approved

- Anastrozole (class)
- ATRA
- Bendamustine
- Bicalutamide
- Capecitabine
- Cisplatin
- Fludarabine

Gemcitabine
Imatinib
Irinotecan
Leuprolide (class)
Oxaliplatin (not for early stage rectal ca)
Rituximab
Trastuzumab
Vinorelbine
G-CSF

Denied

- Dasatinib
- Nilotinib

- Erlotinib
- Gefitinib

- Arsenic trioxide

- Diethylstilbesterol

Keeping the EML Current – Process started March 2016

- Review the 29 disease-based documents delivered in December 2014
- Will likely re-recommend molecular analyses and targeted therapies for Non-small cell lung cancer
- Will likely re-recommend second line Tyrosine kinase inhibitors for chronic myeloid leukemia only after disease progression on imatinib
- Will develop a document proposing bisphosphonates for treatment of malignant bone disease
- No new diseases added
- Present recommendations to WHO in December 2016 for consideration in April 2017

Some considerations….

Being on the WHO EML is different from a drug being available to a patient

Regulatory issues, prequalification, cost considerations, supply chain management, quality assurance, new vendors, training of personnel, service delivery, and so on

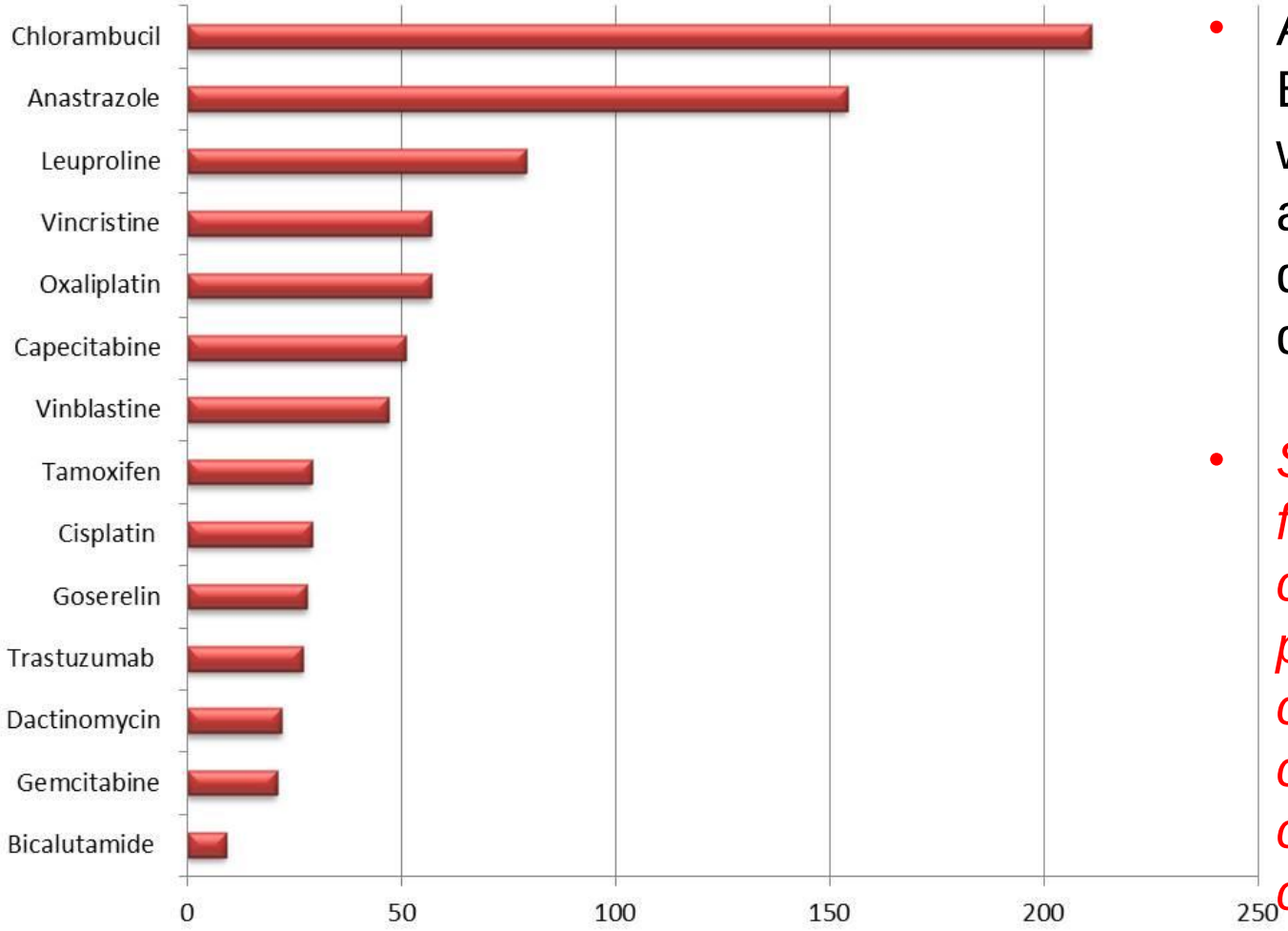
Comparing Country EMLs with the 2013 and 2015 WHO EMLs

- Countries with GNI < $25,000 and with data available reviewed (135)
- These data do not necessarily reflect what medicines countries purchase
- These data do not necessarily reflect what medicines are available or affordable

Jane Robertson[1] PhD, Ronald Barr[2] MD, Lawrence N Shulman[3] MD, Gilles B Forte[4] PhD, Nicola Magrini[4] MD, manuscript in press, WHO Bulletin

WHO Region (number of countries)	Median number of medicines listed (minimum, maximum)		
	Medicines in WHO EML 2013 (30 medicines)	Medicines added in 2015 (16 medicines)	Medicines not added in 2015 (6 medicines)
Overall (n= 135)	17 (0, 25)	3 (0, 15)	0 (0, 4)
Africa (n=37)	13 (1, 23)	1 (0, 14)	0 (0, 1)
Americas (n=29)	19 (3, 25)	6 (0, 15)	0 (0, 4)
Eastern Mediterranean (n=14)	23.5 (0, 25)	6.5 (0, 15)	0 (0, 4)
Europe (n=26)	18.5 (1, 25)	10 (0, 15)	0 (0, 4)
South East Asia (n=11)	21 (2, 24)	1 (0, 13)	0 (0, 0)
Western Pacific (n=18)	7 (0, 25)	0.5 (0, 15)	0 (0, 2)
Western Pacific (n=9)*	19 (9, 25)	2 (1, 15)	0 (0, 2)

Analysis of Chemotherapy Stock-out



- At least 40% of Botswana NEML were out of stock for a mean and median duration of 48 and 30 days respectively.
- *Stock-outs affected first-line chemotherapy for potentially curable cancers - cervical cancer, breast cancer, and colorectal cancer.*

Costing

- Ideally a patient anywhere should have access to best therapy

- But cost *is* a factor for many countries

Cancer Treatment in Resource-Constrained Settings?

“Giving out free cancer drugs would not help the poorest parts of Africa”, the head of a pharmaceutical giant has told the BBC. He said "dramatic" progress was being made in treating tumours, and defended the company's pricing policy. And he said that training doctors, not the cost of drugs, was the biggest issue in the world's poorest countries. Access to treatment has been one of the key themes of the world's biggest cancer conference”

Breast cancer costing: scenario #1
Adjuvant therapy for ER Positive/HER2 Positive Disease

	Unit size and cost	# Units Needed	Total cost (USD)
Doxorubicin 4 cycles	$6.48 per 50mg vial	12 vials	$77.75
Cyclophosphamide 4 cycles	$8.75 per 500mg vial $2.89 per 1g vial	4x 500mg vials + 4x 1g vials	$46.79
Paclitaxel 4 cycles	$7.42 per 100mg vial	12 vials	$178.03
Tamoxifen (5 years)	$0.03 per 20 mg tab-cap	1,825 (daily, 5yrs)	$60.23
TOTAL			$273.03

Trastuzumab not available

Reference: Management Sciences for Health Price Indicator. 2013.

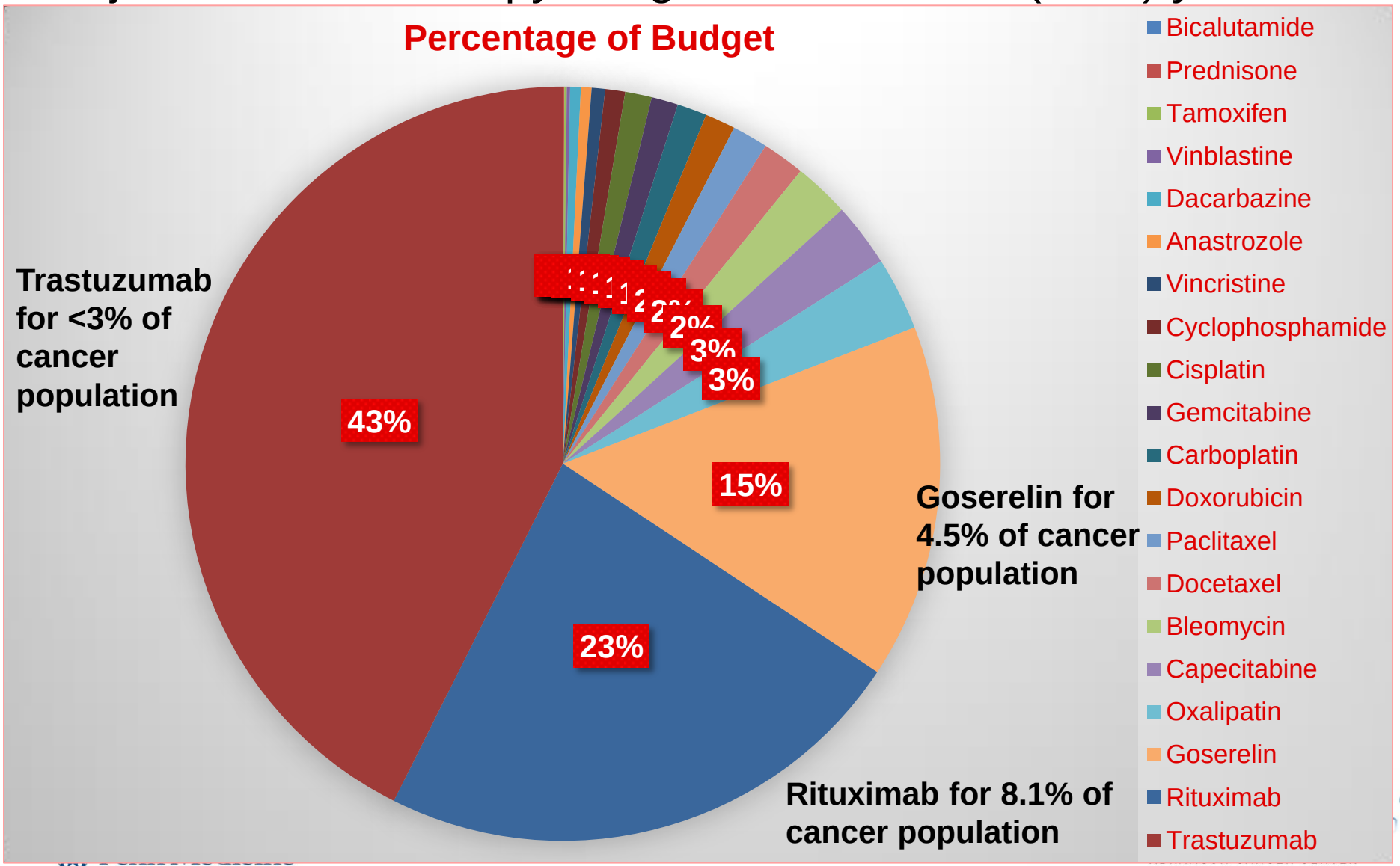
Breast cancer costing: scenario #2
Adjuvant therapy for ER Positive/HER2 Positive Disease

	Unit size and cost	# Units Needed	Total cost (USD)
Doxorubicin 4 cycles	$6.48 per 50mg vial	12 vials	$77.75
Cyclophosphamide 4 cycles	$8.75 per 500mg vial $2.89 per 1g vial	4x 500mg vials + 4x 1g vials	$46.79
Paclitaxel 4 cycles	$7.42 per 100mg vial	12 vials	$178.03
Tamoxifen (5 years)	$0.03 per 20 mg tab-cap	1,825 (daily, 5yrs)	$60.23
Trastuzumab 1 year estimate	$6.27 per mg	6,448mg	$ 40,404.65
TOTAL			$40,767.44

Reference: Management Sciences for Health Price Indicator. 2013.

Chemotherapy Forecasting for Botswana

Projected chemotherapy budget = $2.3 million (USD)/year

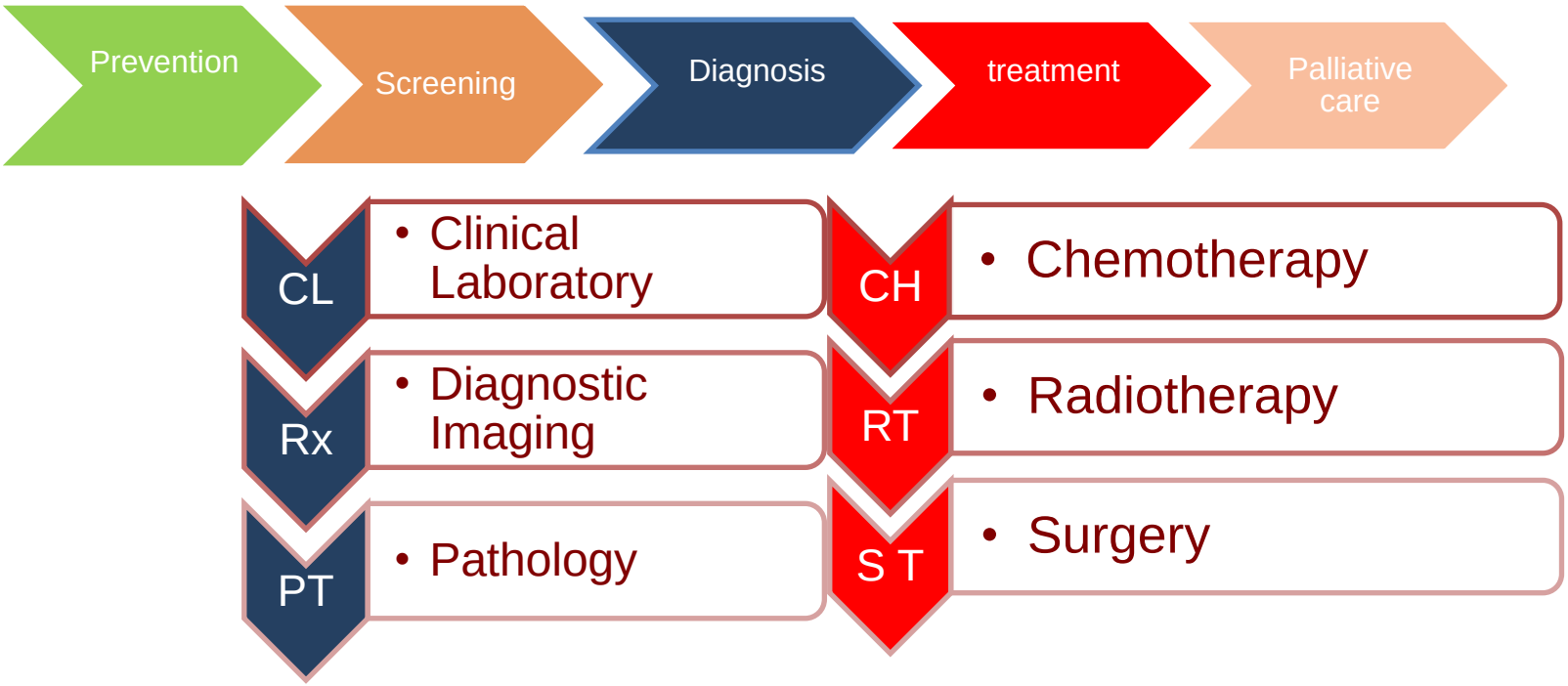


WHO Priority Medical Devices to Diagnose, Treat and Manage Cancer

- "To define a comprehensive tool to guide policy makers and health care mangers in the selection of medical devices for achieving the most appropriate cancer management"

- Cancers targeted: Cervical, breast, prostate, lung, colorectal and leukemia – over the continuum of care

Medical Devices - Continuum of cancer care



WHO Medical Devices for Cancer

- In person meetings of the Steering Group in April and Sept 2015 at WHO
- 60 medical experts from 28 countries and 6 continents, formed workgroups for each area
- Reference book almost complete
- Manuscript describing methodology planned
- First in-country workshop in Sri Lanka

Summary

- Managing chemotherapy needs is complex because of the number of drugs and variation in utilization rates, for the many cancers
- Understanding the number of patients with each disease who you see, and the agreed upon regimens used for those patients can allow you to predict annual volume needs for each drug
- Stock-outs of essential medicines result in sub-optimal therapy being administered, with significant reduction in cure rates, and needless loss of life (ABVD for Hodgkin, R-CHOP for large B-cell lymphoma, etc)
- None of this work is valuable unless it informs countries and ministries and results in improved access to high-quality cancer care for citizens of their countries –

A special thanks to……..

- *UICC and Julie Torode*
- *WHO and Nicola Magrini Magrini and Adriana Velazquez Berumen, and many others*
- *Botswana team – Yehoda Martei, Neo Tapela, Surbhi Grover, Chiyapo Sebathu*