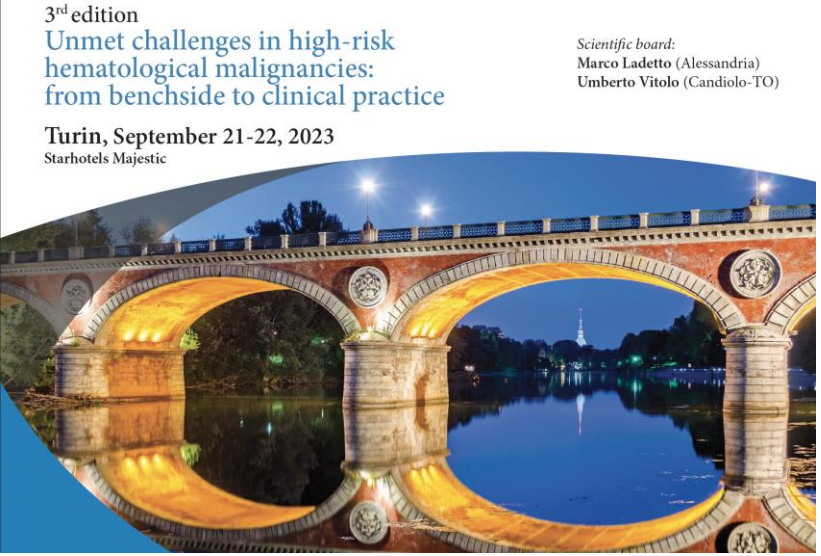

Wordwide disparity of access to clinical trials and novel treatments in clinical practice

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Disclosures

Scientific Advisory Board: AbbVie, Astra Zeneca, BeiGene, Incyte, Janssen, Lilly

Consultant: Bayer

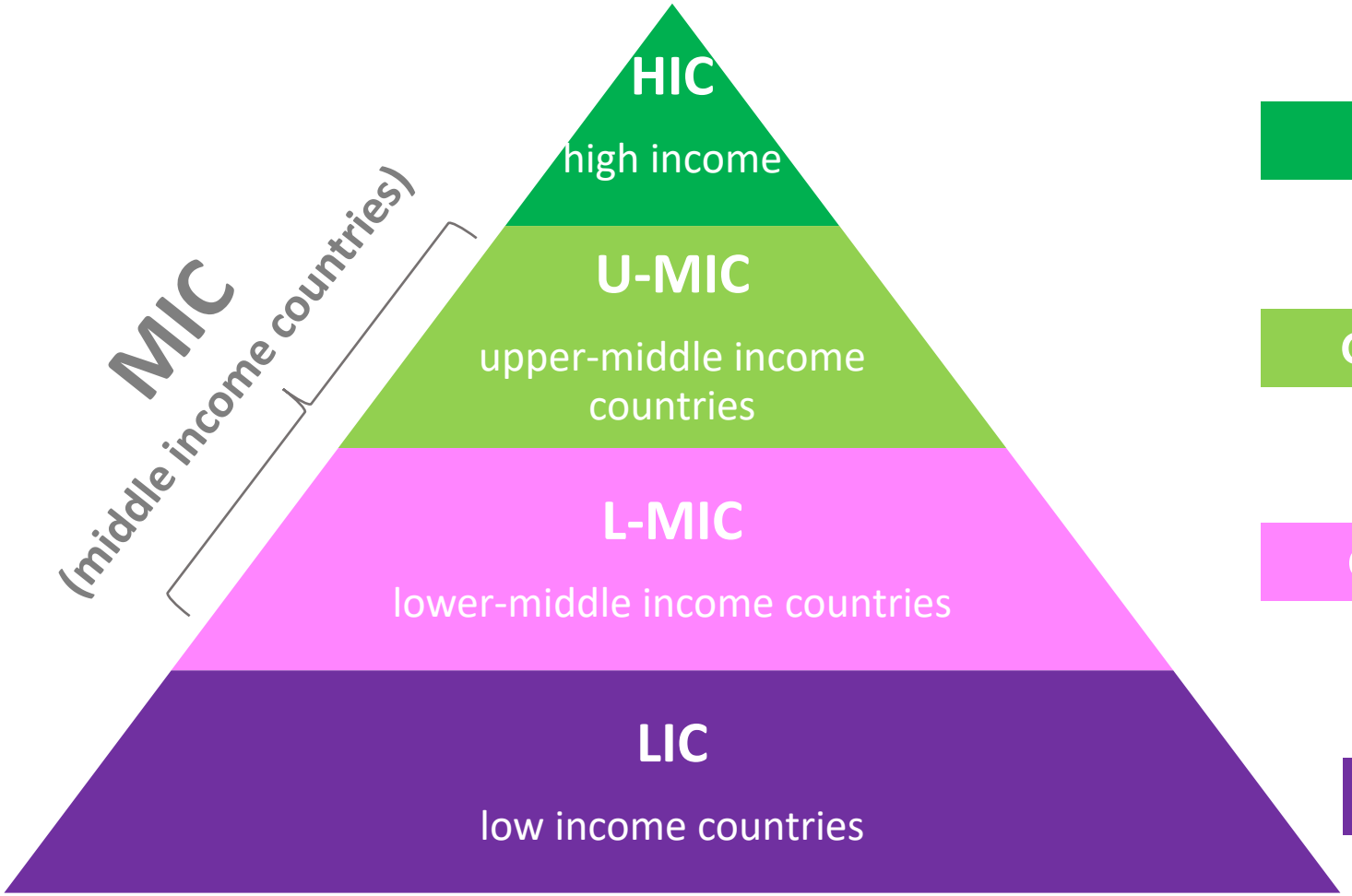
Speakers Bureau: Abbvie, Astra Zeneca, Janssen

Outline

- **Cancer trends in HICs, MICs and LICs**
- Health system models and obstacles to cancer treatment in HICs, MICs and LICs
- Globalization of clinical trials for cancer patients
- Benefit sharing as a goal

World Bank Group country classification by income (FY2024)

The World Bank Group assigns the world's economies to four income groups – low, lower-middle, upper-middle, and high. The classifications are updated each year on July 1, based on the ***GNI (Gross National Income) per capita*** of the previous calendar year.



GNI per capita > $13485

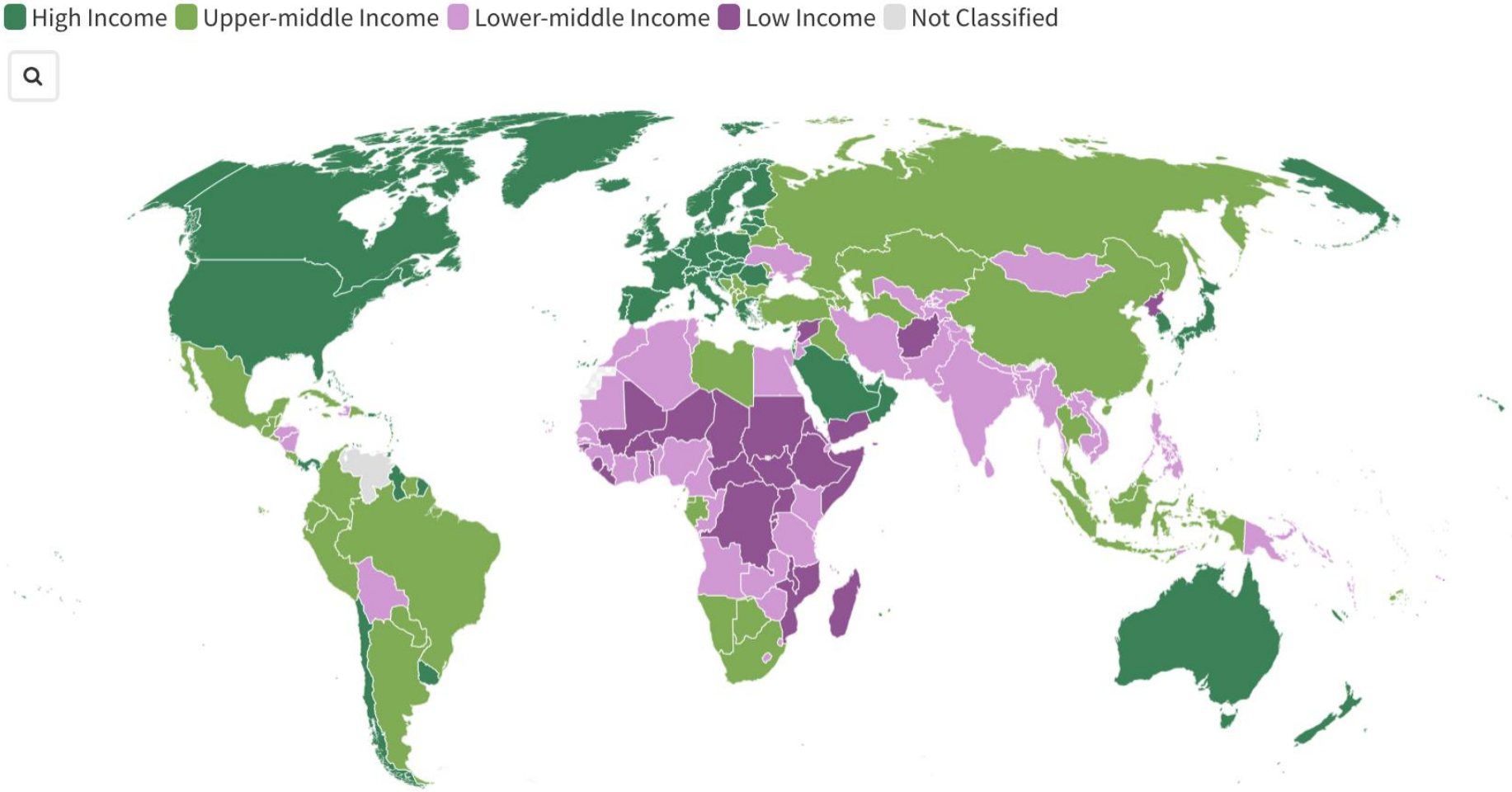
GNI per capita $4466-13485

GNI per capita $1136-4465

GNI per capita ≤ $1135

https://blogs.worldbank.org/opendata/

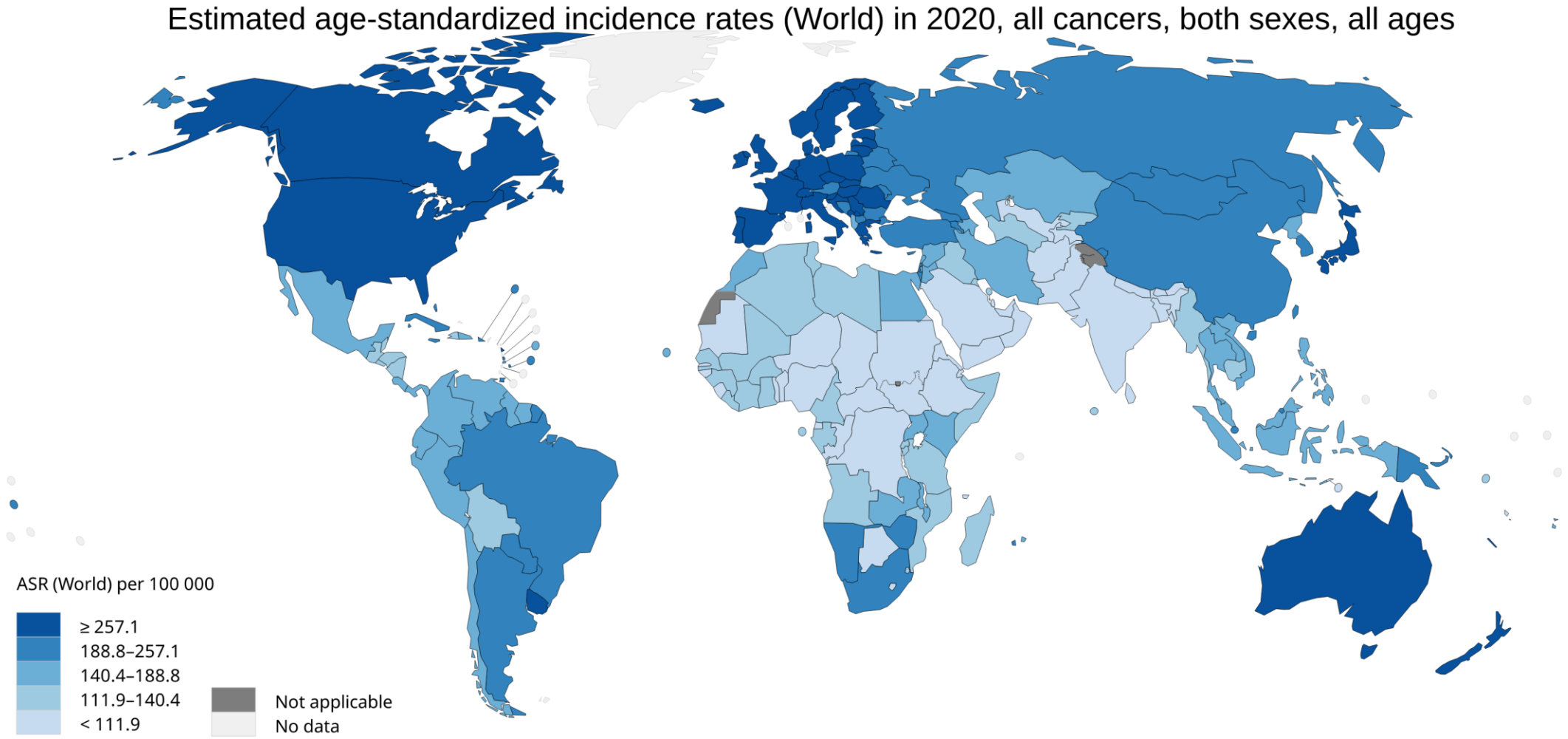
Geography of HICs, U-MICs, L-MICs and LICs according to the World Bank Group



Source: World Bank Income Classifications FY24 • The boundaries, colors, denominations and any other information shown on this map do not imply, on the part of the World Bank Group, any judgment on the legal status of any territory, or any endorsement or acceptance of such boundaries.

https://www.worldbank.org/en/home

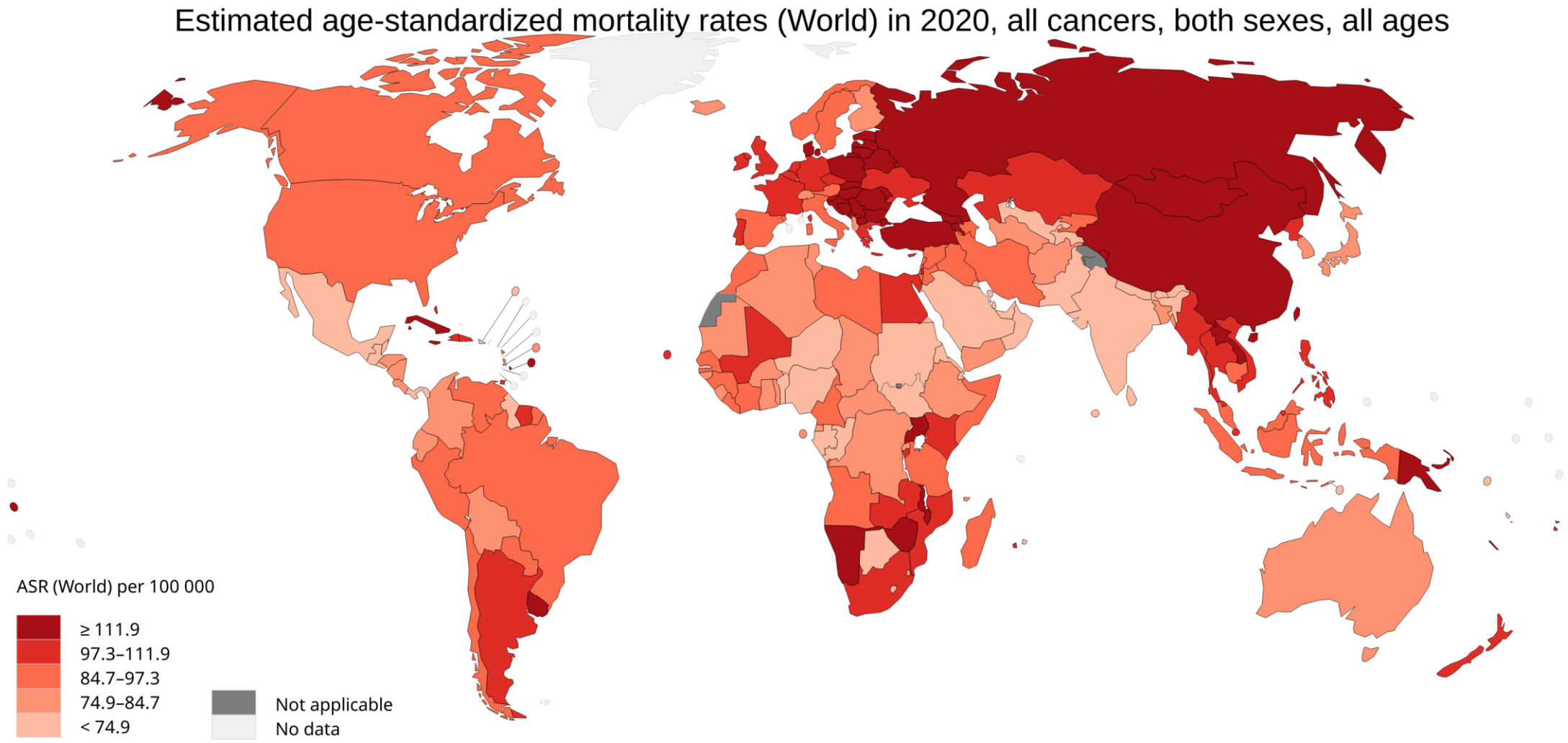
GLOBOCAN cancer incidence in 2020: Geographic distribution



High-income countries (HICs) have a higher cancer incidence rate compared to low- and middle-income countries (LMICS)

IARC, GLOBOCAN 2020; The World Bank (fiscal year 2020)

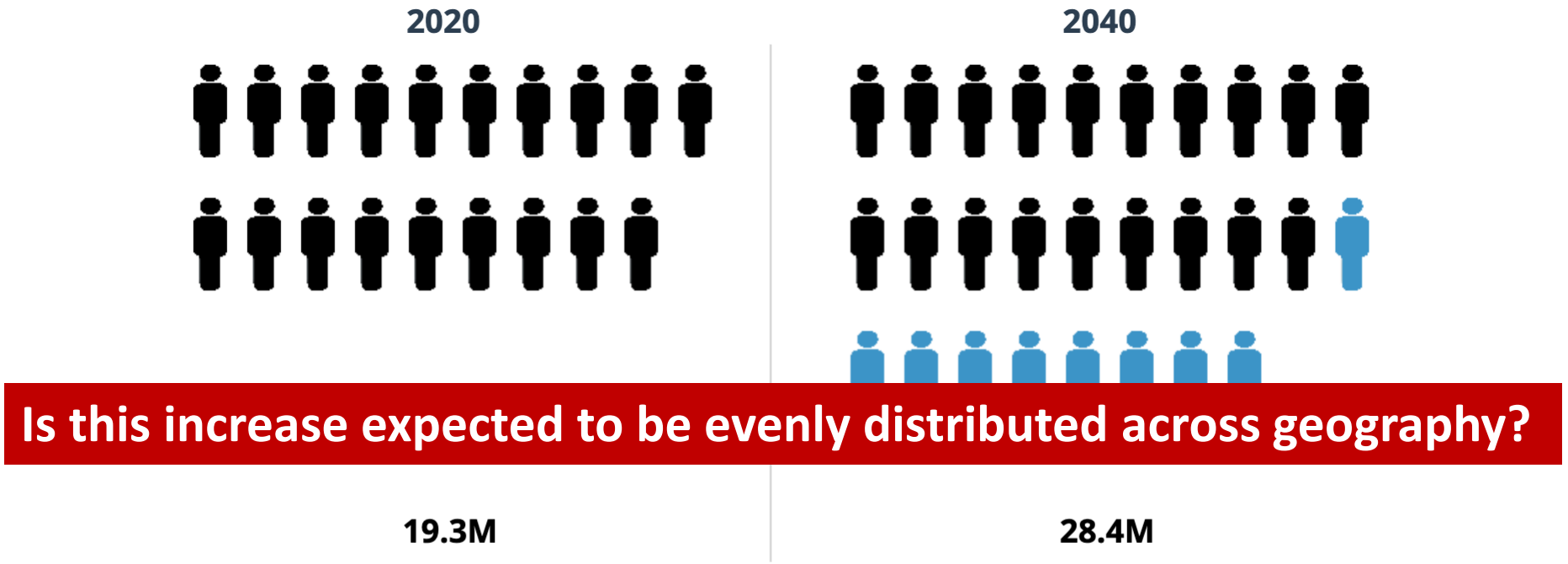
GLOBOCAN cancer mortality in 2020: Geographic distribution



72.4% (7.2/9.95 millions) of cancer deaths occurred in LMICs

IARC, GLOBOCAN 2020

GLOBOCAN cancer estimates for 2040: New cancer cases



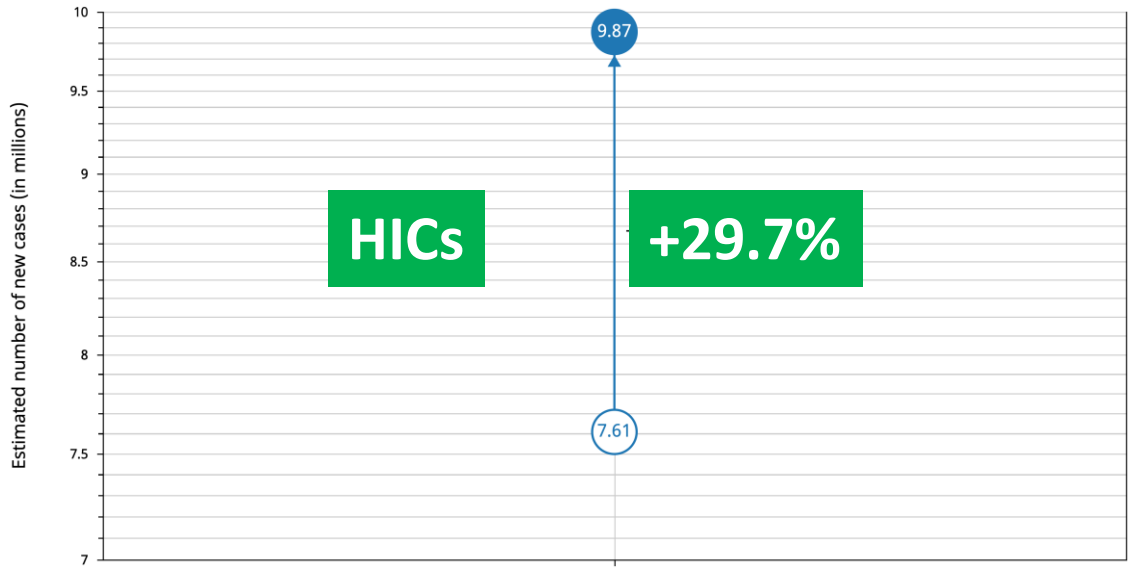
Is this increase expected to be evenly distributed across geography?

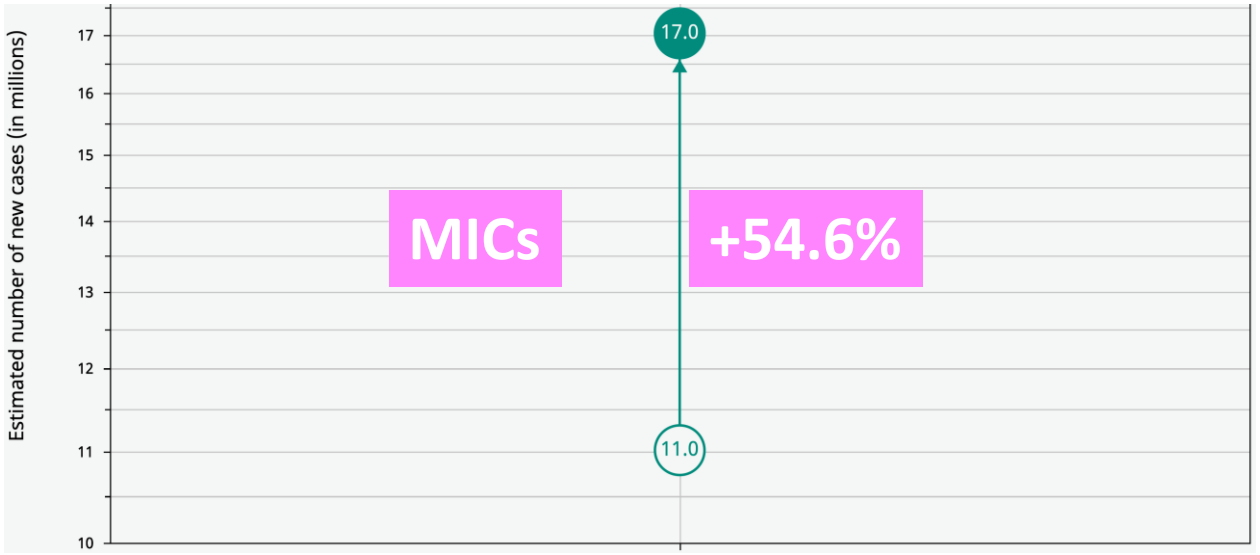
= 1 000 000 Demographic changes

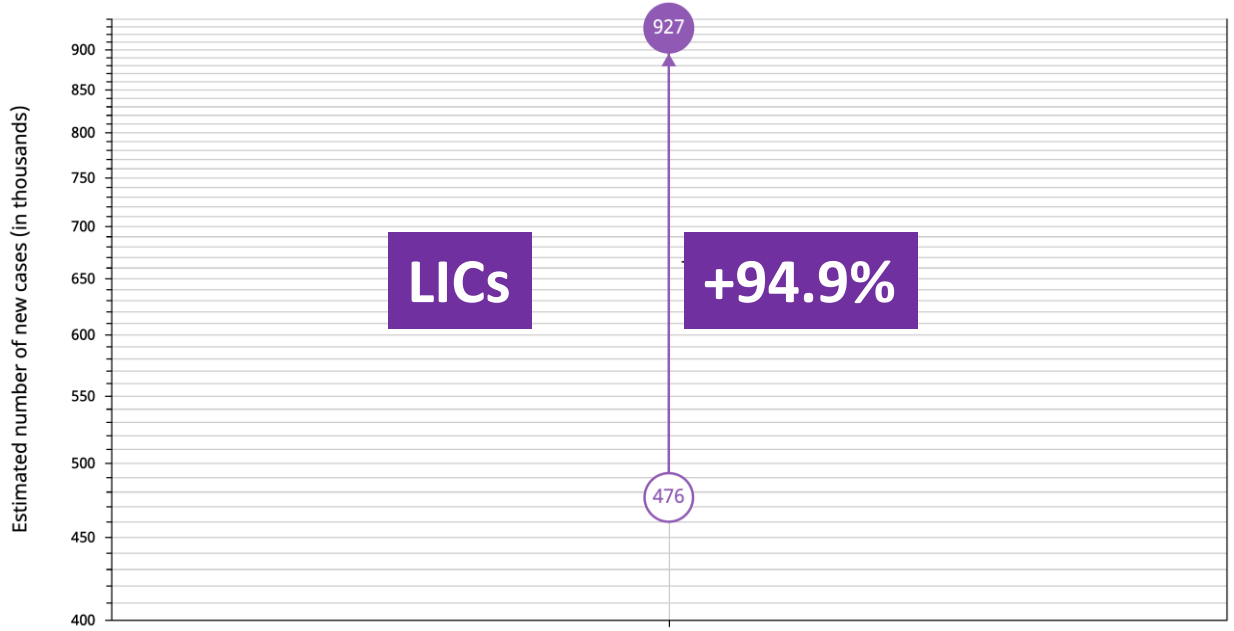
Cancer global incidence is expected to rise by 47.2% between 2020 and 2040

IARC, GLOBOCAN 2020

GLOBOCAN: Estimated increase of new cancer cases from 2020 to 2040 in HICs, MICs and LICs

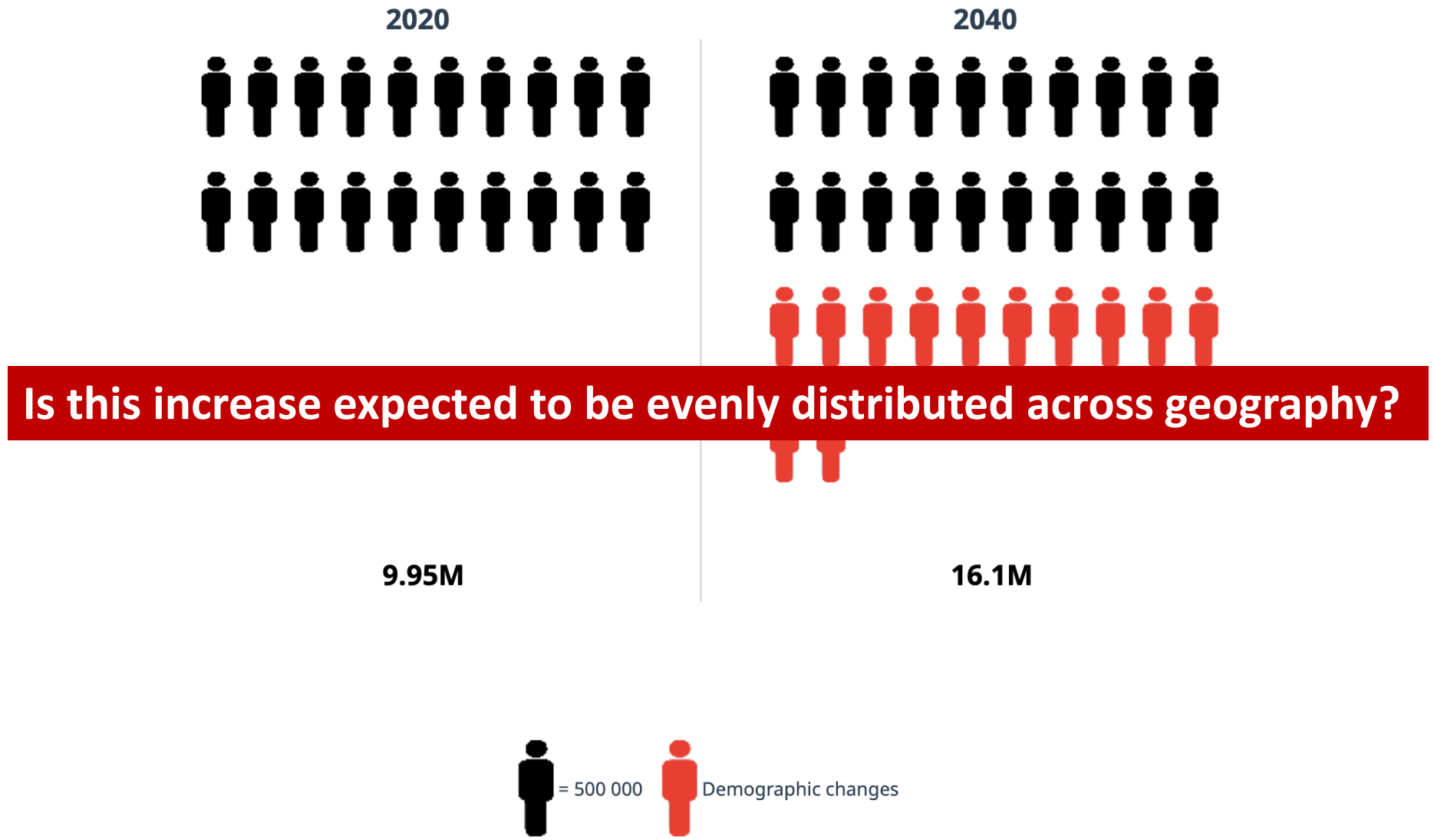






IARC, GLOBOCAN 2020

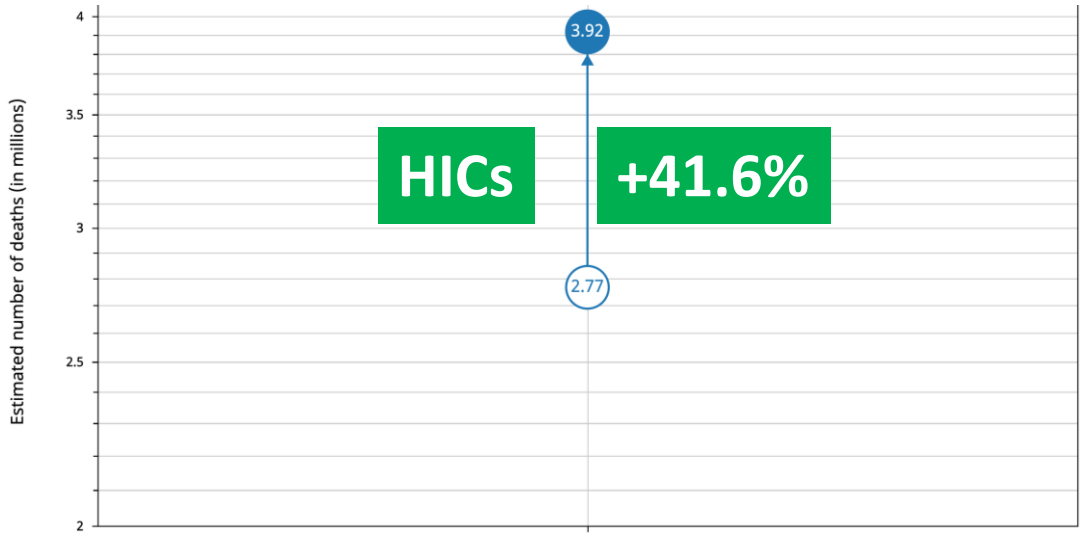
GLOBOCAN cancer estimates for 2040: Cancer deaths

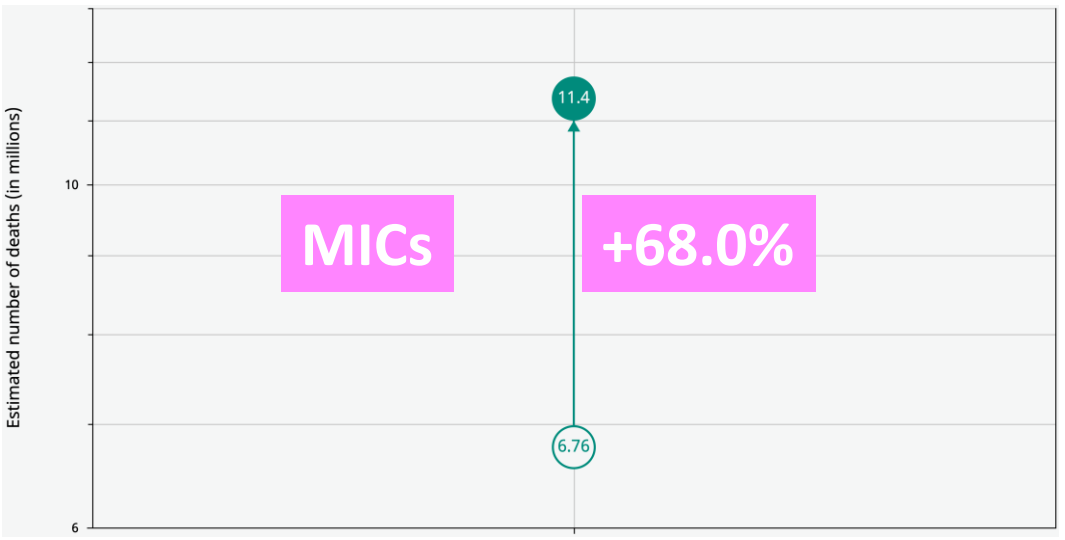


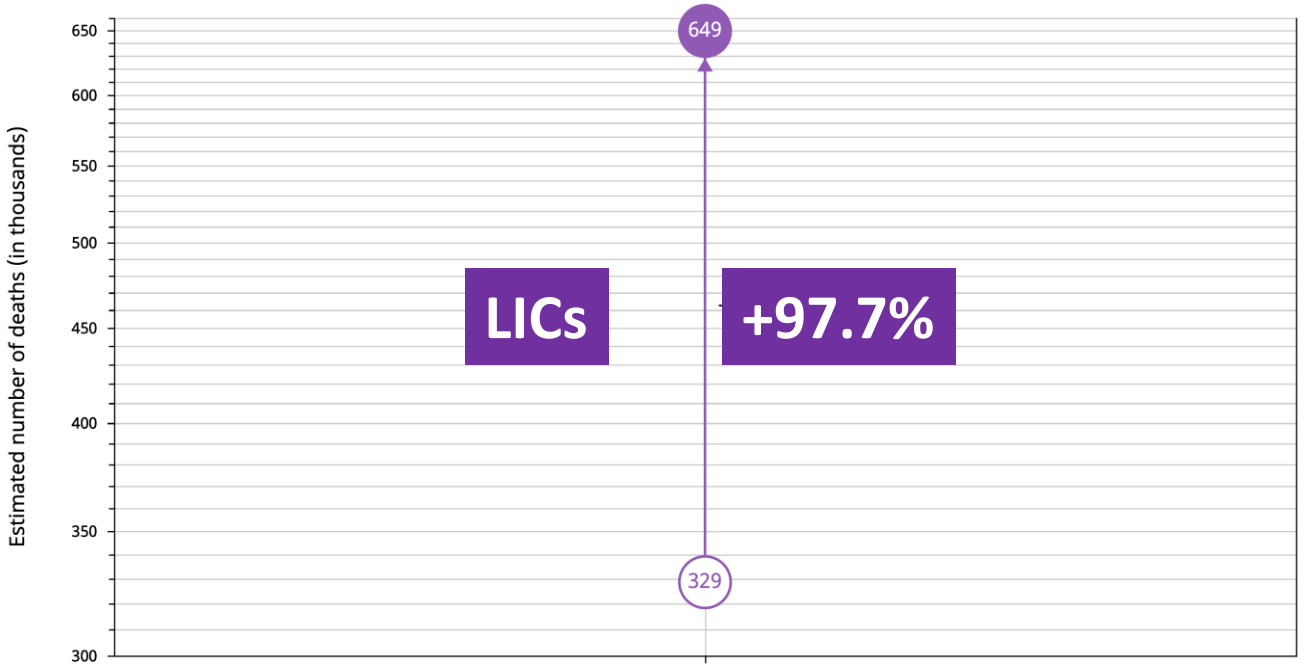
A 61.8% increase of cancer global mortality is expected between 2020 and 2040

IARC, GLOBOCAN 2020

GLOBOCAN: Estimated increase of cancer deaths from 2020 to 2040 in HICs, MICs and LICs





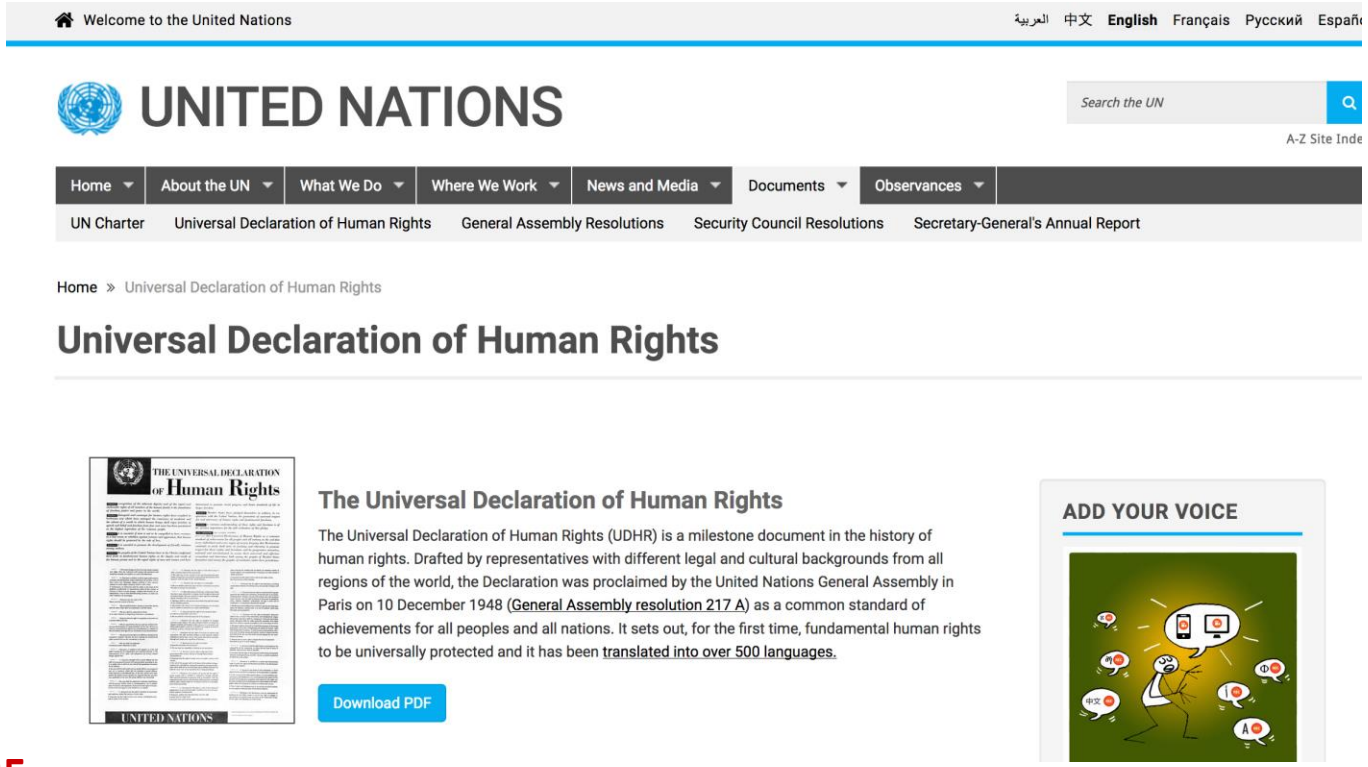


IARC, GLOBOCAN 2020

Outline

- Cancer trends in high (HICs), middle (MICs) and low (LICs) income countries
- **Health system models and obstacles to cancer treatment in HICs, MICs and LICs**
- Globalization of clinical trials for cancer patients
- Benefit sharing as a goal

Universal Declaration of Human Rights (Paris, 1948)

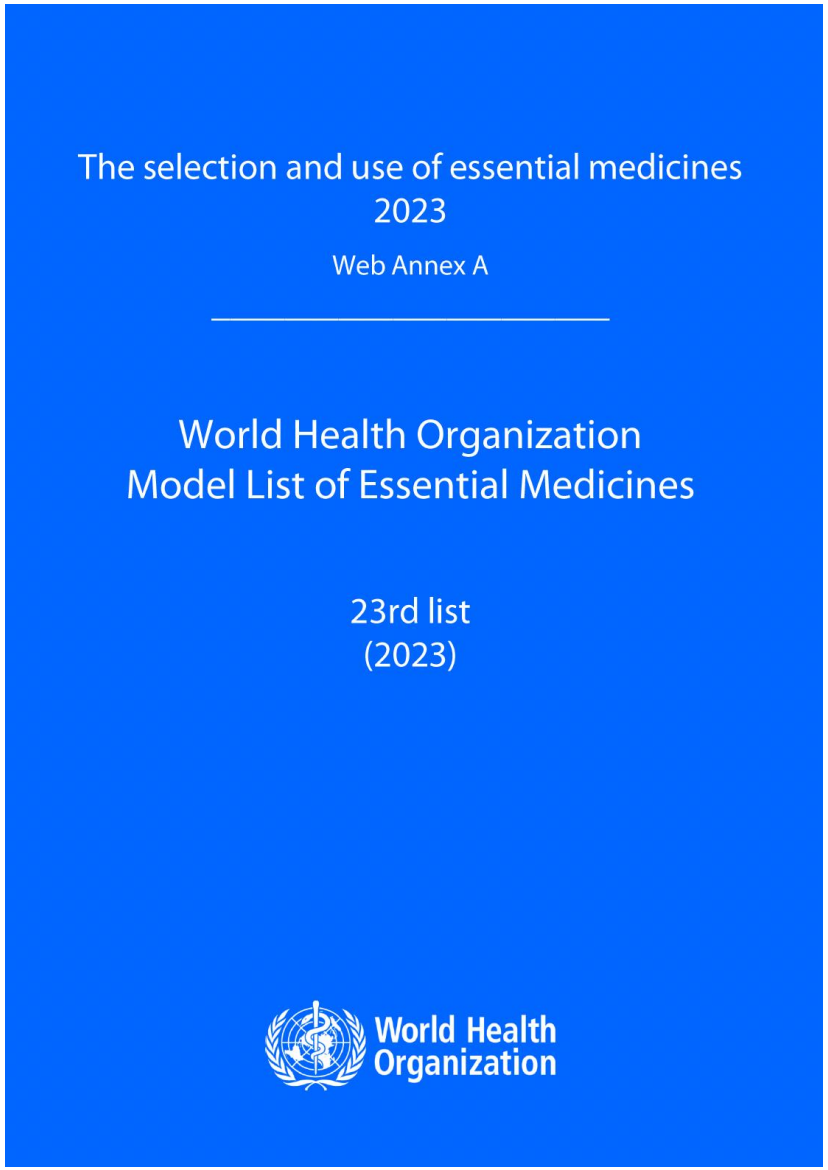



Eleanor Roosevelt holding a poster of the UDHR

Article 25.

(1) **Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including** food, clothing, housing and **medical care** and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control.
(2) Motherhood and childhood are entitled to special care and assistance. All children, whether born in or out of wedlock, shall enjoy the same social protection.

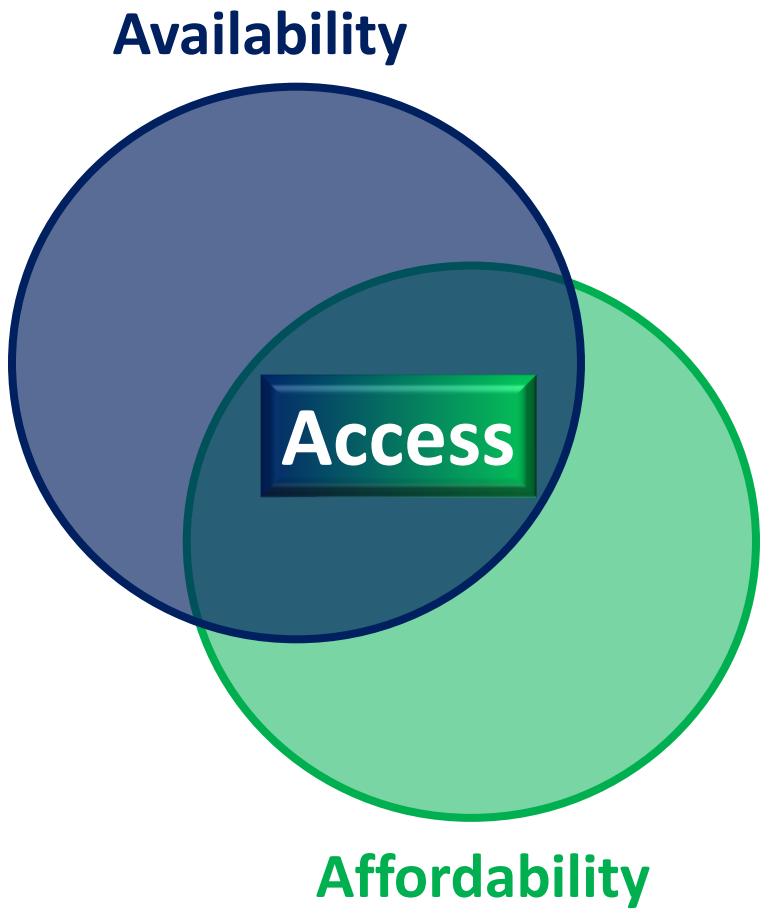
WHO Essential Medicines List (2023): Definition



- Essential medicines are those that satisfy the **priority health care needs of a population**.
- They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness.
- They are **intended to be available in functioning health systems at all times**, in appropriate dosage forms, of assured quality and **at prices individuals and health systems can afford**.

https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

WHO framework for access to essential medicines



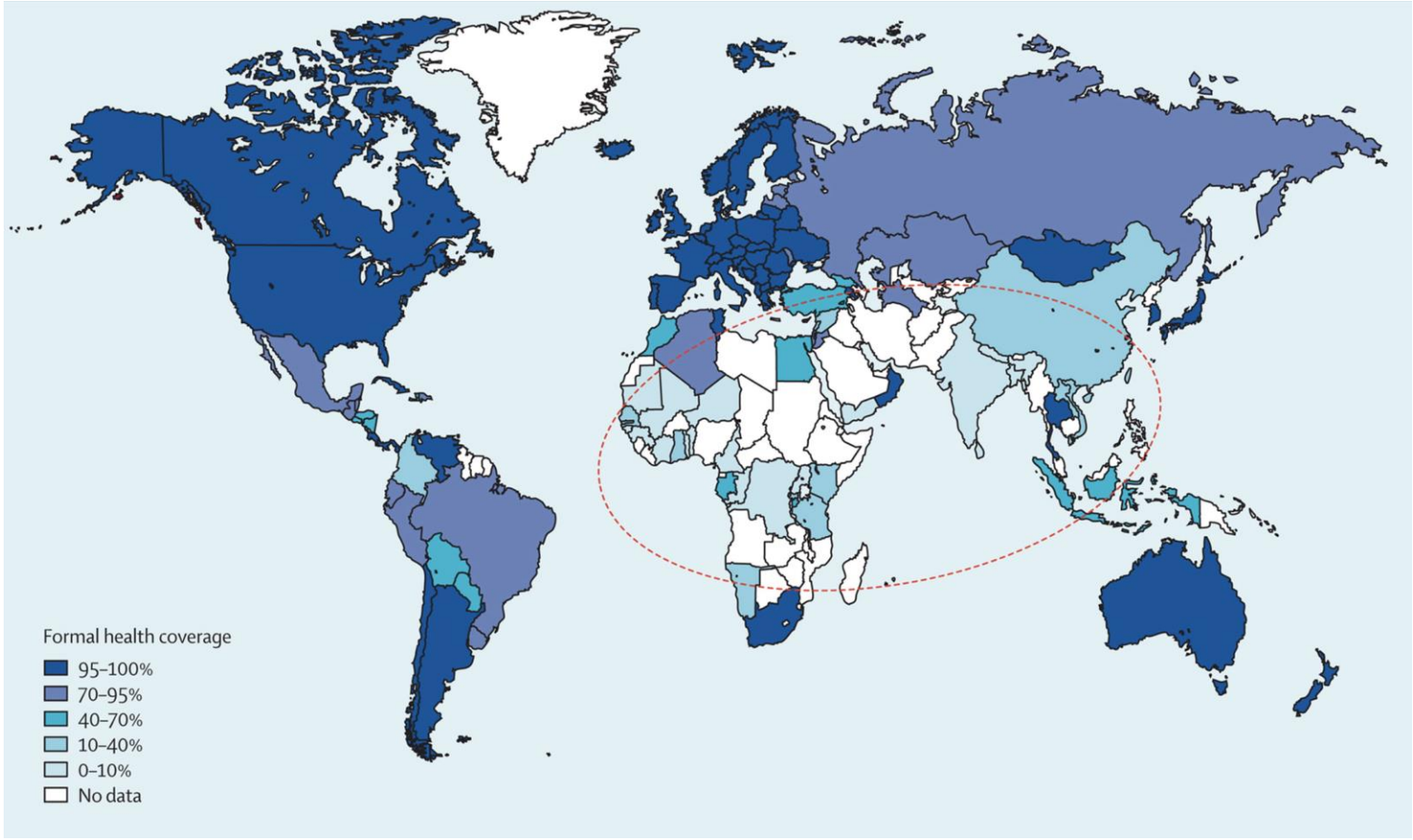
WHO Essential Medicines List (2023): Targeted therapies

WHO Model List of Essential Medicines – 23rd List (2023)

8.2.2 Targeted therapies	
Complementary List	
all-trans retinoid acid (ATRA)	***Capsule:*** *10 mg.* *– Acute promyelocytic leukaemia.*
bortezomib	***Powder for injection:*** *3.5 mg in vial.* *– Multiple myeloma*
dasatinib	***Tablet:*** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.* *– Imatinib-resistant chronic myeloid leukaemia*
☐ *erlotinib* *Therapeutic alternatives:* *- afatinib* *- gefitinib*	***Tablet:*** *100 mg, 150 mg.* *– EGFR mutation-positive advanced non-small cell lung cancer*
everolimus	***Tablet:*** *2.5 mg; 5 mg; 7.5 mg; 10 mg.* ***Tablet (dispersible):*** *2 mg; 3 mg; 5 mg.* *– Subependymal giant cell astrocytoma*
ibrutinib	***Capsule:*** *140 mg.* *– Relapsed/refractory chronic lymphocytic leukaemia*
imatinib	***Solid oral dosage form:*** *100 mg; 400 mg.* *– Chronic myeloid leukaemia* *– Gastrointestinal stromal tumour* *– Philadelphia chromosome positive acute lymphoblastic leukaemia*
nilotinib	***Capsule:*** *150 mg; 200 mg.* *– Imatinib-resistant chronic myeloid leukaemia*
*rituximab** **including quality-assured biosimilars*	***Injection (intravenous):*** *100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.* *– Burkitt lymphoma* *– Diffuse large B-cell lymphoma* *– Chronic lymphocytic leukaemia* *– Follicular lymphoma*
*trastuzumab** **including quality-assured biosimilars*	***Powder for injection:*** *60 mg; 150 mg; 440 mg in vial.* *– Early stage HER2-positive breast cancer* *– Metastatic HER2-positive breast cancer*

https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

Universal health coverage vs Out of the Pocket health



- For many people living in low-income countries, health services are obtained through **out-of-pocket expenditures**. Globally, such costs account for 19% of expenditure on health
- For many **LMICs**, out-of-pocket expenditures account for **more than 50% of the total health expenditures**

Garrett et al, Lancet 2009

The cost of innovative and life-saving drugs for hematologic neoplasia may be unsustainable for LMICs

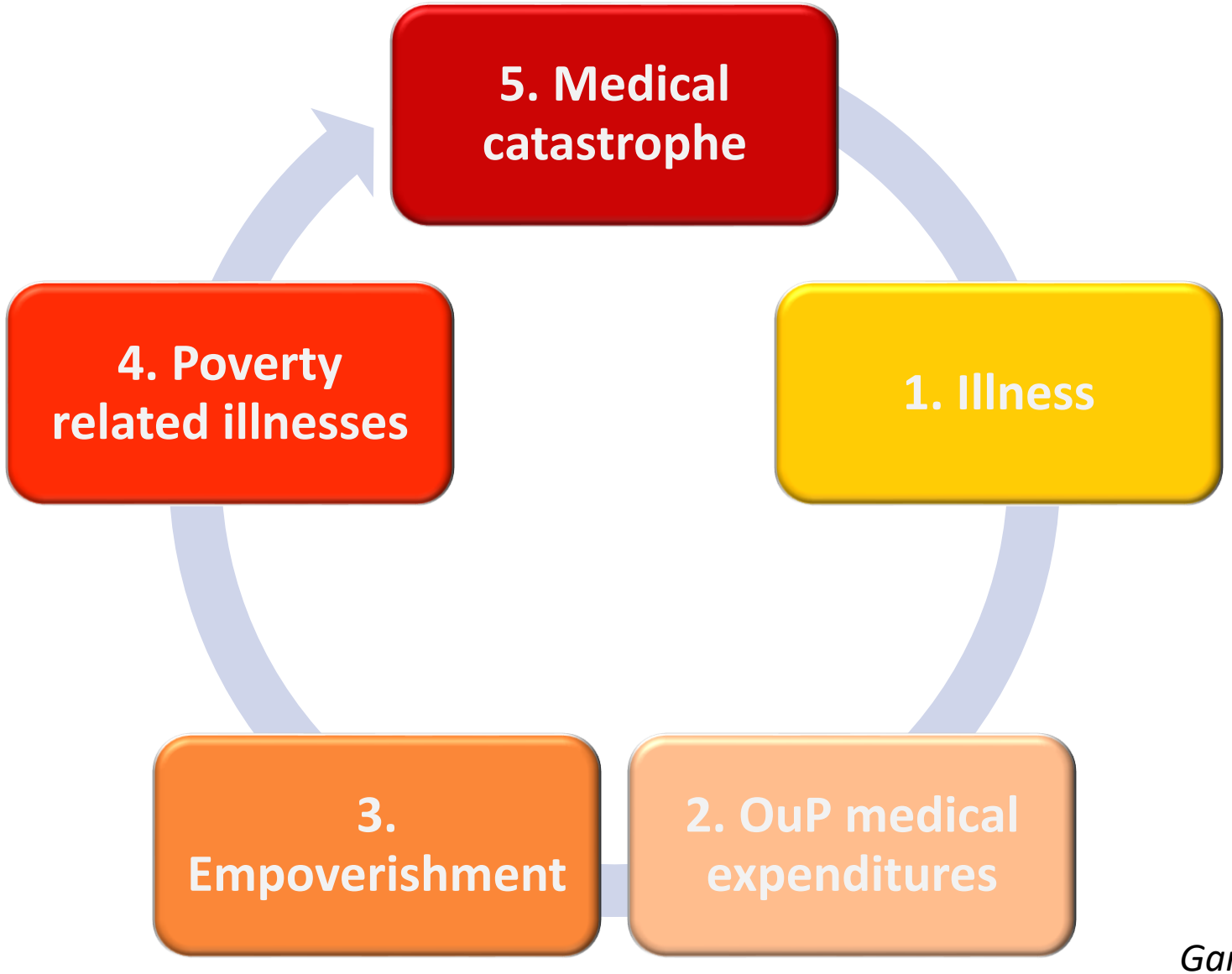
Imatinib treatment for chronic myeloid leukemia in South Africa:

- 40000 USD/year
- **139·3 fold the yearly per capita government expenditure rate** on health ($308·7 in 2012)
- 5·9 fold the GNI per capita ($7190 in 2013)

- In a high income country (eg: Italy), the cost for the same treatment is 10x less compared to per capita government expenditure rate and GNI

Experts in Chronic Myeloid Leukemia, Blood 2013; Ravinetto et al, Lancet Hematol 2014

Vicious cycle of Out of the Pocket (OuP) health systems



Garrett et al, Lancet 2009

Cancer in low and middle income countries (LMICs)

- Current cancer rates are set to rise, especially in low- and middle-income countries (LMICs)[1]
- **Low-income countries** (LICs) suffer from a **generalized lack of access to well established and effective treatment and care**[2]
- In **middle-income countries** (MICs), that are home to 73% of the world's impoverished population[3], cancer **treatment is often only affordable for certain segments of the population**, and good outcomes remain skewed toward those who can pay[2]
- Apart from the high cost per se of innovative drugs globally, access to life-saving, innovative, and costly drugs in MICs may be further reduced by:
  - High poverty rates
  - High out-of-pocket payments for health care
  - Limited health protection coverage

[1]http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf; [2]UNITAID Discussion Paper. Ensuring that essential medicines are also affordable medicines: challenges and options. World Health Organization 2016; [3]Radhakrishnan P. BMJ 2015

A further element of complexity

World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL. CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Ref. RHT/SAV/Alert 3.2017 18 August 2017

Medical Product Alert N° 3/2017

Falsified Avastin (bevacizumab) and Sutent (sunitinib malate) circulating in East Africa

This Medical Product Alert relates to two falsified medicines discovered by the National Drug Authority, Uganda and reported to WHO.

In July 2017 falsified versions of Avastin (bevacizumab) and Sutent (sunitinib malate) were seized by the National Drug Authority, Uganda. Both products were being distributed in the vicinity of various cancer treatment centres in Kampala, Uganda.

The genuine manufacturers of both products have confirmed that they did not manufacture these products.

Details and photographs of both falsified products are shown below:

1: Avastin (Bevacizumab) 400 mg

Product Name	Avastin
Batch Number	NC 1060
Expiry Date	02 - 2019
Stated Active Pharmaceutical ingredient	Bevacizumab
Stated Manufacturer	Astrazeneca/AstraZenaca

Avastin is the trade name of a medicine manufactured by Roche/Genentech for the treatment of various cancers. It is not manufactured by AstraZeneca as stated on the falsified versions.

This falsified version of Avastin is being presented in plastic bottles containing blue/grey tablets. The genuine version of Avastin is supplied only as an injection for intravenous use.

Fig 1. Falsified Avastin

Fig 2. Falsified Avastin

High prices and lack of access

drivers of illegal market and falsification

Outline

- Cancer trends in high (HICs), middle (MICs) and low (LICs) income countries
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Which factors are generally considered when deciding to participate in a multicenter clinical trial?

- Investigational product
- Comparator arm
- Study design
- Absence of competitive trials at the site
- Interest of/for the disease
- …

Geography of sites?

Declaration of Helsinki (2013)

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

This principle reaffirmed by all versions of the Declaration reflects the **need for a direct link between obtainment of scientific results and achievement of health benefits in vulnerable groups**

World Medical Association, JAMA, 2013

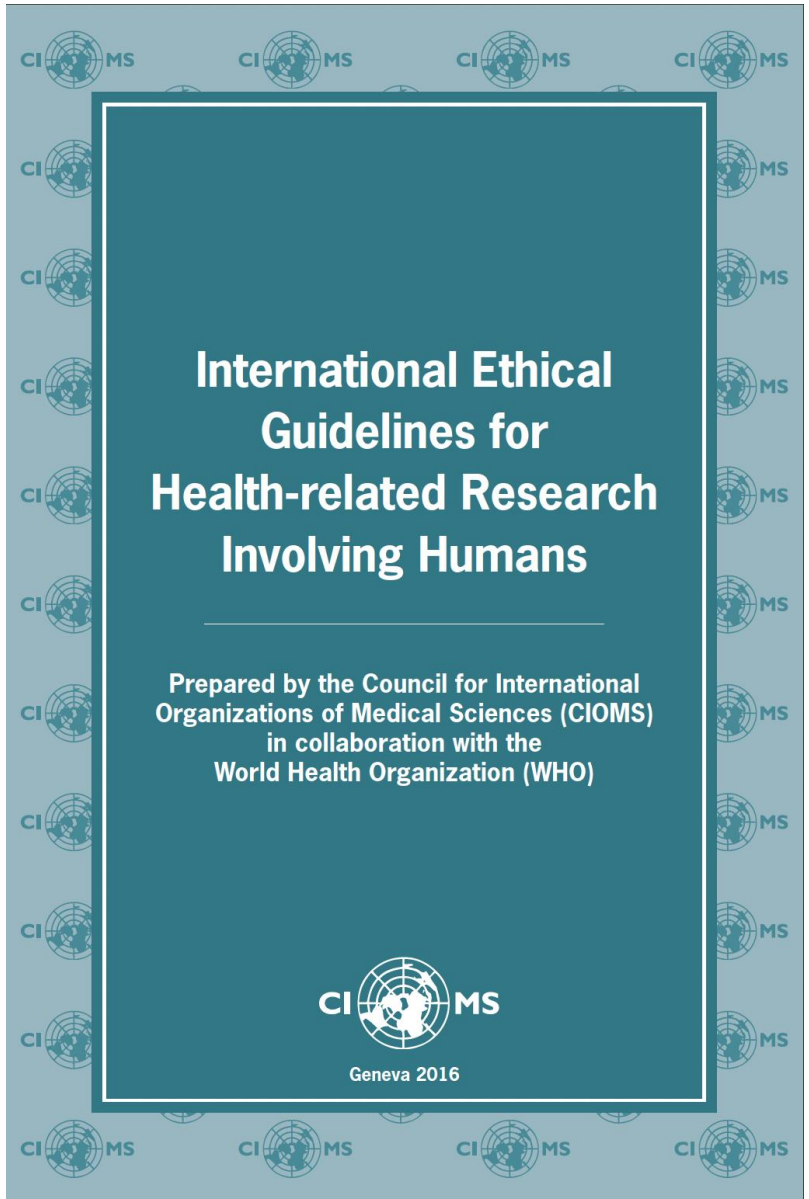
Economical poverty is a criterion for vulnerability in medical research

- the **Belmont Report** includes among vulnerable groups the minorities and the economically disadvantaged.

- In poor countries**, vulnerability** is often linked to poverty, social exclusion and lack of access to health care, and **may drive populations towards participation in clinical trials as a way to secure otherwise unavailable free access to care**

The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979; Pare' Toe et al, PlosONE 2013; Ravinetto et al, Lancet Hematol 2014; Ravinetto et al, Trop Med Int Health, 2015

CIOMS guidelines: implications for research in LMICs (guideline 2)



Before instituting a plan to undertake research in a population or community in low-resource settings, the sponsor, researchers, and relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted.

As part of their obligation, sponsors, and researchers must also:

- **make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity. In some cases, in order to ensure an overall fair distribution of the benefits and burdens of the research, additional benefits such as investments in the local health infrastructure should be provided to the population or community; and**
- **consult with and engage communities in making plans for any intervention or product developed available, including the responsibilities of all relevant stakeholders.**

General considerations. This Guideline pertains to settings in which resources are so limited that the population may be vulnerable to exploitation by sponsors and investigators from wealthier countries and communities. The ethical standards applied should be no less stringent than they

Risk of exploitation of economically vulnerable populations

https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

Hematological neoplasia as a tester for analysing the involvement of MICs in clinical trials

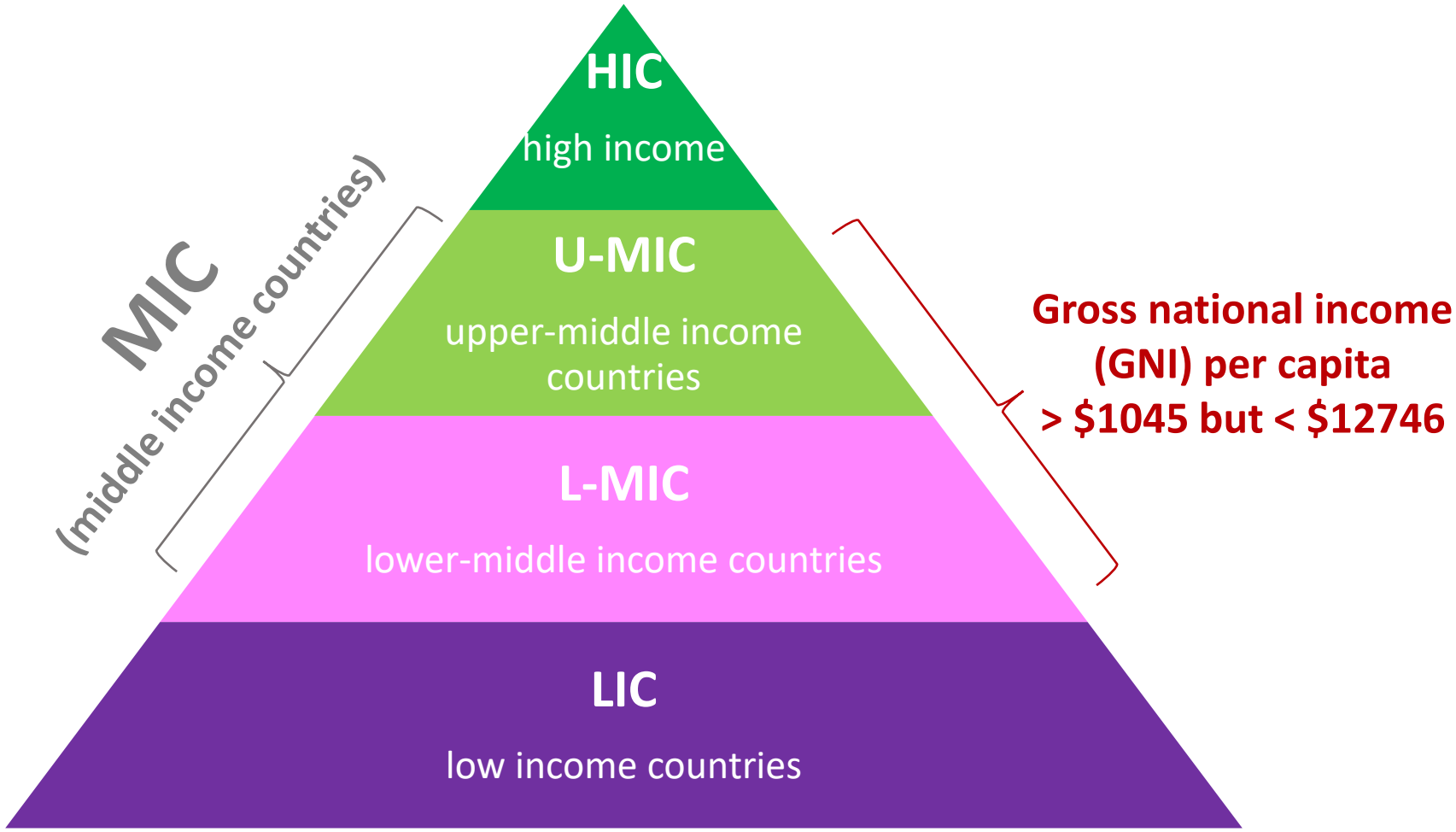
Criteria:

- Non-communicable disease
- Life-saving drugs
- Innovative drugs and costly (small molecules of mAbs)

HEMATOLOGIC NEOPLASIA

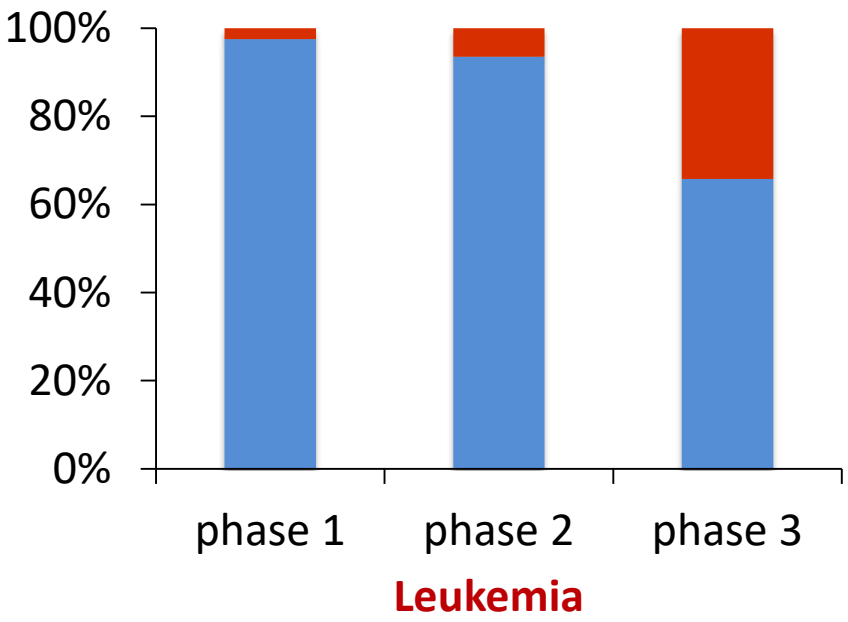
1. Ubiquitous
2. Affects all ages
3. Can be cured or controlled in many patients thanks to innovative drugs

Focus on clinical trials for leukemia, lymphoma and multiple myeloma in MICs

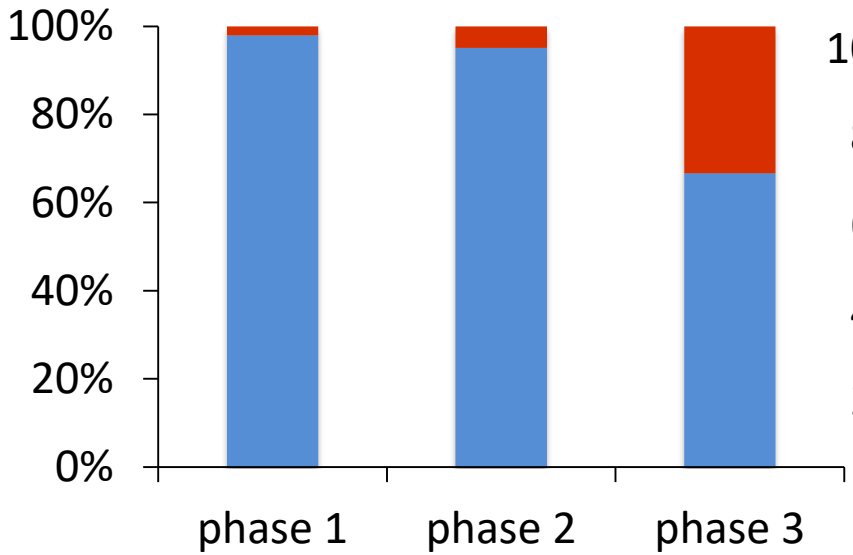


Ravinetto et al, Lancet Hematol, 2014

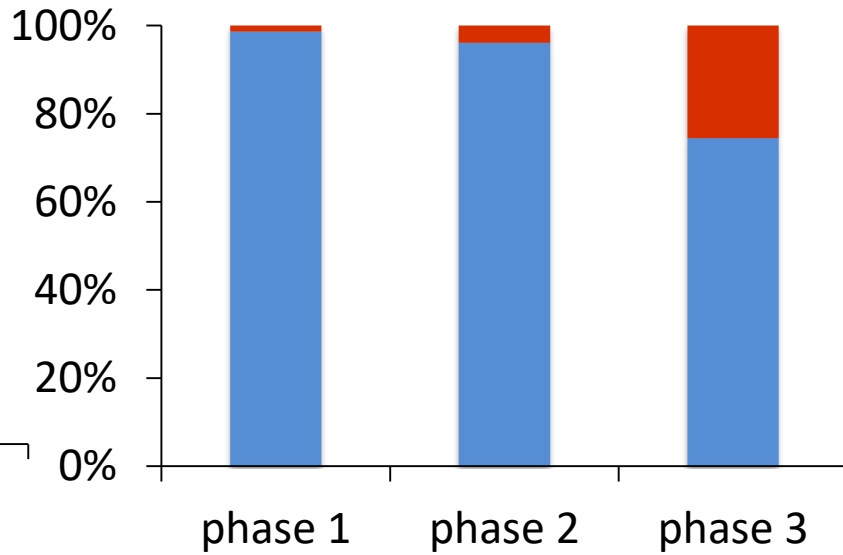
Involvement of MICs in sponsored clinical trials for leukemia, lymphoma and multiple myeloma



Leukemia



Lymphoma

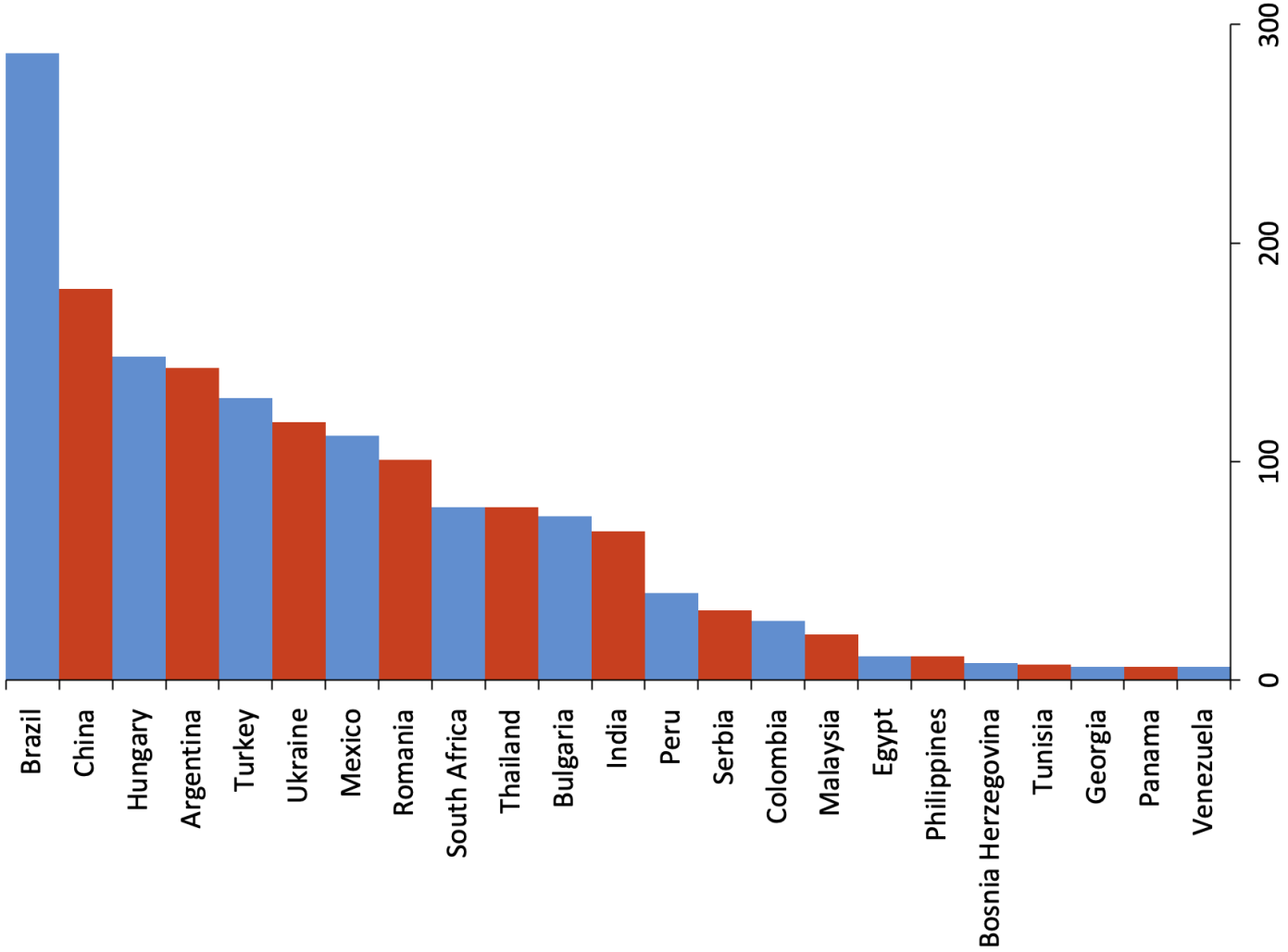


Multiple myeloma

- 30% of phase 3 clinical trials have involved sites in MICs, including both low-middle and upper-middle income countries
- Trials run in MICs targeted all ages, including children or adolescents and the elderly

Ravinetto et al, Lancet Hematol, 2014

MICs with the highest number of sites in industry-sponsored, interventional clinical trials for hematological neoplasms



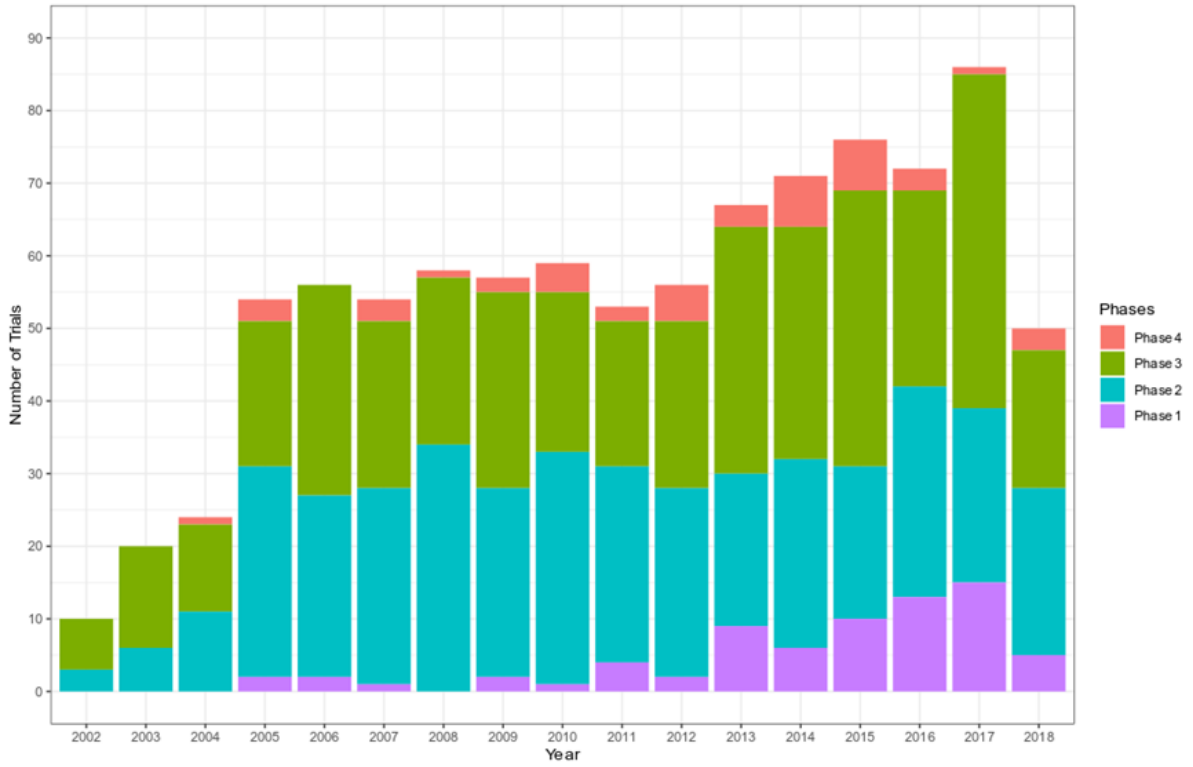
Some phase 3 trials compared drugs close to patent expiration with a second generation compound developed by the same patent holder

Such trials have been conducted in MICs even though the control drug had never been widely accessible, despite its common use for more than a decade in affluent countries

Ravinetto et al, Lancet Hematol, 2014

Global distribution of industry-sponsored breast, lung and colon cancer clinical trials

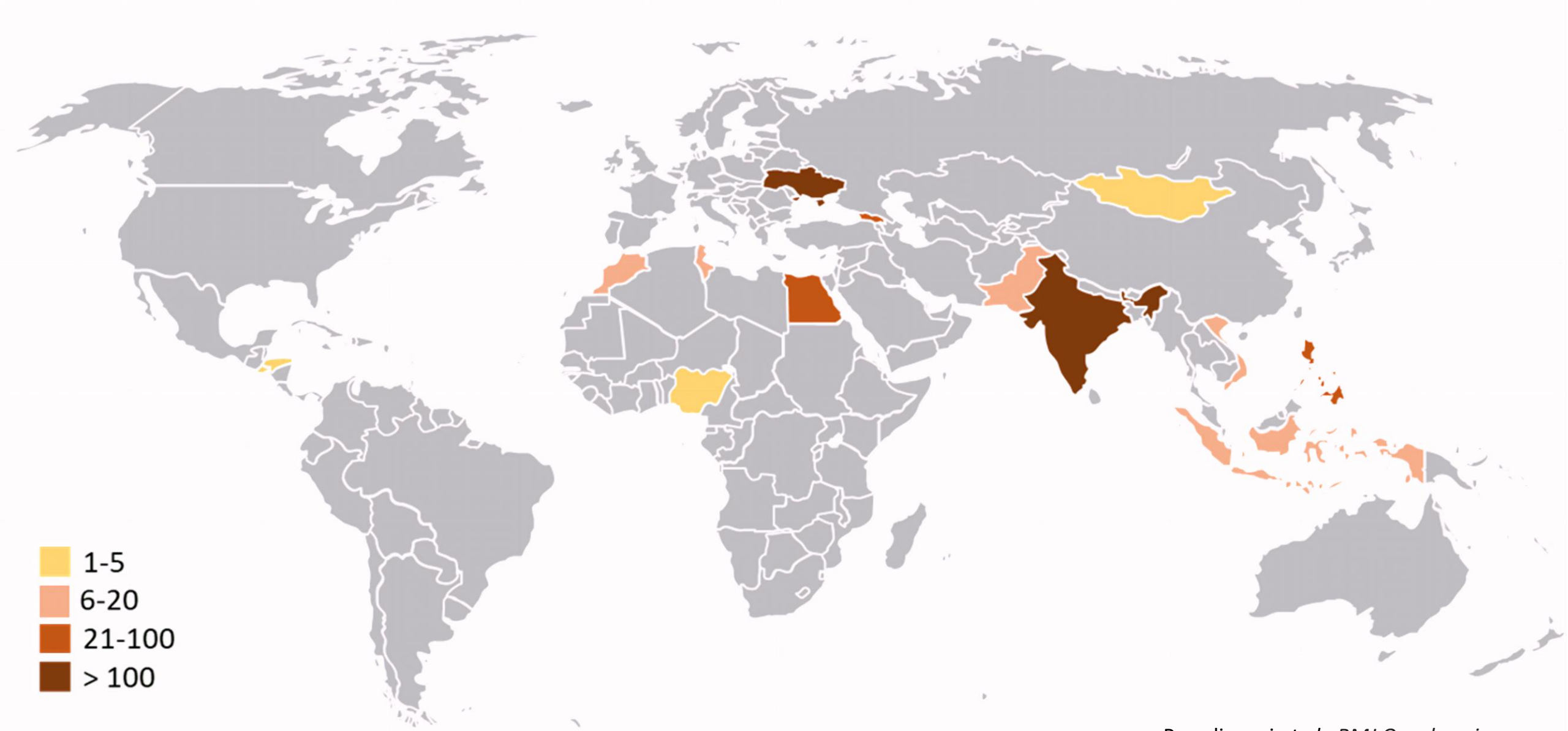
Phases	N. Trials	Involving MICs	%	HICs only	%	p value
I	950	72	7.58%	878	92.42%	<0.001
II	2,450	390	15.92%	2,060	84.08%	<0.001
III	688	416	60.47%	272	39.53%	<0.001
IV	89	45	50.56%	44	49.43%	<0.001
Total	4,177	923	22.10%	3,254	77.90%	



- MICs are significantly involved in phase III and phase IV interventional clinical trials
- No trials were conducted in lower-income countries (LICs) until 2018
- The number of trials in MICs has been constantly rising in the last two decades

Payedimarri *et al.*, *BMJ Oncology in press*

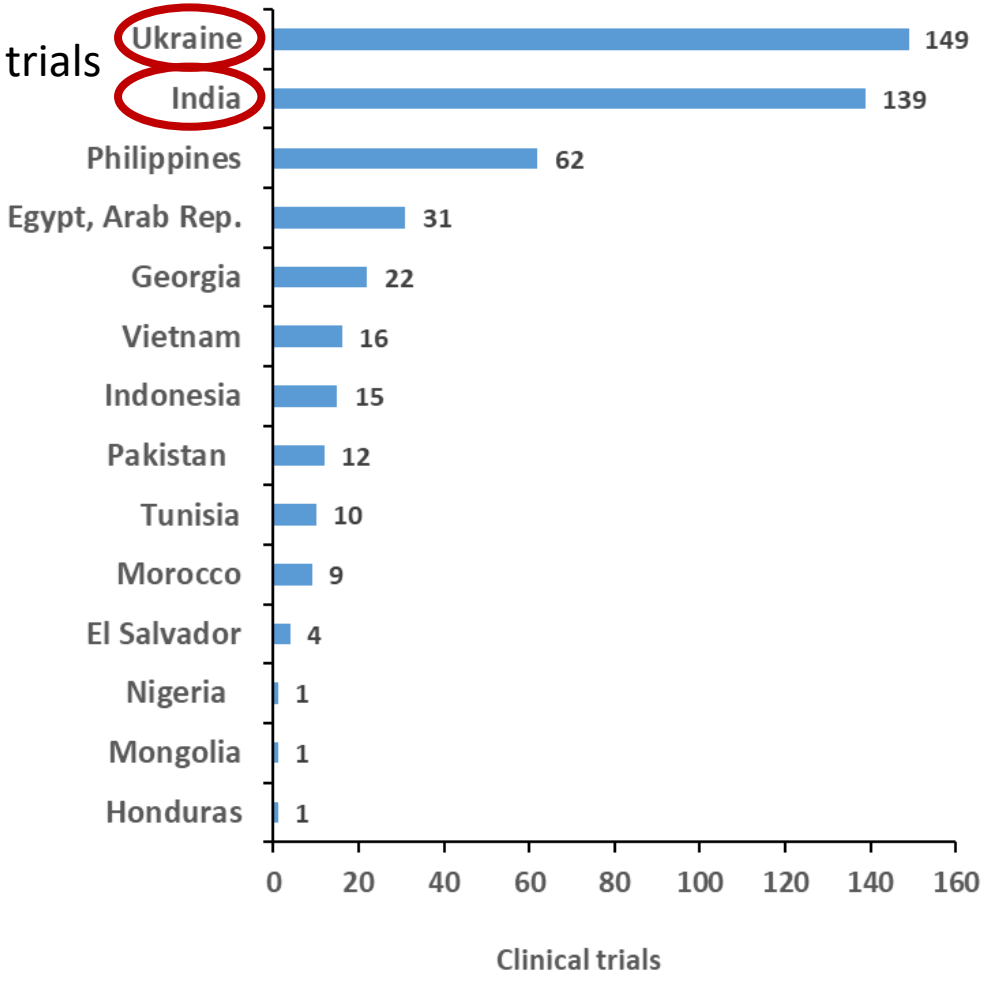
Distribution of industry-sponsored breast, lung and colon cancer clinical trials in L-MICs

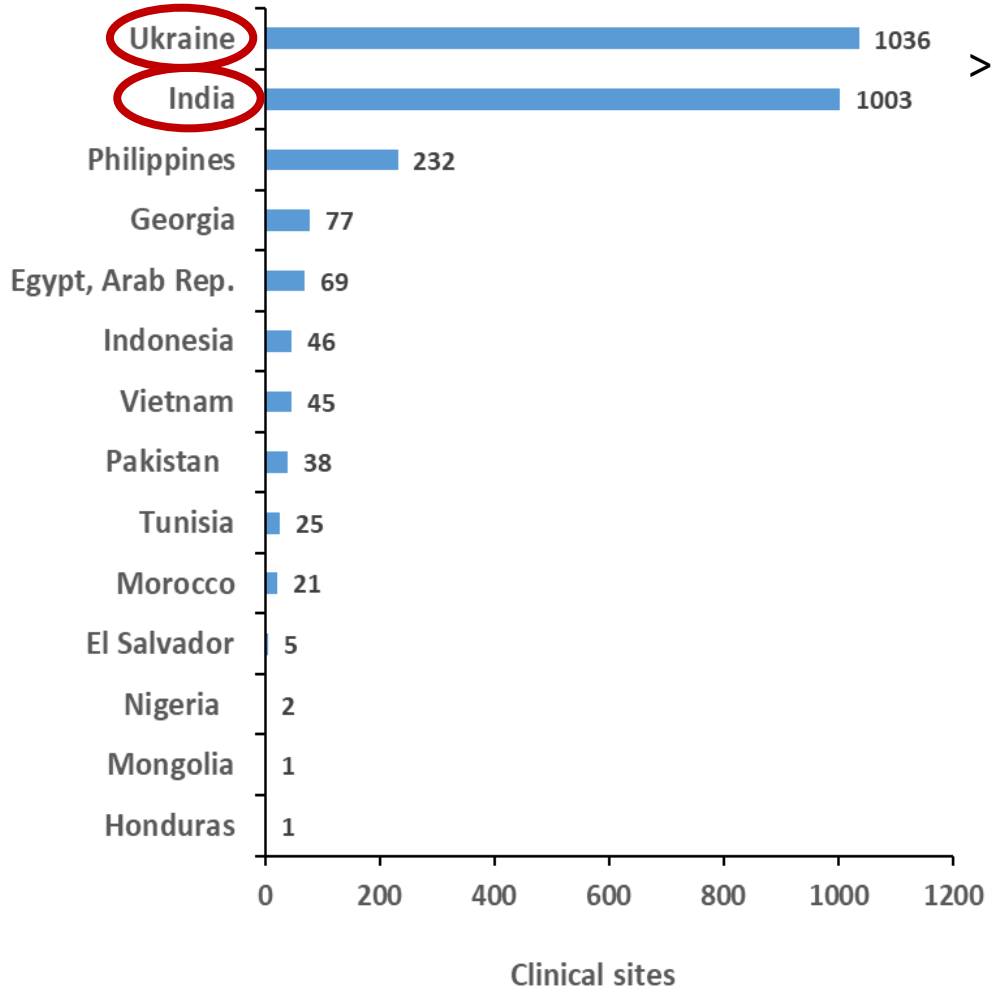


Payedimarri *et al.*, *BMJ Oncology in press*

Distribution of industry-sponsored breast, lung and colon cancer clinical trials in L-MICs

> 100 trials

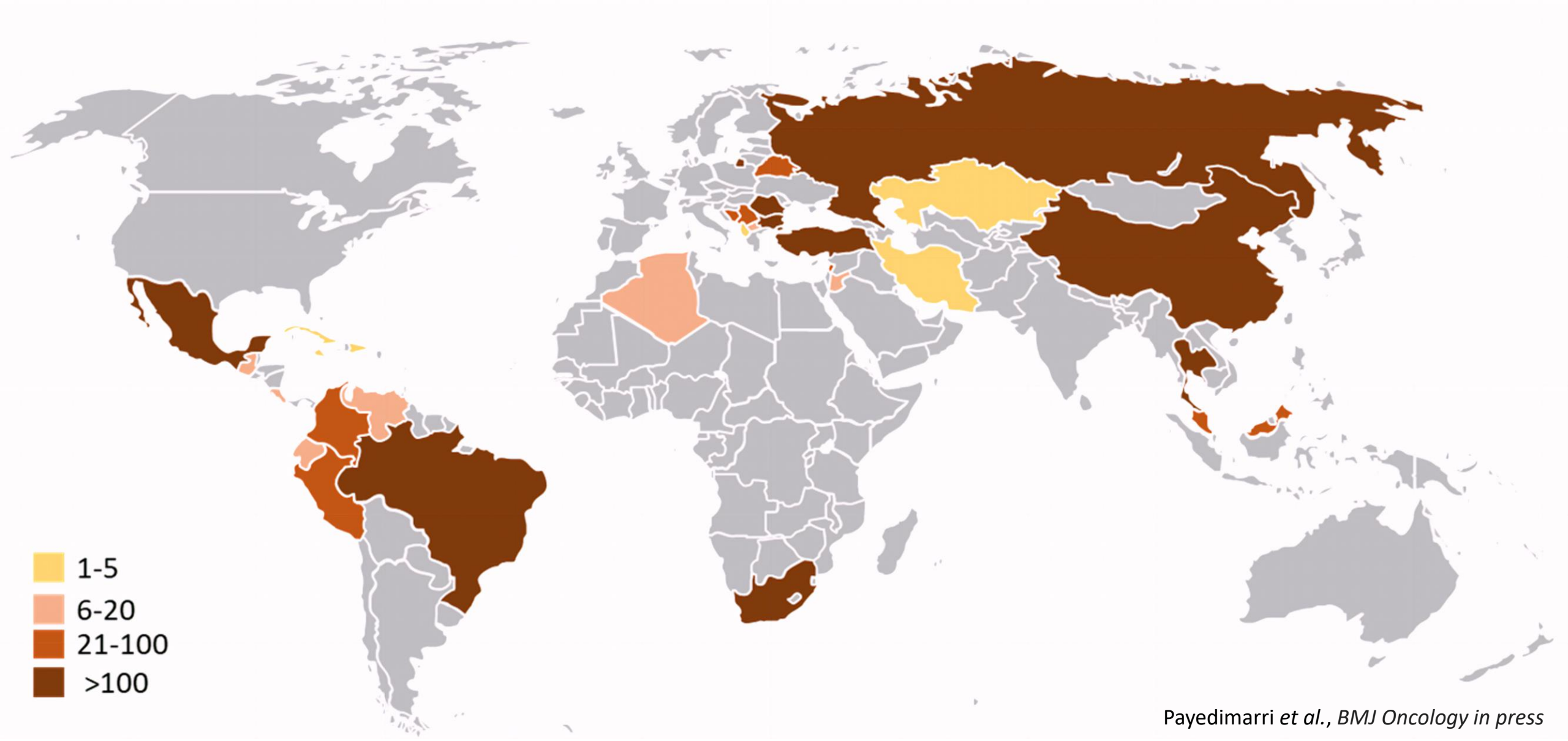




> 1000 sites

Payedimarri *et al.*, *BMJ Oncology in press*

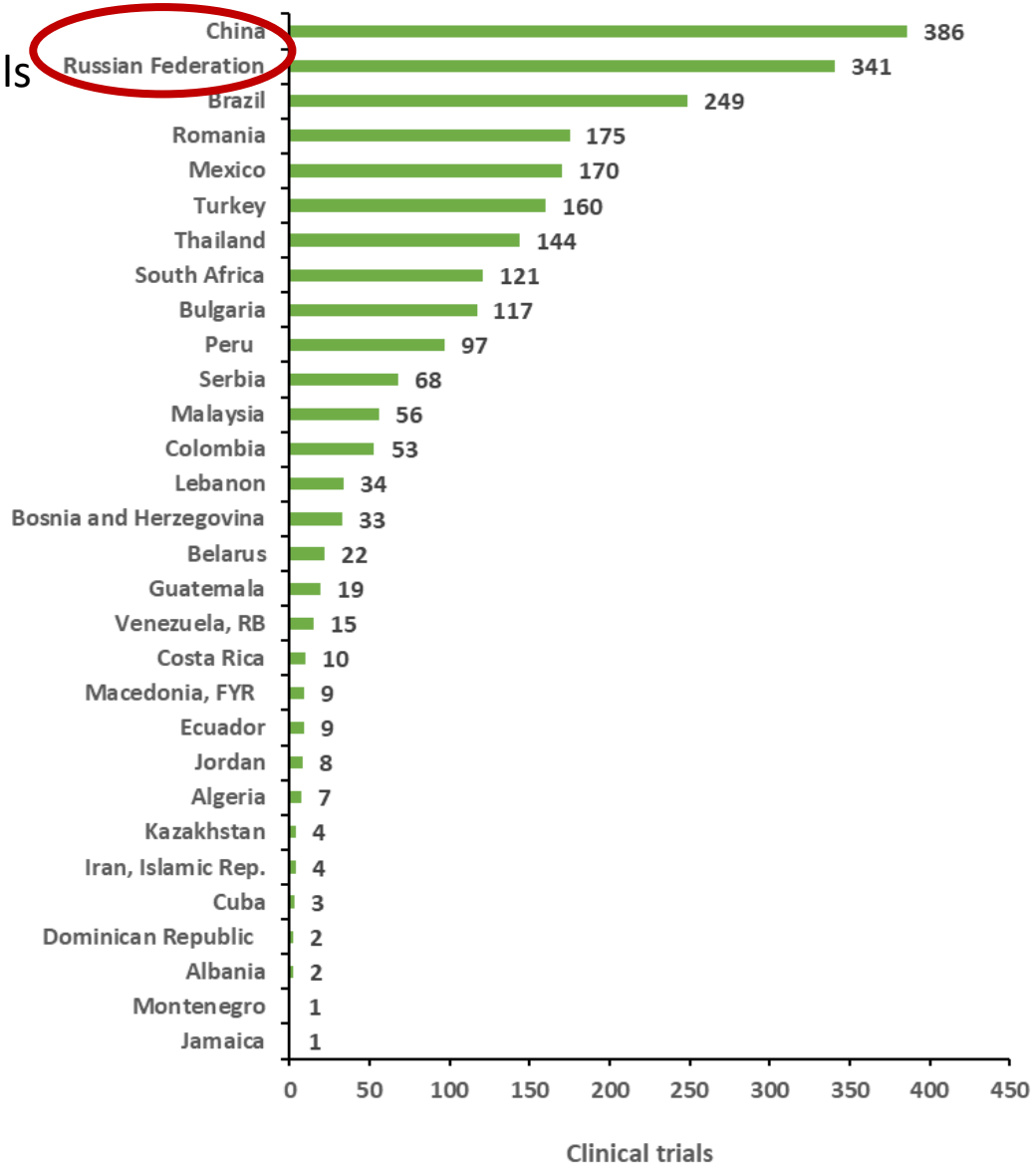
Distribution of industry-sponsored breast, lung and colon cancer clinical trials in U-MICs



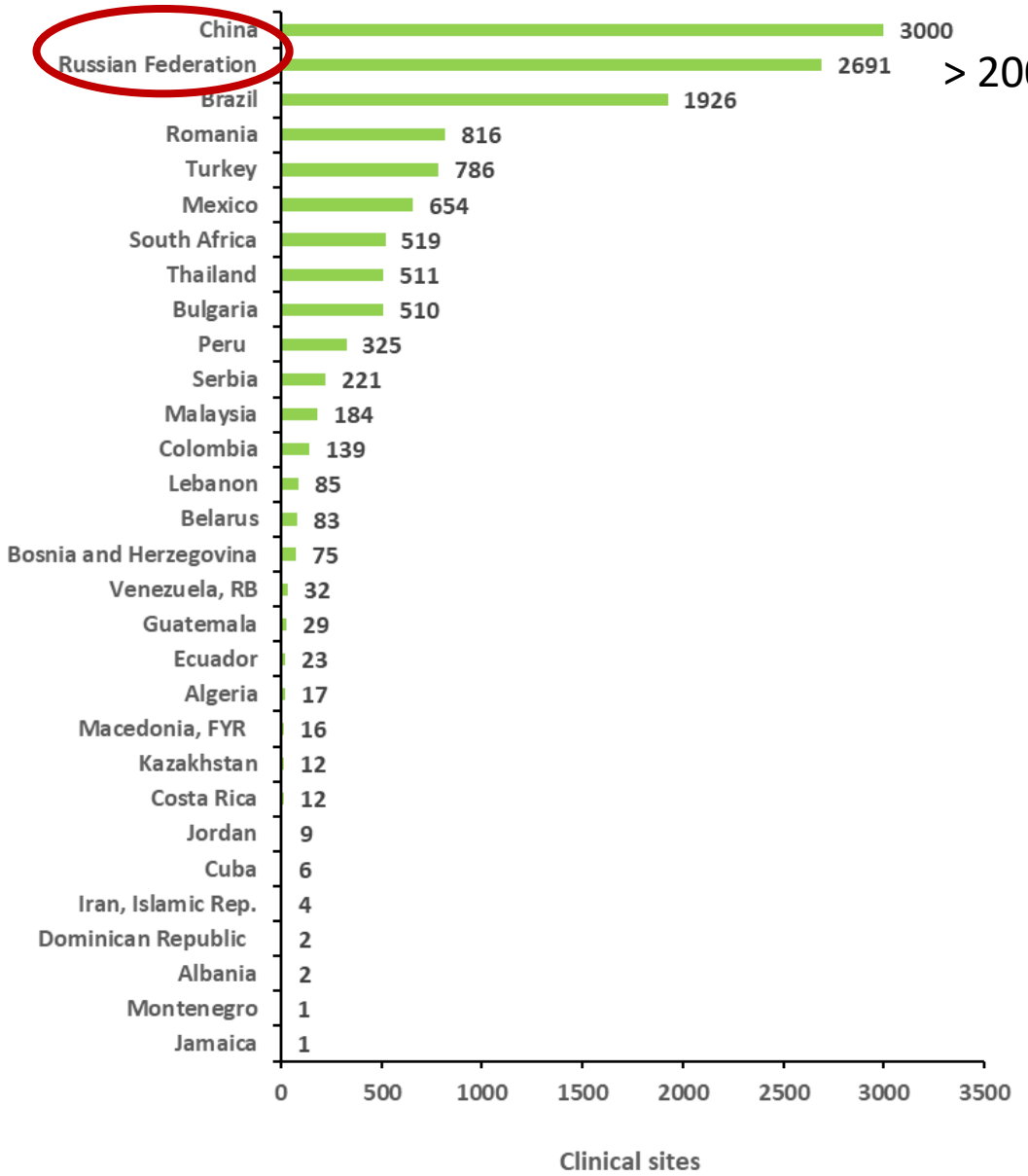
Payedimarri *et al.*, *BMJ Oncology in press*

Distribution of industry-sponsored breast, lung and colon cancer clinical trials in U-MICs

> 300 trials

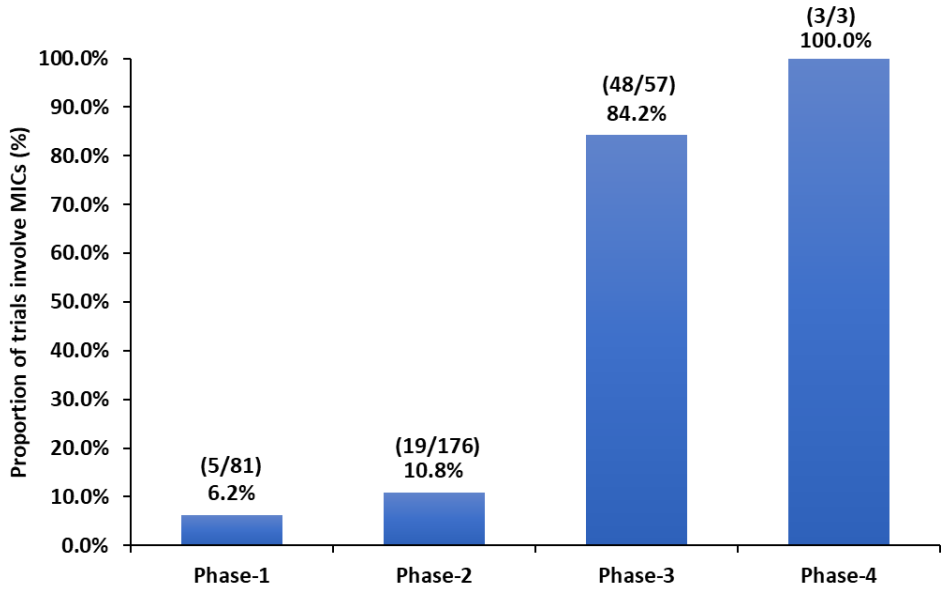


> 2000 sites

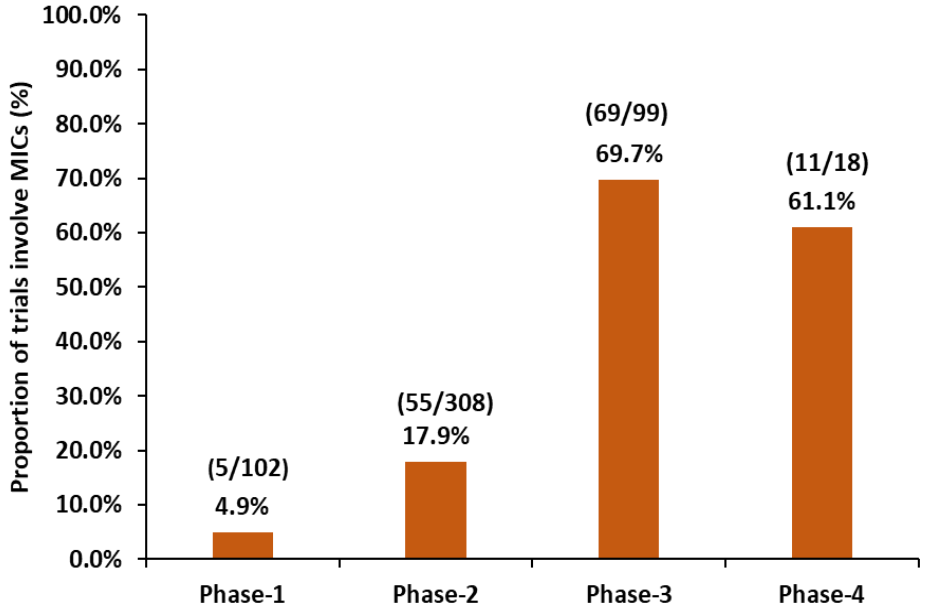


Payedimarri *et al.*, *BMJ Oncology in press*

Immune checkpoint inhibitors and target therapy trials for lung cancer in MICs



Industry-sponsored lung cancer clinical trials on **immune checkpoint inhibitors** with at least one site in MICs conducted until 2018



Industry-sponsored lung cancer clinical trials on **EGFR and/or VEGFR inhibitors** with at least one site in MICs conducted until 2018

Payedimarri *et al.*, *BMJ Oncology in press*

The «algebra» of clinical trial globalisation in MICs

Reasons

- Lower research costs
- Administrative convenience
- Availability of larger pools of potential participants

Concerns

- Acceptance *a priori* of a trial as the only option for receiving treatment
- Less stringent oversight
- Recognition of authorship to local researchers

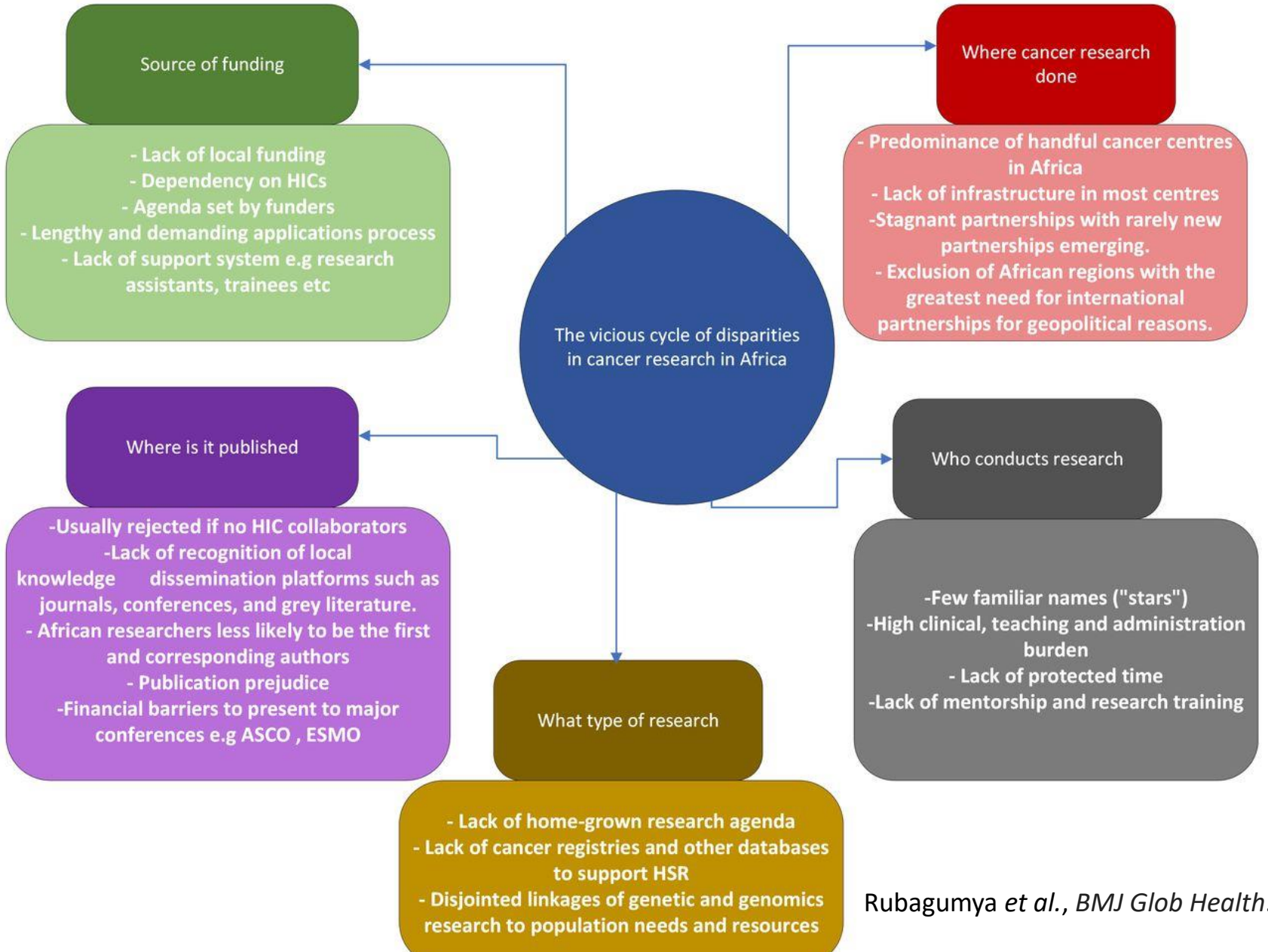
Benefits

- Involvement of MICs in international research
- Implementation of clinical facilities
- Prompting toward request for access to drugs

Glickman et al, NEJM 2009; The Belmont Report; Ravinetto et al, Lancet Hematol 2014

Inequalities in cancer research in LMICs: Lack of recognition of local researchers

More than 30% of HIC-led oncologic RCTs that included LMIC patients did not list LMIC authors in the publications



Rubagumya *et al.*, *BMJ Glob Health*. 2023

A poorly explored issue: phase 1 facilities in LICs and MICs

Facilities dedicated to:

- FIH trials (single ascending dose, multiple ascending dose)
- Proof of concept trials
- Drug-Drug interactions
- Phase I PK in renal and hepatic impairment

Examples of locations in Europe:

- Ukraine
- Romania
- Moldova
- Georgia

Risk of exploitation based on Helsinki Declaration and CIOMS Guidelines

Outline

- Cancer trends in high (HICs), middle (MICs) and low (LICs) income countries
- Health system models and obstacles to cancer treatment in HICs, MICs and LICs
- Globalization of clinical trials for cancer patients
- **Benefit sharing as a goal**

Benefit sharing

- The concept of benefit sharing deals with the concern of what participants and communities ought to gain as a result of their participation in biomedical research
- Research sponsors gain generalizable knowledge and profit from interventions that have been proven effective
- Ethically, participants/communities should also gain something in return for contributing to research endeavor

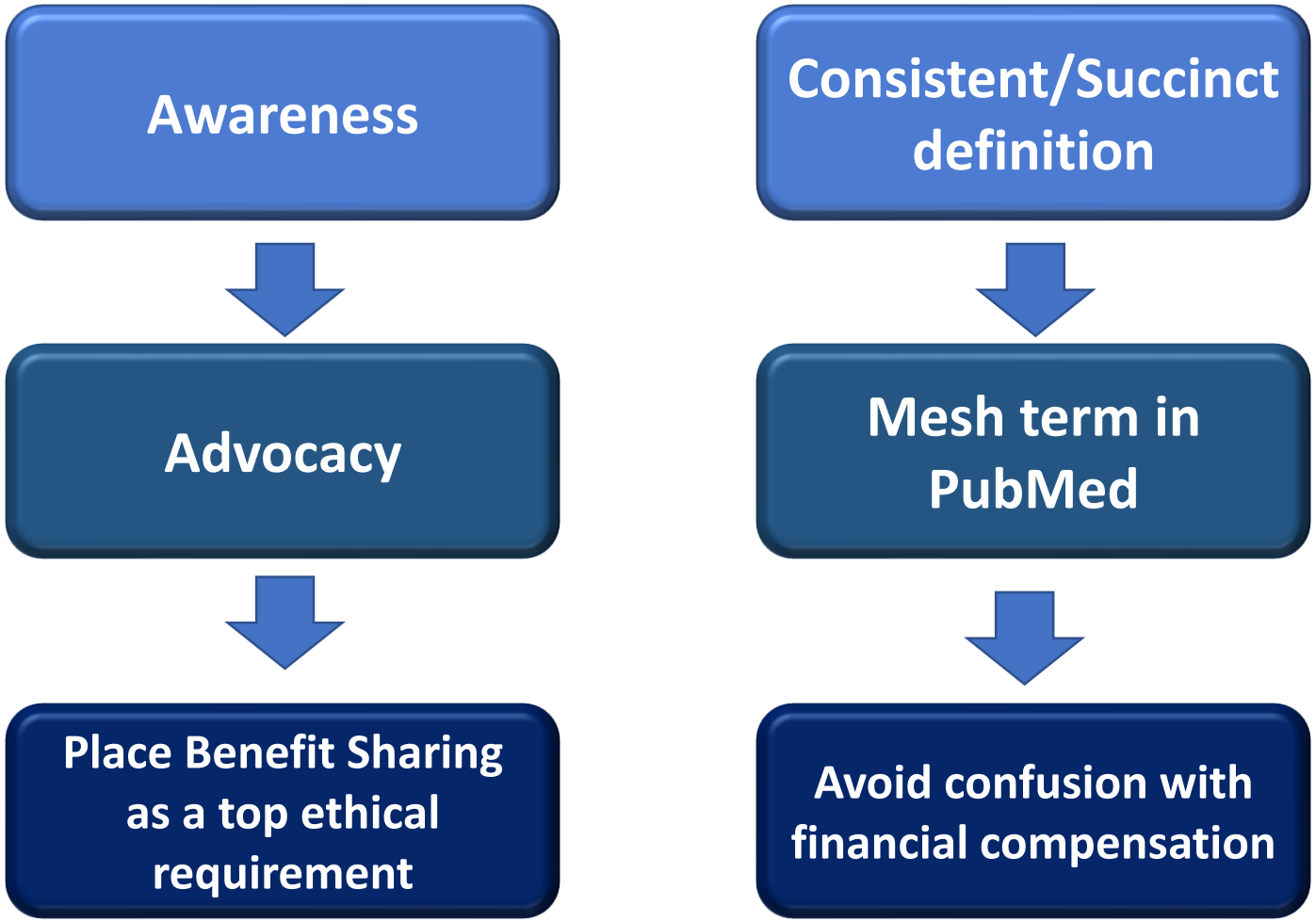
- **Benefit fairly shared with participants and communities**
  - Upgrade diagnostic/clinical capacity
  - Access to interventions developed by research
  - *Prior dialogue with industry, health authorities, advocacy*
  - *An explicit "access" plan*
- **Data sharing** beyond a specific study or consortium
- **Ownership of samples** exported abroad (ex. Ebola)

Schulz-Baldes et al, EMBO Reports, 2007

Courtesy of Raffaella Ravinetto

Benefit sharing

What needs to be improved



Legal instruments on benefit sharing would require a careful implementation process

Courtesy of Raffaella Ravinetto

Summing up

- Globalization of cancer research is a growing phenomenon with potential benefits for LMICs, but also risks (e.g. lack of benefit-sharing and subsequent access to medicinal product)

- An active role of MICs in clinical research with innovative medicines is beneficial provided that there is a reasonable likelihood that their populations will benefit from the research

- The shift in geographical boundaries should prompt a quest for ethically acceptable solutions rather than being perceived as an obstacle toward MICs involvement

- Regulatory and legislative measures are required to ensure the availability and affordability of innovative medicines in countries that participated in industry-sponsored trials

- Research institutions in MICs should receive adequate recognition in authorship and be empowered to take on a leading role in the cancer research agenda and

Proposals

- Scientific journals should publish a complete list of the trial sites and the number of cases/site, in line with the CONSORT guidelines
- Regulatory agencies should require an “ethical clause” that binds the marketing authorization holders to register it in all MICs involved in the trials, to make it available at tiered prices
- Physicians and patients from MICs, hopefully joined by their peers in affluent countries, should lobby for getting a *juxtum pretium* (i.e., a morally justifiable “just price”) for the drugs tested in their countries
- The cancer research and development agenda should include LICs, in order to address their specific unmet needs in cancer care

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