CANCER CARE AND ACCESS TO CANCER DRUGS IN ASIA-PACIFIC

Main report

Thomas Hofmarcher
George Keel
Peter Lindgren

IHE Report
2021:3

CANCER CARE AND ACCESS TO CANCER DRUGS IN ASIA-PACIFIC

This is the main report and all the sub-reports are included as separate chapters

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George Keel
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IHE - The Swedish Institute for Health Economics

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CANCER CARE AND ACCESS TO CANCER DRUGS IN ASIA-PACIFIC

Introduction of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

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Foreword

Cancer is one of the most intensely discussed health policy issues globally. The aging population in societies around the world leads to an increased disease burden caused by cancer, both to patients and to the health care system as a whole. At the same time, significant scientific advancements have been made in the diagnosis and treatment of cancer in recent decades. Lack of access to innovative diagnostic and treatment modalities remains a major challenge that needs to be addressed.

The Swedish Institute for Health Economics (IHE) has for many years now published regular updates on the burden of cancer and access to cancer drugs in Europe. This report expands IHE's expertise in this research area to Asia-Pacific. Covering almost half of the world population, Asia-Pacific is a diverse region consisting of high-income countries that strive to offer state-of-the-art health care to all its citizens and middle-income countries that still need to fully implement universal health coverage. Despite the different starting points, all countries face the challenge of achieving the best possible outcomes for patients given constrained health care resources.

This report builds on a comparative analysis of 14 countries and locations in Asia-Pacific. It intends to raise awareness on the size of the burden of cancer, the resources currently used to tackle the burden, the challenges faced by patients in accessing innovative treatment modalities, and possible ways to improve the status quo.

The present report is divided into several documents: The complete report (this document) and separate sub-reports consisting of the executive summary and the five main chapters in this report.

The report was funded by Merck Sharp & Dohme (MSD). Responsibility for the analysis, interpretations, and conclusions, as well as errors or omissions lies solely with the authors.

Lund, May 2021

Peter Lindgren
Managing Director, IHE

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Three external experts provided feedback on early results of the analysis. We thank Isao Kamae (University of Tokyo), Zaheer Ud Din Babar (University of Huddersfield), and Michael Wonder (Wonder Drug Consulting) for sharing their thoughts and helping source additional material.

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Introduction

Cancer is a growing challenge for health systems around the world. The global number of newly diagnosed cancer cases is expected to increase by almost 50%, from around 19 million cases in 2020 to 29 million cases in 2040 (1). Similarly, the number of cancer deaths is also expected to increase by 64% over 2020-2040, from around 10 to 16 million deaths (1). The increasing cancer burden is driven by demographic changes reflecting the growth and aging of population, along with changes in the prevalence of cancer risk factors (e.g., smoking, unhealthy diet, obesity, physical inactivity). According to the WHO, 30-50% of cancer cases are caused by known risk factors and the implementation of effective prevention measures (e.g., tobacco control) is key to address the increasing cancer burden (2).

Cancer patients have very different chances of survival depending on where in the world they live. For example, for patients diagnosed with lung cancer during 2010-2014, 5-year survival was 33% in Japan but only 4% in India. For breast cancer, 5-year survival was 90% in the USA but in the range of only 65-66% in other countries such as Malaysia and India (3). Trends in survival have been generally increasing for most cancer types in the past, owing to advancements in screening, diagnosis, and treatment (3). To ensure continued progress in patient outcomes in the leading countries and for other countries to catch up with these countries, additional investment in effective cancer control policies along the whole patient pathway are vital.

Geographic scope of the report

In this report, cancer care and access to cancer drugs in Asia-Pacific is described. 14 countries and locations, referred to as "*markets*" in the remainder of the report, are included in the analysis. They are grouped into two sets based on the classification system of the World Bank: 7 *high-income markets* (Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan) and 7 *middle-income markets* (China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam). Figure 1 shows the gross domestic product (GDP) per capita of the 14 markets, ranging from just over $2,000 in India to $65,000 in Singapore in 2019.

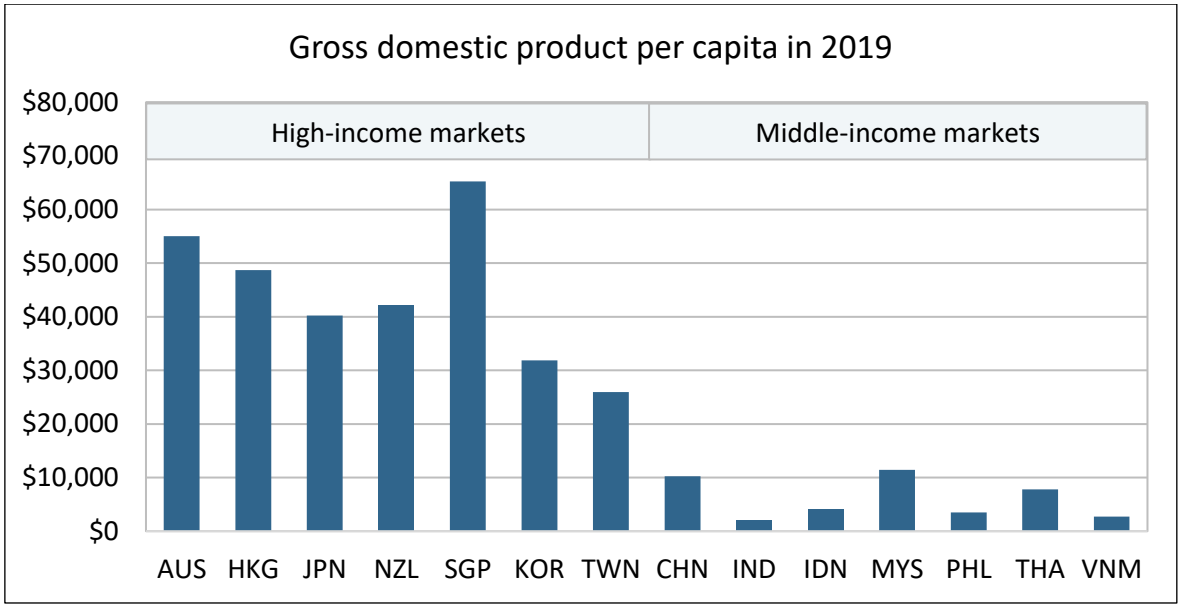

Figure 1: Gross domestic product (GDP) per capita in US$ in Asia-Pacific, 2019

Notes: Numbers are in current prices and not adjusted for differences in purchasing power parity.
Source: World Bank (4) and National Statistics Bureau (5).

The 14 markets in Asia-Pacific account for a sizable share of the world population and also of the world's total GDP. Almost half (47%) of the world population resides in this region, most of them in middle-income markets; see Figure 2. China and India are the largest markets with almost 1.4 billion inhabitants each, while New Zealand is the smallest with 5 million inhabitants; see Table 1. Figure 2 shows also that around one third (34%) of the world's economic wealth is created in Asia-Pacific, with high-income markets almost creating four times more wealth in relation to their population.

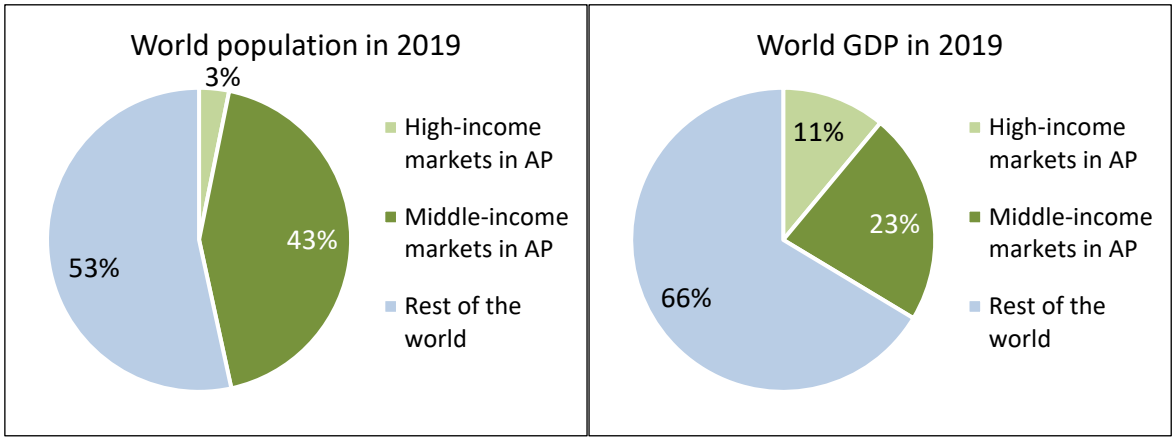

Figure 2: Total GDP and total population in high-income and middle-income markets in Asia-Pacific (AP) in comparison to the rest of the world, 2019

Notes: Numbers do not sum to 100% due to rounding.
Source: World Bank (4), National Statistics Bureau (5) and Department of Household Registration (6).

Table 1: Total population in Asia-Pacific, 2019

High-income markets		Population in 2019 (million)	Middle-income markets		Population in 2019 (million)
AUS	Australia	25.4	CHN	China	1,397.7
HKG	Hong Kong	7.5	IND	India	1,366.4
JPN	Japan	126.3	IDN	Indonesia	270.6
NZL	New Zealand	4.9	MYS	Malaysia	31.9
SGP	Singapore	5.7	PHL	Philippines	108.1
KOR	South Korea	51.7	THA	Thailand	69.6
TWN	Taiwan	23.6	VNM	Vietnam	96.5

Source: World Bank (4) and Department of Household Registration (6).

Content of the report

The increasing burden of cancer is becoming a growing challenge throughout Asia-Pacific. Demands on health care are increasing not only because of a rising number of cancer patients but also because of growing expectations of patients to receive high-quality care. Significant progress in cancer research has led to a rapid inflow of new treatment options for cancer patients in recent years, in particular in the area of drug treatment. Advancements in both the cutting-edge science and treatment outcomes are changing the profile of cancer from a life-threating to a chronic disease, transforming cancer care, and most importantly improving cancer patient survival.

New cancer treatment modalities are often considered to be costly and raise concerns about the budget impact and sustainability of health systems, especially in markets with deprived health care systems. However, the value of any new treatment modality is not only determined by its costs, but also by the benefits it offers to patients. Finding effective strategies to balance constrained health care budgets with access to innovative treatments with significant clinical benefits to patients is crucial for health policy makers.

This report aims to corroborate the developments described above with concrete numbers. As cancer is just the collective name of a group of over 100 diseases, the report puts greater focus on a handful of selected cancer types. Five cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, lung cancer – that are responsible for around half of all cancer cases across Asia-Pacific are considered.

The report is divided into five sub-reports, each answering a set of research questions:

1. **The burden of cancer**
    a. What is the size of the cancer burden in relation to other diseases?
    b. What is the trend in the cancer burden at the population level and at the individual level?
    c. What might be the size of the cancer burden in 2040?
2. **Health spending on cancer care**
    a. What is the level and proportion of health spending funded by public and private sources in general and what is known about the level of health spending on cancer?
    b. Is there an association between health spending and cancer patient outcomes?
    c. What is the proportion of households in financial catastrophe because of cancer?
3. **Access to innovative cancer drugs**
    a. What is the proportion of innovative cancer drugs in the national formulary?
    b. How long is the period from regulatory approval to reimbursement approval for innovative cancer drugs?
    c. How many patient life years could be saved by faster reimbursement approval of innovative cancer drugs?
4. **Health spending on cancer drugs and unmet patient needs**
    a. What is the level of total health spending on cancer drugs?
    b. What is the level of public health spending on innovative cancer drugs?
    c. Is health spending on cancer drugs sufficient to meet patient needs?
5. **Pricing policies for off-patent cancer drugs**
    a. What is the general price pattern of originator drugs before and after the availability of generics/biosimilars?
    b. How much expenditure could be saved if effective pricing mechanisms are applied to originator drugs after patent expiry?

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Executive summary of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

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Executive summary

Cancer is a growing challenge for health systems around the world. The global numbers of newly diagnosed cancer cases and cancer deaths are predicted to rise by 50% and 64%, respectively, between 2020 and 2040. The increasing cancer burden is driven by demographic changes reflecting the growth and aging of population, along with changes in the prevalence of cancer risk factors (e.g., smoking, unhealthy diet, obesity, physical inactivity). Cancer is already now the leading cause of death in many high-income countries around the globe. It will increasingly become a major public health issue in middle-income countries as well, based on current trajectories.

Cancer patients have very different chances of survival depending on where in the world they live. For example, for patients diagnosed with lung cancer during 2010-2014, 5-year survival was 33% in Japan but only 4% in India. Trends in survival have been generally increasing for most cancer types in the past, owing to advancements in screening, diagnosis, and treatment. To ensure continued progress in the leading countries and for other countries to catch up with these countries, additional investment in effective cancer control policies along the whole patient pathway are vital.

Treatment options for cancer patients are advancing rapidly, in particular in the area of drug treatment. New treatment modalities are often considered to be costly and raise concerns about the budget impact and financial sustainability of health systems, especially in countries with deprived health systems. However, the value of any new treatment modality is not only determined by its costs, but also by the benefits it offers to patients. Finding effective strategies to balance constrained health care budgets with access to innovative treatments with significant clinical benefits to patients is crucial for health policy makers.

Geographic scope of the report

In this report, cancer care and access to cancer drugs in Asia-Pacific is described. 14 countries and locations, referred to as "*markets*" in the report, are analyzed. They are grouped into 7 *high-income markets* – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 *middle-income markets* – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam. Together these markets

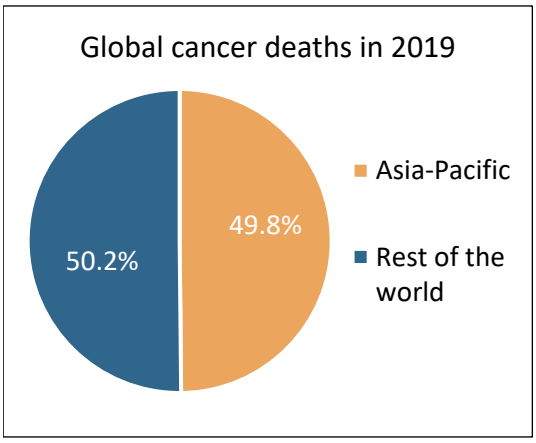

Figure 1: Global distribution of cancer deaths, 2019

account for almost half (47%) of the world population and around one third (34%) of the world's economic wealth.

Content of the report

This report provides a comparative analysis of the 14 markets in Asia-Pacific. It is divided into five sub-reports focusing on:

1. The burden of cancer
2. Health spending on cancer care
3. Patient access to innovative cancer drugs
4. Health spending on cancer drugs and unmet patient needs
5. Pricing policies for off-patent cancer drugs

1. The burden of cancer

Cancer patient numbers have been growing steadily along with the incoming silver tsunami

The number of newly diagnosed cancer cases has increased from 6.6 million to 7.8 million between 2012 and 2018 in Asia-Pacific. Even after accounting for overall population growth in this period, all markets have seen increasing patient numbers; see Figure 2. A key driver in this development is population aging, which is taking place at an unprecedented rate across the region. This "silver tsunami" of elderly people is causing many new cancer cases, as the individual risk of getting cancer increases dramatically with age. However, around 30-50% of all cancer cases would be preventable, according to the WHO. Prevention of major risk factors (e.g., cigarette smoking, obesity, alcohol consumption, infection with hepatitis B and C, human papillomavirus, and *Helicobacter pylori*, air pollution, contamination of water, soil, and food) is key to stem the tide.

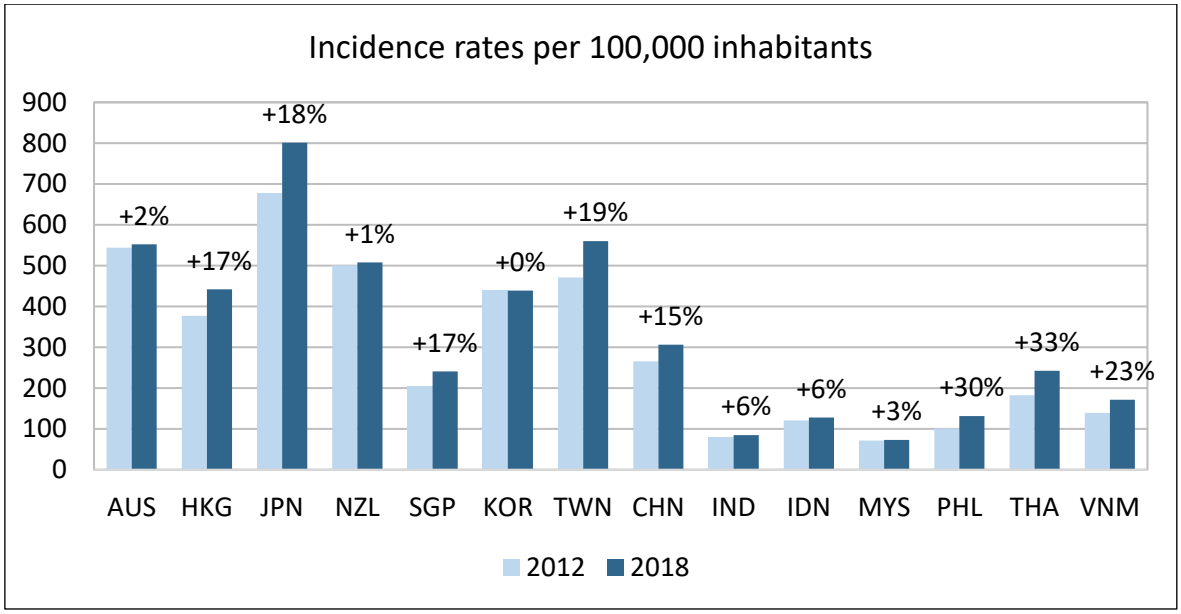

Figure 2: Cancer incidence per 100,000 inhabitants (crude rates), 2012 and 2018

While more and more patients survive cancer in high-income markets, patient outcomes in middle-income markets are at best stagnating

Outcomes of cancer patients differ greatly across Asia-Pacific. Survival (here quantified as the complement of mortality-to-incidence ratio) is a prime measure of patient outcomes. For every 100 patients diagnosed with cancer, around 50-65 of them survive in high-income markets compared to 30-40 in middle-income markets; see Figure 3. Recent developments indicate that the situation for cancer patients in high-income markets continues to improve, while patient outcomes in middle-income markets are at best stagnating. A closer analysis of five major cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, lung cancer – confirms this diverging trend between high-income and middle-income markets. The provision of high-quality cancer care characterized by a rapid adoption of clinical innovations can further increase the odds for cancer survival. The absence of nationwide population-based cancer registries in middle-income markets complicates the monitoring of the effectiveness of cancer control efforts.

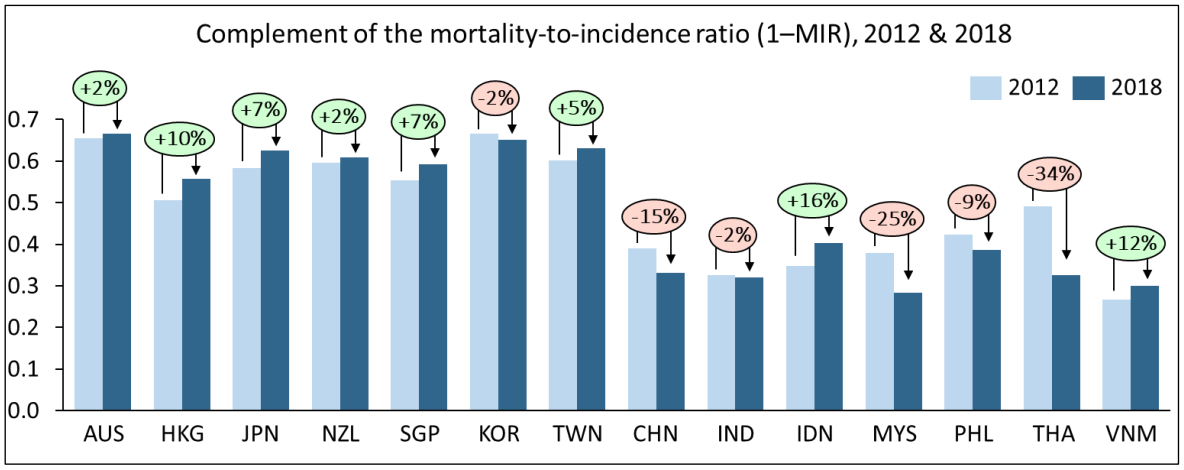

Figure 3: Complement of the mortality-to-incidence ratio of cancer, 2012 and 2018

Notes: The complement of the mortality-to-incidence ratio (1–MIR) (ranging from 0 to 1) serves as a proxy for the 5-year survival rate (0% to 100%), in absence of comparable data from population-based cancer registries in all markets and despite its limitations pointed out in previous literature. Numbers in ellipses show relative changes.

Resolute action is required to address increasing cancer patient numbers in the coming decades

Predictions of the future cancer burden in Asia-Pacific indicate increases in the annual number of newly diagnosed cases by 10-90% and deaths by 20-140% over the next two decades; see Figure 4. Advances and investments in all areas of cancer care – prevention, screening, diagnosis, treatment – are needed to meet the challenge brought upon by the demographic development. A clear prioritization of effective cancer control efforts could spare millions of people from getting cancer and avert millions of deaths of those people who get cancer over the coming decades.

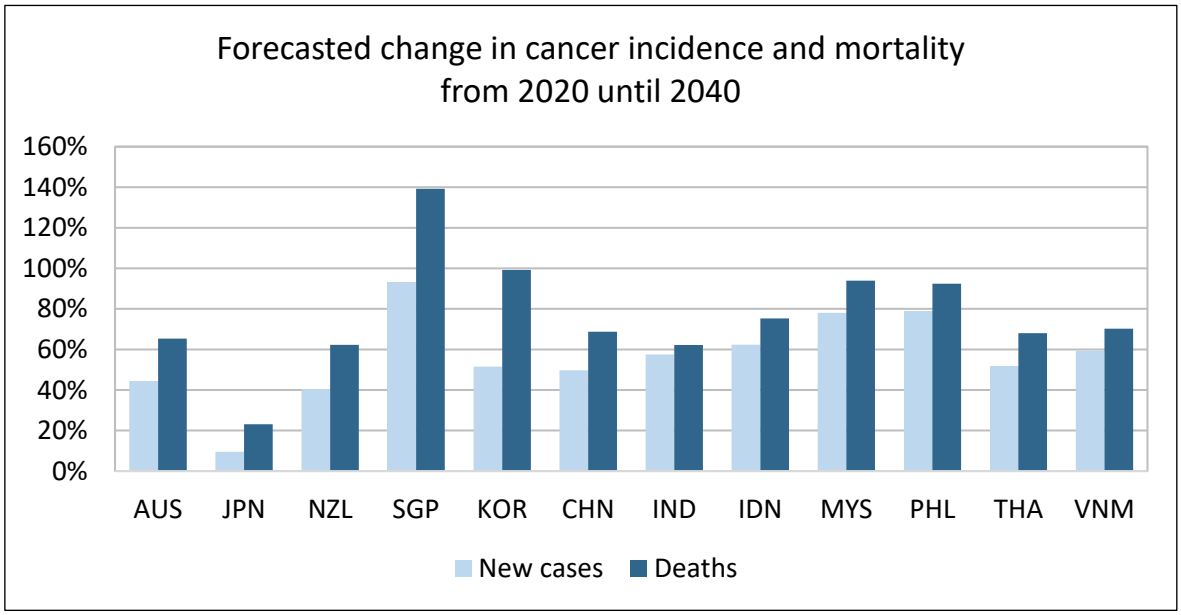

Figure 4: Forecasted change in total cancer incidence and cancer mortality between 2020 and 2040

2. Health spending on cancer care

Most markets miss the informal WHO target of public health spending of 5% of GDP

Access to modern cancer treatment is limited in many markets in Asia-Pacific. This is the result of a lack of universal health coverage, a small package of health services covered, high patient co-payments on covered health services, or a combination thereof. The root cause of this is insufficient public funding of health care. Public health expenditure as a share of gross domestic product (GDP) tend to be much lower in middle-income markets (on average 2%) than in high-income markets (on average 5%) in Asia-Pacific; see Figure 5. Only Australia, Japan, and New Zealand met the informal WHO target of public health spending of 5% of GDP in 2018, despite increases in public health spending relative to GDP in all markets since 2000.

Public health spending per capita is 70 times higher in Australia and Japan than in India, Indonesia, and the Philippines

Public health spending is less than $300 per capita in all middle-income markets, ranging from $289 in China down to $20 in India; see Figure 5. In the top-spending high-income markets – Australia, Japan, and New Zealand – public health spending exceeds $3,000 per capita. Middle-income markets, in particular India and the Philippines, rely much more on out-of-pocket spending from patients in their financing of health care, with an average of 40% of total health spending being out-of-pocket compared to 27% in high-income markets.

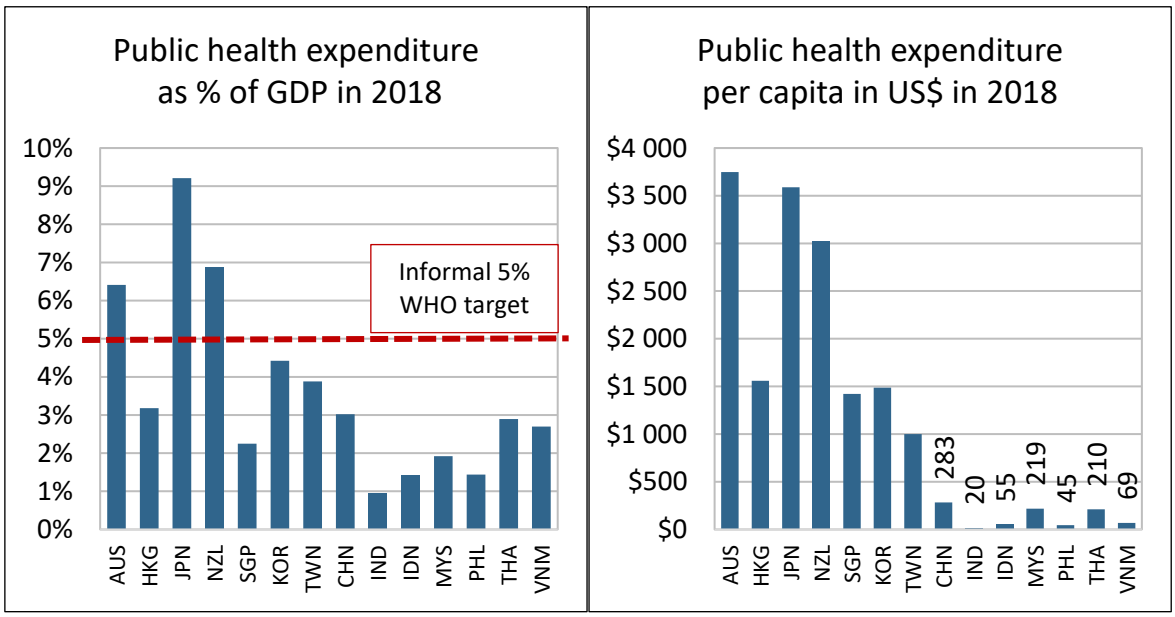

Figure 5: Public health expenditure as % of GDP and per capita in US$, 2018

Cancer accounts for 5-9% of total health spending in high-income markets and only 1-2% (excl. out-of-pocket payments) in some middle-income markets

Limited evidence exists on how much markets spend on cancer care. For markets with available data, health spending on cancer care accounts for 5-9% of total health spending in high-income markets in Asia-Pacific, which is of a similar magnitude as in Europe and the US. Similar proportions have also been reported for China. In Indonesia and Thailand, health spending on cancer care (excluding out-of-pocket payments for cancer treatment) is as low as 1–2% of total health spending.

Insufficient public coverage of medical services and non-medical services means that around 50% of all households affected by cancer face financial catastrophe in most middle-income markets

The consequences of inadequate health coverage can be dire for cancer patients and their families. High out-of-pocket payments for medical services and non-medical services as well as income loss due to reduced or discontinued employment constitute a toxic mix. Indeed, around 50% of all cancer patients and their families face financial catastrophe (here defined as out-of-pockets payments for medical services and non-medical services exceeding annual household income by 30%) in middle-income markets; see Figure 6. An exception is Thailand where “only” a quarter of patients face financial catastrophe, which might be related to well-established universal health coverage granting access to cancer care services at both public and private health care facilities. Even in high-income markets cancer patients may face financial difficulties in conjunction with their diagnosis and care process.

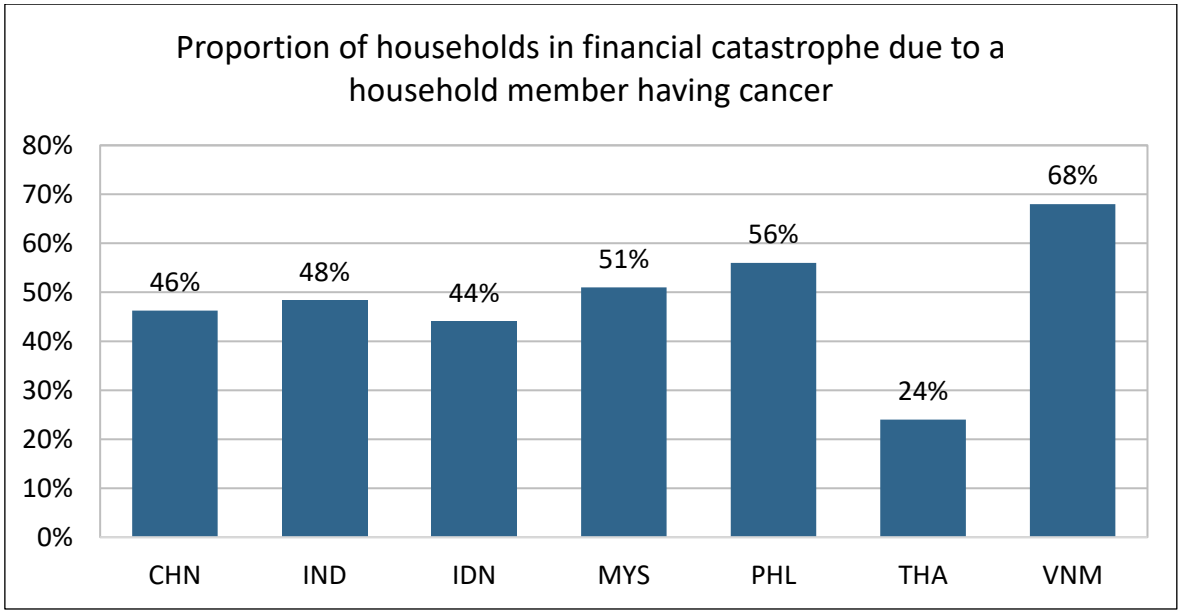

Figure 6: Proportion of households in financial catastrophe due to a household member having cancer

Notes: Financial catastrophe is defined as out-of-pockets payments for medical services and non-medical services exceeding annual household income by 30%. This follows the definition used in the ACTION study that covered many member states of the Association of Southeast Asian Nations.

3. Patient access to innovative cancer drugs

Almost 100 new cancer drugs have been launched over the last decade alone and some are more innovative than others with substantial clinical benefits

New cancer drugs have been introduced at an accelerating pace in recent decades. Almost 100 new cancer drugs have been launched over the last decade alone; see Figure 7. While this is a welcome development for patients, not all drugs offer the same level of innovation and clinical benefits to patients. Value frameworks, such as the Magnitude of Clinical Benefit Scale (ESMO-MCBS) by the European Society for Medical Oncology, have been put forward to help classify cancer drugs with the aim to identify innovative cancer drugs (here defined as ESMO-MCBS score of 4 and 5 or B and A)[1] that should be priorities for rapid reimbursement by national bodies from a clinical perspective.

[1] Drug-indications used in a curative setting receive a score of A, B, or C. A is the highest score and C is the lowest score. Drug-indications used in a non-curative setting receive a score of 5, 4, 3, 2, or 1. 5 is the highest score and 1 is the lowest score. An indication is said to have a "substantial magnitude of clinical benefit" if it receives a score of A or B in the curative setting or a score of 5 or 4 in the non-curative setting. In this report, drug-indications with a "substantial benefit" are called "innovative".

A greater focus on innovative cancer drugs that provide the largest benefit to patients can help constrained health care budgets.

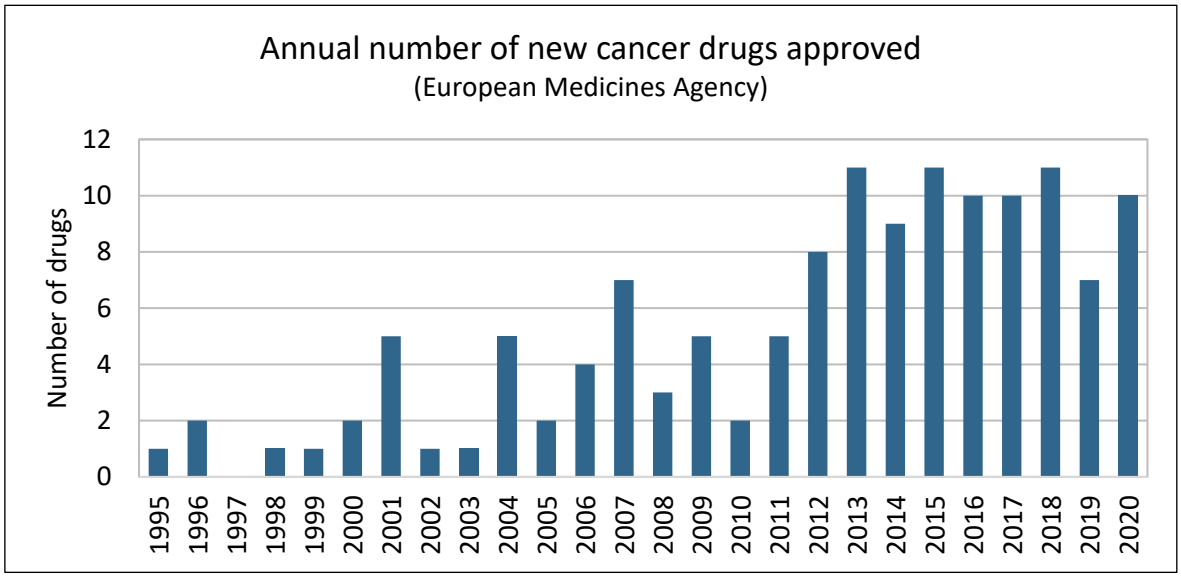

Figure 7: Annual number of new cancer drugs approved by the European Medicines Agency between 1995 and 2020

Of 38 innovative cancer drug-indications approved by the US FDA, around 80% had received regulatory approval across Asia-Pacific, yet only 35% were also reimbursed

Access to innovative cancer drugs through reimbursement is limited in Asia-Pacific. Of 38 innovative drug-indications approved by the US FDA in the treatment of five major cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer) between 1998 and 2020, 80% had received regulatory approval across Asia-Pacific in 2020. Yet only 35% of those indications were also reimbursed in 2020; see Figure 8. High-income markets achieve in general much higher rates of both regulatory approval and reimbursement approval than middle-income markets. Among middle-income markets, China, Indonesia, and Vietnam approve relatively few indications but at the same time reimburse a higher proportion of them, and vice versa in the other markets. Among high-income markets, Japan sticks out due to its policy to reimburse all approved drugs essentially by default, which stands in stark contrast to the restrictive reimbursement policy observed in New Zealand. In Singapore, public health insurance schemes enable patients to pay for approved drugs even though they are not listed on a national formulary as in other markets.

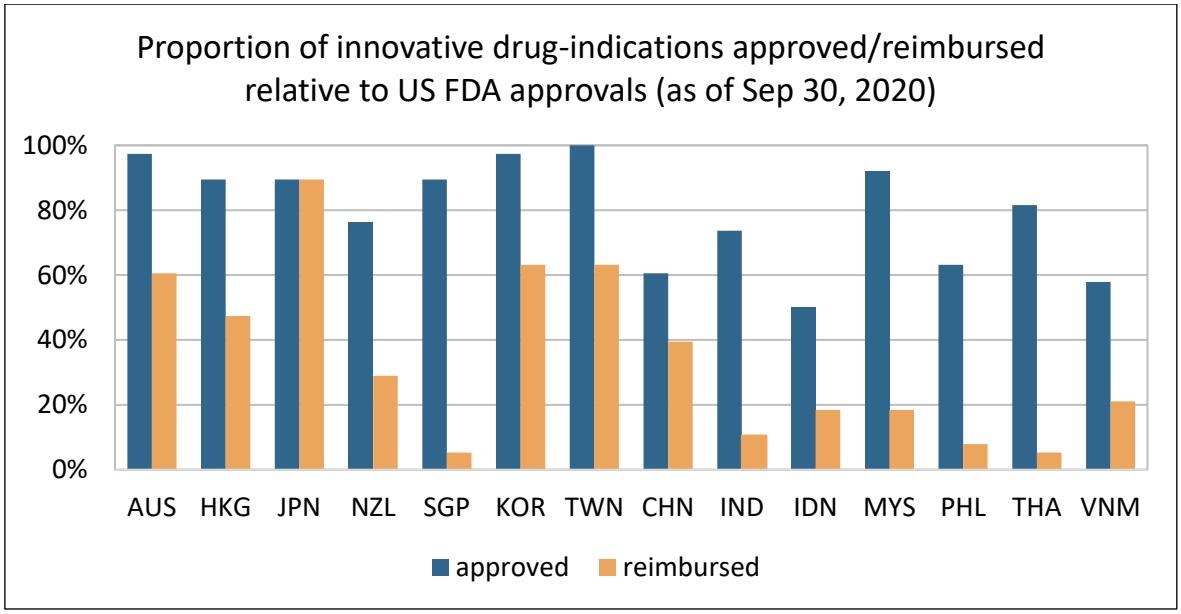

Figure 8: Proportion of innovative cancer drug-indications approved/reimbursed relative to US FDA approvals (as of Sep 30, 2020)

Notes: In Singapore, the proportion of reimbursed drug-indications only refers to drugs on the SDL or MAF while patient's expenditure for approved drugs are mostly covered through the 3M schemes. In India, no reimbursement scheme exists for the whole population and drugs listed in the NLEM are considered here instead.

There is a median delay of around 1.5 to 3 years between regulatory approval and reimbursement approval of innovative cancer drugs in high-income markets and China

Timely reimbursement of innovative cancer drugs is a major challenge in Asia-Pacific. In high-income markets along with China, the median delay between regulatory approval and reimbursement approval is around 1.5 to 3 years; see Figure 9. Yet a full assessment of the delay of recent innovative cancer drugs (defined as US FDA approval since 2010) is not possible as reimbursement approval is still pending for many drugs at the data cut-off in 2020. In most middle-income markets, delays could not be assessed, because there are essentially no recent innovative cancer drugs that have achieved reimbursement listing until 2020. This might indicate delays of 10 years or more in most middle-income markets.

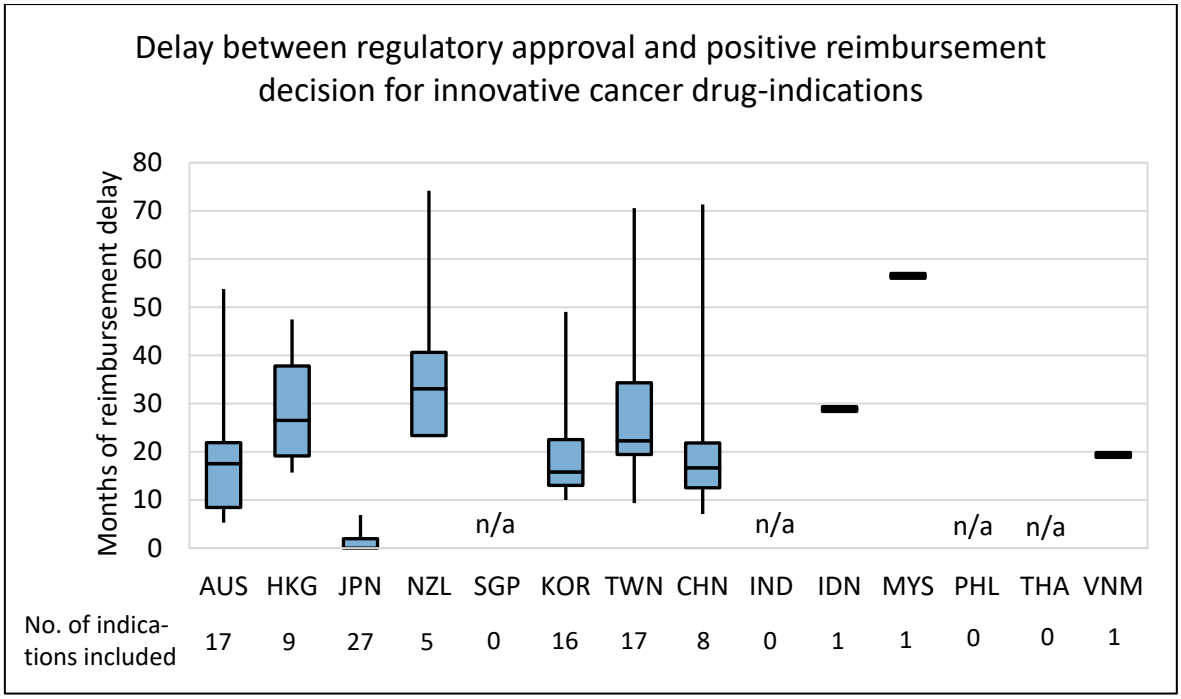

Figure 9: Delay between regulatory approval and positive reimbursement decision for innovative cancer drug-indications (in months)

Notes: n/a = no innovative drugs approved or no information on regulatory/reimbursement approval dates available. Analysis based on a sample of 31 drug-indications.

Almost 1 million patient life years are lost for every year of delay in reimbursement of 10 innovative cancer drug-indications across Asia-Pacific

Timely reimbursement of innovative cancer drugs could save countless patient life years across Asia-Pacific. Drawing on a sample of only 10 innovative drug-indications (out of the 31 innovative drug-indications with US FDA approval since 2010) across five major cancer types, almost 1 million patient life years are lost for every year of delay in reimbursement; see Figure 10. As delays in reimbursement are typically much longer than one year (except in Japan as noted above), patient outcomes could be greatly improved by faster reimbursement decisions. Reasons for delayed reimbursement of innovative cancer drugs vary across markets in Asia-Pacific. In middle-income markets they relate more to limited public health budgets as well as the organization of the reimbursement process with reimbursement listings being infrequently reviewed and updated. In high-income markets, they relate more to the criteria applied in the reimbursement process (e.g., acceptance of surrogate endpoints, comparator in clinical trial reflective of current clinical practice, cost-effectiveness thresholds) and lack of fast-track systems for innovative drugs (e.g., prioritized process with shorter timelines for drug-indications that lack a comparable alternative as in South Korea).

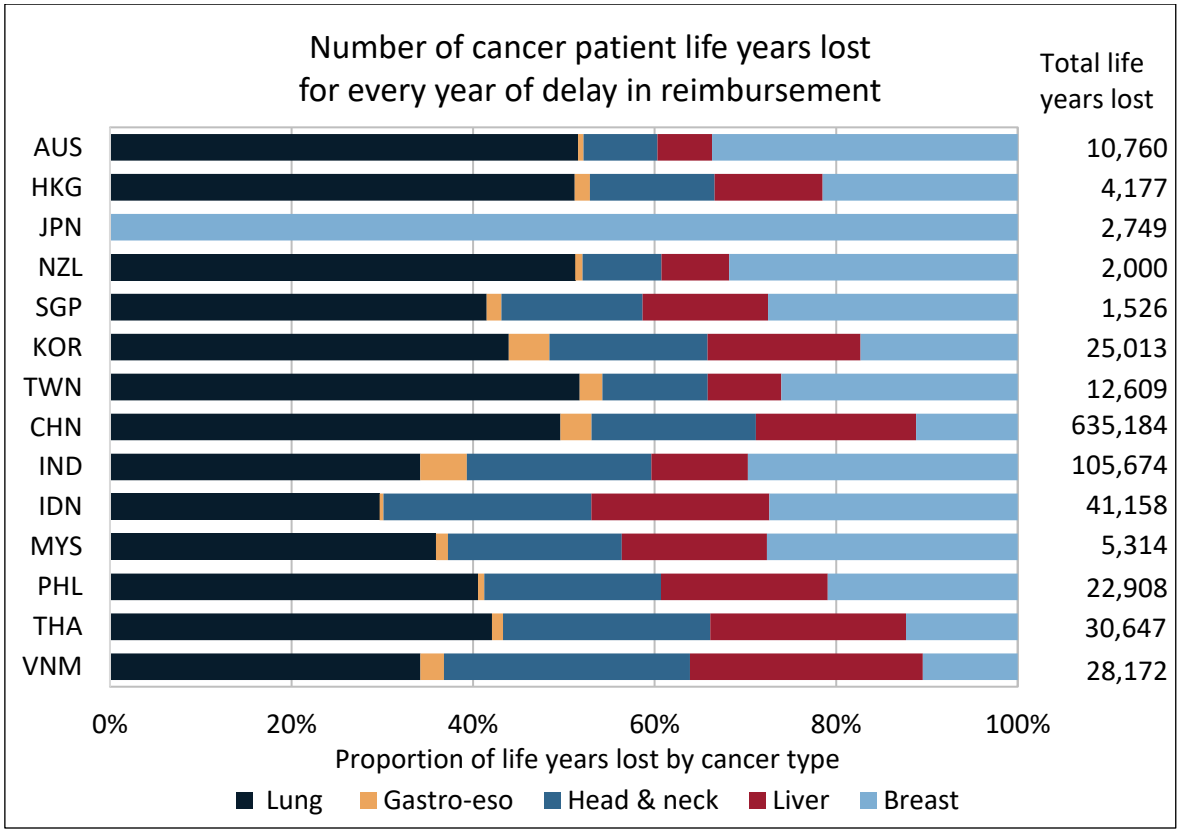

Figure 10: Proportion (left side) and number (right side) of patient life years lost for every year of delay in reimbursement of 10 innovative indications in five cancer types

Notes: Lung = NSCLC, Gastro-eso = gastro-esophageal cancer, Head & neck = head and neck cancer, Liver = liver cancer, Breast = breast cancer. Japan has only life years lost in breast cancer because there was no delay for other cancer types.

4. Health spending on cancer drugs and unmet patient needs

Cancer drugs are an integral part of modern cancer care. The launch of targeted therapies and immunotherapies has changed the standard of care in many cancer types during the last two decades. While such clinical innovation helps address the growing burden of cancer, this poses challenges to health care systems and policy makers with finite health resources available.

High-income markets spend 10–20% of total pharmaceutical expenditure on cancer drugs, while middle-income markets spend 1–9%

High-income markets in Asia-Pacific spent around 10-20% of total pharmaceutical expenditure – financed via public and private sources – on cancer drugs in 2019, whereas middle-income markets spent around 1-9%; see Figure 11. These proportions directed to cancer are comparatively low in relation to the size of the disease burden of cancer. For example, the proportion of cancer deaths

amounted to around 30% of all deaths in high-income markets and 9-25% of all deaths in middle-income markets in 2019.

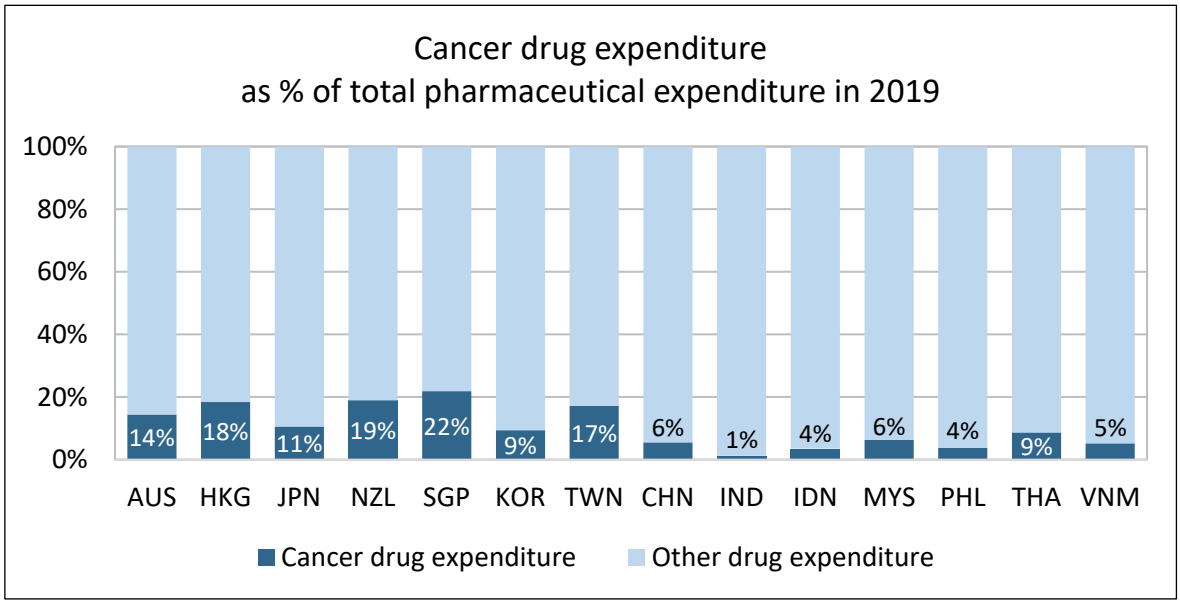

Figure 11: Expenditure on cancer drugs as % of total pharmaceutical expenditure, 2019

Notes: Underlying sales data from IQVIA do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers, which would overestimate the proportion of cancer drug expenditure if the size of rebates for cancer drugs is greater than for other pharmaceuticals.

Total health spending on cancer drugs ranges from $30 to $90 per capita in high-income markets and from $0.2 to $6.6 in middle-income markets

Cancer drug expenditure – financed via public and private sources – are low in most high-income markets in Asia-Pacific compared to Europe. Japan spent the most on cancer drugs per capita with over $90 in 2019, see Figure 12, whereas top-spending countries in Europe spent around $110–$130 per capita. South Korea spent the least on cancer drugs among high-income markets with around $30 per capita, which puts the market at the same level as European countries with lower GDP per capita. Per capita spending levels in middle-income markets ranged from a mere $0.2 in India to $6.6 in Thailand in 2019. Higher numbers of cancer patients in high-income markets might explain some of the vast differences across Asia-Pacific. Yet cancer drug expenditure per cancer case were still less than $600 in India and Indonesia while potentially reaching close to $18,000 in Singapore. Higher list prices of drugs and higher use of drugs with better patient accessibility via reimbursement might explain some of the remaining differences.

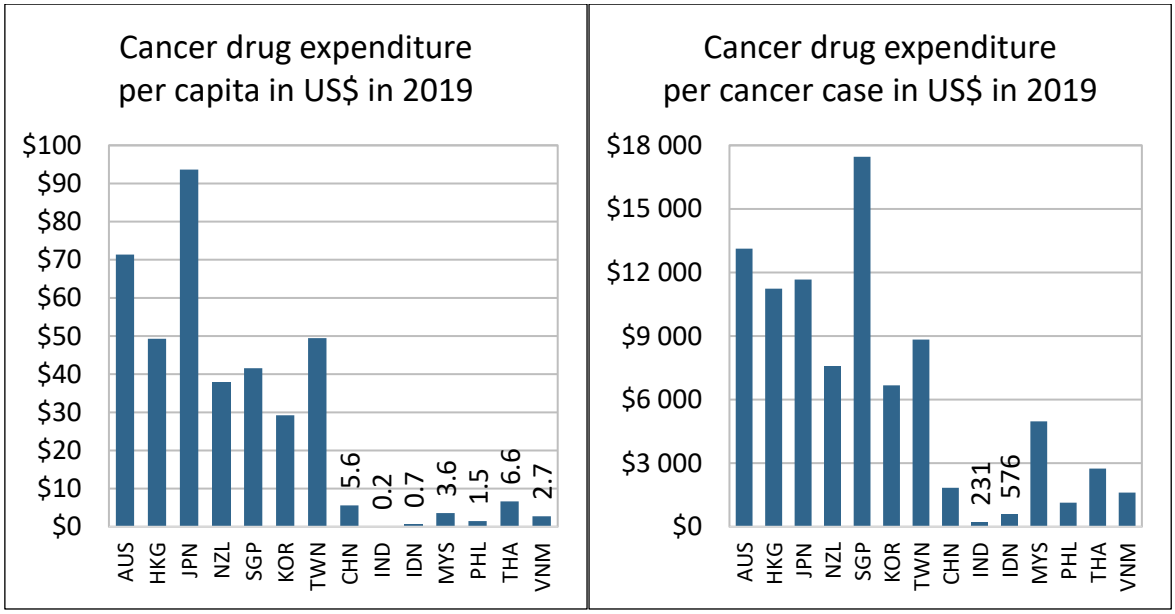

Figure 12: Cancer drug expenditure per capita and per cancer case in US$, 2019

Notes: Cancer drug expenditure are based on sales data from IQVIA, which are based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates. Cancer case is defined as cancer incidence (newly diagnosed cases), and cases in Singapore might be somewhat underestimated.

Despite higher spending on innovative cancer drugs, even high-income markets may struggle to meet patient needs

High-income markets in Asia-Pacific may struggle to meet patient needs for innovative cancer drugs despite much higher levels of spending and high proportions of reimbursement. For older innovative drugs, most high income-markets seem to meet patient needs (here quantified by a comparison of the drug volume needed to treat all eligible patients with the actual drug volume administered), whereas for newer innovative drugs (such as immunotherapies) this might generally not be the case; see Figure 13. Rigid clinical processes and narrow reimbursement criteria might explain this. In middle-income markets, unmet patient needs hinge crucially on whether or not a drug is reimbursed. Without reimbursement, patients are forced to pay the full price out-of-pocket. This exceeds the financial means of most patients even when generic versions for older innovative drugs are already available, leading to high unmet patient needs and subsequently many life years lost.

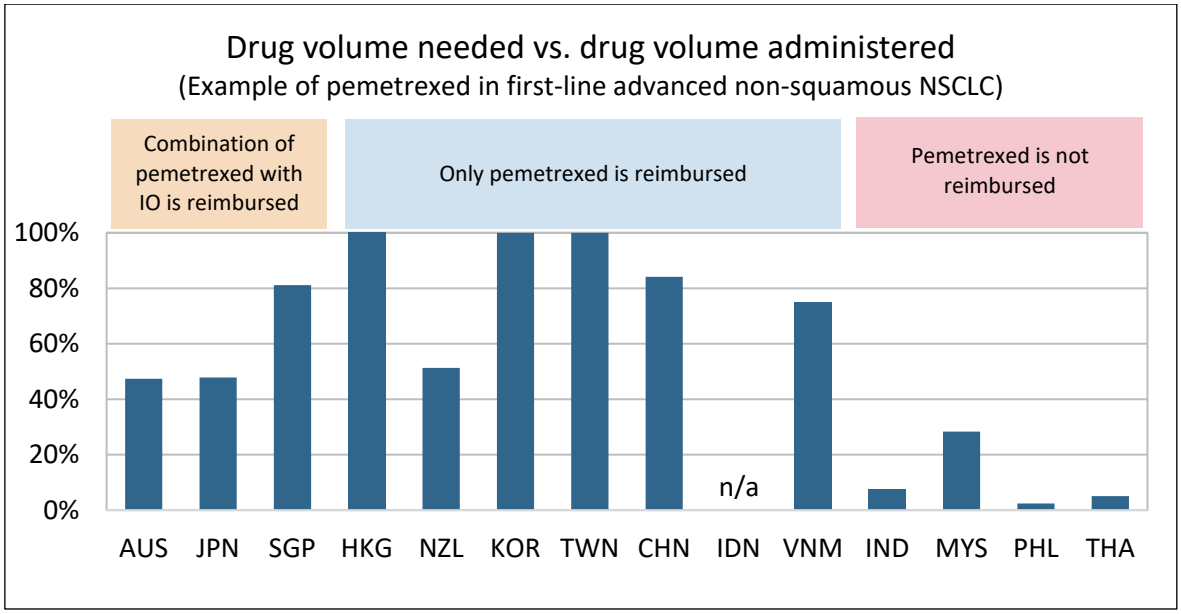

Figure 13: Degree of patient needs met based on drug volume needed vs. drug volume administered of pemetrexed in the third quarter of 2020

Notes: n/a = no data on drug volume administered available. NSCLC = non-small cell lung cancer. IO = immunotherapy. Y-scale = 50% means that half of the total drug volume needed to treat all eligible patients was administered. Drug volume needed (in milligram) based on estimated eligible patient numbers, taking into account decreased eligible patient numbers if EGFR/ALK inhibitors and IO monotherapy for high PD-L1 expression are reimbursed as well as standard dosage and treatment length. Drug volume administered based on IQVIA sales data (in milligram).

There is a clear positive association between the level of cancer drug expenditure and cancer patient outcomes

Low spending on cancer drugs and on cancer care in general is alarming. There is a clear positive association between the level of cancer drug expenditure and patient outcomes across markets in Asia-Pacific; see Figure 14. A relationship of this kind does not need to be causal, but it suggests that the amount of spending on cancer drugs – which typically is a strong indicator of expenditure on cancer care services overall – might be an important driver of success in the treatment of cancer. This mirrors previous analyses of the situation in Europe. In order for middle-income markets to start closing the gap on high-income markets and for high-income markets to ensure continued progress in patient outcomes, increased investment in cancer drugs and cancer care in general is required. This should be guided by evidence-based decision-making on the most efficient allocation of resources along the care process to secure the highest benefits to patients.

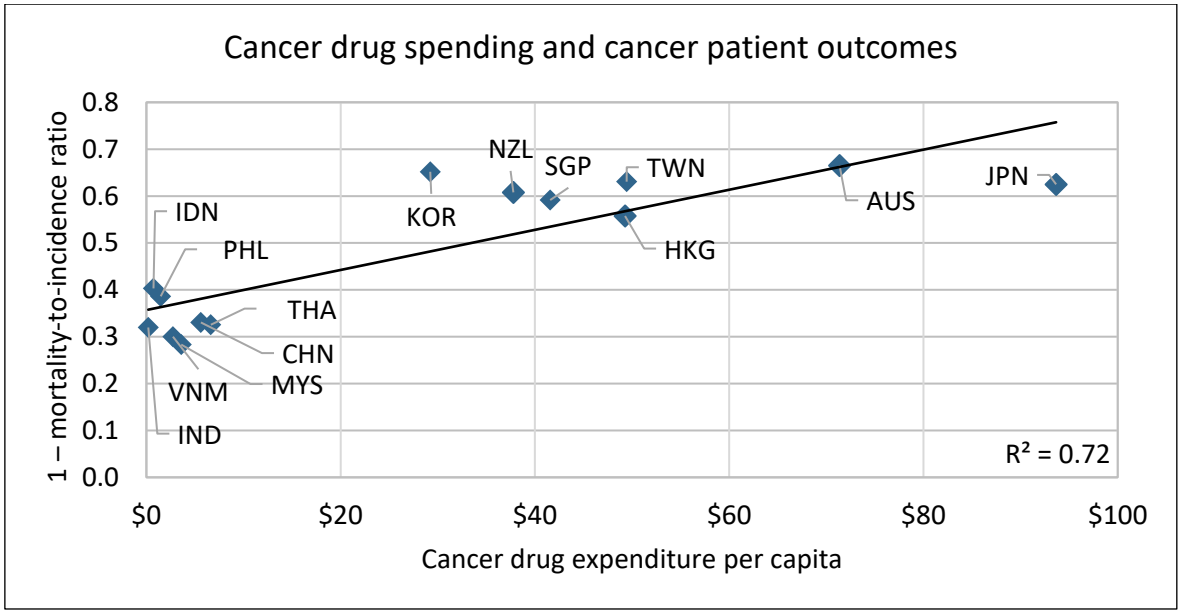

Figure 14: Total cancer drug expenditure per capita and complement of the mortality-to-incidence ratio of cancer, 2018

Notes: The "1 - mortality-to-incidence ratio" is used as proxy for survival, which reflects patient outcomes.

5. Pricing policies for off-patent cancer drugs

Pricing policies for off-patent cancer drugs are not fully effective in many markets

The increasing availability and high cost of innovative cancer drugs together with increasing cancer patient numbers puts financial pressure on the budgets of health care payers. One strategy to balance constrained budgets with patient access to new innovative cancer drugs lies within off-patent pricing mechanisms of older cancer drugs. Once a patent expires, market exclusivity is lost, and generic copies of the originator can enter the market. This stimulates competition between manufacturers and should cause the price of the originator drug to fall. Policies surrounding off-patent pricing mechanisms will affect the magnitude of price decreases of originator drugs, and larger price drops could generate substantial savings. In general, markets in Asia-Pacific react as anticipated with prices of originator drugs overwhelmingly falling after patent expiry (or loss of exclusivity); see Figure 15 for an example. Yet the magnitudes of these price drops vary substantially across drugs and markets, suggesting further efficiency that can be achieved in the health system.

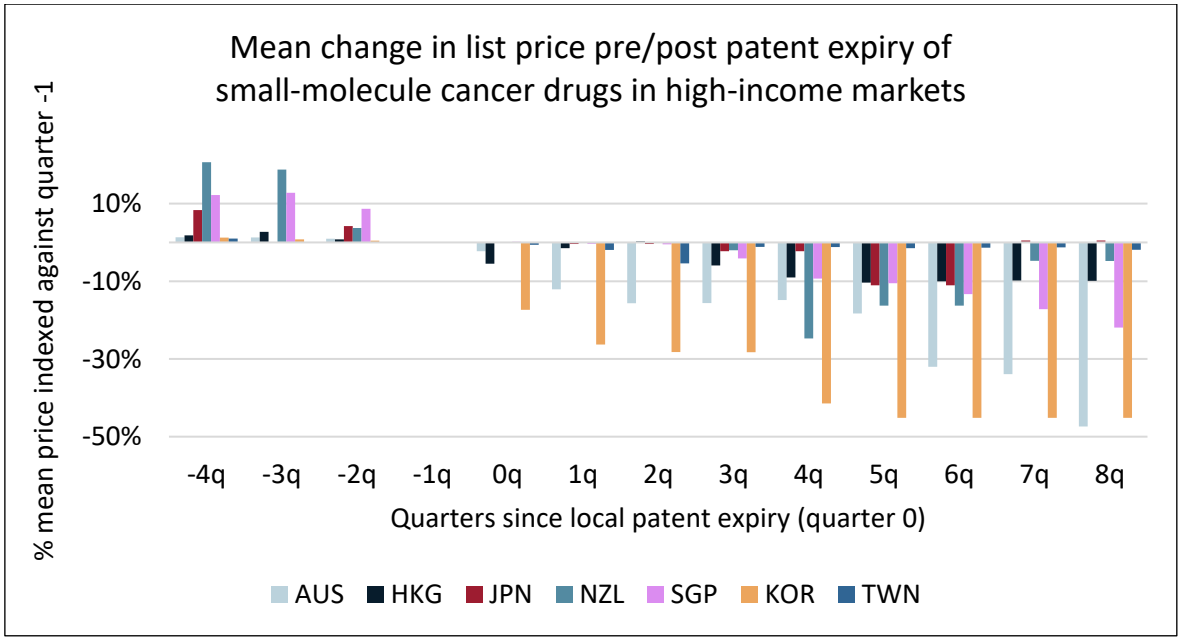

Figure 15: Mean change in list price pre/post patent expiry (or loss of exclusivity) of small-molecule cancer drugs in high-income markets

Notes: Eight major small-molecule cancer drugs with patent loss between 2010 and 2020 were included in the analysis. Quarter 0 refers to the quarter during which a drug's patent expired or (if the former information was not available) to the quarter during which the first generic version received regulatory approval or started being sold.

Effective pricing policies for off-patent cancer drugs could free up substantial resources for re-investment in new innovative cancer drugs

If more effective off-patent pricing mechanisms were adopted, markets in Asia-Pacific could achieve lower prices of originator drugs post patent expiry or loss of exclusivity. This could generate substantial savings. Drawing on a limited sample of 11 major cancer drugs with patent loss between 2010 and 2020, estimates indicate that the potential savings range from 3% to 20% of total cancer drug expenditure; see Figure 16. In middle-income markets where access to originator drugs is low, price drops associated with effective off-patent pricing mechanisms would likely trigger increased sales volumes, thus compounding the savings. Patent expiry should be viewed as an opportunity where effective policy can improve access to drugs and free up resources, thus creating budget headroom for reimbursing new innovative drugs. Ultimately, an effective re-channeling of resources from off-patent drugs to new innovative drugs could offer a more sustainable financing model of innovative drugs.

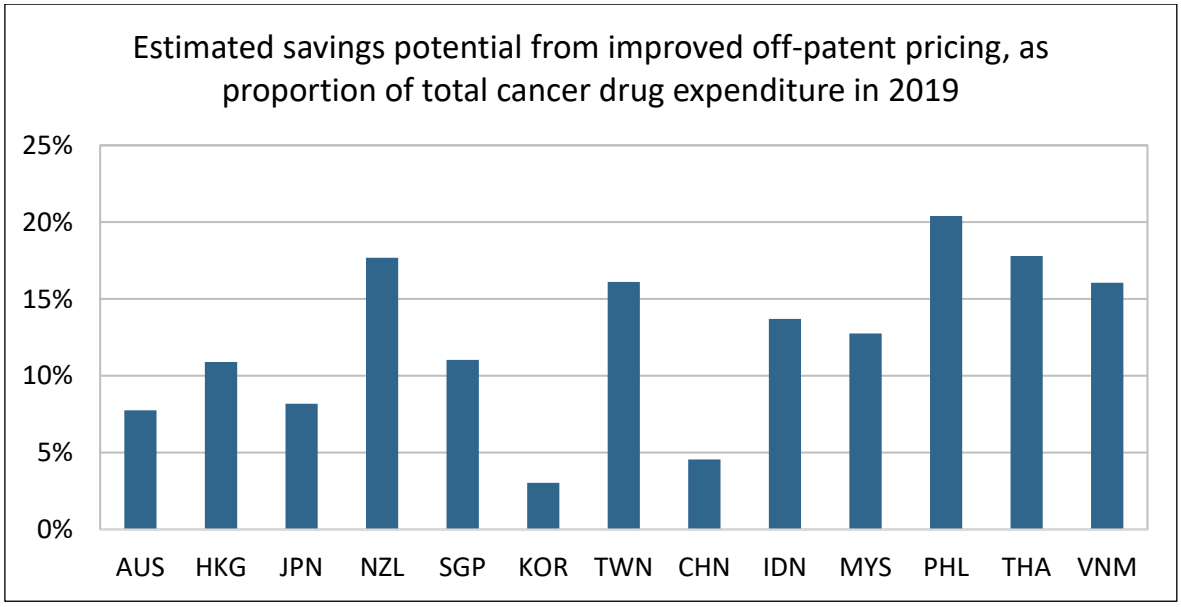

Figure 16: Estimated savings from more effective off-patent pricing outcomes of 11 cancer drugs as a proportion of total expenditure on all cancer drugs

Notes: No data available for India. Effectiveness is here defined as achieving the lowest possible price for the originator drug after patent expiry or loss of exclusivity. The analysis is based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers.

Call to action

Cancer is a growing challenge for health systems that requires political leadership across markets in Asia-Pacific. Instructive examples from other parts of the world are the Nixon administration's "*War on Cancer*" in 1971 in the United States or the Delors Commission's first "*Europe Against Cancer*" program in 1987 and the von der Leyen Commission's "*Europe's Beating Cancer Plan*" in 2021 in Europe. Policy makers in Asia-Pacific can learn from these examples and start prioritizing effective and comprehensive cancer control efforts to address the many challenges ahead. To this end, the WHO advocates National Cancer Control Programs to tackle cancer in a strategic way.

This report provides the following lessons learned:

1. The burden of cancer is growing, and a two-fold strategy is needed to tackle it. First, prevention efforts addressing major risk factors need to be reinforced to reduce the number of newly diagnosed cancer cases. Second, treatment provision needs to be improved to enable patient access to equitable and high-quality care to improve survival.
2. Success in the treatment of cancer is associated with the amount of spending on cancer drugs and more generally also with the amount of spending on health care and cancer care. Access to modern cancer treatment is limited in many markets in Asia-Pacific today. This is the result of a lack of universal health coverage, a small package of health services covered, high patient co-payments on covered health services, or a combination thereof. The root cause of this is insufficient public funding of health care.
3. Increased public spending on cancer care is needed to protect patients from financial hardship and to save lives. Reimbursement of cancer drugs is key for the vast majority of patients to gain access and to meet their clinical needs. Without reimbursement, patients are forced to pay the full price out-of-pocket. This exceeds the financial means of most patients even in cases when generic versions for older innovative drugs are available.
4. The recent wave of cancer drugs offers new treatment options for many patient groups. Not all drugs are equally effective and an increased focus on innovative drugs with the greatest clinical benefits to patients is needed. Use of health technology assessment can support evidence-based decision-making in reimbursement and allocation of constrained health resources to maximize patient outcomes.
5. Increasing efficiency in health systems deserves greater attention. For example, more effective measures are needed to stimulate competition between generic producers and to control prices of originator drugs after patent expiry. This can create considerable budget headroom, which can be reinvested in innovative cancer drugs that offer substantial clinical benefits to patients.

THE BURDEN OF CANCER IN ASIA-PACIFIC

Sub-report 1 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

Thomas Hofmarcher
George Keel
Peter Lindgren

IHE - The Swedish Institute for Health Economics

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Report summary

The burden of cancer is high in Asia-Pacific, accounting for approximately half of the global cancer deaths. Cancer is currently the leading cause of death in most high-income markets. It will increasingly become a major public health issue in middle-income markets based on current trajectories and experiences from other regions of the world.

The number of newly diagnosed cancer cases has increased from 6.6 million to 7.8 million between 2012 and 2018 in Asia-Pacific. A key driver in this development is population aging, which is taking place at an unprecedented rate across the region. While preventive measures (e.g., tobacco control cessation) could address around 30-50% of all new cancer cases, the provision of high-quality cancer treatment is key to reduce the risk of death for cases that cannot be prevented. Evidence from Europe and the United States shows that health investment in screening and treatment helps to improve outcomes of cancer patients.

Outcomes of cancer patients differ greatly across Asia-Pacific. For every 100 patients diagnosed with cancer, around 50-65 of them survive in high-income markets as compared to 30-40 in middle-income markets, based on estimates derived from mortality-to-incidence ratios. Recent developments also indicate that the situation for cancer patients in high-income markets continues to improve, while patient outcomes in middle-income markets are at best stagnating. A closer analysis of five major cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, lung cancer – confirms these different patterns observed in high-income and middle-income markets.

Predictions of the future cancer burden indicate increases in the number of newly diagnosed cases and deaths by around 50-60% until 2040 across Asia-Pacific. Advances and investments in all areas of cancer care – prevention, screening, diagnosis, treatment – are needed to meet the challenges brought upon by the demographic development. A clear prioritization of effective and comprehensive cancer control efforts could spare millions of people from getting cancer and simultaneously improve the lives of the millions of cancer patients over the coming decades. To this end, the WHO advocates National Cancer Control Programs (NCCP) to tackle cancer in a strategic way.

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1. The burden of cancer

Cancer is the second-leading cause of death globally, with around 1 in 6 deaths being due to cancer (3). In 2018, there were 18.1 million new cancer cases diagnosed, and 9.6 million cancer deaths worldwide (4). Across the 14 markets in Asia-Pacific[1] studied in this report, there were 7.8 million new cancer cases and 4.8 million cancer deaths. The region, which is home to around 47% of the global total population, thus accounted for almost 50% of the global cancer deaths (1, 2); see Figure 1.

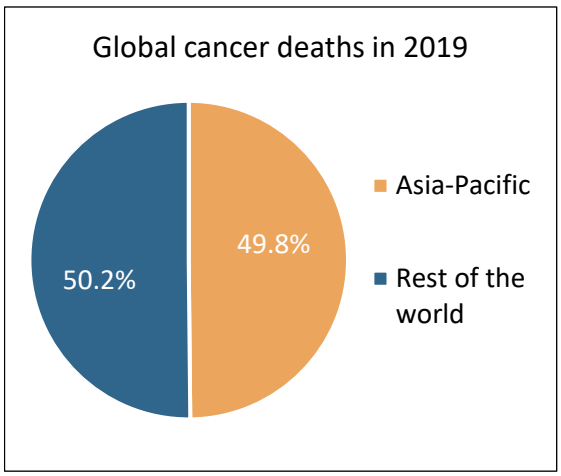

Figure 1: Global distribution of cancer deaths, 2019

Notes: Asia-Pacific consists of the 14 markets considered in this report. All WHO member states and Taiwan are included.
Source: WHO (1) and Taiwan Ministry of Health and Welfare (2).

The global distribution of cancer is uneven. Europe and North America have relatively more new cancer cases in relation to their total population, while Africa has relatively fewer cases. Asia-Pacific falls somewhere in between (4).

The uneven global distribution of cancer points to one of the root causes of cancer: aging. Although cancer can affect people of all ages, the probability of a person to get cancer increases dramatically with age. This is partly because the cellular repair mechanisms become less effective as a person grows older and partly because of an accumulation and exposure to risks[2] over a person's lifetime (3). As people live to older ages and the proportion of elderly increases within a population, naturally the number of cancer incidence would increase. Asia-Pacific has been facing this very scenario of "population aging" in the past decades (5). Since 2000, population aging has been the result of both longer life expectancy (6-year increase in low and lower-middle income countries, 4-year increase in upper-middle and high-income countries) and declining fertility rates (falling from 2.6 to 2.1 per woman of reproductive age). This development is predicted to continue in the coming decades (5), and will exert a substantial upward pressure on cancer numbers (6).

[1] Asia-Pacific consists in this report of 7 high-income markets – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 middle-income markets – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam.
[2] These risks include, for instance, tobacco use, alcohol use, unhealthy diet, physical inactivity, infection with carcinogenic viruses (such as human papillomavirus (HPV) and hepatitis B virus) or with *Helicobacter pylori*, indoor and outdoor air pollution, and ionizing and ultraviolet radiation.

While cancer is a critical public health issue that will become increasingly important to address in Asia Pacific, there is a silver lining. First of all, around 30-50% of all cancer cases are preventable and prevention is key to stem the tide, as emphasized by the World Health Organization (WHO) (3, 7). Second, for all cancer cases that cannot be prevented, the risk of death can be reduced through the provision of high-quality cancer treatment. Evidence from Europe and the United States analyzing the development in recent decades shows that improvements in screening and treatment have helped to improve the prospects of cancer patients (8-11). A clear political commitment, such as the Nixon administration's "War on Cancer" in 1971 in the United States or the Delors Commission's first "Europe Against Cancer" program in 1987 in Europe, was certainly beneficial in this regard (12, 13). Policy makers in Asia-Pacific can learn from these examples and prioritize cancer control efforts to address the challenges ahead. However, a prerequisite for effective cancer control is a good understanding of the magnitude of the burden of cancer.

1.1 Measuring the burden of cancer

Population-level and individual-level measures are needed to characterize the burden of cancer.

- **Population-level measures**: How many new cancer cases and cancer deaths are there in a country?
    - Newly diagnosed cases (**incidence**): The number of new cancer cases diagnosed in a certain year in a specific geographical area; commonly expressed per 100,000 inhabitants ("incidence rate").
    - Deaths (**mortality**): The number of deaths caused by cancer in a certain year in a specific geographical area; commonly expressed per 100,000 inhabitants ("mortality rate").

Incidence rates and mortality rates are presented as "crude rates" in this report, i.e., raw data on incidence and mortality divided by the total local population (per 100,000 inhabitants). Crude rates are needed, because countries differ in population size and also themselves experience changes in population size over time. Crude rates are also a relevant measure for policy makers to look at, as for instance a growing total population per se is not a problem, provided that a growing population entails more income earners and taxpayers who can help finance the health care system.[3]

[3] Age-standardized rates are not considered in this report. In addition to standardizing incidence and mortality numbers by total population size, they take into account different age structures between countries or within the same country over time. This erases the influence of population aging on incidence and mortality statistics. Yet population aging is one of the key challenges in Asia-Pacific, as explained in section 2.

- **Individual-level measures**: Will a patient survive cancer?
    - **5-year survival rate**: The proportion of patients diagnosed with cancer in a certain year that is still alive after five years; commonly expressed in %.
    - **Complement of the mortality-to-incidence ratio** (1–MIR): The number of deaths divided by the number of newly diagnosed cases in a certain year (MIR), with this ratio being subtracted from 1 to make it resemble survival rates; commonly expressed as a raw number.
    - **Disability-adjusted life years** (DALYs) **lost per patient**: One DALY represents one year of healthy life lost (14). DALYs are computed as the sum of two components; Years of Life Lost (YLL) due to premature death caused by a disease and Years of Life Lost to Disability (YLD) due to an impaired health state caused by a disease. In this report, DALYs are standardized by the number of newly diagnosed cancer cases.

The complement of the MIR (1–MIR) is used as a proxy for survival in this report, despite its limitations pointed out in previous literature (15, 16). The ideal measure would be the 5-year survival rate. However, many markets in Asia-Pacific do not have reliable data on this due to the lack of high-quality population-based cancer registries. DALYs lost per patient are used as an additional measure of the cancer burden in this report, as it considers morbidity on top of mortality.

1.2 Aim of the sub-report

The aim of this sub-report is to describe the burden of cancer in Asia-Pacific.

- Section 2 explains the past development of the cancer burden leading up to the current status.
- Section 3 focuses on the past development of five selected cancer types.
- Section 4 provides an outlook of the future development of the cancer burden.

2. The burden of cancer over time

This section describes the burden of cancer in Asia-Pacific with the help of different population-level and individual-level measures. It aims to answer the following questions: What is the size of the cancer burden in relation to other diseases? What is the trend in the cancer burden at the population level? What is the trend in the cancer burden at the individual level?

2.1 Method and data

Different kinds of data sources were combined to obtain relevant information on the burden of cancer. To compare cancer to other diseases, data on the causes of death were obtained. The main source was the "Cause-specific mortality" database maintained by the WHO (1). For Hong Kong and Taiwan, this information was directly obtained from respective local authorities (2, 17).

Information on cancer incidence and cancer mortality was primarily obtained from publicly available national cancer registries or publications that provide estimates on incidence and mortality based on data from regional cancer registries. For countries without such data, estimates from GLOBOCAN (Global Cancer Observatory) – a global database on cancer statistics maintained by the International Agency for Research on Cancer (IARC), part of the WHO – were obtained. Data for the years 2012 and 2018 (or nearest year) were sourced for all 14 markets; see Table A1 in the Appendix for further information and links to sources. Cancer was defined as all malignant cancer sites but non-melanoma skin cancer[4] (ICD-10 C00-C97/C44) wherever possible.

Box 1: Data quality of the national cancer registry in Malaysia

In Malaysia, the national cancer registry publishes reports covering 5-year periods (18). The latest report covers the period 2012-2016 and reported 115,238 incidence cases and 82,601 deaths, up from 103,507 cases and 64,275 deaths, respectively, in the period 2007-2011. The numbers for 2012-2016 correspond to yearly average of 23,048 new cases and 16,520 deaths. In comparison to these yearly averages, GLOBOCAN estimates that there were 43,372 new cases (88% difference) and 26,207 deaths (59% difference) in 2018, based on its own methodology to derive cancer statistics in countries with low-quality data (19). This echoes cautions by the Breast Cancer Welfare Association Malaysia of grave underreporting of cancer cases in Malaysia (20).

The foundation for analyses of trends in the cancer burden are solid data from population-based nationwide cancer registries. Most middle-income markets either lack such cancer registries or have national/regional registries of poor quality; see Box 1. Therefore, results from the analysis of both the size of the cancer burden and trends over time should

[4] Non-melanoma skin cancer is commonly excluded from incidence data (and sometimes also from mortality data), as its registration is often incomplete and inaccurate, as it is usually non-fatal and treated in primary care.

be taken as directional and considered with caution across middle-income markets. Some high-income markets also either publish annual key statistics on cancer with rather long delays (more than 2 years in Australia, New Zealand, and South Korea) or fail to publish comprehensive key statistics (incidence, prevalence, mortality, survival) in annual reports (e.g., South Korea does not include information on mortality). Singapore publishes no annual reports and only covers five-year periods – the latest report covering 2013–2017; see also Box 2.

Box 2: GLOBOCAN data, WHO data, and national cancer registry data in Singapore

In Singapore, the national cancer registry reported 71,265 new cases and 27,730 deaths during 2013-2017 (21), corresponding to yearly averages of 14,253 new cases and 5,546 deaths. The Ministry of Health reported around 29,400 cancer deaths (6% difference) during 2013-2017 (22). GLOBOCAN estimates that there were 25,770 new cases (81% difference) and 13,066 deaths (136% difference) in 2018 (19). GLOBOCAN data seem to seriously overestimate the number of new cases and of deaths. The WHO Global Health Estimates report 7,898 cancer deaths in 2019 compared to 26,834 total deaths (1), which are both higher numbers than reported by the Ministry of Health, but the proportion of cancer deaths is very similar.

Information on disability-adjusted life years (DALY) caused by cancer (defined as malignant neoplasms) were obtained from the WHO (23), and combined with information on newly diagnosed cancer cases from the sources indicated above.

2.2 Results

The burden of cancer in relation to other diseases

Cancer is one of the leading causes of death in Asia-Pacific. During the past two decades, the number of cancer deaths has increased from 3.2 million in 2000 to 4.7 million in 2019.[5] In 2000, cancer was already the leading cause of death in three high-income markets (Hong Kong, Japan, Taiwan) and one middle-income market (Thailand); see Figure 2. In 2019, cancer had become the leading cause of death (accounting for 29-31% of all deaths) in all high-income markets except in Singapore where cardiovascular diseases are still narrowly leading. Across all middle-income markets, the proportion of deaths attributed to cancer has also expanded between 2000 and 2019; it ranged from 9% of deaths in the Philippines to 25% of deaths in China in 2019.

The development in Asia-Pacific parallels the development in Europe in recent decades. While cancer is still the second-leading cause of death behind cardiovascular disease across the continent, in some countries (Denmark, France, Netherlands, and the UK) cancer is already the major killer

[5] Estimated numbers of cancer deaths differ from source to source. As noted in section 1, there were 4.8 million deaths in 2018 based on data from national cancer registries and GLOBOCAN, whereas the estimate of 4.7 million deaths in 2019 here is based on data from the WHO and the local authorities in Taiwan.

(24). With the shifting demographics and changing lifestyles, there is an urgent need to address growing demands in health care to maintain the well-being of the population.

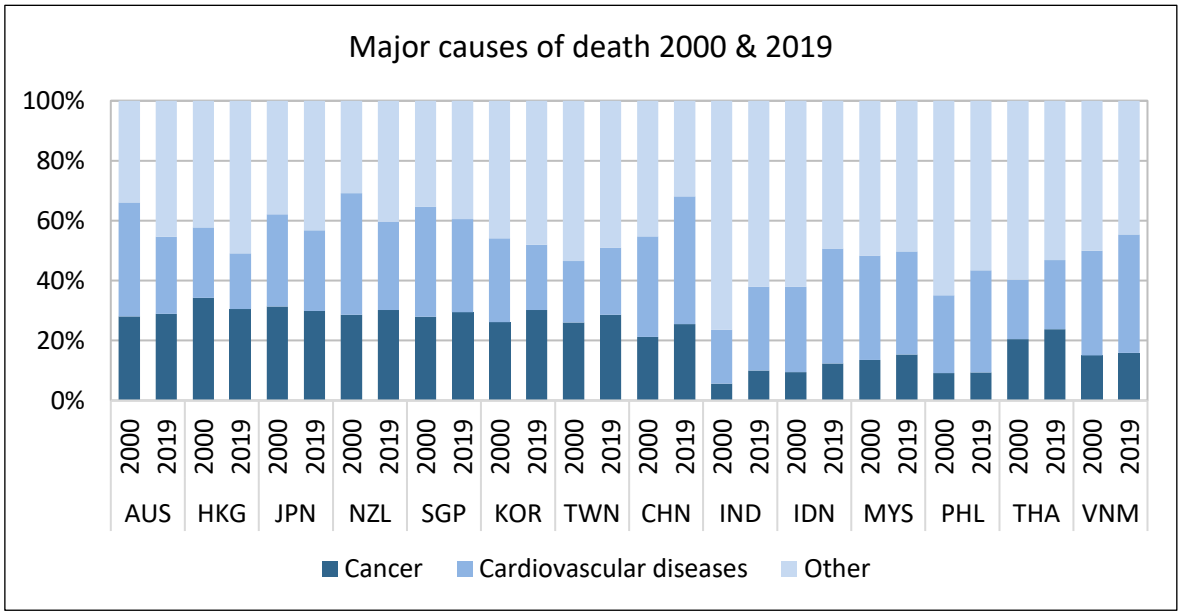

Figure 2: Major causes of death, 2000 and 2019

Notes: Cancer is defined as malignant neoplasms in all markets. Cardiovascular diseases (ICD-10: I00-I99) are somewhat underestimated in HKG (only include ICD-10: I00-I09, I11, I13, I20-I51, I60-I69) and in TWN (only include ICD-10: I01-I02.0, I05-I09, I10-I15, I20-I25, I27, I30-I52, I60-I69, I71). Numbers in 2000 in HKG and TWN refer to 2001 due to lack of data.
Source: WHO (1), except for HKG (17) and TWN (2).

The burden of cancer at the population level

The number of newly diagnosed cancer cases has increased from 6.6 million to 7.8 million between 2012 and 2018 in Asia-Pacific. To take into account the influence of overall population growth in this period, Figure 3 shows incidence rates of cancer per 100,000 inhabitants for all 14 markets. There are two key observations to be made. First, incidence rates differ largely in magnitude between markets, ranging from below 100 new cases per 100,000 inhabitants in India and Malaysia to over 800 new cases per 100,000 inhabitants in Japan in 2018. In comparison, the crude incidence rate in Europe was just below 600 in 2018 (24). The differences in magnitude are largely explained by differences in the age-specific composition of the population in the different markets. The incidence of cancer rises dramatically with age (3), meaning that a population consisting of a larger proportion of older people will record more cancer cases. In fact, Figure 4 shows that the proportion of people aged 65 years or above ranged from around 6-7% in India, Indonesia, Malaysia, and the Philippines to 28% in Japan in 2020. This four-fold difference should be kept in mind when seeing the eight-fold difference in incidence rates between Japan and middle-income markets in Figure 3.

The second key observation from Figure 3 is that the number of newly diagnosed cancer cases has been increasing between 2012 and 2018 in all markets, despite the limited time period. Increases were minimal in South Korea, New Zealand, and Australia during this period, yet a look further back in time in the respective national cancer registries reveals large increases (e.g., 110% increase in the crude rate between 2000 and 2017 in South Korea) (25-27). This is also similar to the situation in some of the Nordic countries in Europe which have experienced shorter periods of stagnating cancer incidence rates, whereas long-term trends are unambiguously going up (28).

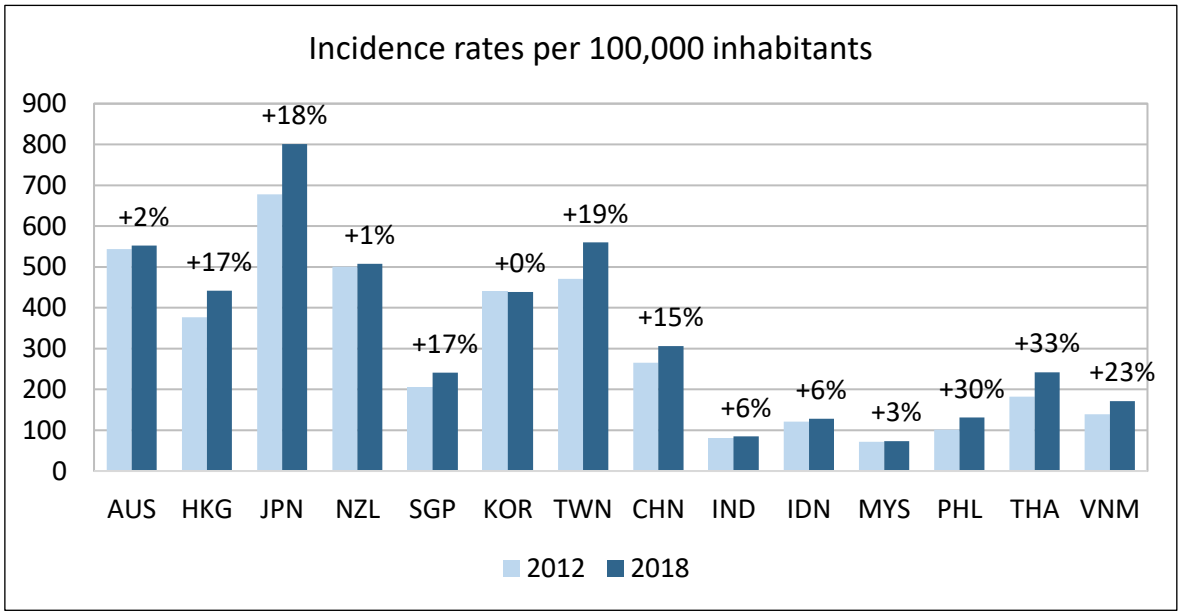

Figure 3: Cancer incidence per 100,000 inhabitants (crude rates), 2012 and 2018

Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

In general, increases in cancer incidence in Asia over time have been documented before (29). Major factors explaining increasing cancer incidence rates are as follow:

- **Population aging**: As the risk of getting cancer increases with age, an aging population contributes to an increasing number of cancer cases. Figure 4 shows the age structure of all 14 markets in 2000 and 2020. The proportion of people aged 65 years or above has been increasing considerably in all markets. In several markets the proportion more than doubled.
- **Risk factors**: Several lifestyle factors are linked to cancer (7).[6] The WHO estimates that around 30-50% of all newly diagnosed cancer cases relate to these factors and are therefore

[6] The latest World Cancer Report of the WHO lists tobacco consumption, infectious agents (e.g., *Helicobacter pylori*, human papillomaviruses, hepatitis B and C viruses), alcohol consumption, sunlight and ultraviolet radiation, ionizing radiation (from both natural sources and artificial sources such exposure to medical radiation), diet and nutrition (high intake of processed meat and red meat and low intake of fruits and

assumed to be preventable (3). Not all risk factors are equally carcinogenic. Smoking is the most important risk factor globally (7). In fact, recent studies for Sweden, the UK, and the US show that cigarette smoking is responsible for almost half of all preventable cancer cases (30-32). Recent studies for East Asia also point to smoking as major public health problem (33). Changing smoking behaviors and changing patterns in all other risk factors (e.g., obesity, HPV infection rates) over time will eventually affect cancer incidence rates. However, several decades may pass between the exposure to a carcinogen and the diagnosis of cancer (called latency period) (34).

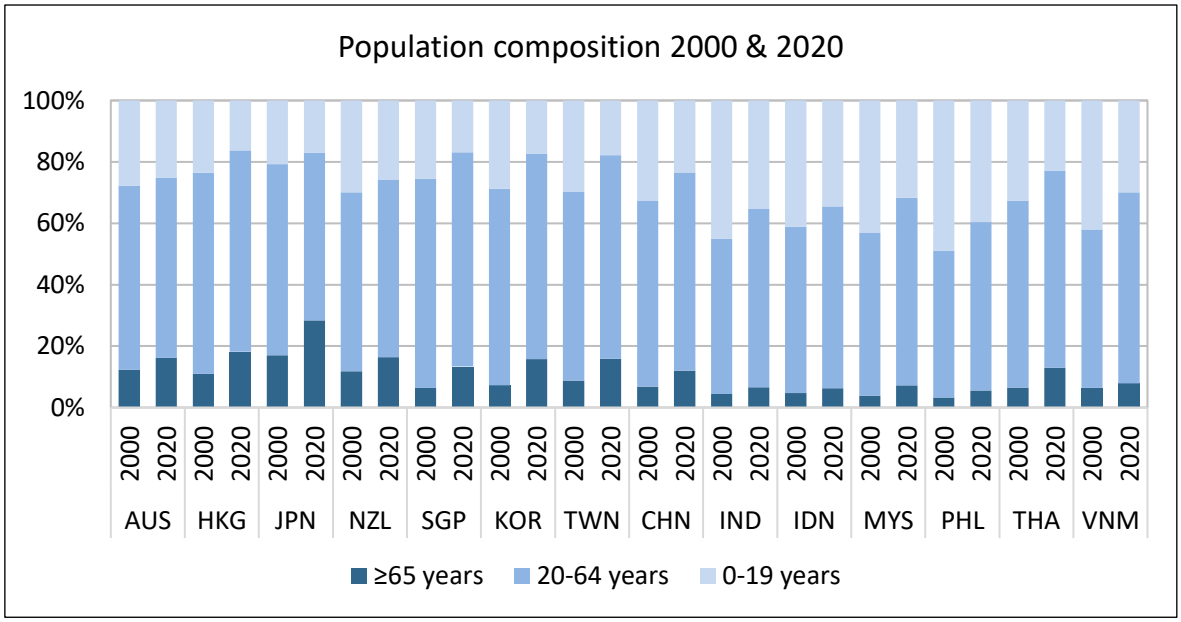

Figure 4: Population composition by age group, 2000 and 2020

Notes: Numbers for 2020 are based on the "medium fertility variant". Source: United Nations (35).

- **Screening**: Established screening methods are available for some cancer types; breast cancer, cervical cancer, colorectal cancer, lung cancer, prostate cancer. In high-income markets in Asia, population-based screening programs for breast cancer exist and opportunistic screening is also done in middle-income markets (36). Similarly, opportunistic prostate cancer screening is common in some markets (37). Lung cancer screening for people who are or have been heavy smokers is comparatively new and has been trialed mostly in China, Japan, and South Korea (38). Even though screening is vital for early detection of

vegetables), physical inactivity, obesity, dietary carcinogens (e.g., aflatoxin and aristolochic acid), contamination of air (airborne particulate matter originating from, e.g., fuel combustion for transportation or and domestic heating and cooking.), water, soil, and food (e.g., through arsenic), occupational carcinogens (e.g., asbestos, polycyclic aromatic hydrocarbons, heavy metals), pharmaceutical drugs (e.g., hormonal contraceptives) (7).

cancer, some screening methods – mammography for breast cancer and PSA testing for prostate cancer – also lead to the detection of a considerable proportion of cases of latent disease that never would have become symptomatic, i.e., overdiagnosis (39, 40). The implementation of such screening programs or greater participation and use of screening in general inflates cancer incidence rates over time.

- **Competing risks of death**: The risk of getting cancer is influenced by the epidemiological development in other diseases. More people are nowadays surviving previously fatal diseases (e.g., myocardial infarction) as a result of improvements in health care and medicine. This is especially true for many cardiovascular diseases; see the declining share of cardiovascular diseases in Figure 2 in most high-income markets. As more people reach an advanced age, this leaves more people at risk of getting cancer (41).

The number of cancer deaths has increased from 3.8 million to 4.8 million between 2012 and 2018 in Asia-Pacific. Figure 5 shows mortality rates of cancer per 100,000 inhabitants for all 14 markets. These numbers should not be interpreted in isolation but rather interpreted together with the numbers for incidence rates in Figure 3. There are two observations to be made. First, mortality rates differ largely in magnitude between markets, ranging from around 50 deaths per 100,000 inhabitants in India and Malaysia to 300 deaths per 100,000 inhabitants in Japan in 2018. In comparison, the crude mortality rate in Europe was 275 in 2018 (24). A high mortality rate of a market does not necessarily indicate something about that country's effectiveness of cancer care. As Japan had by far the highest incidence rate in 2018, it is not surprising to find that it also had the highest mortality rate, and vice versa for India and Malaysia.

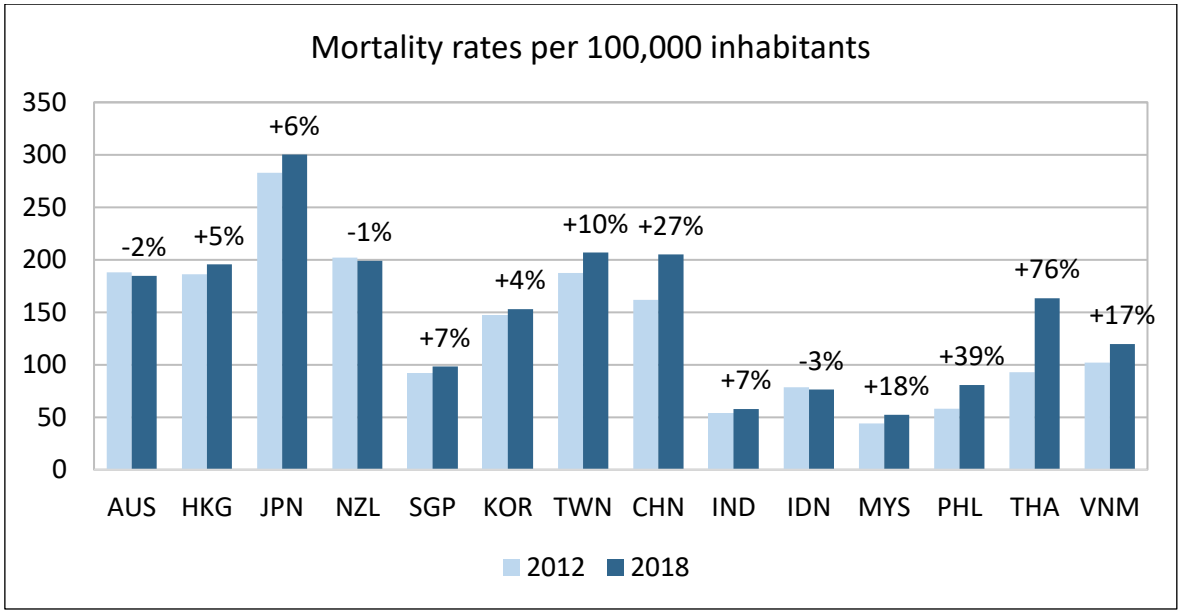

Figure 5: Cancer mortality per 100,000 inhabitants (crude rates), 2012 and 2018

Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

The second observation from Figure 5 is that the number of cancer deaths has been increasing between 2012 and 2018 in most markets. This mirrors the observed development for incidence rates, as more new cancer cases imply, ceteris paribus, more deaths. Trends in explaining incidence (population aging, risk factors, screening programs, epidemiological development in other diseases) are thus also relevant for explaining trends in mortality. In addition, trends in the quality of cancer care (diagnostics and treatment) influence trends in mortality. Australia and New Zealand managed to achieve small reductions in mortality rates between 2012 and 2018.[7] Such small reductions have also been observed in several countries in Europe between 1995 and 2018 (24). Trends in middle-income markets, such as the small reduction in Indonesia and the massive increase in Thailand, should be interpreted with caution, as changes to GLOBOCAN's methodology and data inputs to estimate cancer cases might heavily affect the results (42, 43). Yet, despite the data limitations, the trajectories in middle-income markets are undoubtedly increasing; see also section 4.

[7] South Korea is an example where mortality rates increased slightly despite a stagnation in incidence rates. Such patterns are rather unusual and do not necessarily indicate that the quality of cancer treatment has become worse. An explanation could be shifting proportions in cancer types with different survival profiles, such as an increase in the incidence of pancreatic cancer and an equally large decrease in the incidence of breast cancer.

The burden of cancer at the individual level

The cancer burden at the population level is also a reflection of the burden at the individual level. Success in the fight against cancer is often judged by looking at survival rates, which indicate the proportion of diagnosed patients that are still alive after a certain period of time (typically after 5 years as an indication of being "cured"). In the absence of comparable data on survival rates across all 14 markets in Asia-Pacific, the complement of the mortality-to-incidence ratio (1–MIR) is considered as a proxy. A higher 1–MIR implies a higher survival rate.

Figure 6 shows the 1–MIR for all 14 markets in 2012 and in 2018. Both levels and trends in the 1–MIR are noteworthy. All high-income markets achieve much higher 1–MIRs than the middle-income markets. For every 100 patients diagnosed with cancer, around 50-65 of them would survive in high-income markets as compared to 30-40 in middle-income markets. In China, India, Malaysia, Thailand, and Vietnam around twice as many newly diagnosed patients die from cancer as in Australia and South Korea. These vast differences can also be observed for actual 5-year survival rates shown in Figure A1 in the Appendix for a selected number of cancer types and markets with available data in the CONCORD-3 study (44). This study concluded that patients in the USA and Canada in the Americas, in Australia and New Zealand in Oceania, and in Finland, Iceland, Norway, and Sweden in Europe tended to have the highest survival for most cancers around the world in patients diagnosed in 2010 to 2014.

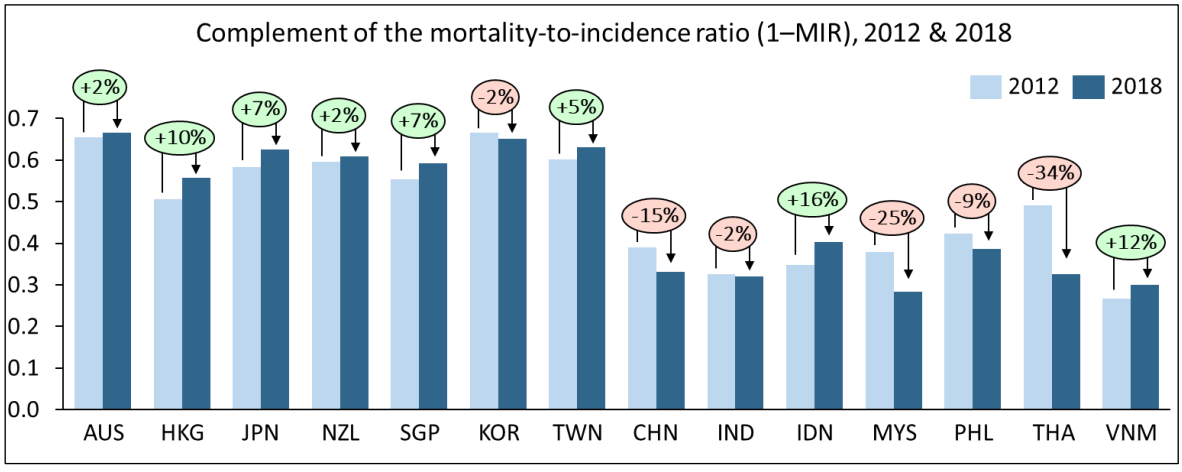

Figure 6: Complement of the mortality-to-incidence ratio of cancer, 2012 and 2018

Notes: Numbers in ellipses show relative changes. Differences in the frequency of common cancer types with differing survival rates impede market comparisons.
Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

Trends in the 1–MIR between 2012 and 2018 in Figure 6 suggest improvements in cancer treatment in most high-income markets. This resembles the development in Europe where the 1–MIR increased

slightly by 2% in relative terms during the same period (24). Trends in middle-income markets[8] need to be interpreted with caution in the absence of data from nationwide population-based cancer registries. Nonetheless, the decrease in the 1–MIR in middle-income markets foreshadows difficulties in maintaining even modest quality levels in cancer treatment in the face of the increasing patient numbers shown in Figure 3. Comprehensive cancer control plans and actions are required to halt this negative development.

Another measure to gauge the burden of cancer at the individual level is DALYs lost per patient. Figure 7 shows results for this measure and both levels and trends are again noteworthy. In all high-income markets fewer DALYs are lost per patient than in the middle-income markets. This is in line with the findings from the 1–MIR-analysis, where middle-income markets have lower 1–MIR. However, a lower burden in terms of DALYs per patient can be the result of both longer survival and higher quality-of-life. Trends over time indicate a stagnating cancer burden in most high-income markets, whereas the picture is more mixed in middle-income markets.

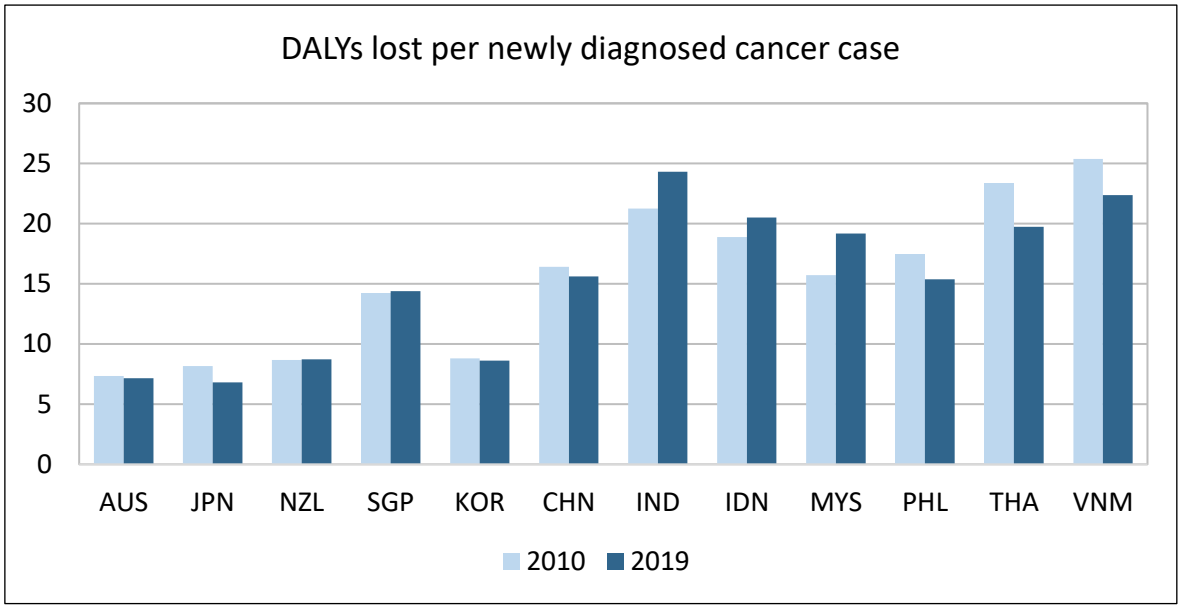

Figure 7: DALYs of cancer lost per newly diagnosed cancer case, 2010 and 2019

Notes: No comparable data for DALYs are available for HKG and TWN. In SGP, DALYs might be overestimated and cancer incidence underestimated (see Box 2), resulting in a too high estimate in this figure. Estimates of cancer incidence from 2012 and 2018 (see Table A1 in the Appendix) were used to standardize total DALYs in 2010 and 2019, respectively.
Source: WHO for DALYs (23), and national cancer registries and GLOBOCAN for incidence; see Table A1 in the Appendix.

[8] In China, the latest national estimates based on data from regional registries indicate that the 1–MIR has remained unchanged at 0.39 between 2012 (45) and 2015 (46). This might indicate that the GLOBOCAN estimate of 0.33 for 2018, and hence the 15% relative decrease in Figure 6, is overestimated.

3. The burden of selected cancer types

Cancer is the collective name of a group of over 100 diseases that are characterized by uncontrolled growth and division of cells. This section describes the burden of five major cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, lung cancer – in Asia-Pacific with the help of different population-level and individual-level measures. It aims to answer the following questions: What is the extent of the disease burden from these cancer types in relation to other cancer types? What is the trend in the burden of these cancer types at the individual level?

3.1 Method and data

Five major cancer types that are responsible for around half of all cancer cases across Asia-Pacific were selected for a deeper analysis in this and subsequent sub-reports. These are breast cancer (ICD-10 C50), gastro-esophageal cancer (C15-C16), head and neck cancer (C00-C14, C30-C32)[9], liver cancer (C22), and lung cancer (C33-34). Information on cancer incidence and cancer mortality was obtained from national cancer registries and GLOBOCAN as described in section 2.1; see also Table A1 in the Appendix for further information and links to sources.

3.2 Results

Cancers are commonly classified based on their primary site, i.e., based on the organ where the first tumor forms. Some cancer types are much more common than others, and the proportion of different cancer types may vary both across countries and within a country over time. Figure 8 shows the proportions of five major cancer types across the 14 markets for both incidence and mortality in 2018. Even though a diverse pattern is discernable, there are some similarities. Lung cancer and breast cancer each account for 6-18% of incidence, while lung cancer is responsible for around 20% of deaths in most markets. The five cancer types are jointly responsible for two thirds of deaths in China and Vietnam, but only about one third of deaths in Australia and New Zealand.

There are several noticeable patterns in Figure 8 that previous studies have related to differences in risk factors between markets.

[9] Some national cancer registries and GLOBOCAN do not report small sub-types of head and neck cancer. In Japan, C30-31 is missing; in New Zealand C30-32; in GLOBOCAN C14 and C30-31.

- Liver cancer is particularly common (more than 5% of total incidence and mortality) in China, Hong Kong, the Philippines, South Korea, Taiwan, Thailand, and Vietnam and has been linked to high infection rates with hepatitis B virus and hepatitis C virus (47, 48).
- Gastric cancer is particularly common in China, Hong Kong, India, Japan, Malaysia, South Korea, Singapore, Taiwan, Thailand, Vietnam and has been linked to high prevalence of *Helicobacter pylori* infection, higher consumption of salt and salt-preserved foods, as well as smoking (in men) (49, 50).
- Esophageal cancer is particularly common in China and almost half of all newly diagnosed cases globally occur there, but conclusive evidence on risk factors (such as indoor air pollution, exposure to polycyclic aromatic hydrocarbons) has not been reached yet (51-53).
- Head and neck cancer is particularly common in India. Head and neck cancer is generally associated with tobacco consumption, alcohol consumption, and human papillomavirus infection (54, 55), but the high rates in India have been linked to chewing of the "betel quid" containing the carcinogenic areca nut (56, 57).

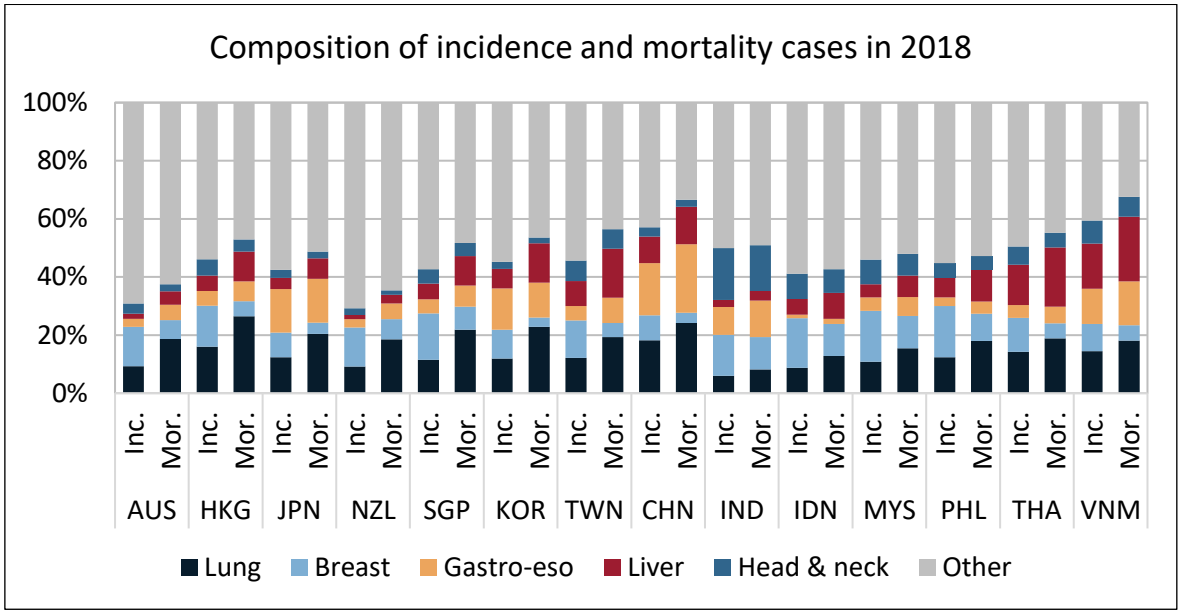

Figure 8: Proportion of selected cancer types in cancer incidence and mortality, 2018

Notes: Inc. = Incidence, Mor. = Mortality, Lung = NSCLC, Breast = breast cancer, Gastro-eso = gastro-esophageal cancer, Liver = liver cancer, Head & neck = head and neck cancer, Other = all remaining malignant cancer types.
Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

The burden of the five cancer types at the individual level differs considerably. Figure 9 shows the 1–MIR for the five types in all 14 markets. Breast cancer has the highest 1–MIR (indicating highest survival; see also Figure A1 in the Appendix) in all markets, whereas liver cancer has the lowest 1–

MIR in almost all markets closely followed by lung cancer and gastro-esophageal cancer.[10] The 1–MIRs for all cancer types are higher in high-income markets than in middle-income markets, indicating better cancer treatment in high-income markets in line with the results in section 2.2. A noticeable outlier among the high-income markets is gastro-esophageal cancer, with Japan and South Korea recording much higher 1–MIRs. This has been attributed to specific clinical factors, particularly earlier stage at diagnosis (58, 59).

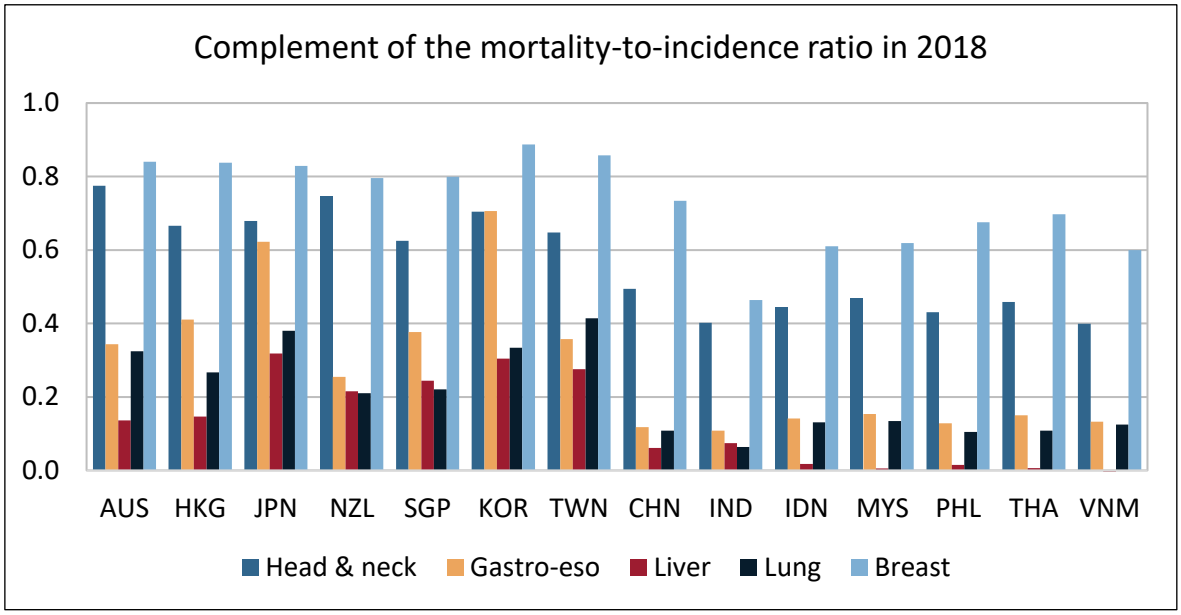

Figure 9: Complement of the mortality-to-incidence ratio of selected cancer types, 2018

Notes: Lung = NSCLC, Breast = breast cancer, Gastro-eso = gastro-esophageal cancer, Liver = liver cancer, Head & neck = head and neck cancer.
Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

Developments in the 1–MIR for the five cancer types between 2012 and 2018 are shown in Figure 10 (high-income markets) and Figure 11 (middle-income markets). Lung cancer and breast cancer experienced improvements (i.e., increase in the 1–MIR) in nearly all high-income markets, whereas 1–MIRs stagnated in Japan and New Zealand during this period; see Figure 10. Improved breast cancer screening leading to early detection and better treatment have been suggested as reasons behind the recent improvement in these markets (36). For lung cancer, screening was not available during this period but several drug treatments targeting a common genomic alteration (EGFR) in Asian lung cancer patients were introduced during this period (60); see sub-report 3. By contrast, the magnitudes of improvements made in liver cancer and head and neck cancer were smaller (especially

[10] The 1–MIR and the 5-year survival rate match quite closely for most cancer types. For example, Australia recorded 5-year survivals of 91% in breast cancer, 31% in gastric cancer, 22% in esophageal cancer, 71% in head and neck cancer, 20% in liver cancer, and 19% in lung cancer in the period 2012-2016 (25).

if compared the low baseline 1–MIR), which might be explained by a lack of clinical advancement with more effective treatment modalities (61-63).

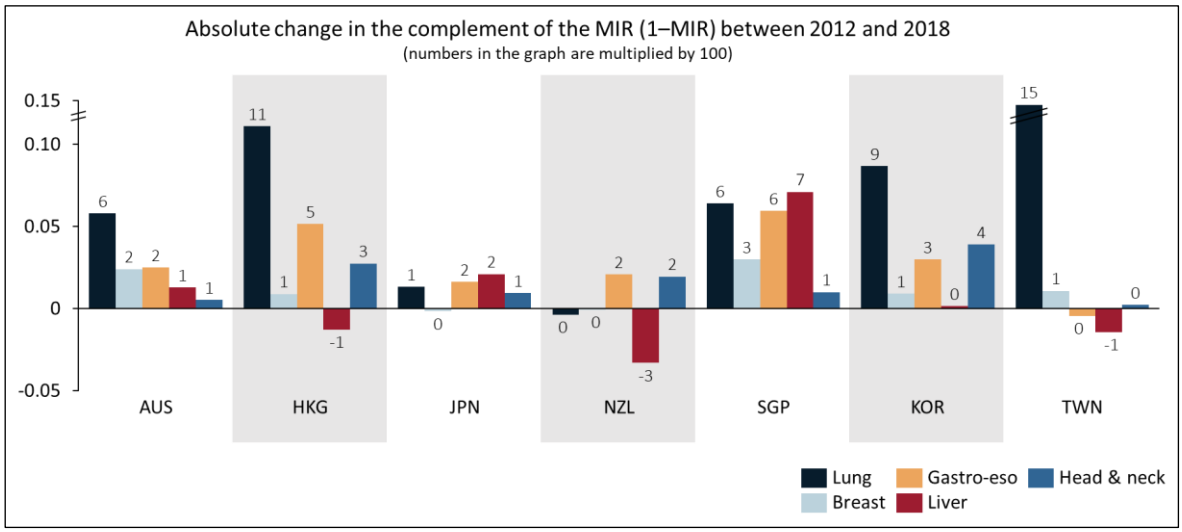

Figure 10: Absolute change in the complement of the mortality-to-incidence ratio between 2012 and 2018 in high-income markets

Notes: Lung = NSCLC, Breast = breast cancer, Gastro-eso = gastro-esophageal cancer, Liver = liver cancer, Head & neck = head and neck cancer. Numbers next to bars are multiplied by 100.
Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

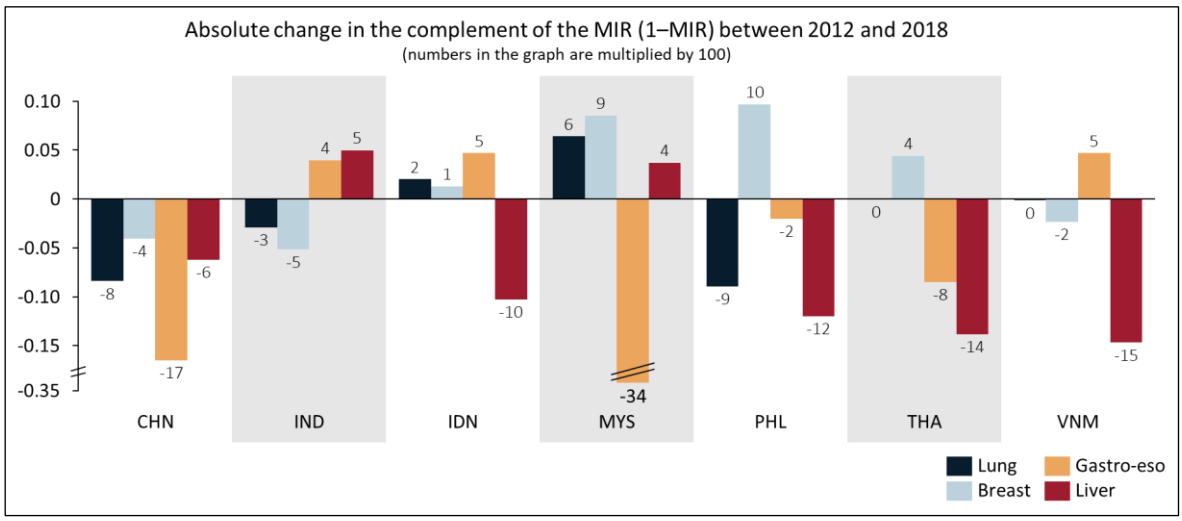

Figure 11: Absolute change in the complement of the mortality-to-incidence ratio between 2012 and 2018 in middle-income markets

Notes: Lung = NSCLC, Breast = breast cancer, Gastro-eso = gastro-esophageal cancer, Liver = liver cancer, Head & neck = head and neck cancer. No data available for head and neck cancer in any market in 2012. Numbers next to bars are multiplied by 100.
Source: National cancer registries and GLOBOCAN; see Table A1 in the Appendix.

As mentioned in section 2.2, trends in the 1–MIR in middle-income markets need to be interpreted with caution in the absence of data from nationwide population-based cancer registries. Recent developments in the 1–MIR, shown in Figure 11, suggest limited improvements across the considered cancer types. The only notable exception is breast cancer in Malaysia, the Philippines, and Thailand which showed significant improvements. This might be explained by increased awareness among women, decreased belief in ineffective traditional and alternative therapies, as well as improved treatment options (e.g., trastuzumab became available to patients in these markets during this period; see sub-report 3), although robust studies on this are lacking (36).

4. Future development of the cancer burden

This section provides an outlook of the future development of the cancer burden in Asia-Pacific. It aims to answer the following question: What might be the size of the cancer burden in 2040?

4.1 Method and data

Predictions of the future cancer burden are naturally uncertain. GLOBOCAN provides a tool to gauge the future development until 2040 in terms cancer incidence and cancer mortality (6). It uses two inputs in its predictions. First, national age-specific cancer incidence/mortality rates for the base year (here 2020) are calculated. It is assumed that these rates do not change in the prediction period until 2040. Thus, changes in risk factors associated with cancer such as smoking habits, obesity levels, etc. are not incorporated. Second, data from the United Nations on predicted changes in total population size and age structure until 2040 are used.[11] The expected number of new cancer cases or deaths in a country are computed by multiplying the age-specific incidence/mortality rates with the corresponding expected population sizes of different age groups in 2040. The predictions thus capture only the effect of the expected demographic development.

To better understand the underlying demographic development until 2040, data from the United Nations were also obtained (35).

4.2 Results

The expected demographic development in the 14 markets between 2020 and 2040 is depicted in Table 1 and Figure 12. In most high-income and middle-income markets, the total population is expected to grow by around 10-20%, while population numbers are expected to stagnate in South Korea, Taiwan, China, and Thailand and to decrease by 10% in Japan; see Table 1. A growing/declining population will accelerate/slow down the growth in the cancer burden. However, the changing composition of all populations in Asia-Pacific is much more important for the future development of the cancer burden. Figure 12 shows that the share of elderly people aged 65 years and above will increase in all markets. In China, Indonesia, Singapore, South Korea, Thailand, and Vietnam population aging will proceed at a noticeably rapid pace, with the proportion of elderly people expected to double within the course of the next 20 years. In Hong Kong, Japan, and South

[11] These numbers are based on the “medium fertility variant”.

Korea around one third of the population will be aged 65 years and above in 2040. This means that a considerable proportion of the population is of an age when the risk to get cancer is very high.

Table 1: Forecasted change in total population size between 2020 and 2040

	AUS	HKG	JPN	NZL	SGP	KOR	TWN
Relative change 2020 to 2040	+20%	+9%	-10%	+13%	+10%	-3%	-1%
	CHN	**IND**	**IDN**	**MYS**	**PHL**	**THA**	**VNM**
Relative change 2020 to 2040	+1%	+15%	+16%	+20%	+24%	-1%	+11%

Notes: Numbers for 2020 and 2040 are based on the "medium fertility variant".
Source: United Nations (35).

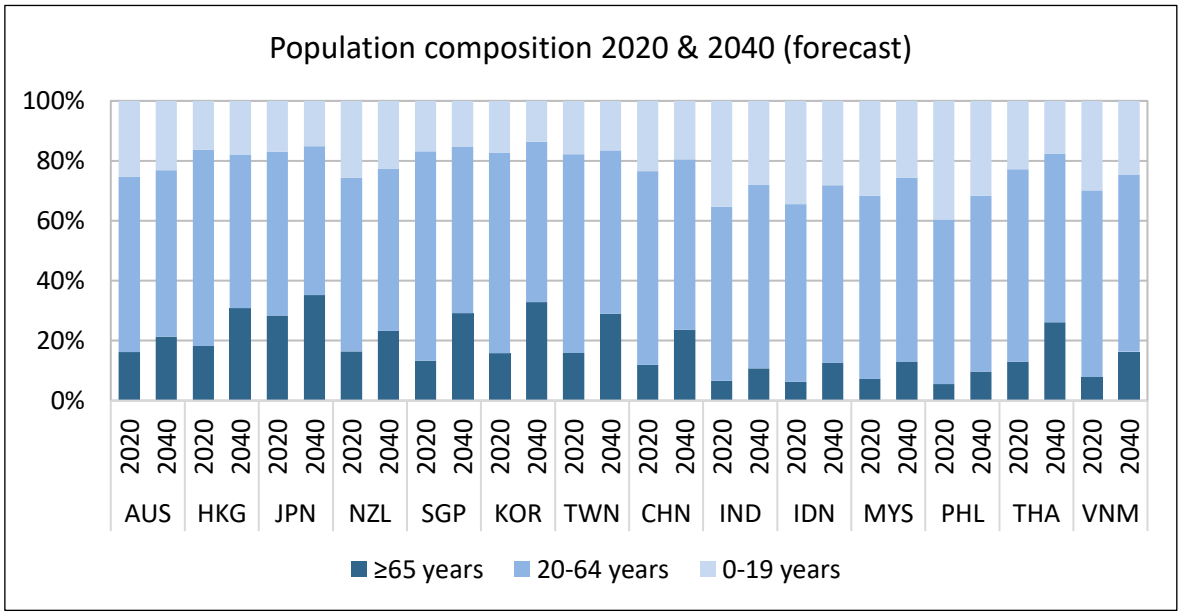

Figure 12: Forecasted population composition by age group, 2020 and 2040

Notes: Numbers for 2020 and 2040 are based on the "medium fertility variant".
Source: United Nations (35).

Against the backdrop of the expected demographic development (population aging in all markets and changing overall population sizes in some markets), Figure 13 illustrates the expected development of the cancer burden between 2020 and 2040. It shows what would happen if the status quo (base year 2020) remains, i.e., in the absence of further improvements in cancer treatment and prevention. All markets would be expected to record increases in incidence cases, ranging from 9% in Japan to 93% in Singapore, and in deaths, ranging from 23% in Japan to 139% in Singapore. Across the 12

markets in Figure 13, an additional 3.93 million incidence cases (up from 8.25 to 12.18 million) and 3.29 million deaths (up from 5.01 to 8.30 million) are expected to occur in 2040 compared to 2020.[12]

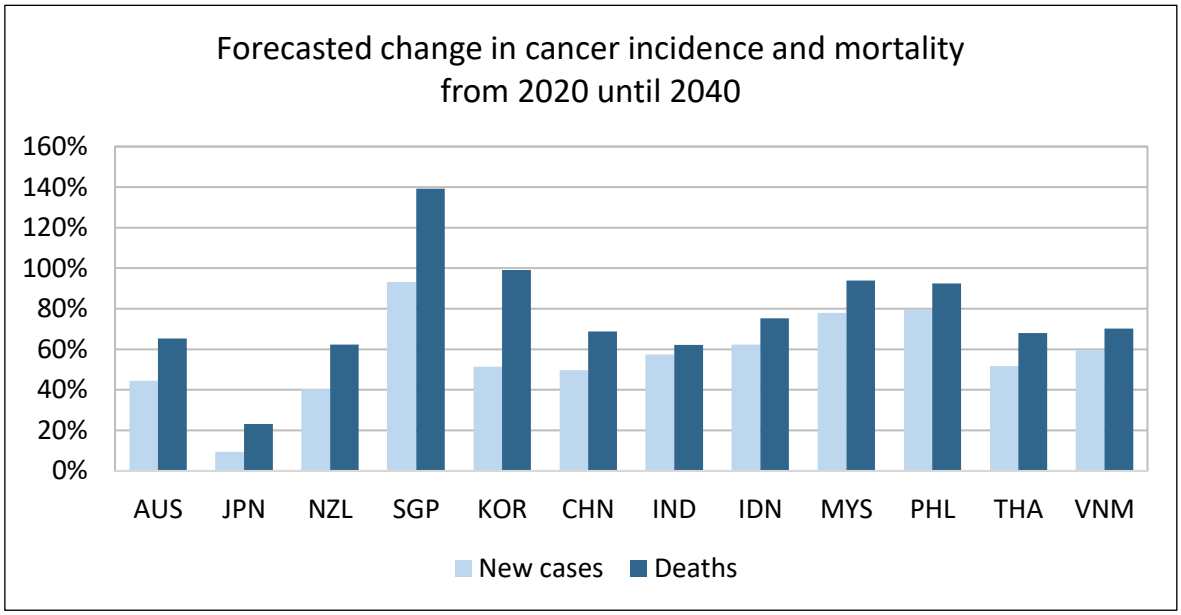

Figure 13: Forecasted change in total cancer incidence and cancer mortality between 2020 and 2040

Notes: Changes refer to total number of cases. "Cancer" refers to all cancers excl. non-melanoma skin cancer. No comparable data are available for HKG and TWN.
Source: GLOBOCAN (6).

The forecasted development in Figure 13 prompts urgent action by all governments across Asia-Pacific. Advances and investments in all areas of cancer care – prevention, screening, diagnosis, treatment – are needed to meet the challenges brought upon by the demographic development and to achieve a lasting turnaround in cancer incidence and mortality. A clear prioritization of effective and comprehensive cancer control efforts could spare millions of people from getting cancer and simultaneously improve the lives of the millions of cancer patients over the coming decades. To this end, the WHO advocates National Cancer Control Programs (NCCP) to tackle cancer in a strategic way (64).

[12] There is a larger relative increase in deaths than in incidence cases in all markets. This would suggest that the 1–MIR becomes worse in the future, contrary to the recent development observed in high-income markets in section 2. GLOBOCAN forecasts are based on age-specific incidence and mortality rates in 2020. The shape of the age-specific incidence/mortality curves differs particularly at older ages, when mortality increases much faster than incidence (opposite at middle ages). Together with the forecasted rapid increase of the elderly population, this leads to larger increases for mortality.

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Appendix

Table A1: Sources for cancer incidence and cancer mortality

	Market	Incidence		Mortality	
		2012	**2018**	**2012**	**2018**
HIGH-INCOME MARKETS	Australia	National registry (25)	National registry (25)	National registry (25)	National registry (25)
	Hong Kong	National registry (65)	National registry (65)	National registry (65)	National registry (65)
	Japan	National registry (66)	National registry (66)	National registry (66)	National registry (66)
	New Zealand	National registry (26)	National registry (26); 2017	National registry (26)	National registry (26); 2017
	Singapore	National registry (21); average in 2008-2012	National registry (21); average in 2013-2017	National registry (21); average in 2008-2012	National registry (21); average in 2013-2017
	South Korea	National registry (67)	National registry (68); 2017	National registry (67)	National registry (68); 2017
	Taiwan	National registry (69)	National registry (69)	National registry (69)	National registry (69)
MIDDLE-INCOME MARKETS	China	National estimate from regional registries (45)	GLOBOCAN (19)	National estimate from regional registries (45)	GLOBOCAN (19)
	India	GLOBOCAN (70)	GLOBOCAN (19)	GLOBOCAN (70)	GLOBOCAN (19)
	Indonesia	GLOBOCAN (70)	GLOBOCAN (19)	GLOBOCAN (70)	GLOBOCAN (19)
	Malaysia	National registry (18); average in 2007-2011*	National registry (18); average in 2012-2016*	National registry (18); average in 2007-2011*	National registry (18); average in 2012-2016*
	Philippines	GLOBOCAN (70)	GLOBOCAN (19)	GLOBOCAN (70)	GLOBOCAN (19)
	Thailand	GLOBOCAN (70)	GLOBOCAN (19)	GLOBOCAN (70)	GLOBOCAN (19)
	Vietnam	GLOBOCAN (70)	GLOBOCAN (19)	GLOBOCAN (70)	GLOBOCAN (19)

Notes: Total numbers on incidence and mortality were obtained from the sources cited in the table. These numbers were combined with information on the total population from the World Bank (71) and from the Department of Household Registration in Taiwan (72) to calculate crude rates in a standardized manner across all markets. * Data from the registry in Malaysia were only used in section 2, whereas data from GLOBOCAN were used in section 3.

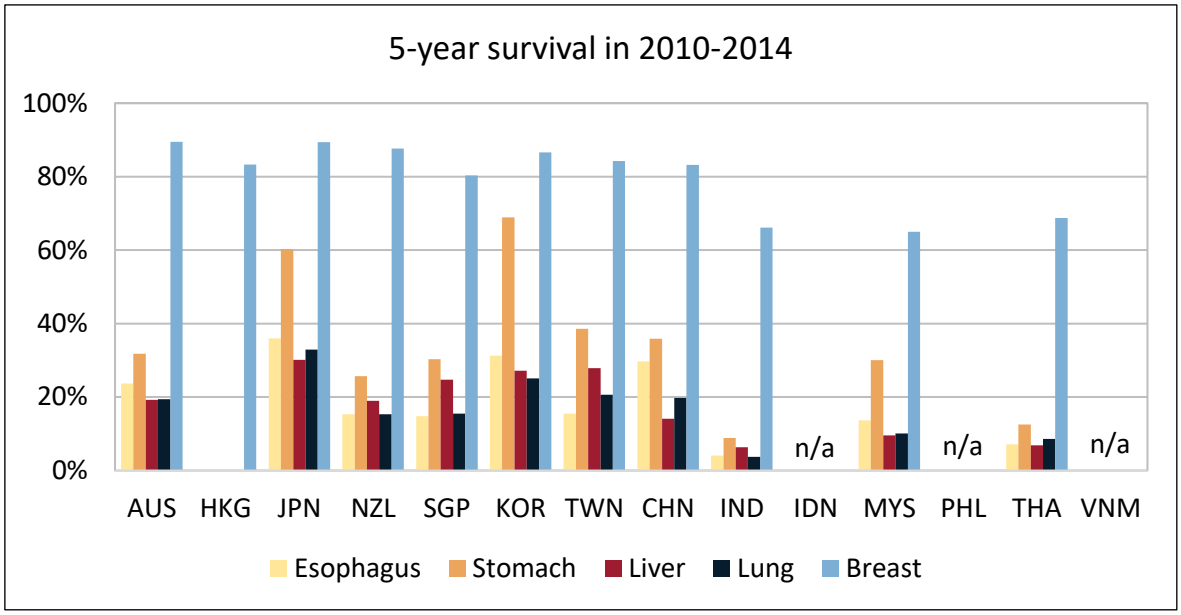

Figure A1: 5-year age-standardized net survival rates in adult patients (15–99 years), 2010–2014

Notes: Esophagus = esophageal cancer, Stomach = gastric cancer, Liver = liver cancer, Lung = lung cancer, Breast = breast cancer. No data are available for head and neck cancer. n/a = no data available. For HKG, only data for breast cancer are available. Coverage of the underlying population is 100% in AUS, HKG, NZL, SGP, KOR, TWN, 40.6% in JPN, 2.3% in CHN, 0.1% in IND, 5.2% in MYS, 20.3% in THA.
Source: CONCORD-3 (44).

HEALTH SPENDING ON CANCER IN ASIA-PACIFIC

Sub-report 2 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

Thomas Hofmarcher
George Keel
Peter Lindgren

IHE - The Swedish Institute for Health Economics

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www.ihe.se | ihe@ihe.se

Report summary

Adequate and effective health care investment is critical in cancer control. Today, access to cancer treatment is limited in many markets in Asia-Pacific – in terms of population covered, services covered, and/or costs of services covered. This affects patient outcomes negatively, and the lack of access conflicts with an individual's right to health. Cancer has also seen much advancement in medical treatment that brings substantial clinical benefit to cancer patients in recent years. This necessitates governments to reconsider the allocation of health care resources to achieve the highest benefits to patients. Being able to link health investment to patient outcomes is pivotal to inform decision-making in this regard.

Total health expenditure (financed via public and private sources) as a share of GDP in middle-income markets (4% on average) were approximately half of that in high-income markets (8%) in Asia-Pacific in 2018. Very large differences in per capita health spending can be observed with spending levels in high-income markets ranging from $1,600 in Taiwan to $5,400 in Australia and in middle-income markets from $70 in India to $500 in China.

The proportion of public health spending tends to be higher in high-income markets than in middle-income markets. Notable exceptions are Hong Kong and Singapore with a comparatively low proportion of public health spending due to different health care organizations, and Thailand with a comparatively high proportion with progress towards universal health coverage. In India and the Philippines, out-of-pocket expenditures dominate total health spending.

The question of what defines an adequate level of public health spending is debatable, with targets of public health expenditure relative to GDP often used in tracking progress towards universal health coverage. On average, public health expenditure as share of GDP in middle-income markets (2%) are less than half of that in high-income markets (5%) in 2018. Only Australia, Japan, and New Zealand met the informal WHO target of public health spending of 5% of GDP, despite relative increases in public health spending in all markets since 2000. Australia, Japan, and New Zealand were also the top-spending high-income markets with public health spending exceeding $3,000 per capita. Public health spending was less than $300 per capita in all middle-income markets, ranging from $289 in China down to $20 in India.

Limited evidence suggests that health spending on cancer care accounts for around 5-9% of total health spending in high-income markets in Asia-Pacific, which is of a similar magnitude as in Europe and the US. Similar proportions of spending on cancer care have been reported for China. In Indonesia and Thailand, cancer care spending levels are as low as 1-2% of total health spending, excluding out-of-pocket payments for cancer treatment.

The consequences of inadequate health coverage can be dire for cancer patients and their families. High out-of-pocket payments for medical services and non-medical services as well as income loss due to reduced or discontinued employment constitute a toxic mix. Indeed, around 50% of all cancer patients and their families face financial catastrophe in middle-income markets. An exception is Thailand where "only" a quarter of patients face financial catastrophe, which might be related to well-established universal health coverage granting access to cancer care services at both public and private health care facilities. Even in high-income markets cancer patients may face financial difficulties in conjunction with their diagnosis and care process.

Health coverage and overall spending on health care are vital for patient outcomes. Health care expenditure per capita correlate strongly with cancer patient outcomes. In Asia-Pacific, just as in Europe, markets with higher health expenditure per capita achieve higher survival rates. This signals a clear need, in particular in middle-income markets, to secure additional health funding to improve patient outcomes. Effective allocation of additional resources across the health system through evidence-based decision-making is pivotal to achieve the highest benefits to patients.

Table of contents

1. Health spending and health coverage

Adequate and effective health care investment is critical in cancer control. Ensuring equal access for a rising number of cancer patients (see sub-report 1), represents a major challenge for many markets in Asia-Pacific. Today, access to modern cancer treatment is limited in many markets in Asia-Pacific (1-3). This affects patient outcomes negatively, and lack of access conflicts with an individual's right to health. This right was enshrined in the Constitution of the World Health Organization (WHO) in 1946 and in the Universal Declaration of Human Rights of the United Nations (UN) in 1948 (4, 5). The 2030 Agenda for Sustainable Development, adopted by all UN member states in 2015, also calls for action to get closer to achieving the right to health. The Sustainable Development Goals 3.8 states: "*Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines*[1] *and vaccines for all [until 2030].*" (7).

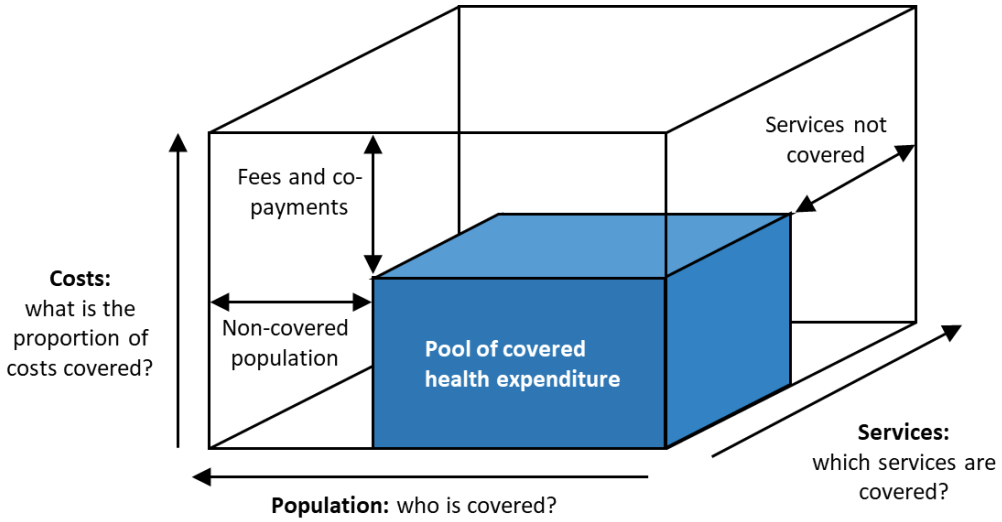

Figure 1: Dimensions of universal health coverage

Source: Adapted from WHO (8).

Figure 1 shows the dimensions of universal health coverage (UHC) as described by the WHO (8). There are three dimensions: the population covered, the services covered, and the proportion of costs of services covered. These dimensions apply to health care in general but also to cancer care. The implementation of UHC is still in the making in some middle-income markets in Asia-Pacific (9). The achievement of UHC is often only measured in terms of the population covered, thus neglecting the importance of the other two dimensions for patient outcomes. While access to cancer care might

[1] The WHO defines essential medicines as "a subset of the total range of pharmaceuticals that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and cost–effectiveness." (6).

be free for the whole population, many modern services along the patient pathway (e.g., MRI examination, radiotherapy through linear accelerators, tumor genotyping, immunotherapy drugs) might not be offered at all or only in a restricted manner (e.g., only a limited number of drug treatment cycles are for free). For those services that are offered, high out-of-pocket payments might arise (e.g., co-payments for every radiotherapy session and every prescribed drug), which can lead to unaffordability in the absence of annual caps on co-payments or other types of financial safety nets.

The amount of health spending by governments determines the size of the "pool of covered health expenditure" in Figure 1. Governments may prioritize certain dimensions over others, but in order to mitigate socio-economic differences in both access to care and patient outcomes, coverage in all dimensions is necessary. Suboptimal coverage may deprive patients not only of achieving good health outcomes but also put them and their families in a situation of financial distress. This is especially the case for diseases such as cancer, which require the consumption of many different health services within a relatively short period of time.

Cancer has also seen much advancement in medical treatment that brings substantial clinical benefit to cancer patients in recent years (see sub-report 3 and sub-report 4). The "services" dimension in Figure 1 is thus continuously expanding, necessitating governments to reconsider the allocation of resources to achieve the highest benefits to patients. Being able to link health investment to patient outcomes is pivotal to inform decision-making in this regard.

1.1 Aim of the sub-report

The aim of this sub-report is to describe health spending on cancer in Asia-Pacific.[2]

- Section 2 describes health spending in general and spending on cancer care.
- Section 3 showcases the consequences for cancer patients and their families of inadequate health coverage.
- Section 4 explores how the level of health spending relates to cancer patient outcomes.

[2] Asia-Pacific consists in this report of 7 high-income markets – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 middle-income markets – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

2. Health spending

This section describes the level of health spending across all markets in Asia-Pacific. It aims to answer the following questions: What is the level and proportion of health spending funded by public and private sources? What is known about the level of health spending on cancer care?

2.1 Method and data

Comparable data on health expenditure were retrieved from the Global Health Expenditure Database by the WHO (10). For Hong Kong and Taiwan, this information was obtained directly from local authorities (11, 12). The latest available data for all markets is for the year 2018.

The WHO relies on the System of Health Accounts 2011 (SHA 2011) reporting standard to ensure a common definition of health expenditure. In this analysis, "current health expenditure" was used. It measures the final consumption of health care goods and services, including personal health care (curative care, rehabilitative care, long-term care, ancillary services, and medical goods) and collective services (prevention and public health services as well as health administration).

Health expenditure are financed by a mix of sources. This includes government spending and compulsory health insurance, voluntary private health insurance, out-of-pocket payments by individuals, and funds by foreign donors (i.e., development aid).

A shortcoming of the WHO SHA 2011 framework is the lack of reporting of health expenditure by disease area. This makes it difficult to answer the question: What is the level of health spending on cancer? The OECD has promoted the idea of disease-specific health accounts, but few countries provide such data within the SHA 2011 framework (13). In the absence of such data, cost-of-illness studies, that quantify all costs of a particular disease, are an alternative source of information (14).

2.2 Results

To compare statistics on health spending across markets, results are presented in two fashions. The first approach presents health spending relative to gross domestic product (GDP). The second approach presents health spending levels in US dollars per capita in current prices.

Total health spending

Figure 2 shows total health expenditure (financed via public and private sources) across the 14 markets in Asia-Pacific in 2018. On average, health expenditure as share of GDP in middle-income

markets (4%) were approximately half of that in high-income markets (8%). There are considerable variations across middle-income markets, ranging from 3% in Indonesia to 6% in Vietnam, and also across high-income markets, ranging from 4% in Singapore to 11% in Japan. In comparison, total health expenditure as a share of GDP was 10% in Europe in 2018, ranging from 5% in Romania to 12% in Switzerland (15). In general, total health expenditure as a share of GDP reflect policy choices made by governments in the organization of their overall health financing system, as well as differences in epidemiological patterns, as noted by the WHO (16). The latter point alludes to the fact that populations with a larger proportion of elderly people might face a greater need for health care. As shown in sub-report 1, high-income markets have an older population than middle-income markets in Asia-Pacific, which thus might explain some of the variation observed here.

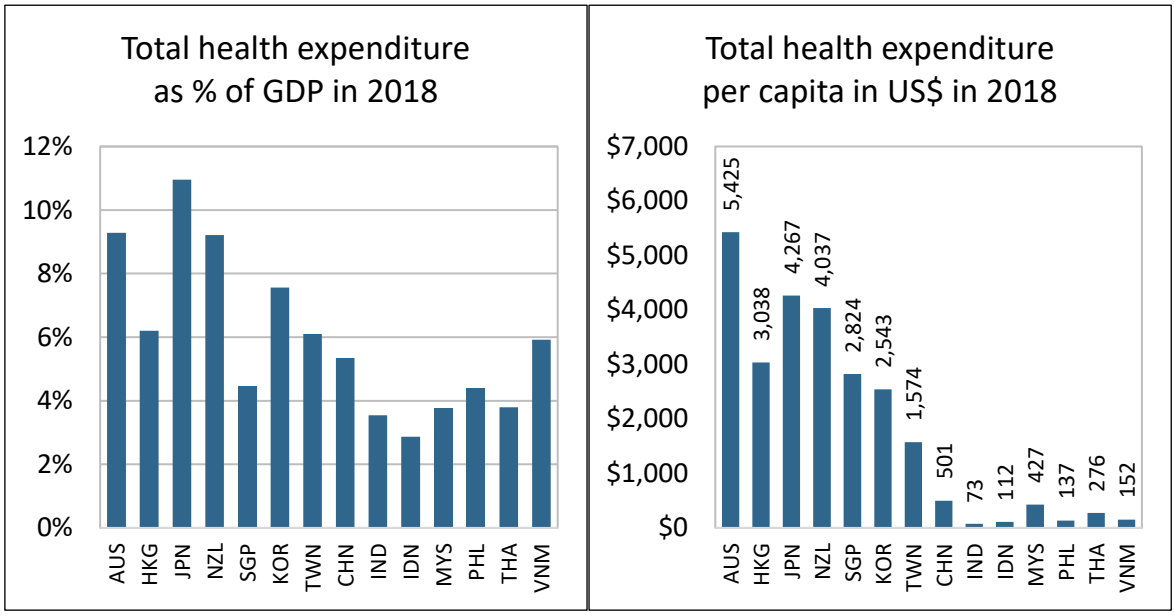

Figure 2: Total health expenditure as % of GDP and per capita in US$, 2018

Notes: Total health expenditure includes financing from public and private sources. Expenditure are in current prices not adjusted for differences in purchasing power parity. GDP = gross domestic product.
Source: WHO (10), Department of Health for HKG (11), Ministry of Health and Welfare for TWN (12).

Very large differences in per capita health spending can be observed across Asia-Pacific in Figure 2. This is mainly a reflection of differences in levels of economic wealth (GDP), but the differences in health spending as % of GDP also add to it. Spending levels among high-income markets ranged from around $1,600 in Taiwan to $5,400 in Australia and among middle-income markets from $70 in India to $500 in China. In comparison, total health expenditure per capita was around $3,700 in Europe in 2018, ranging from $690 in Romania to $9,900 in Switzerland (15).

Composition of total health spending

Total health expenditure is financed through a mix of sources, with public spending typically accounting for the greatest contribution. Analysis of health spending data across the globe in 2018 illustrated that the sources of health spending could vary notably across country income groups. High-income member states had larger share of public financing (government transfers and social health insurance contributions) at 70% and lower out-of-pocket spending (OOPs) at 21% in total health spending. In comparison, lower middle-income and upper middle-income member states had a lower share of public financing at 41-55% and a higher share of OOPs at 35-42% (16).

In Asia-Pacific, most of the high-income markets tended to have relatively high proportions of public health spending aligned with the findings by the WHO; see Figure 3. Japan had the highest proportion with 84% in 2018. Hong Kong and Singapore had both comparatively low proportions of around 50%. In Hong Kong this has been attributed to the large role of the private sector in outpatient medical services (around 70% of all services), while in Singapore this has been attributed to the government's longstanding principle of fiscal prudence and common use of co-payments (17-20).

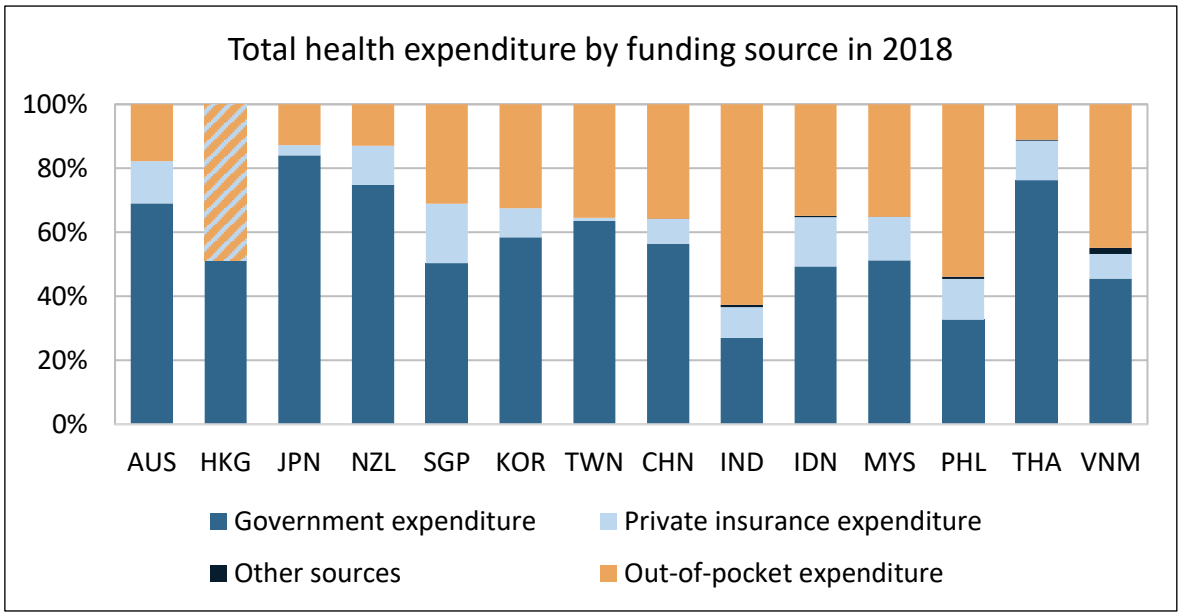

Figure 3: Total health expenditure by funding source, 2018

Notes: "Other sources" encompass non-domestic funding, such as development aid. No distinction between out-of-pocket expenditure and private insurance expenditure possible for HKG.
Source: WHO (10), Department of Health for HKG (11), Ministry of Health and Welfare for TWN (12).

There was great variation in the share of public financing in total health spending in middle-income markets; see Figure 3. Thailand had by far the highest proportion with 76%. This is a result of Thailand's early move towards universal health coverage in 2002, backed by general taxation to finance the health care sector without relying on contributions from members (21). Public spending

in China, Indonesia, Malaysia, and Vietnam amounts to around 45-55% of total spending, while OOPs amount to around 35-45% of total spending. While Vietnam is the only lower middle-income markets among those markets as classified by the World Bank, the share of its public spending was in line with the upper middle-income markets and reflects its efforts to achieve UHC with the government setting a national social health insurance coverage target at 95% by 2025 (22).

For India and the Philippines, the situation of these two lower-middle income markets was different even when compared to the average figures reported by the WHO. While OOPs was 42% and public spending at 41% on average in lower middle-income countries worldwide, OOPs dominated in India and the Philippines, accounting for 63% and 54% of total health spending respectively. Public spending contributed to only one third or less of total health expenditure. In India, previous research has attributed this to the small role of the public health care sector due to it being "*perceived as being unreliable, of indifferent quality and generally is not the first choice, unless one cannot afford private care*" (23, 24), and with initial moves towards UHC only having begun since 2017 (25, 26). In the Philippines, explanations are the lack of infrastructure and human resources and inadequate coverage of health services by the social health insurance (PhilHealth) (27, 28).

Public health spending

Public health researchers have proposed that setting explicit targets with public health expenditure relative to GDP is one of the possible measures in tracking progress towards UHC (29). The question of what defines an adequate level of public health spending has engaged scholars and the WHO in recent decades (30). The 2010 World Health Report of the WHO notes in relation to public health spending that it is "*difficult to get close to universal health coverage at less than 4-5% of GDP [p.98]*" (8). This informal target is thus not officially endorsed but the 5%-reference keeps being used as a benchmark by the WHO (31). It is also acknowledged that, for instance, Thailand managed to achieve UHC at a rate of public spending of around 2-3% of GDP (31). Yet UHC in Thailand refers here more the population and costs of services covered, whereas the range of services covered (i.e., the third dimension in Figure 1) in cancer care is comparatively low (see sub-report 3), possibly responsible for poor patient outcomes (see sub-report 1).

On average, public health expenditure as share of GDP in middle-income markets (2%) were less than half of that in high-income markets (5%) in 2018; see Figure 4.[3] Variations are substantial within middle-income markets, ranging from 1% in India to 3% in China, Thailand, and Vietnam, and even

[3] In some markets, public health spending is also low in comparison to other areas of public spending, such as military spending. In fact, military spending as % of GDP in 2018 was higher than public health spending in India (2.4% of GDP) and Singapore (3.1% of GDP) (32).

greater within high-income markets, ranging from 2% in Singapore to 9% in Japan. Only three markets – Australia, Japan, and New Zealand – managed to meet the 5% of GDP target across Asia-Pacific in 2018 and South Korea and Taiwan would have met a lower target of 4% of GDP.

Figure 4 also shows that the level of public health expenditure differed by more than a factor of 10 between all middle-income markets and the top-spending high-income markets, Australia, Japan, and New Zealand, which spent more than $3,000 per capita. In fact, all middle-income markets spent less than $300 per capita, ranging from $289 in China down to $20 in India. This is equivalent to spending $0.8 on health care per inhabitant on a daily basis in China and $0.05 in India.

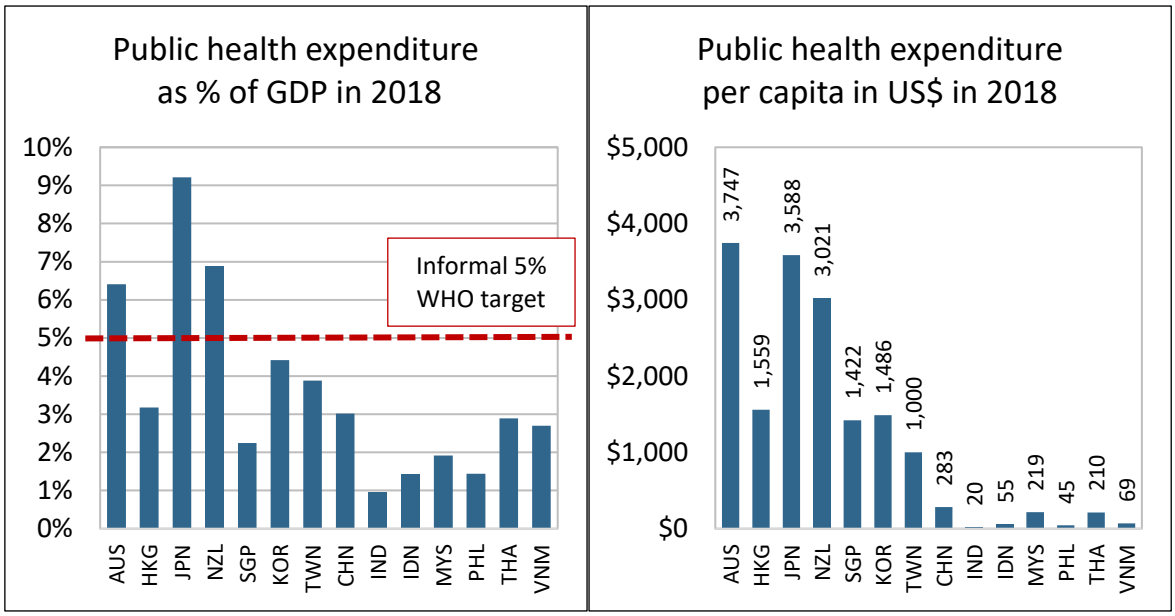

Figure 4: Public health expenditure as % of GDP and per capita in US$, 2018

Notes: Expenditure are not adjusted for differences in purchasing power parity. GDP = gross domestic product.
Source: WHO (10), Department of Health for HKG (11), Ministry of Health and Welfare for TWN (12).

Figure 5 portrays the development of public health spending since 2000. It shows that in all markets, public health spending as percentage of GDP has increased over time. This has brought all markets closer to the 5%-benchmark. China has tripled its public spending, while Indonesia and South Korea have also more than doubled public spending over 2000-2018. By contrast, the increases in the Philippines and India were minimal.

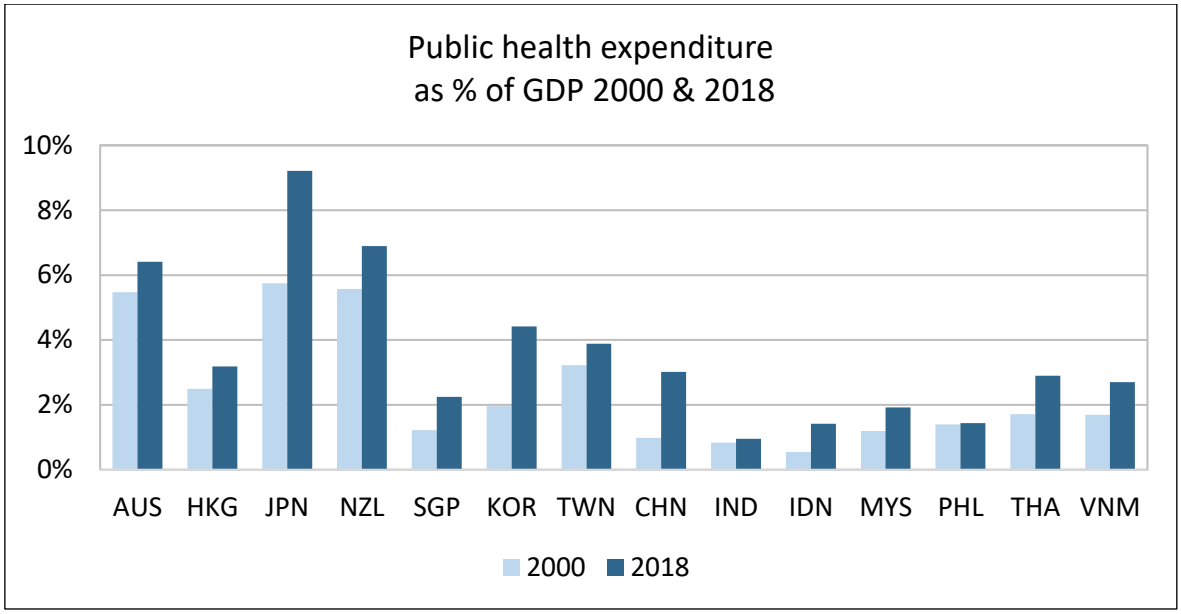

Figure 5: Public health expenditure as % of GDP, 2000 and 2018

Notes: Expenditure are not adjusted for differences in purchasing power parity. GDP = gross domestic product. Proportion in 2000 in HKG refers to earliest available fiscal year of 2006/2007.
Source: WHO (10), Department of Health for HKG (11), Ministry of Health and Welfare for TWN (12).

Health spending on cancer care

In Europe, previous studies show that health spending (from public and private sources) on cancer care accounted for 6% of total health spending in 2018, ranging from 4-7% in most countries (15, 33). Interestingly, there is no correlation between GDP per capita and the percentage of total health spending on cancer care in Europe, with some wealthier countries, such as Germany and the Netherlands, spending around 7% on cancer care and other wealthier countries, such as Norway and Sweden, spending around 4% on cancer care. There is also no correlation between the number of newly diagnosed cancer cases (incidence crude rate) and the percentage of total health spending on cancer care in Europe (15).

In the US, previous studies show that health spending (from public and private sources) on cancer care has been fluctuating around 5% of total health spending between 1963 and 1995 (34). In 2010, the proportion was still around 5% (expenditure on cancer care of $124.57 billion (35), and total health expenditure of $2,450.5 billion (10)), but edged up to 6% in 2015 (expenditure on cancer care of $183 billion (36), and total health expenditure of $3,045.5 billion (10)). This rather stable pattern of the cancer-specific proportion of total health expenditure has also been observed in Europe, where it was around 6% between 1995 and 2018 (33, 37).

In high-income markets in Asia-Pacific, existing estimates of the size of health spending on cancer care indicate roughly a similar magnitude[4] as in Europe and the US:

- **Australia**: Health spending on cancer care was estimated to AUD 6.3 billion in 2013 (38), corresponding to around 4.5% of total health spending (AUD 140 billion in 2013, according to the WHO (10)).
- **Japan**: Health spending on cancer care was JPY 4,525.6 billion in the fiscal year 2018 (39), corresponding to around 7.5% of total health spending (JPY 59,929 billion in 2018, according to the WHO (10)).
- **South Korea**: Health spending on cancer care was estimated to be 9.1% of total health spending in 2009 by the OECD (13).

In middle-income markets in Asia-Pacific, existing estimates of the size of health spending on cancer indicate either a similar or much lower magnitude as in Europe and the US:

- **China**: Health spending on cancer care was estimated to be CNY 221.4 billion in 2015 (40), corresponding to around 6.5% of total health spending (CNY 3,418 billion in 2015, according to the WHO (10)).
- **Indonesia**: Health spending on cancer care (solid types and leukemia) by the Healthcare & Social Security Agency (BPJS) was IDR 3,904 billion in 2019 (41), corresponding to around 0.9% of total health spending (IDR 425,583 billion in 2018, according to the WHO (10)). Out-of-pocket payments are not included in this number and might be considerable as noted above.
- **Thailand**: Health spending on cancer care by the National Health Security Office (NHSO), the payer of the Universal Coverage Scheme (UCS), was USD 297 million in 2018, with the UCS covering 72.2% of the population (42). Total health spending was USD 19,549 million in 2018, according to the WHO (10). This would correspond to a cancer-specific spending proportion of 1.5%, but if the remaining population covered by two other schemes would have a similar consumption of cancer care resources, the proportion would be around 2.1%. Out-of-pocket payments are not included in this number.

It is difficult to infer an optimal proportion of health expenditure to be spent on cancer care, as epidemiological patterns differ greatly across Asia-Pacific (see sub-report 1). However, considering that around 30% of deaths are because of cancer in high-income markets and 9–25% in middle-

[4] Differences in underlying methodology might complicate a valid comparison across markets.

income markets, the proportions of health spending on cancer care found here appear low. The combination of low overall health spending levels and low percentages of spending going into cancer care in middle-income markets render it difficult to finance a comprehensive set of cancer care services. This comes with negative consequences both for individual coverage against high OOP payments (see section 3) and patient outcomes (see section 4).

3. Financial burden of cancer treatment

This section explores the financial consequences for cancer patients and their families from inadequate health coverage for cancer treatment across all markets in Asia-Pacific. It aims to answer the following question: What is the proportion of households in financial catastrophe because of cancer treatment?

3.1 Method and data

A pragmatic literature review on financial catastrophe because of cancer treatment was performed. The review was conducted in PubMed/MEDLINE based on a pre-defined search strategy for each of the 14 markets in Asia-Pacific as well as for Asia as a whole.[5] Titles and abstracts were screened for relevancy. Relevant articles were reviewed with respect to the definition of "financial catastrophe" used. The initial search was limited to the articles published between Jan 1, 2018 and Sep 30, 2020, and, due to few relevant search hits, extended to articles published between Jan 1, 2015 and Sep 30, 2020. The limitation to articles published in recent years is motivated by the fact that public health spending has been on an increasing trajectory in most markets in recent decades, as shown in Figure 5 in section 2, which might have improved the financial safety net available to patients.

There is not yet a formal definition of financial catastrophe, also referred to as financial toxicity or economic/financial hardship, and different definitions exist in the literature (43-45). Financial toxicity is largely contributed by high OOP medical payments by patients and reduced income while being treated or recovering from the disease. Despite relatively rich data covered by qualitative studies on the topic, there are limited quantitative studies with a need for standardized tools to advance research in the field.

In general, financial catastrophe is defined at the household level rather than at the individual level. This is based on the idea that a sick household member will receive financial help from other household members. Health-related expenditure include both OOPs for medical services and for non-medical services such as costs for transportation and accommodation in relation to care provision. These OOPs are typically compared to the annual household income. Thresholds for OOPs exceeding annual household income by 10% to 40% have been used in the literature and there is no consensus

[5] For example, for Australia the search strategy was: ("cancer*"[Title/Abstract] OR "neoplasm*"[MeSH Terms]) AND ("hardship" [Title/Abstract] OR ("catastroph*" [Title/Abstract] OR "financ*"[Title/Abstract]) OR ("catastroph*" [Title/Abstract] "econ*"[Title/Abstract]) OR "low econ*"[Title/Abstract] OR "minimal econ*"[Title/Abstract] OR "limited means" [Title/Abstract] OR "circumstances" [Title/Abstract] OR "economic status" [Title/Abstract]) AND "Australia"[Title/Abstract] AND ("2018/01/10"[Date - Publication] : "3000"[Date - Publication]).

on which one is best suited to represent financial catastrophe (43-45). In this report, financial catastrophe is defined as OOPs for medical services and non-medical services exceeding annual household income by 30%. This choice was primarily driven by the definition used in the ACTION study carried out in multiple markets in Asia-Pacific.

3.2 Results

As newly diagnosed cancer patients go through their treatment journey (consisting of diagnostics and treatment, such as surgery, radiotherapy, and/or systemic treatment), costs incur along the way. This includes both OOPs for medical services and for non-medical services such as costs for transportation and accommodation in relation to care provision. At the same time, some patients might face income loss due to reduced or discontinued employment during treatment and when cancer survivors return to work. Adequate health coverage is vital in these circumstances. This is especially true for diseases such as cancer, which come with a high health care need within a relatively short period of time upon diagnosis.[6] If there is no safety net through social health insurance or (mandatory) private insurance, patients face a double burden of high OOPs and income loss, creating financial difficulties.

Figure 7 summarizes recent estimates of the extent of financial catastrophe due to cancer across middle-income markets in Asia-Pacific. Around half of all cancer patients face financial catastrophe, defined as OOPs for medical services and non-medical services exceeding annual household income by 30%. Vietnam is the market with the highest proportion of cancer patients in financial catastrophe with 68% as reported by the international ACTION study (46). For Malaysia, a recent country-specific study put this proportion to 51% (as shown in Figure 7) (47), similar to the result obtained in the ACTION study at 45% (46).

Thailand is the market with the lowest proportion of cancer patients in financial catastrophe with 24% from the same ACTION study (46). While both Malaysia and Thailand have had achieved UHC long time before the study, households in Malaysia appeared to be less shielded from financial toxicity than those in Thailand. The authors of the ACTION study emphasized differences in the structures of their health care systems as a possible explanation. In Thailand, public insurance funds finance a package of cancer care services which citizens can access from both public and private health care facilities. In Malaysia, publicly financed health care is only provided in public health care

[6] This situation sets cancer apart from other diseases, such as diabetes or multiple sclerosis, which do not stop people from continuing to work upon diagnosis and where annual medical treatment costs are comparatively low but instead occur throughout several years or even decades.

facilities, which are characterized by long waiting times, which in turn might force many patients to pay OOP for health care services in the private health care facilities (46).

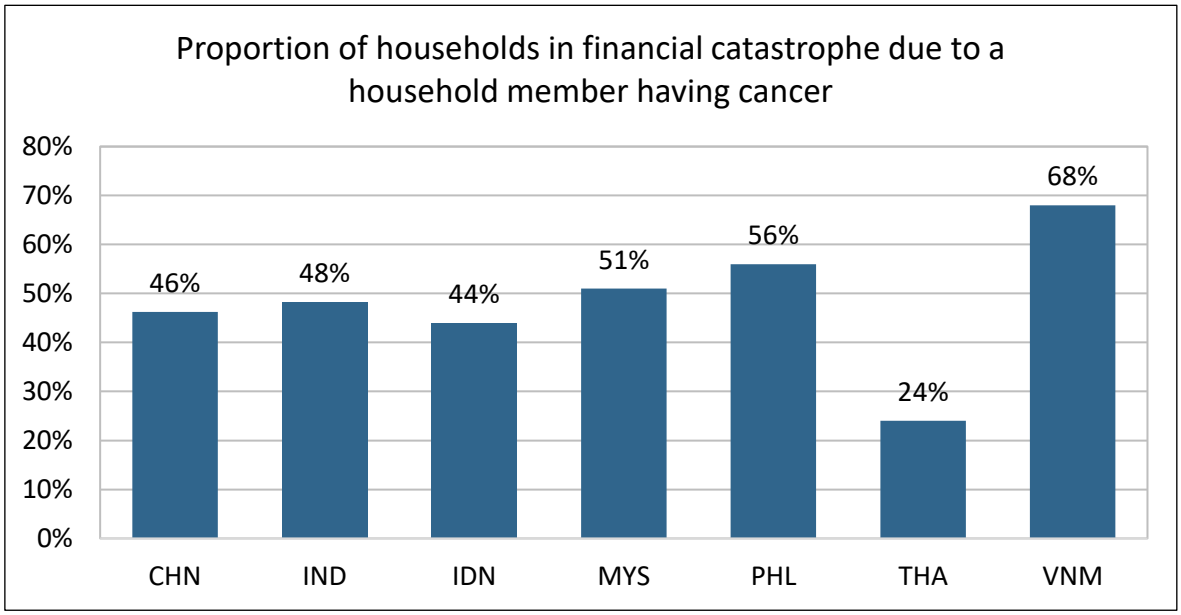

Figure 6: Proportion of households in financial catastrophe due to a household member having cancer

Notes: Financial catastrophe is defined as out-of-pocket medical and non-medical expenditure ≥30% annual household income. For China, the numerator of financial catastrophe only comprises medical expenditure and thus leads to an underestimation of the proportion of households in financial catastrophe, whereas the denominator is household non-food expenditure, which is a smaller amount than household income and thus leads to an overestimation of the proportion of households in financial catastrophe. For India, the proportion shown is the average of the proportion of affected households using a 20% and 40% threshold, and with estimates for the public sector and the private sector weighted based on the proportion of patients treated in these sectors. In India, the numerator of financial catastrophe only comprises medical expenditure related to inpatient treatment and thus leads to an underestimation of the proportion of households in financial catastrophe, whereas the denominator is household expenditure, which might be a smaller amount than household income and thus leads to an overestimation of the proportion of households in financial catastrophe. No comparable data were identified for high-income markets.
Source: CHN (48), IND (49), MYS (47), IDN+PHL+THA+VNM (46).

In high-income markets in Asia-Pacific, no comparable studies on financial catastrophe of cancer patients were identified. However, cancer patients in these markets may also financial difficulties, even though possibly not to the extent in middle-income markets. In Australia, cancer patients in rural areas may face high OOPs due to the cost of travelling far away from their homes for treatment, or from the relatively high co-payments for treatment by working-age patients without concession cards (50, 51). The latter is similar to the situation in Japan, where younger cancer patients face a higher risk of financial problems due to the higher co-payment rates on medical services (30% instead of 10% for people aged 70 or older) (52). In South Korea, 6% of male cancer patients and 19% of female cancer patients reported OOPs for medical expenditure in excess of 10% of annual household income. Patients with private insurance that cover health services and treatment that are not

reimbursed through the national health insurance were less likely to experience financial toxicity. (53).

Further research is warranted on financial catastrophe due to its complexity, lack of a firm definition of the topic, and limited quantitative studies. The subjective perception of financial distress and its effects on patients in general is also an under-researched area (44). There is also limited evidence regarding the effect of OOPs on health seeking behavior and subsequent patient outcomes, as patients might become reluctant to seek care with the prospect of potential high OOPs (54). This burden falls disproportionally on poor patients, making them more likely to subsequently present at late-stage disease with worse prognosis.

The provision of a comprehensive safety net to prevent high OOPs is imperative in the quest of governments seeking to guarantee equitable and good-quality care through UHC. For cancer care services offered under UHC, some factors are especially noteworthy, such as:

- Ensuring that the public health system has the capacity to cater to the needs of all patients, thus avoiding patients being forced to seek care in the private sector
- Reviewing the size of co-payments on health services and imposing an annual cap on co-payments
- Seeking ways to cover non-medical costs such as costs of travel in conjunction with care provision

4. Health spending and cancer patient outcomes

This section explores how the level of health spending relates to cancer patient outcomes across all markets in Asia-Pacific. It aims to answer the following question: Is there an association between health spending and cancer patient outcomes?

4.1 Method and data

Two types of input were combined for the analysis. Health spending was defined as total health expenditure per capita; see section 2. This is a measure of the financial value of resources used in health care and demarcates the fundamental boundaries within which health is produced through the public and private health care sector.

Outcomes of cancer patients were defined as the complement of the mortality-to-incidence ratio (1–MIR) as a proxy for survival; see section 2 in sub-report 1. While 1–MIR is a cruder measure than survival, it allows international comparisons due to its simplicity and availability of incidence and mortality data for most markets.

Both data inputs refer to the year 2018 in all markets. Linear regression analysis was used to examine the strength of the correlation between the two measures.

4.2 Results

Linking inputs in the health care process to patient outcomes is fundamental in assessing the efficiency of health care systems. Measuring such inputs and patient outcomes comprehensively is challenging as both consist of several relevant dimensions (e.g., survival and quality of life may both be relevant patient outcomes).

Figure 6 shows how total health expenditure per capita (inputs) correlate with the complement of the mortality-to-incidence ratio (1–MIR) of cancer (patient outcomes). Each dot in Figure 6 represents a market and the drawn (unweighted) line represents the relationship between inputs and outputs inferred based on the 14 markets. The following observation can be made. There is a clear positive correlation between health expenditure and the 1–MIR across Asia-Pacific. This indicates that markets with higher health spending tend to achieve better patient outcomes, while markets with

lower health spending tend to achieve worse patient outcomes. The strength of this association is high[7], as indicated by a correlation coefficient of 0.75 (0 is no correlation and 1 is perfect correlation).

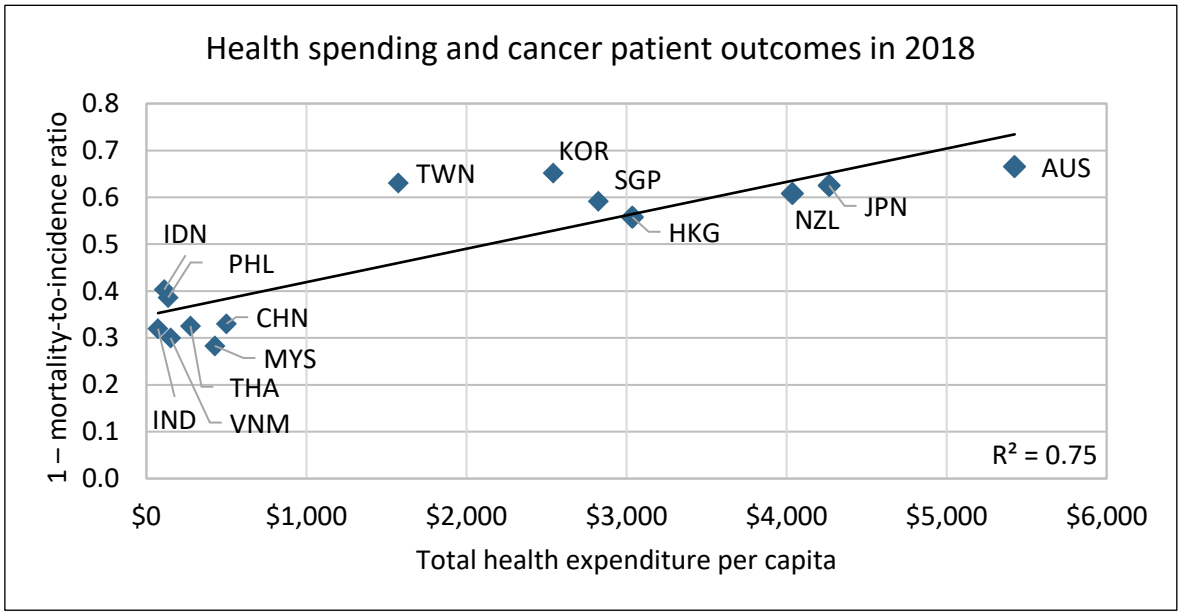

Figure 7: Total health expenditure per capita and complement of the mortality-to-incidence ratio of cancer, 2018

Notes: Total health expenditure includes financing from public and private sources. Expenditure are not adjusted for differences in purchasing power parity.
Source: National cancer registries and GLOBOCAN for the mortality-to-incidence ratio (see Figure 6 in sub-report 1) and WHO, Department of Health for HKG, Ministry of Health and Welfare for TWN for health expenditure (see Figure 1).

A positive relationship between health spending and cancer patient outcomes has been documented previously in other parts of the world. This includes analyses of OECD countries, studying the relationship between total health spending per capita and 5-year cancer survival rate (55), and the relationship between a measure of the quality of health systems and the cancer MIR (56). Analyses of the relationship between cancer-specific health spending per capita and 5-year cancer survival rates in European countries further supported the positive correlation between health investment and outcomes (15, 57).

The positive relationship between health spending and patient outcomes in Figure 6 does not need to be causal, but it suggests that health spending might be a stronger driver of patient outcomes. It signals to health policy makers that sufficient health care investment is vital for patient outcomes. Furthermore, health spending only represents the overall monetary value of all resources used. Effective allocation of such resources across the health system through evidence-based decision-making is pivotal to achieve the greatest benefits to patients (58).

[7] Note that the associations could potentially also be driven by some third factor (e.g., the level of education in a country) that is related to both the amount of health expenditure and patient outcomes.

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PATIENT ACCESS TO INNOVATIVE CANCER DRUGS IN ASIA-PACIFIC

Sub-report 3 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

Thomas Hofmarcher
George Keel
Peter Lindgren

IHE - The Swedish Institute for Health Economics

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Report summary

Cancer drugs are essential for improving patient outcomes. Almost 100 new cancer drugs have been launched over the last decade alone. While this is a welcome development for patients, not all drugs offer the same level of innovation. Constrained health care budgets could be aided by an increased focus on innovative cancer drugs that provide the greatest benefit to patients. Value frameworks, such as ESMO-MCBS, have been put forward to help classify cancer drugs with the aim to identify "*innovative*" cancer drugs (in this report defined as drugs with a "*substantial clinical benefit*" with an ESMO-MCBS score of 4 and 5 or B and A) that should be priorities for rapid reimbursement by national bodies from a clinical perspective.

Access to innovative cancer drugs through reimbursement is quite limited in Asia-Pacific. Of 38 innovative drug-indications approved by the US FDA in treatment of five major cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer) between 1998 and 2020, 80% had received regulatory approval across Asia-Pacific in 2020. Yet only 35% of those indications were also reimbursed in 2020. The approved proportion of cancer drugs in general (141 indications in the five cancer types) was around 71% in Asia-Pacific compared to the US FDA, and the proportion of drug-indications with a positive reimbursement status was 39%.

A clear division in access to innovative cancer drugs exists between high-income and middle-income markets in Asia-Pacific. High-income markets achieve much higher proportions of both regulatory approval and reimbursement approval rates (91% and 59%, respectively) than middle-income markets (68% and 17%, respectively). Among the latter group, China, Indonesia, and Vietnam approve relatively fewer indications but at the same time reimburse a higher proportion of them. Among high-income markets, Japan sticks out due to its policy to reimburse all approved drugs essentially by default, which stands in stark contrast to the restrictive reimbursement policy observed in New Zealand.

Timely reimbursement of innovative cancer drugs is a major challenge in all markets in Asia-Pacific except in Japan. In high-income markets along with China, the median delay between regulatory approval and reimbursement approval was around 1.5 to 3 years. Yet a full assessment was not possible as reimbursement was still pending for many indications at the data cut-off. In all middle-income markets except China, delays could not be assessed, because there are essentially no recent innovative indications (launched globally during the last 10 years) that have ever achieved reimbursement listing.

The lack of timely reimbursement of innovative cancer drugs results in a great loss of patient life years. For every year of delay in reimbursement, almost 1 million patient life years are lost across

Asia-Pacific, drawing on a limited sample of only 10 innovative drug-indications. As cancer patients across Asia-Pacific typically face much longer delays in access to innovative cancer drugs than one year, their health outcomes could be greatly improved by faster reimbursement decisions.

Reasons for delayed reimbursement of innovative cancer drugs vary across markets in Asia-Pacific. In middle-income markets, they relate more to limited public health budgets as well as the organization of the reimbursement process with listings being infrequently reviewed and updated. In high-income markets, they relate more to the criteria applied in the reimbursement process (e.g., acceptance of surrogate endpoints, comparator in clinical trial reflective of current clinical practice, cost-effectiveness thresholds) and the lack of fast-track systems for innovative drugs (e.g., prioritized process with shorter timelines for drug-indications that lack a comparable alternative as in South Korea).

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1. Innovative cancer drugs

Cancer drugs are essential for improving patient outcomes (1). The last decade has seen a surge in the number of new cancer drugs being launched in the US (2). The situation is similar in Europe, where 92 new cancer drugs received marketing authorization between 2011 and 2020 compared to 35 new cancer drugs between 2001 and 2010; see Figure 1. New drugs offer new treatment options to patients, but they also represent a challenge for health care system. As the standard of care evolves rapidly in certain cancer types, medical staff needs to be trained continuously to be able to use the new treatments and clinical guidelines need to be updated frequently. In addition, health care budgets are constrained and health care payers around the world struggle to absorb the recent wave of new cancer drugs.

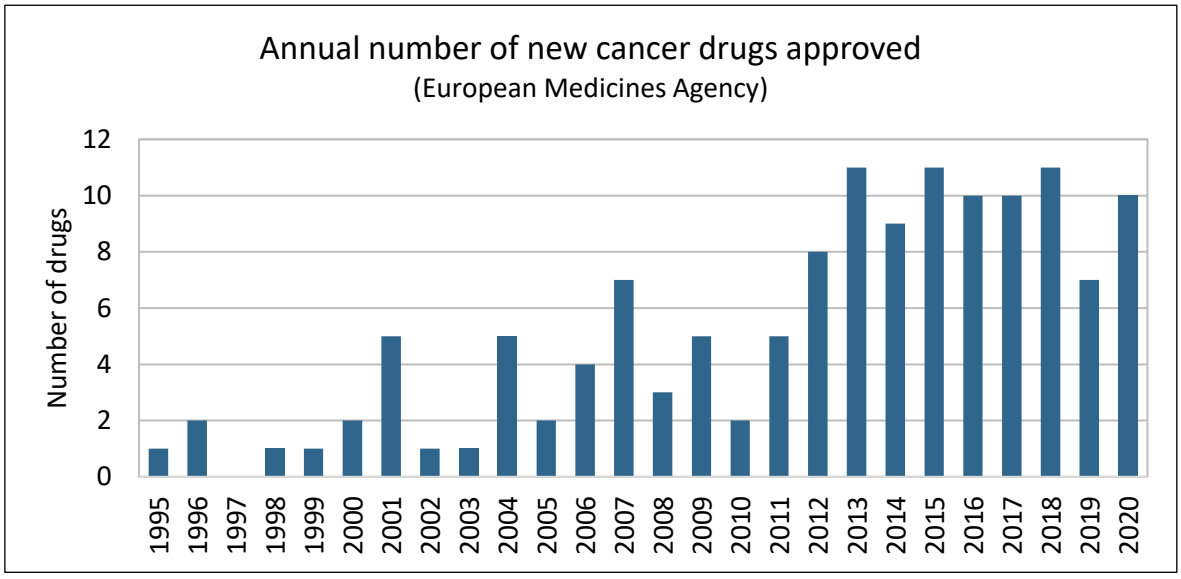

Figure 1: Annual number of new cancer drugs approved by the European Medicines Agency between 1995 and 2020

Source: EMA (3).

In fact, the price of new cancer drugs and the budget impact of cancer drugs as a whole are frequently debated topics. In the US, cancer patients might face financial hardship due to out-of-pocket expenses towards insurance co-payments, coinsurance, deductibles for prescription and non-prescription drugs, hospitalization, outpatient services and other medical care (4-9). It was estimated that 10%-20% of patients might decide to compromise on their treatment plan or not to take treatment due to considerations of these out-of-pocket expenses (10). In Europe, the debate focuses more on the sustainability of increasing public health expenditure on cancer drugs, because public payers (governments or sickness funds) cover the vast majority of the cost of cancer care (including cancer drugs) for the whole population (11, 12). In Asia-Pacific, the debate is also characterized by considerations of financial toxicity (see sub-report 2), especially in markets without comprehensive

universal health coverage, as well as of sustainability of publicly-funded health systems (13). Yet cancer drugs only account for between 1-22% of total pharmaceutical expenditure across markets in Asia-Pacific (see sub-report 4).

The value of a new cancer drug, as with any other new therapeutic intervention, is determined by its clinical benefit compared to its costs (14). Within budget-constrained health system, considerations of value can guide decision makers and help adopt new cancer drugs that are cost-effective and provide value-for-money. While costs of new cancer drugs may vary from country to country, the clinical benefit for an individual patient should be relatively constant across countries. In order to enable a meaningful discussion on the value of new cancer drugs, two major value frameworks to measure clinical benefit have been launched in recent years: the American Society of Clinical Oncology Value Framework (ASCO VF) and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (15, 16).

Clinical benefit in the context of the value frameworks refers to the added (i.e., relative) benefit compared with a control which, ideally, reflects the current standard of care. Consideration of the relative clinical benefit is important, as not all new drugs offer the same improvement over the existing treatment standard. In addition, value frameworks such as the ESMO-MCBS do not consider drugs at the molecular level but align with the specific indication and addressable patient population considered in pivotal clinical trials. This means that relative clinical benefit is closely geared to the use of a drug in a certain tumor type (e.g., lung cancer), tumor subtype (e.g., EGFR-positive non-small cell lung cancer), line of therapy (e.g., first line or later-line therapy), and treatment setting (curative or metastatic).

A scoring system for clinical benefit of cancer drugs can help national reimbursement bodies to distinguish between innovative and non-innovative drugs. Indeed, the ambition of the ESMO-MCBS is to be just that, a tool to inform the process of prioritization of access to cancer drugs when resources are limited (15, 17). It is also advantageous that this scoring system is provided directly by physicians through an international organization (European Society for Medical Oncology) which ensures objectivity and transparency and makes it less susceptible to the influence of external stakeholders with vested interests (e.g., individual country governments, pharmaceutical industry, patient organizations).

1.1 Aim of the sub-report

The aim of this sub-report is to describe patient access to innovative cancer drugs in Asia-Pacific.[1]

- Section 2 explores the regulatory approval and reimbursement status of cancer drugs.
- Section 3 examines the delay between regulatory and reimbursement decisions.
- Section 4 showcases the consequences for patients of delayed reimbursement.
- Section 5 discusses reasons for delayed reimbursement.

[1] Asia-Pacific consists in this report of 7 high-income markets – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 middle-income markets – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

2. Innovative cancer drugs in national formularies

This section explores the regulatory approval status and the reimbursement status of cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: What is the proportion of innovative cancer drugs in the national formulary?

2.1 Method and data

The following steps were taken to assess the availability of innovative cancer drugs in all 14 markets in Asia-Pacific. The first step involved the definition of a sample of innovative cancer drugs. We focused on drugs used in the same five cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer (NSCLC)) as in sub-report 1. For all cancer types, we retrieved data on approved indications by the Food and Drug Administration (FDA) in the United States. The cut-off date was September 30, 2020. This yielded 141 indications of 72 drugs, approved between 1959 and 2020; see Table A1 in the Appendix for the full list. Figure 2 summarizes the proportion of the 141 indications across the five cancer types and shows that most approved indications are found in breast cancer (43%) and NSCLC (35%).

In the next step, we added information on the innovation status to the list of FDA-approved indications. To this end, we used the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS); see Box 1. Indications with an ESMO-MCBS score of 4 and 5 or A and B were classified as innovative; see Table A1 in the Appendix for the ESMO-MCBS score of each indication. The cut-off date was once again September 30, 2020. In total, 38 indications could be classified as "innovative", approved between 1998 and 2020.[2] NSCLC had the highest absolute number of innovative

Box 1: ESMO-MCBS and innovative drugs

Launched in 2015, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) provides scores for new indications of cancer drugs used in solid tumors. The scale considers overall survival, progression-free survival, disease free survival, hazard ratio, response rate, quality of life, prognosis of the condition, and toxicity (18).

- Indications in a curative setting receive a score of A, B, or C. A is the highest score and C is the lowest score.
- Indications in a non-curative setting receive a score of 5, 4, 3, 2, or 1. 5 is the highest score and 1 is the lowest score.

An indication is said to have a "*substantial magnitude of clinical benefit*" if it receives a score of A or B in the curative setting or a score of 5 or 4 in the non-curative setting. In this report, indications with a "*substantial clinical benefit*" are called "*innovative*".

[2] It should be noted that most indications approved before 2010 lack an ESMO-MCBS score, because ESMO-MCBS was launched in 2015 and only few indications before that time were scored retroactively. Several indications approved in 2020 also lacked an ESMO-MCBS score at the time of data retrieval.

indications (18), whereas head and neck cancer the highest relative number of innovative indications (4 out of 11; 36%); see Figure 2.

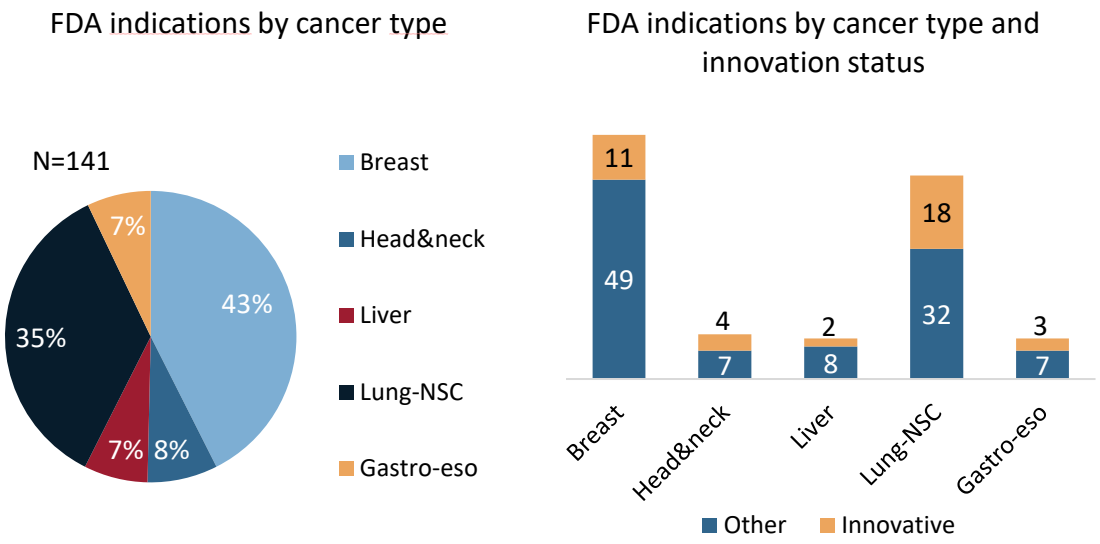

Figure 2: Overview of the sample of FDA-approved indications by cancer type

Notes: Breast = breast cancer, Head&neck = head and neck cancer, Liver = liver cancer, Lung-NSC is non-small cell lung cancer, Gastro-eso = gastro-esophageal cancer.
Source: FDA (19) and ESMO-MCBS (18).

In the final step, publicly available information [3] on the regulatory approval status and the reimbursement status of all 141 FDA-approved indications was retrieved in all 14 markets as of September 30, 2020. Table A2 in the Appendix provides an overview of the relevant national regulatory agencies responsible for drug approval (i.e., marketing authorization) as well as national reimbursement schemes for drugs (i.e., the national formulary) considered in the analysis. Analysis of reimbursement schemes are more complicated in certain markets and the following choices were made:

- India: A scheme for the entire population is lacking, partly due to its decentralized health system (20); the National List of Essential Medicines (NLEM) was used as a proxy for inferring reimbursement status instead.
- Singapore: Two schemes, Standard Drug List (SDL) and Medication Assistance Fund (MAF), were used to infer reimbursement status. In reality, three additional public health

[3] Table A3 in the Appendix provides an overview of the level of granularity in public information in the respective market. In general, information on the indication level was available in most markets. Information only at the drug level was available in (1) Hong Kong for regulatory approval status and reimbursement status in the Hospital Authority Drug Formulary, (2) India for reimbursement status inferred from the National List of Essential Medicines, (3) Japan for regulatory approval status and reimbursement status of drugs launched before 2004, (4) the Philippines for regulatory approval status, (5) Vietnam for reimbursement status.

insurance schemes (MediShield Life, MediSave, MediFund) can be used to cover treatment costs of approved cancer drugs (see Box 1 in sub-report 4) (21, 22).

- Thailand: The National List of Essential Medicines (NLEM) was used as all three main public health insurance schemes (CSMBS, SSS, UCS) provide drugs on this list, and only the CSMBS, covering 8% of the population, through the Oncology Prior Authorization (OCPA) covers a slightly longer list of cancer drugs (23).

2.2 Results

To explore and compare the availability of cancer drugs in terms of regulatory approval status and reimbursement status within and across markets, results are presented with two different approaches. The first uses a common benchmark: approved indications by the US FDA. The second uses a local benchmark: approved indications by the national regulatory agency in the respective market. Results are also presented separately using either the whole sample of 141 indications across the five cancer types (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, NSCLC) or the smaller sample of 38 innovative indications.

Sample of all indications

Figure 3 shows the proportions of drug-indications with positive regulatory approval status and positive reimbursement status compared to the US FDA benchmark as of Sep 30, 2020. Among the 141 drug-indications approved by the US FDA, around 71% had also received regulatory approval across Asia-Pacific. Across high-income markets, close to 80% of drug-indications had received regulatory approval, except for New Zealand at 65%. In middle-income markets, the average proportion was 62%, but there was great variation between markets ranging from around 50% in China and Indonesia to around 70% in India, Malaysia, and Thailand.

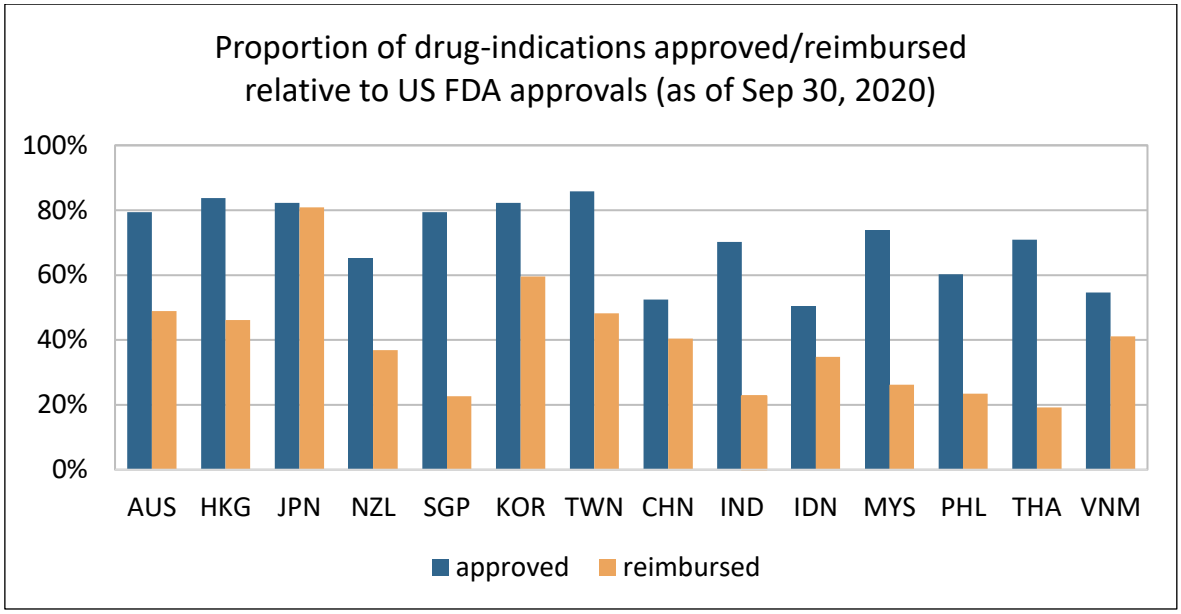

Figure 3: Proportion of drug-indications approved/reimbursed relative to US FDA approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all 141 US FDA indications approved on Sep 30, 2020. Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

The proportion of drug-indications with a positive reimbursement status (39% across all markets) is generally much smaller compared to the regulatory approval status in Figure 3. The only exception is Japan. This is due to the Japanese system of including all drugs in the National Health Insurance (NHI) list once a drug is approved by the Pharmaceuticals and Medical Devices Agency (PMDA) (24). In other high-income markets, the proportion (compared to the US FDA benchmark) ranges from 37% in New Zealand to 60% in South Korea. Among the middle-income markets, China and Vietnam achieved the highest proportions of reimbursed indications of around 40%, thus exceeding New Zealand. The lowest proportion of only 19% was observed in Thailand. These proportions should also be interpreted against the backdrop of availability of generics/biosimilars in 2020. At the global level, generics/biosimilars were available for drugs that cover around 40% of all indications included in the analysis. Yet some of these older drugs might no longer be standard of care and their non-reimbursement will not affect patients as long as the newer drugs they were replaced with are reimbursed.

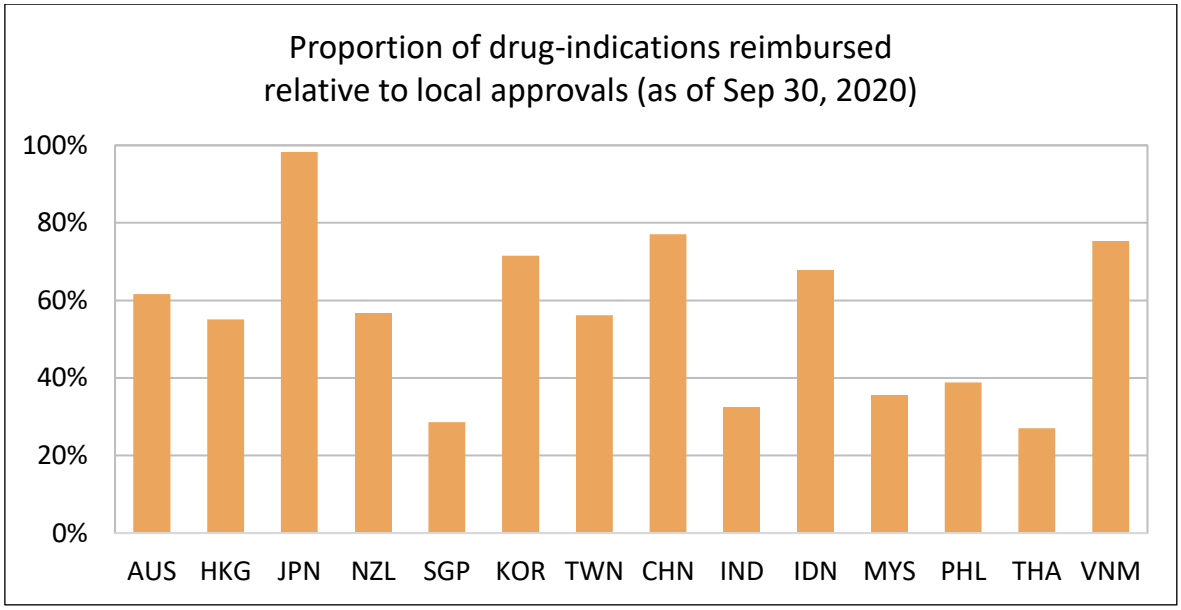

Figure 4: Proportion of drug-indications reimbursed relative to local approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all locally approved indications (max = 141). Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

In general, only locally approved drug-indications can be included in the local drug formulary. Therefore, Figure 4 shows the proportion of approved drug-indications that are made available to the general public through national reimbursement coverage in the respective local market.[4] Across Asia-Pacific, just more than half (56%) of locally approved indications were also reimbursed. Among the high-income markets, Japan (for reasons noted above) followed by South Korea achieved reimbursement proportions higher than the Asia-Pacific average. Middle-income markets fall into two categories; those that achieve a comparatively high reimbursement proportion (China, Indonesia, Vietnam, which at the same time are the three markets with the lowest regulatory approval proportion in Figure 3) and those that achieve a comparatively low proportion (India, Malaysia, Philippines, Thailand).

Sample of innovative indications

Innovative drugs are characterized by greater relative clinical benefit compared with the existing standard of care. Figure 5 shows the proportions of innovative drug-indications with positive regulatory approval status and positive reimbursement status compared to the US FDA benchmark as of Sep 30, 2020. Among the 38 innovative drug-indications approved by the US FDA, around

[4] Such a comparison eliminates the influence of factors related to the absence or delay of regulatory approval (e.g., differential timing of submissions for marketing authorization by pharmaceutical companies and length of the marketing authorization process) compared to the US FDA approval.

80% of them had received regulatory approval across Asia-Pacific. This is a higher proportion than the one observed for the whole sample of 141 drug-indications (71%). In high-income markets (average of 91%), the proportion is close to 100% in Australia, South Korea, and Taiwan, whereas it is the lowest in New Zealand at 76%. There is greater variation in the middle-income markets (average of 68%), with proportions ranging from 50% in Indonesia to 92% in Malaysia.

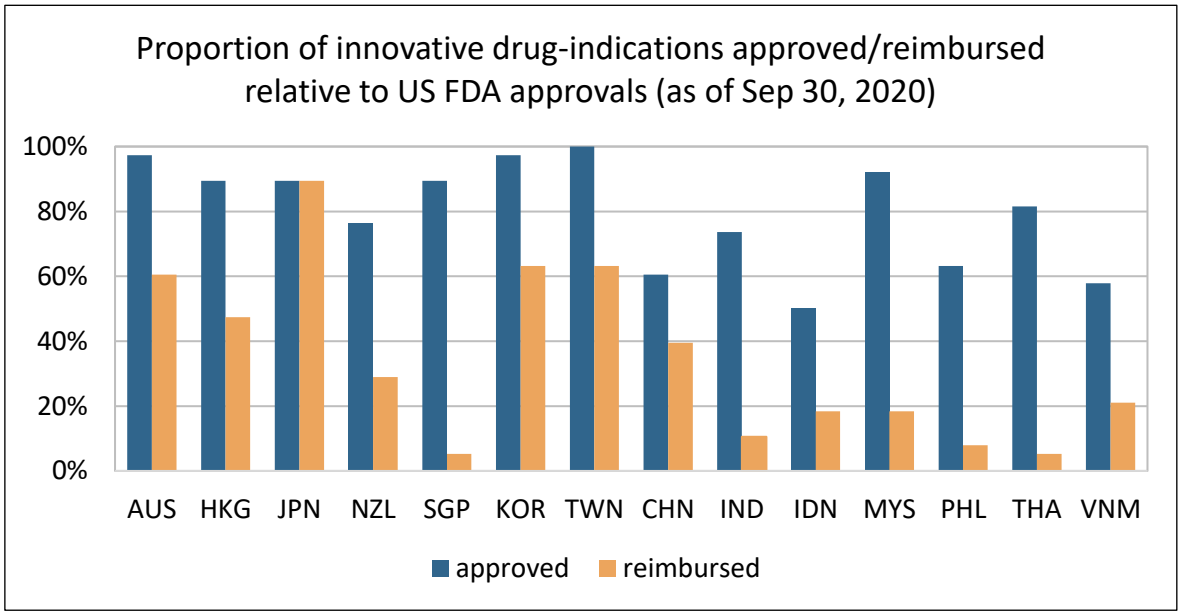

Figure 5: Proportion of innovative drug-indications approved/reimbursed relative to US FDA approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all 38 US FDA indications approved on Sep 30, 2020. Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

A defining feature of the considered innovative drug-indications is the big gap between regulatory approval status and reimbursement status in many markets. Figure 5 shows that the proportion of reimbursed indications (compared to the US FDA benchmark) is on average 35% across all markets. Yet in high income-markets it is 59% (excluding Singapore), ranging from 29% in New Zealand to 89% in Japan. In middle-income markets, it is merely 17% on average, ranging from 5% in Thailand to 39% in China. As noted above, these proportions should be interpreted against the backdrop of availability of generics/biosimilars in 2020. At the global level, generics/biosimilars were available for drugs that cover around 18% of all innovative indications included in the analysis.

A demarcation in terms of reimbursement of innovative drug-indications between high-income and middle-income markets can also be read off in Figure 6. Despite local regulatory approval, middle-income markets achieve only a reimbursement rate of 27%, ranging from 6% in Thailand to 65% in China. China, Indonesia (37%), and Vietnam (36%) have relatively higher reimbursement proportions than the other four middle-income markets, mirroring the pattern observed in Figure 4.

In comparison, around 64% of locally approved indications are reimbursed in high-income markets (excluding Singapore). Japan once again achieved 100% reimbursement of all locally approved innovative indications. For the other high-income markets, the proportion of reimbursed indications overall (Figure 4) and of innovative indications (Figure 6) is remarkably similar, suggesting no preferential treatment of innovative indications. An exception is New Zealand which reimburses distinctly fewer approved innovative indications (38%) than approved indications overall (57%).

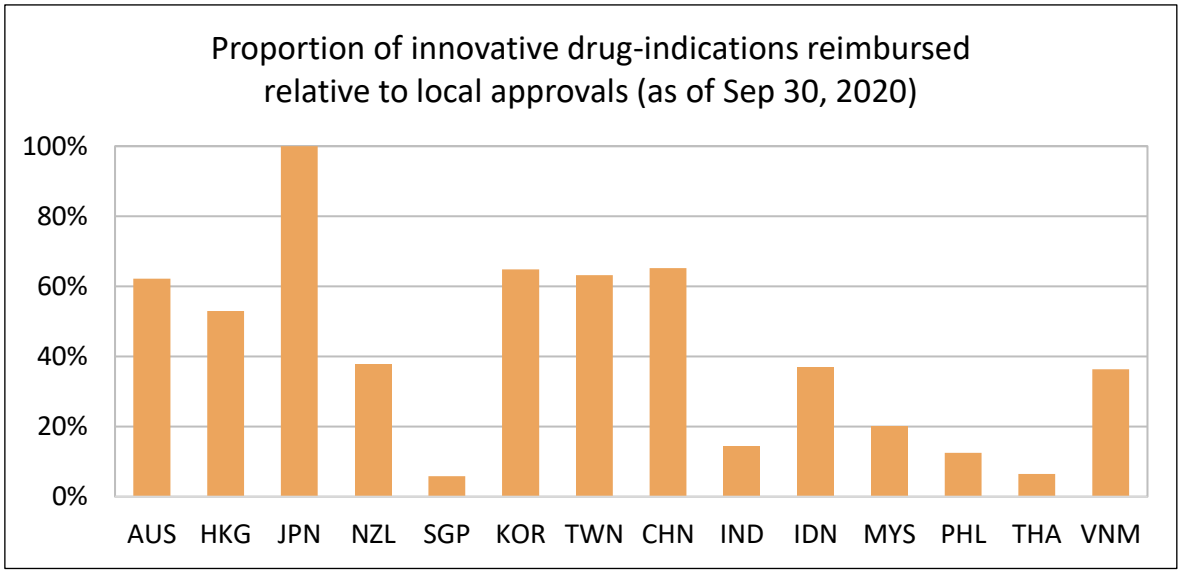

Figure 6: Proportion of innovative drug-indications reimbursed relative to local approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all locally approved indications (max = 38). Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

Figure 7 presents the same analysis as Figure 6 but separately for indications approved in breast cancer (left figure) and in NSCLC (right figure). The proportion of reimbursed innovative drug-indications for the treatment of these two cancer types varies between markets. All markets recorded higher proportions for NSCLC than for breast cancer, apart from China (same proportions) and New Zealand (higher proportion of breast cancer indications). Much of the lower proportion in breast cancer across markets is driven by a lack of reimbursement of the three CDK4/6 kinase inhibitors (abemaciclib, palbociclib, ribociclib) and the first PARP inhibitor (olaparib).

Advancement in medical research has enabled the use of precision medicines that target the abnormal biology of tumor cells or leverage biomarkers to predict response towards specific drugs (25, 26). For example, the discovery of specific oncogenic drivers in lung cancer (e.g., EGFR, ALK, etc.) along with the development of tyrosine kinase inhibitors have enabled significant improvements in the outcomes of patients with these activating mutations since the late 2000s. More recently, immunotherapy has further transformed the treatment landscape in lung cancer by offering

therapeutic options for patients without sensitizing mutations. Similar developments of personalized therapies could also be seen in other cancer types such as breast cancer.

With better understanding of tumor biology and the availability of innovative precision medicines that could offer significant benefits to specific patient sub-groups, it would be interesting to explore if there is sufficient access to address the clinical unmet needs of these different sub-groups.

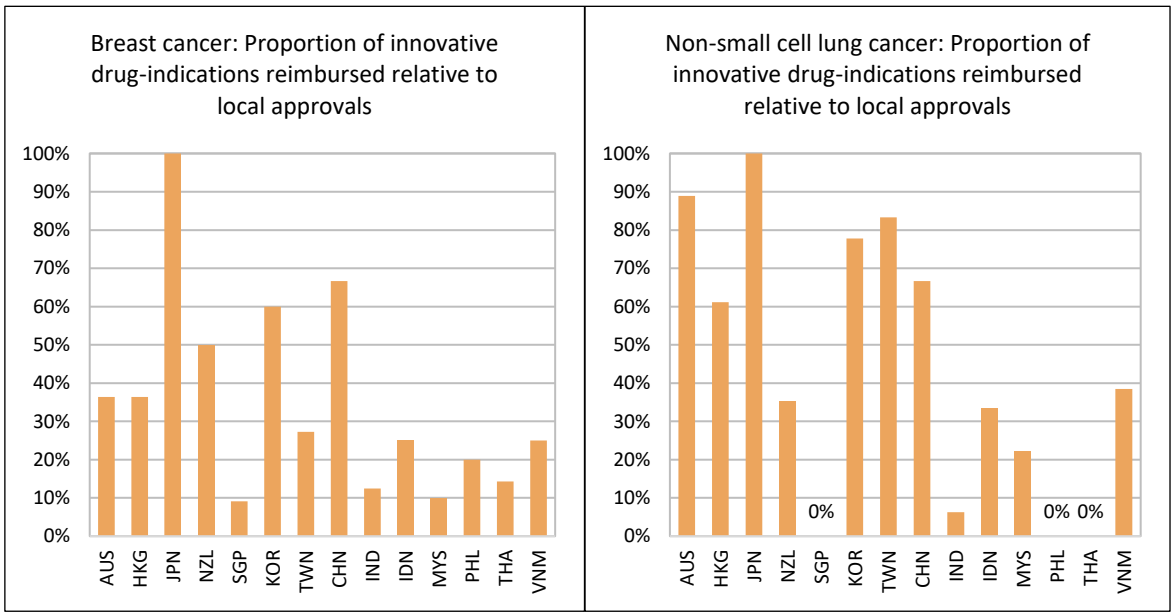

Figure 7: Proportion of innovative drug-indications reimbursed in breast cancer and NSCLC relative to local approvals (as of Sep 30, 2020)

Notes: Numbers reflect the status on Sep 30, 2020. 100% refers to all locally approved indications (max = 11 for breast cancer; max = 18 for NSCLC). Reimbursement in IND is based on the NLEM 2015. Reimbursement in SGP is underestimated as MediShield Life (MSL) can be used to cover most prescriptions.

Comparison with previous studies

There are few comparative studies looking at the issue of regulatory approval status and reimbursement status of cancer drugs. A recent study coordinated by ESMO assessed the availability of cancer drugs in most of the 14 markets considered in this report (13, 27). This study distinguished between drugs on the 2015 WHO Model List of Essential Medicines and newer drugs with an ESMO-MCBS score>2 not on the WHO list, with availability being assessed through survey answers in 2015.

The general finding for drugs on the WHO Model List of Essential Medicines (e.g., chemotherapy, trastuzumab, imatinib) was that accessibility in high-income countries and many upper-middle income countries was generally good. However, barriers to access were reported in some lower-middle income countries (especially in India and to a lesser extent in Indonesia, Philippines,

Vietnam) due to reasons such as the lack of reimbursement, budget capitation, and/or the lack of or unreliable suppliers.

For newer drugs with an ESMO-MCBS score>2, the study found that in most middle-income markets, drugs were hardly reimbursed or simply lacked regulatory approval. In high-income markets (including Australia, New Zealand, Japan, South Korea, and Singapore), the accessibility of these drugs varied. While most drugs were listed in the formulary and usually available in Japan followed by Australia, over half of them were not included in the formulary in New Zealand and Singapore. Interestingly, other barriers to access such as the lack of or unreliable suppliers and parallel exports were also reported for some instances (e.g., in New Zealand). Overall, the findings in this study align well with the patterns observed in this section.

Another study focusing on middle-income markets in Asia-Pacific assessed actual use of cancer drugs per patient, drawing on drugs listed on the 2017 WHO Model List of Essential Medicines (28). This study distinguished between traditional chemotherapy drugs, targeted drugs, and hormonal drugs. During most of the study period from 2007 to 2017, use of drugs of all three categories was the highest in Malaysia and Thailand, and distinctly lower in China, the Philippines and lastly Indonesia. The relatively higher level of access to cancer drugs in China reported in the current report study might be explained by the regular annual updates of the National Reimbursement Drug List (NRDL) since 2017, which is a promising sign of accelerated access as the list had remained unchanged in 2009-2017 (29, 30).

The analysis in this section has provided a snapshot of the approval and reimbursement status of innovative cancer drugs as of Sep 30, 2020. Clear differences in approval and reimbursement rates between markets could be observed in the region. Even though some high-income markets achieve relatively higher reimbursement rates than most middle-income markets, patient access can still be negatively affected by long delays between regulatory approval and reimbursement.

3. Delay in reimbursement of innovative cancer drugs

The previous section has established that there is a large gap between the proportion of drugs with positive regulatory approval status and positive reimbursement status. This section explores the delay between regulatory approval and positive reimbursement decision for innovative cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: How long is the period from regulatory approval to reimbursement approval for innovative cancer drugs?

3.1 Method and data

The following steps were taken to assess the length of the delay between regulatory approval and positive reimbursement decision for innovative cancer drugs in all 14 markets in Asia-Pacific. The list of innovative indications described in section 2.1 was used as a starting point. Older innovative drugs that were approved by the US FDA between January 1, 1998 and January 1, 2010 were excluded. This reduced the number of innovative indications from 38 to 31; see Table A1 in the Appendix. This restriction was motivated by the fact that delays calculated in this section are supposed to be reflective of the current institutional setting and current standard of care. In addition, this restriction means that the analysis can capture a maximum delay of 10.75 years (Jan 1, 2010 to Sep 30, 2020).

Publicly available information on the exact dates of regulatory approval and/or reimbursement approval was retrieved in all 14 markets; see Table A2 in the Appendix for the relevant national regulatory agencies and national reimbursement schemes considered in the analysis. The level of granularity in public information regarding exact dates was sub-optimal in several markets; see Table A3 in the Appendix. These markets typically only provide dates of initial regulatory approval of a drug but no dates of subsequent extensions of the label to additional indications, whereas data availability for reimbursement approval dates by indication is generally better. An online search for company press releases was conducted to fill data gaps. Reimbursed indications with unclear regulatory approval dates or reimbursement approval dates were excluded from the analysis. India was excluded from the analysis as it lacks a reimbursement scheme for the entire population. In Singapore, no reimbursement dates were available although some older innovative indications were listed in the SDL or the MAF (31). In Hong Kong, only some indications in the

Box 2: Number of innovative drug-indications included in the analysis (see Table A4 in the Appendix)

AUS = 17	CHN = 8
HKG = 9	IND = 0
JPN = 27	IDN = 1
NZL = 5	MYS = 1
SGP = 0	PHL = 0
KOR = 16	THA = 0
TWN = 17	VNM 1

Community Care Fund (CCF) could be considered because of the lack of public information on reimbursement dates (32).

3.2 Results

Figure 8 presents the results of the analysis of the delay between regulatory approval and positive reimbursement decision. Across the innovative drug-indications, high-income markets generally record a median delay of 1.5 years (Australia and South Korea) to 3 years (Hong Kong and New Zealand). At the same time, the minimum delay is almost 1 year while the maximum delay is 4-6 years. Japan is the big exception. The median delay is 0 months in this analysis, because all new drugs with regulatory approval are in principal included within at most 60-90 days in the NHI list and all subsequent extensions of the drug's label to additional indications are reimbursed without any delay (24, 33, 34).

For middle-income markets, there is either no or very limited reimbursement. The delays in Indonesia (2.5 years), Malaysia (4.5 years), and Vietnam (1.5 years) are only based on a single indication and in no way reflective of a median delay. These numbers rather present the minimum reimbursement delay in these markets, as there remains no access to the other 30 innovative indications. The underlying sample for China is bigger and the median delay is 1.5 years, which is on par with some of the faster high-income markets. The Chinese numbers should also be interpreted in the light of the findings in section 2, where the emerging pattern was that comparatively few indications obtain regulatory approval (which suggests a long delay until regulatory approval), but relatively many of those are reimbursed. This is also influenced by the long delay in the update of the NRDL between 2009 and 2017 and more regular updates since then, as noted in section 2.

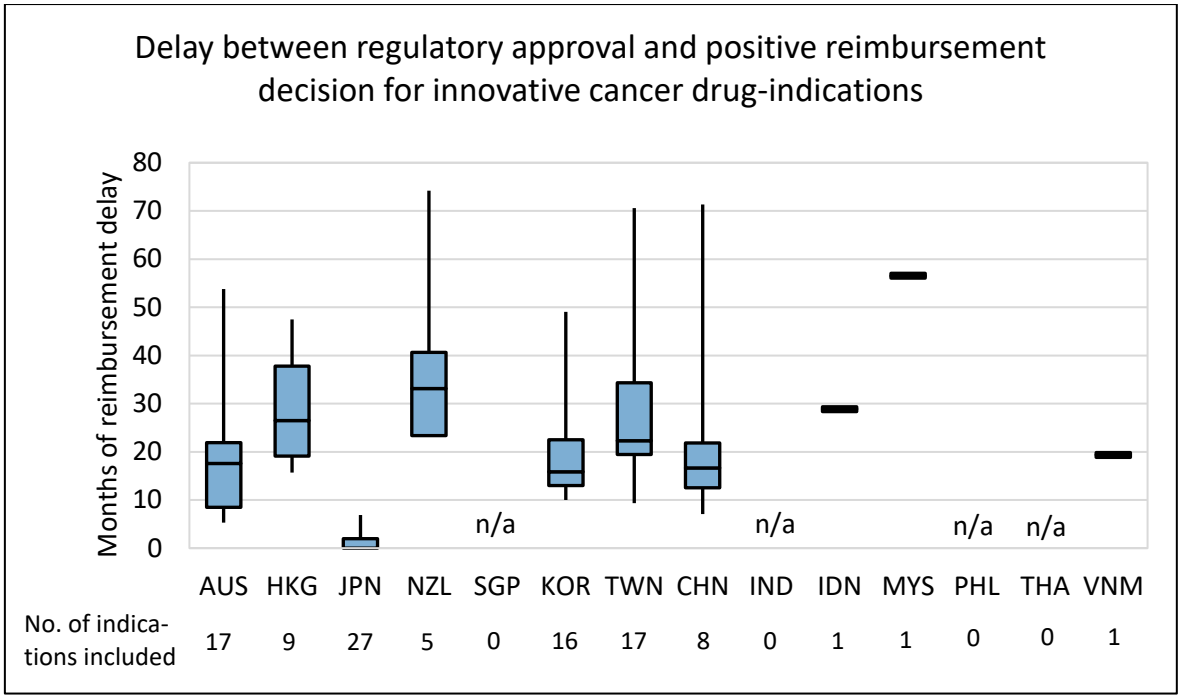

Figure 8: Delay between regulatory approval and positive reimbursement decision for innovative cancer drug-indications (in months)

Notes: The base sample contains 31 innovative drug-indications approved between Jan 1, 2010 and Sep 30, 2020 by the US FDA (see Table A1 in the Appendix), but local sample size differs (see Box 2). N/A = no innovative drugs approved or no information on regulatory/reimbursement approval dates available.
Interpretation of the boxplot: The lower/upper tips of the vertical lines denote the minimum and maximum delay, the borders of the blue boxes define the interquartile range (25th to 75th percentile), and the horizontal line inside the blue box denotes the median delay.

In general, all numbers in Figure 8 need to be interpreted with caution, especially those with few underlying indications (see Box 2). The main caveat is that only indications with a positive reimbursement decision were included in the analysis. An indication approved in 2012 still waiting for reimbursement in 2020 would have faced an 8-year delay but is not included. Delays of 8 years or longer are in fact the reality in many middle-income markets. Markets with fairly high regulatory approval rates (Malaysia, Philippines, Thailand) fail to reimburse innovative cancer drugs. This conclusion is in line with the report conducted by ESMO and described in section 2, which showed that even generic availability of cancer drugs does not entail a positive reimbursement decision (13, 27).

Comparison with previous studies

Previous studies assessing the delay between regulatory approval and reimbursement decision generally found similar results to this report. For Japan, the above-mentioned studies confirmed that new drugs are generally reimbursed within the timeframe of 60-90 days (24). For Taiwan, an analysis of the time from application submission to reimbursement listing found a median delay of 1.5 years (561 days, average delay of 742 days) for new cancer drugs approved between Jan 2013 and Sep

2017, compared to 2 years in this study (35). For South Korea, a recent analysis of 59 new cancer drugs approved between 2007 and 2018 found a median delay of 26 months. This is longer than the 16 months found in this report but might be partly explained by a different sample (all new cancer drugs vs. innovative indications of both new and existing cancer drugs for selected cancer types) and partly by the more recent time period studied here. The latter is important as the analysis here incorporates a longer time period since the introduction of the "risk-sharing agreement pathway" in 2014, a fast-track system for certain types of drugs including cancer drugs that has been shown to have reduced delays (36).

Studies comparing national formularies in Australia and New Zealand have repeatedly found that only around half of new drugs achieving reimbursement listing in Australia do so in New Zealand (37-39). They have also shown that reimbursement listing in New Zealand occurs on average 2.5 years after Australia. In this report, the methodology to calculate the gap between Australia and New Zealand is different but would suggest a shorter delay (18 months vs. 33 months). However, the real median delay in New Zealand is longer, as the current numbers are only based on 5 indications. For instance, the first indication in NSCLC of an immunotherapy drug (nivolumab) was approved in April 2016 but in September 2020 reimbursement listing was still pending, whereas in Australia it was reimbursed in August 2017 after a regulatory approval in January 2016.

Although Japan might appear as an outlier in the analysis of high-income markets in Asia-Pacific, some countries in Europe also have a reimbursement delay of only a few months. A survey, conducted by the European Federation of Pharmaceutical Industries and Associations (EFPIA), showed that the average delay between regulatory approval of all new cancer drugs approved by the European Medicines Agency (EMA) between 2015 and 2018 and patient access (defined as first sales of a drug in a local market, which typically coincides with reimbursement in the local market in Europe) was less than 6 months in Denmark and Germany (40).

4. Consequences of delayed reimbursement of innovative cancer drugs

The previous sections have established that many cancer drugs with regulatory approval lack positive reimbursement status. They have also shown that timely reimbursement is a major challenge and several years of delay is the rule rather than the exception. This section quantifies some of the consequences for patients with delayed reimbursement of innovative cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: How many patient life years could be saved by faster reimbursement approval of innovative cancer drugs?

4.1 Method and data

To quantify the consequences of delayed reimbursement, patient life years lost was used as a metric. The following steps were taken to calculate the number of patient life years lost. The first step involved the definition of a sample of innovative drug-indications, drawing from the pool of innovative indications identified in section 2. For each of the five cancer types in scope, two innovative indications were selected. All 10 drug-indications were considered in every market, even if regulatory approval in a market was still pending in September 2020 as this is a prerequisite for reimbursement. Table 1 provides an overview of the 10 selected indications.

In the second step, the annual number of eligible patients was calculated. Eligibility was defined according to the approved label (using the local approved label or the US FDA label in case of no local approval). The exact calculation of patient numbers was done in the following top-down manner. Newly diagnosed cases (incidence) in 2018 of the selected tumor type (breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, lung cancer) served as the starting point (see sub-report 1). These numbers were then adjusted for the proportion of tumor subtype (e.g., non-small cell lung cancer), genomic alterations (e.g., HER2-positive in breast cancer), disease stage (e.g., metastatic disease), and line of therapy; see Table 1 for the level of detail used. Market-specific estimates were retrieved for these adjustment factors; in case these were not available, Asia-specific (Europe-specific for Australia and New Zealand) or global estimates were used.

In the third step, median survival gain per eligible patient was calculated. The survival gain was based on the gain in overall survival (OS) observed in key clinical trials; see Table 1. In cases when the comparator drug used in the key clinical trial lacked regulatory approval in a specific market, an indirect comparison was made, based on the key clinical trial of the comparator drug and the current standard of care.

Table 1: Innovative cancer drug-indications and their clinical benefit

Cancer type	Drug	Indication	ESMO-MCBS	Comparator drug	OS gain (months)	Clinical trial
Breast cancer	Abemaciclib	2nd line, combo with fulvestrant, HR+ HER2-, metastatic	4	Fulvestrant	9.4	(41)
Breast cancer	Pertuzumab	1st line, combo with trastuzumab + docetaxel, HER2+, metastatic	4	Trastuzumab + docetaxel	15.7	(42)
Esophageal cancer	Nivolumab	2nd line, mono, ESCC, metastatic	4	Paclitaxel or docetaxel	2.5	(43)
Gastric cancer	Trifluridine & tipiracil	3rd line, mono, gastric or GEJ AC, metastatic	3*	Placebo (best supportive care)	2.1	(44)
Head and neck cancer	Cetuximab	1st line, combo with platinum + fluorouracil, HNSCC, metastatic	3*	Platinum + fluorouracil	2.7	(45)
Head and neck cancer	Pembrolizumab	1st line, combo with platinum + fluorouracil, HNSCC, metastatic	4	Cetuximab + platinum + fluorouracil	2.3	(46)
Liver cancer	Atezolizumab^	1st line, combo with bevacizumab, HCC, Child-Pugh class A, advanced	5	Sorafenib	9.6	(47)
Liver cancer	Regorafenib	2nd line, mono, HCC, Child-Pugh class A, advanced	4	Placebo (best supportive care)	2.8	(48)
Lung cancer	Osimertinib	1st line, mono, NSCLC, EGFR+, metastatic	4	Erlotinib or gefitinib	6.8	(49)
Lung cancer	Pembrolizumab	1st line, combo with pemetrexed + platinum, NSCLC, NSQ, EGFR- ALK-, metastatic / 1st line, combo with carboplatin + (nab-)paclitaxel, NSCLC, SQ, EGFR- ALK-, metastatic	4 / 4	Pemetrexed + carboplatin / carboplatin + (nab-)paclitaxel	11.3 / 5.5	(50, 51)

Notes: AC = adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GEJ = gastroesophageal junction, HCC = hepatocellular carcinoma, NSQ = non-squamous, OS = overall survival, SCCHN = squamous cell carcinoma of the head and neck, SQ = squamous.

* Indications with ESMO-MCBS score of 3 (moderate clinical benefit) used in the absence of other GEJ and head & neck drug-indications with higher scores of 4/B+

^ Indication received ESMO-MCBS score after main data collection.

Clinical trials for indirect comparison were used in some markets for osimertinib (average of erlotinib (52) and gefitinib (53)), for atezolizumab (sorafenib (54)), and for pembrolizumab in head and neck cancer (cetuximab (45)).

In the final step, information on the delay between regulatory approval and reimbursement approval was added (see section 3). However, as shown in the previous section, the median delay differs greatly between markets and many markets had failed to reimburse most of the 10 indications considered here by September 2020. In order to obtain comparable estimates of the consequences of delayed reimbursement, the following strategy was used. The annual number of eligible patients and the median survival gain per patient was first combined. This yielded number patient life years lost. This number also presents the patient life years lost *per year*, as it is based on the *annual* number of eligible patients. In instances when the actual delay between regulatory approval and reimbursement approval was shorter than one year (in Japan for all 10 indications, in Australia for 2 indications[5], and in South Korea for 1 indication[6]), the actual delay was used rather than one year of delay.

4.2 Results

Reimbursement of cancer drugs to facilitate patient access is vital. Timely reimbursement of new innovative drug-indications is important to improve survival outcome and avoid the loss of patient life years. Figure 9 presents the results of the analysis of patient life years lost due to delayed reimbursement. Across the 14 markets in Asia-Pacific, 928,000 patient life years are lost for every year of reimbursement delay of only 10 innovative indications across 5 cancer types. Compared to the number of eligible patients of 1.53 million diagnosed every year, this equals more than 7 months of life lost per patient.

The lion's share of the total loss in patient life years in Asia-Pacific occurs in China with 635,000 life years lost per year of delay, corresponding to more than two thirds of the total loss. This is naturally owed to the large cancer patient population in China (see sub-report 1), both in absolute terms and in relative terms for the five cancer types considered. At the other end of the spectrum are the two markets with the smallest cancer patient populations, Singapore and New Zealand, with 1,500 to 2,000 life years lost.

Japan is the only market where the numbers in Figure 9 present actual loss of patient life years due to delay as all 10 indications had received reimbursement by September 2020. There were minimal delays of around 2 months between regulatory approval and reimbursement of the breast cancer indications, which were new drugs listed on NHI within the 60-90 days period as mentioned previously. In the other 13 markets in Asia-Pacific, the numbers in Figure 9 would need to be multiplied with the actual time period it took (or will take) to receive reimbursement to get

[5] Trifluridine & tipiracil and pembrolizumab in lung cancer (squamous type).
[6] Regorafenib.

comparable numbers to Japan. For example, section 3 showed that the median reimbursement delay of innovative indications is around 2 years in Taiwan. The annual life years lost here amounts to 12,600, but the final number might be around 25,000 assuming a 2-year delay. For markets where reimbursement might take 10 years or more, such as the Philippines as shown in section 3, the final number would amount to ten times the numbers presented here – 230,000 patient life years lost in the case of the Philippines.

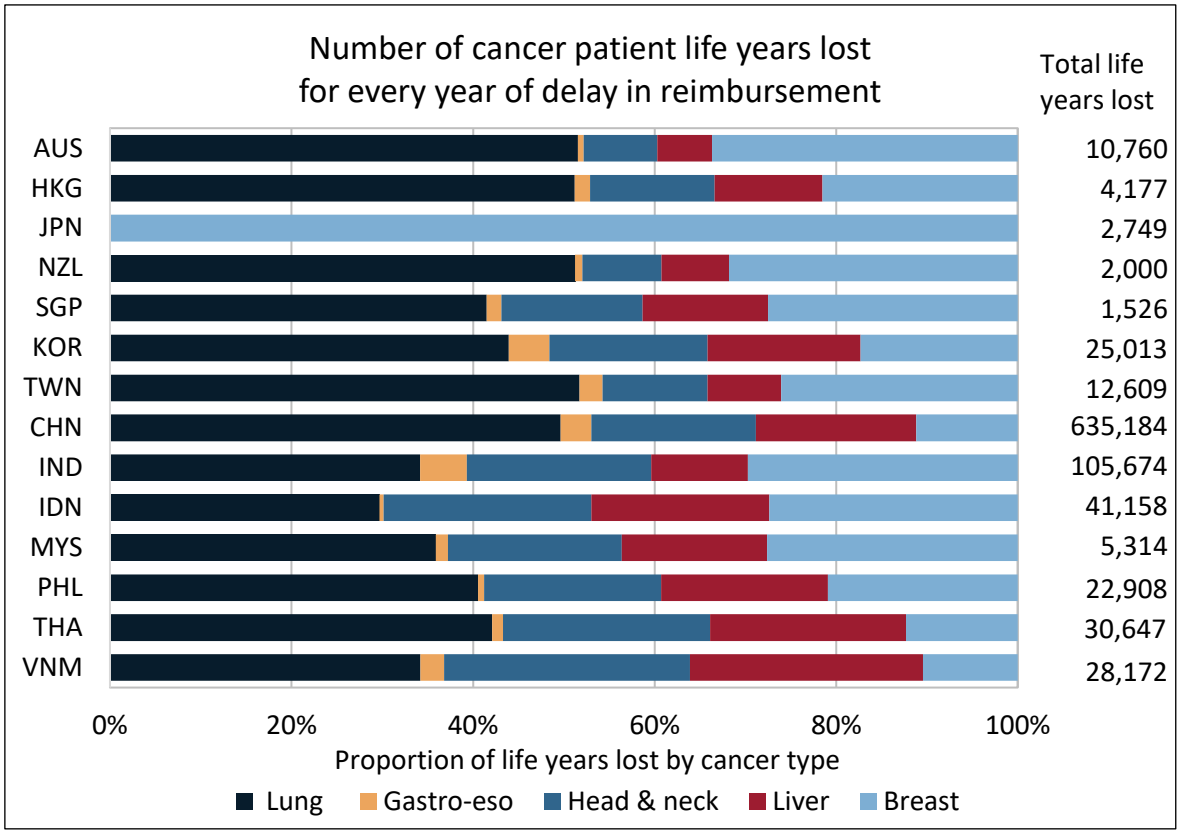

Figure 9: Number (right side) and proportion (left side) of patient life years lost for every year of delay in reimbursement of 10 innovative indications in 5 cancer types

Notes: Lung = NSCLC, Gastro-eso = gastro-esophageal cancer, Head & neck = head and neck cancer, Liver = liver cancer, Breast = breast cancer.

Figure 9 also presents a split of the loss in patient life years by cancer type. In all markets (except Japan), the greatest number of life years that could be saved was in lung cancer followed by breast cancer (except in Vietnam) with better access to innovative treatment. These numbers partly reflect larger numbers of eligible patients in these two cancer types (see sub-report 1), but also greater absolute survival gains that could be offered by the select drug-indications based on pivotal trial data (see Table 1). Japan has only patient life years lost from delays in reimbursement of both breast cancer drug-indications, as these were the initial indications approved for these drugs, which comes along with some delay (at most 60-90 days as noted above).

Comparison with previous studies

Comparable studies on the topic of patient life years lost due to delays in reimbursement of cancer drugs are scarce in Asia-Pacific.[7] In Europe, a recent study used two cancer drugs – abiraterone and ipilimumab – to study life years lost during the delay between approval by the European Medicines Agency and initial patient access (defined as first sales registered in the IQVIA MIDAS database) in a large sample of countries (57). The approach to use first sales as a proxy for patient access (thought of in terms of reimbursement) makes more sense in the European health care systems, where few sales occur before reimbursement. However, this is different in Asia-Pacific (see sub-report 4). In terms of conclusion, the European study echoes the findings in this report that cancer patients face long delays in access to innovative cancer drugs in most markets and their health outcomes could be greatly improved by faster reimbursement decisions.

It should also be noted that the estimated number of almost 1 million patient life years lost in this report is only based on 10 innovative drug-indications. As explained in section 3, there were 31 innovative drug-indications approved by the US FDA between 2010 and 2020 for the five cancer types considered in this report. For other cancer types, there are also innovative cancer drugs available, and they might face similar challenges with reimbursement delays. Thus, the estimate of almost 1 million patient life years lost per year of reimbursement delay is likely a great underestimation of the actual loss across all innovative cancer drugs and cancer types.

[7] There is a vast literature on the topic of years of life lost (YLL) due to premature death of cancer and other diseases. The WHO regularly provides statistics on this measure for countries around the globe (55). Recently, studies on COVID-19 and YLL have been published (56), and they are closer to the topic considered here, as they indirectly quantify the YLL due to delay in access to an effective vaccine.

5. Reasons for delayed reimbursement of innovative cancer drugs

This section discusses reasons for delayed reimbursement of innovative cancer drugs across all markets in Asia-Pacific. It aims to answer the following question: What are the reasons for the delay in access to innovative cancer drugs in the different markets in Asia-Pacific and also compared to the situation in Europe?

5.1 Method

An ad-hoc literature search was performed to extract relevant articles and reports published in the grey literature. Material reviewed during the data collection of regulatory approval and reimbursement dates, described in section 3.1, was also used.

5.2 Results

Delays in patient access to innovative cancer drugs is not just a challenge in Asia-Pacific. Countries in Europe share the same challenge, despite a more favorable basis to start from. In Europe, the European Medicines Agency (EMA) was established in 1995 and has taken over the responsibility for regulatory approval of most new drugs, including all cancer drugs. However, individual countries are responsible for the reimbursement decision. The time for these decisions varies considerably. The survey by EFPIA mentioned in section 3, showed that the average delay between regulatory approval by the EMA and patient access ranged from less than 6 months in Denmark and Germany to over 2 years in many (less wealthy) Eastern European countries, for cancer drugs approved between 2015 and 2018 (40).

Similar to Asia-Pacific, Europe also consists of countries of different sizes and with varying economic wealth (although the variations are distinctly smaller), which provides them with different means to make reimbursement decisions for innovative cancer drugs. A recent survey among different European stakeholders has uncovered 9 key factors that are causing delay to innovative cancer drugs (58); see Table 2. These factors generally relate to three broad categories: the organization of the reimbursement process, the criteria applied in this process, and the readiness of the health care system to absorb the drugs. A description of these three categories applied to the different markets in Asia-Pacific is provided below.

Table 2: Factors delaying patient access to innovative cancer drugs in Europe

Category	Factors causing delay	Description
Process	Late start of the process	Late company submission or late start of the national process after EMA approval
	Lack of clearly defined national timelines	Absence of (or no compliance with) a maximum duration of the process
	Multiple layers of decision-making	Subnational enforcement or financing of a reimbursement decision
Value assessment criteria	Misalignment of evidence requirements	Differences between EMA and national HTA bodies, and between HTA bodies (endpoints, comparator, population, etc.)
	Unpredictability of requirements	Unclear or inconsistently applied evidence requirements and pricing and reimbursement thresholds
	Limited compatibility of existing HTA and value assessment methodology with innovation	More evidence gaps arising from latest innovations (novel endpoints, trial designs, etc.)
Health system readiness	Limited resources to implement decisions	Resource and budget insufficiency hampering prescription and use
	Lack of up-to-date clinical guidelines	Latest innovations are often not included in the guidelines
	Suboptimal health care infrastructure and care pathways	Care organization hampers optimal prescription and use

Notes: EMA = European Medicines Agency, HTA = health technology assessment. Source: (58).

Reimbursement process

An exact description of the reimbursement process in every market goes beyond the scope of this report. However, there are some institutional features worth highlighting in relation to patient access. Even if the process leading up to a reimbursement decision is carried out at different times for different drugs, patient access is only realized once the decision comes into force. This typically coincides with the time when the reimbursement scheme (national formulary) is updated. Table 2 provides an overview of the frequency at which reimbursement schemes used in this report are usually updated.

Table 3: Reimbursement schemes and frequency of update

	Market	Reimbursement scheme	Frequency of reimbursement scheme update*
HIGH-INCOME MARKETS	Australia	Pharmaceutical Benefits Scheme (PBS) list	Monthly
	Hong Kong	Hospital Authority Drug Formulary (HADF), Samaritan Fund (SF), Community Care Fund (CCF)	Every 2-4 months
	Japan	National Health Insurance (NHI) list	Every 1-3 months
	New Zealand	Pharmaceutical Management Agency (PHARMAC) list	Monthly
	Singapore	Standard Drug List (SDL), Medication Assistance Fund (MAF)	Every 3-4 months
	South Korea	National Health Insurance (NHI) list	Monthly
	Taiwan	National Health Insurance (NHI) list	Monthly
MIDDLE-INCOME MARKETS	China	National Reimbursement Drug List (NRDL)	Most recent updates in Feb 2017 and Aug/Nov 2019, Dec 2020
	India	(no scheme for entire population)	n/a
	Indonesia	National Formulary (Fornas)	Most recent updates Apr 2018, Apr 2019, Apr 2020
	Malaysia	Ministry of Health Medicines Formulary (MOHMF)	≈3 times per year
	Philippines	Philippine National Formulary (PNF)	8th edition of PNF-EML in 2017 and full PNF update in Sep 2019
	Thailand	National List of Essential Medicines (NLEM)	Most recent updates Jul 2018, Mar 2019, Oct 2020
	Vietnam	Reimbursement Drug List (RDL)	Most recent updates Jan 2015, Jan 2019

Notes: * Reimbursement committees could meet at different intervals across the markets than the cited update of the reimbursement scheme. n/a = not applicable.

In high-income markets, reimbursement listings tend to be updated every 1-4 months. This limits the potential delay between the actual reimbursement decision and the decision to come into effect.

By contrast, reimbursement listings are reviewed and updated much less frequently across most middle-income markets; see Table 3. For instance, China got its first national formulary in 2000 (back then called the China National Formulary, CNF), which was subsequently updated in 2004, in 2009, and in 2017 (29). During the update in 2009 and 2017, around 70 new cancer drugs were launched in Europe alone (see Figure 1), but without inclusion in the CNF/NRDL none of them could reach patients in China on a large scale. Since 2017, China has significantly improved on the frequency of updates and now aims for updates on an annual basis (59, 60).

The fast-paced development of new cancer drugs coming into the market in the recent decade together with the infrequent updates of reimbursement listings means that there could be growing numbers of cancer patients with limited access to the latest treatment options in many middle-income markets. For instance, during the four years between the two most recent updates of the RDL in 2015 and 2019 in Vietnam, 42 new cancer drugs were launched in Europe alone (see Figure 1). Removing these kinds of institutional barriers is an important step towards driving change and improving patient outcomes in middle-income markets.

Value assessment criteria – the role of HTA

The reimbursement process of a new drug is typically informed by an analysis of the clinical benefits and costs of treatment. The systematic evaluation of the properties and effects of a new drug, typically also including a comparison with the existing standard of care, is called health technology assessment (HTA). Evaluations of clinical trials data naturally hold a level of uncertainty around a drug's performance in the real world, which in turn can cause delays in reimbursement decisions by HTA bodies. To address this issue, health care payers, HTA bodies, and the pharmaceutical industry have adopted formal arrangements, called risk-sharing agreements (RSA), patient access schemes (PAS), or managed entry agreements (MEA), to share the financial risks associated with new drugs when their value is not fully observable at the time of launch (61). Many European countries have adopted RSA, although success is mixed due to their complexity and administrative burden (62, 63). The use and comprehensiveness of HTA to inform reimbursement decisions as well as of RSA differs across markets in Asia-Pacific.

Japan did not use to carry out any HTA, but after conducting a pilot-program between 2016 and 2019, the submission of cost-effectiveness evidence to the Central Social Insurance Medical Council (Chuikyo) has become mandatory for selected drugs (33). The evaluation of this evidence only informs pricing decisions and happens *after* the reimbursement decision and thus will not delay the latter. By contrast, Australia, New Zealand, South Korea, and Taiwan perform HTA routinely and carry out their assessments *before* reimbursement. The speed of these assessments thus crucially influences delay in access to innovative cancer drugs.

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) bases its recommendations for reimbursement on a number of criteria, but cost-effectiveness is imperative. Most applications are initially declined and have to be revised several times, according to information from the public registry of PBAC (64). In New Zealand, the Pharmaceutical Management Agency (PHARMAC) also conducts a thorough review and is doing broad consultations with different stakeholders, but this also causes significant delays. A review of the public registry of PHARMAC and major immunotherapy

drugs (e.g., nivolumab or pembrolizumab) shows that consultations have been going on since 2016 but no decisions have been reached by the end of 2020 (65). These delays have potentially resulted in thousands of patient life years lost, as shown in section 4.

In South Korea, HTA has been performed by the Health Insurance Review and Assessment service (HIRA) since 2006, and drugs are assessed in different tracks depending on whether an alternative drug is available or not. In 2014, a special RSA fast-rack pathway to improve patients' access to cancer drugs (and drugs for rare disease) was introduced, which was shown to have reduced reimbursement delays (36, 66). In Taiwan, HTA has been performed since 2007 by the Center for Drug Evaluation (CDE) to inform inclusion of drugs on the National Health Insurance list (67). RSA to reduce reimbursement delay and manage financial impact were announced to be piloted for cancer drugs in September 2018 by the Ministry of Health and Welfare (68, 69).

In Singapore, HTA has been conducted to a limited extent by the Agency for Care Effectiveness (ACE) since 2015 (22). ACE seems to apply a comparatively strict approach, as evidenced by an evaluation of first-generation and second-generation EGFR inhibitors for NSCLC in 2018 (70). In its evaluation ACE did not recommend inclusion in the Medial Assistance Fund, because the drugs provided "*uncertain clinically meaningful benefits for patients*" and have "*unacceptable cost-effectiveness*", despite being reimbursed in all other high-income markets and even some middle-income markets.

Some middle-income markets have also started to adopt HTA to inform reimbursement decisions. In Thailand, the use of HTA in facilitating decision making started with the revision of the 2004 NLEM, which included economic aspects as a criterion for drug selection (71). The Health Intervention and Technology Assessment Program (HITAP) was established in 2007, yet resources to conduct proper HTA remain limited (71). In Malaysia, the Malaysian Health Technology Assessment Section (MaHTAS) carries out HTA and has also strengthened its capacity to conduct economic evaluations since 2015 (72). In China, HTA efforts are underway but have not been formally implemented (66). The Philippines launched its first HTA process and methods guidelines in September 2020 (73). By contrast, in Indonesia and in Vietnam HTA is not yet used to guide the selection of drugs to be listed in the national formulary (74, 75).

Health system readiness

As shown in sub-report 2, all middle-income markets in Asia-Pacific invest comparatively little in health care – both in relation to GDP and in absolute terms. Budgetary restrictions and the resulting lack of reimbursement have been pointed out as the root cause for low patient access to newer cancer drugs in middle-income markets, in the survey by ESMO described in section 2 (13). Limited

resources delay positive reimbursement decisions. However, as pointed out by the WHO, the wealth of a country is just a general determinant of health spending whereas political commitment to allocate sufficient investment for the provision of high-quality health care (which includes access to innovative drugs) also matters (76). The latter might explain why New Zealand incurs comparatively long delays in reimbursement of innovative cancer drugs among high-income markets.

All health care payers, albeit by different extent potentially, face the same challenges in allocating limited health resources. Therefore, there is a need for clear prioritization of drugs with high clinical benefit to achieve an allocation of resources that maximizes patient outcomes. The analysis in section 4 of this report has demonstrated the positive impact on patient survival outcomes that could potentially be achieved by investing in innovative treatment options and ensuring timely patient access.

Reimbursement decisions of innovative drugs also have to be well thought through in terms of the auxiliary health services needed to administer them. Sub-optimal health care infrastructure can hamper the use of innovative drugs. For instance, to administer targeted therapies in NSCLC, an assessment of genomic alterations is a prerequisite. Drugs targeting EGFR, ALK, ROS1, BRAF, NTRK, RET, and MET mutations have been approved by the US FDA during the last decade (see Table A1 in the Appendix). Sequential testing for these alterations is challenging due to the number of different tests warranted, resulting in depletion of tumor tissue samples and incomplete assessments. Extensive mutational profiling using next generation sequencing (NGS) has emerged as the main alternative to meet the clinical need, but this technology is still relatively costly as compared to other more traditional molecular methods. In Europe, this is one of the reasons why countries with limited economic means also provide limited access to drugs targeting these mutations (77).

The analysis in this report offers a nuanced view on reimbursement of cancer drugs, emphasizing the need to focus on innovative drugs that provide clear clinical benefits to patients. Yet access to innovative cancer drugs through reimbursement is quite limited in Asia-Pacific and a clear division between high-income and middle-income markets is noticeable. Even in markets with greater access, patients have to wait for several years to get access due to delays in reimbursement decisions, resulting in a great loss of patient life years. Reasons for delayed reimbursement of innovative cancer drugs vary across markets in Asia-Pacific. In middle-income markets they relate more to the budgetary readiness of the health care system to absorb new drugs (see sub-report 5 for potential solutions) as well as the organization of the reimbursement process. In high-income markets, they relate more to the criteria applied in the reimbursement process and the lack of fast-track systems for innovative drugs.

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Appendix

Table A1: List of US FDA-approved indications and ESMO-MCBS score (Sep 30, 2020)

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Abemaciclib	BC	2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	28-Sep-2017	4	Innovative
Abemaciclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	26-Feb-2018	3	Others
Abemaciclib	BC	2L, mono, HR+ HER2-, advanced or metastatic	28-Sep-2017		Others
Afatinib	LUC	1L, mono, EGFR+, metastatic	12-Jan-2018 (12-Jul-2013)	4	Innovative
Afatinib	LUC	2L, mono, SQ, metastatic	15-Apr-2016	2	Others
Alectinib	LUC	1L, mono, ALK+, metastatic	6-Nov-2017	4	Innovative
Alectinib	LUC	2L, mono, ALK+, metastatic	11-Dec-2015	4	Innovative
Alpelisib	BC	2L, combo with fulvestrant, HR+ HER2- PIK3CA+, advanced or metastatic	24-May-2019	3	Others
Anastrozole	BC	2L, mono, advanced	27-Dec-1995		Others
Anastrozole	BC	1L, mono, HR+, advanced or metastatic	1-Sep-2000		Others
Anastrozole	BC	Adjuvant, HR+	5-Sep-2002		Others
Atezolizumab	LUC	2L, mono, metastatic	18-Oct-2016	5	Innovative
Atezolizumab	BC	1L, combo with nab-paclitaxel, triple-negative, PD-L1+, advanced or metastatic	8-Mar-2019	3	Others
Atezolizumab	LIC	1L, combo with bevacizumab, HCC, metastatic	29-May-2020		Others
Atezolizumab	LUC	1L, combo with bevacizumab + paclitaxel + carboplatin, NSQ, EGFR- ALK-, metastatic	6-Dec-2018	3	Others
Atezolizumab	LUC	1L, combo with nab-paclitaxel + carboplatin, NSQ, EGFR- ALK-, metastatic	3-Dec-2019	3	Others
Atezolizumab	LUC	1L, mono, PD-L1+ EGFR- ALK-, metastatic	18-May-2020		Others
Bevacizumab	LIC	1L, combo with atezolizumab, HCC, metastatic	29-May-2020		Others
Bevacizumab	LUC	1L, combo with carboplatin + paclitaxel, NSQ, metastatic	11-Oct-2006	2	Others
Bleomycin	HNC	1L, mono, SCCHN, metastatic	31-Jul-1973		Others
Brigatinib	LUC	1L, mono, ALK+, metastatic	22-May-2020 (2-Oct-2017)	3	Others
Cabozantinib	LIC	2L, mono, HCC, metastatic	14-Jan-2019	3	Others
Capecitabine	BC	2L/3L, mono, metastatic	30-Apr-1998		Others
Capecitabine	BC	2L, combo with docetaxel, metastatic	7-Sep-2001		Others
Capmatinib	LUC	1L, mono, MET+, metastatic	6-May-2020		Others
Ceritinib	LUC	1L, mono, ALK+, metastatic	26-May-2017 (29-Apr-2014)	4	Innovative
Cetuximab	HNC	1L, combo with radiation therapy, SCCHN, advanced	1-Mar-2006		Others
Cetuximab	HNC	2L, mono, SCCHN, metastatic	1-Mar-2006		Others
Cetuximab	HNC	1L, combo with platinum + fluorouracil, SCCHN, metastatic	7-Nov-2011	3	Others
Crizotinib	LUC	1L, mono, ALK+ or ROS1+, metastatic	21-Jul-2017 (26-Aug-2011)	4 / 3	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Cyclophosphamide	BC	1L, mono	[16-Nov-1959]		Others
Dabrafenib	LUC	1L, combo with dabrafenib, BRAF V600E+, metastatic	22-Jun-2017	2	Others
Dacomitinib	LUC	1L, mono, EGFR+, metastatic	27-Sep-2018	3	Others
Docetaxel	GEC	1L, combo with cisplatin + fluorouracil, gastric or GEJ AC, advanced	22-Mar-2006	A	Innovative
Docetaxel	BC	2L, mono, advanced or metastatic	22-Jun-1996 (14-May-1996)		Others
Docetaxel	BC	Adjuvant, combo with doxorubicin and cyclophosphamide, node-positive	18-Aug-2004		Others
Docetaxel	HNC	1L, combo with cisplatin + fluorouracil, SCCHN, advanced	28-Sep-2007 (17-Nov-2006)		Others
Docetaxel	LUC	2L, mono, advanced or metastatic	23-Dec-1998		Others
Docetaxel	LUC	1L, combo with cisplatin, advanced or metastatic	27-Nov-2002		Others
Doxorubicin	BC	1L, mono, metastatic	[7-Aug-1974]		Others
Doxorubicin	BC	Adjuvant, combo	8-May-2003		Others
Doxorubicin	GEC	1L, mono, gastric, metastatic	[7-Aug-1974]		Others
Durvalumab	LUC	2L, mono, stage III	16-Feb-2018	4	Innovative
Entrectinib	LUC	1L, mono, ROS1+, metastatic	15-Aug-2019	3	Others
Epirubicin	BC	Adjuvant, combo	15-Sep-1999		Others
Eribulin	BC	3L, mono, metastatic	15-Aug-2010	2	Others
Erlotinib	LUC	1L or laterL, mono, EGFR+, metastatic	18-Oct-2016 (18-Nov-2004)	4	Innovative
Everolimus	BC	2L, combo with exemestane, HR+ HER2-, advanced	20-Jul-2012	2	Others
Exemestane	BC	2L, mono, advanced	21-Oct-1999		Others
Exemestane	BC	Adjuvant after tamoxifen, ER+	5-Oct-2005		Others
Fluorouracil	GEC	Perioperative, combo with cisplatin, gastric or GEJ or esophageal AC, resectable	[25-Apr-1962]	A	Innovative
Fluorouracil	BC	1L, mono, AC	[25-Apr-1962]		Others
Fulvestrant	BC	2L, mono, HR+, advanced	25-Aug-2017 (25-Apr-2002)	2	Others
Fulvestrant	BC	2L, combo with palbociclib or abemaciclib, HR+ HER2-, advanced or metastatic	14-Nov-2018 (2-Mar-2016)		Others
Fulvestrant	BC	1L, mono, HR+ HER2-, advanced	25-Aug-2017	2	Others
Fulvestrant	BC	1L/2L, combo with ribociclib, HR+ HER2-, advanced or metastatic	11-Mar-2019		Others
Gefitinib	LUC	1L, mono, EGFR+, metastatic	13-Jul-2015 (3-May-2003)	4	Innovative
Gemcitabine	BC	1L, combo with paclitaxel, metastatic	19-Mar-2010 (19-May-2004)		Others
Gemcitabine	LUC	1L, combo with cisplatin, metastatic	19-Mar-2010 (25-Aug-1998)		Others
Goserelin	BC	1L, mono, advanced	31-Aug-2009 (1989)		Others
Hydroxyurea	HNC	1L, combo with chemoradiation, SCCHN, advanced	[7-Dec-1967]		Others
Ipilimumab	LIC	2L, combo with nivolumab, HCC, metastatic	10-Mar-2020		Others
Ipilimumab	LUC	1L, combo with nivolumab, PD-L1+ EGFR- ALK-, metastatic	15-May-2020		Others
Ipilimumab	LUC	1L, combo with nivolumab + Pt-based chemo, EGFR- ALK-, metastatic	26-May-2020		Others

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Ixabepilone	BC	3L, combo with capecitabine, metastatic	16-Oct-2007		Others
Ixabepilone	BC	4L, mono, metastatic	16-Oct-2007		Others
Lapatinib	BC	2L, combo with capecitabine, HER2+, advanced or metastatic	13-Mar-2007	3	Others
Lapatinib	BC	1L, combo with letrozole, HR+ HER2+, metastatic	29-Jan-2010		Others
Larotrectinib	LUC	1L, mono, NTRK+, metastatic	26-Nov-2018	3	Others
Lenvatinib	LIC	1L, mono, HCC, unresectable	15-Aug-2018	4	Innovative
Letrozole	BC	1L/2L, mono, HR+, advanced	2-Mar-2010 (25-Jul-1997)		Others
Letrozole	BC	Adjuvant after tamoxifen	29-Oct-2004		Others
Letrozole	BC	Adjuvant, HR+	28-Dec-2005		Others
Lorlatinib	LUC	2L/3L, mono, ALK+, metastatic	2-Nov-2018	3	Others
Methotrexate	BC	1L, mono	[10-Aug-1959]		Others
Methotrexate	HNC	1L, mono, epidermoid	[10-Aug-1959]		Others
Methotrexate	LUC	1L, mono, SQ	[10-Aug-1959]		Others
Mitomycin	GEC	1L, combo with chemo, gastric AC, metastatic	1-Jan-1974		Others
Necitumumab	LUC	1L, combo with gemcitabine + cisplatin, SQ, metastatic	24-Nov-2015	1	Others
Neratinib	BC	Adjuvant-extended, mono, HER2+	1-Oct-2018 (17-Jul-2017)	A	Innovative
Neratinib	BC	3L, combo with capecitabine, HER2+, metastatic	25-Feb-2020		Others
Nivolumab	HNC	2L, mono, SCCHN, metastatic	10-Nov-2016	4 / 5	Innovative
Nivolumab	LUC	2L, mono, metastatic	9-Oct-2015 (4-Mar-2015)	5	Innovative
Nivolumab	LIC	2L, mono or combo with ipilimumab, HCC, metastatic	10-Mar-2020 (22-Sep-2017)		Others
Nivolumab	LUC	1L, combo with ipilimumab, PD-L1+ EGFR- ALK-, metastatic	15-May-2020		Others
Nivolumab	LUC	1L, combo with ipilimumab + Pt-based chemo, EGFR- ALK-, metastatic	26-May-2020		Others
Nivolumab	GEC	2L, mono, ESCC, metastatic	10-Jun-2020	4	Innovative
Olaparib	BC	2L, mono, gBRCAm+ HER2-, metastatic	12-Jan-2018	4	Innovative
Osimertinib	LUC	2L, mono, EGFR-T790M+, metastatic	13-Nov-2015	4	Innovative
Osimertinib	LUC	1L, mono, EGFR+, metastatic	18-Apr-2018	4	Innovative
Paclitaxel	BC	2L, mono, metastatic	13-Apr-1994		Others
Paclitaxel	BC	Adjuvant, combo with doxorubicin-based chemo, node-positive	25-Oct-1999		Others
Paclitaxel	LUC	1L, combo with cisplatin, metastatic	30-Jun-1998		Others
Paclitaxel-nab	BC	2L, mono, metastatic	7-Jan-2005		Others
Paclitaxel-nab	LUC	1L, combo with carboplatin, advanced or metastatic	11-Oct-2012		Others
Palbociclib	BC	2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	19-Feb-2016	4	Innovative
Palbociclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	31-Mar-2017 (3-Feb-2015)	3	Others
Pembrolizumab	HNC	1L, mono, SCCHN, PD-L1+, metastatic	17-Jun-2019	4 / 5	Innovative
Pembrolizumab	HNC	1L, combo with platinum + fluorouracil, SCCHN, metastatic	17-Jun-2019	4	Innovative
Pembrolizumab	HNC	2L, mono, SCCHN, metastatic	5-Aug-2016	4	Innovative
Pembrolizumab	LUC	2L, mono, PD-L1+, metastatic	24-Oct-2016 (2-Oct-2015)	5	Innovative
Pembrolizumab	LUC	1L, mono, PD-L1+ EGFR- ALK-, stage III or metastatic	11-Apr-2019 (24-Oct-2016)	5	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Pembrolizumab	LUC	1L, combo with pemetrexed + carboplatin, NSQ, EGFR- ALK-, metastatic	30-Oct-2018 (17-May-2017)	4	Innovative
Pembrolizumab	LUC	1L, combo with carboplatin + (nab-)paclitaxel, SQ, metastatic	30-Oct-2018	4	Innovative
Pembrolizumab	LIC	2L, mono, HCC, metastatic	9-Nov-2018		Others
Pembrolizumab	GEC	3L, mono, gastric or GEJ AC, PD-L1+, metastatic	22-Sep-2017		Others
Pembrolizumab	GEC	2L, mono, ESCC, PD-L1+, metastatic	30-Jul-2019		Others
Pemetrexed	LUC	2L maintenance, NSQ, advanced or metastatic	2-Jul-2009	4	Innovative
Pemetrexed	LUC	1L, como with cisplatin, NSQ, advanced or metastatic	11-Oct-2017 (26-Sep-2008)	4	Innovative
Pemetrexed	LUC	2L, mono, NSQ, metastatic	11-Oct-2017 (19-Aug-2004)		Others
Pemetrexed	LUC	1L, combo with pembrolizumab + carboplatin, NSQ, EGFR- ALK-, metastatic	30-Jan-2019 (4-Jun-2018)		Others
Pertuzumab	BC	1L, combo with trastuzumab + docetaxel, HER2+, metastatic	8-Jun-2012	4	Innovative
Pertuzumab	BC	Adjuvant, combo with trastuzumab + chemotherapy, HER2+	20-Dec-2017	B	Innovative
Pertuzumab	BC	Neoadjuvant, combo with trastuzumab + chemotherapy, HER2+	20-Dec-2017 (30-Sep-2013)	C	Others
Pralsetinib	LUC	1L, mono, RET+, metastatic	4-Sep-2020		Others
Ramucirumab	LIC	2L, mono, HCC, metastatic	10-May-2019	1	Others
Ramucirumab	LUC	2L, combo with docetaxel, metastatic	12-Dec-2014	1	Others
Ramucirumab	LUC	1L, combo with erlotinib, EGFR+, metastatic	29-May-2020	3	Others
Ramucirumab	GEC	2L, mono or combo with paclitaxel, gastric or GEJ AC, metastatic	12-Dec-2014 (21-Apr-2014)	2	Others
Regorafenib	LIC	2L, mono, HCC, metastatic	27-Apr-2017	4	Innovative
Ribociclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	18-Jul-2018 (13-Mar-2017)	3 / 5	Innovative
Ribociclib	BC	1L or 2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	18-Jul-2018	4	Innovative
Sacituzumab govitecan	BC	3L, mono, triple-negative, metastatic	22-Apr-2020		Others
Selpercatinib	LUC	1L, mono, RET+, metastatic	8-May-2020		Others
Sorafenib	LIC	1L, mono, HCC, metastatic	16-Nov-2007		Others
Talazoparib	BC	1L, mono, gBRCAm+ HER2-, advanced or metastatic	16-Oct-2018	4	Innovative
Tamoxifen	BC	1L, mono, metastatic	29-Oct-1998 (30-Dec-1977)		Others
Tamoxifen	BC	Adjuvant, mono	29-Oct-1998 (30-Dec-1977)		Others
Thiotepa	BC	1L, mono, metastatic	9-Mar-1959		Others
Toremifene	BC	1L, mono, ER+, metastatic	20-Nov-1997		Others
Trametinib	LUC	1L, combo with dabrafenib, BRAF V600E+, metastatic	22-Jun-2017		Others
Trastuzumab	BC	Adjuvant / 1L / laterL, mono/combo, HER2+, all stages	18-Jan-2008 (25-Sep-1998)	A	Innovative
Trastuzumab	GEC	1L, mono, gastric or GEJ AC, metastatic	20-Oct-2010		Others
Trastuzumab deruxtecan	BC	3L, mono, HER2+, metastatic	20-Dec-2019	2	Others
Trastuzumab emtansine	BC	2L, mono, HER2+, metastatic	19-Aug-2013	4	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Trastuzumab emtansine	BC	Adjuvant, mono, HER2+	3-May-2019		Others
Trifluridine & tipiracil	GEC	3L, mono, gastric or GEJ AC, metastatic	22-Feb-2019	3	Others
Tucatinib	BC	2L, combo with trastuzumab and capecitabine, HER2+, advanced or metastatic	17-Apr-2020	3	Others
Vinblastine	BC	2L, metastatic	[25-Nov-1965]		Others
Vinorelbine	LUC	1L, mono, metastatic	14-Mar-2014 (23-Dec-1994)		Others
Vinorelbine	LUC	1L, combo with cisplatin, advanced or metastatic	14-Mar-2014 (23-Dec-1994)		Others

Notes: BC = breast cancer, GEC = gastro-esophageal cancer, HNC = head and neck cancer, LIC = liver cancer, LUC = non-small cell lung cancer. AC = adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GEJ = gastroesophageal junction, HCC = hepatocellular carcinoma, NSQ = non-squamous, SCCHN = squamous cell carcinoma of the head and neck, SQ = squamous. FDA approval dates in parenthesis () indicate original date of approved indication that has been replaced by the current one, and brackets [] indicate drug approval date in absence of information on indication approval date.

Table A2: National regulatory drug agencies and national drug reimbursement schemes

	MARKET	REGULATORY AGENCY	REIMBURSEMENT SCHEME
HIGH-INCOME MARKETS	Australia	Therapeutic Goods Administration (TGA)	Pharmaceutical Benefits Scheme (PBS) list
	Hong Kong	Drug Office (DO)	Hospital Authority Drug Formulary (HADF), Samaritan Fund (SF), Community Care Fund (CCF)
	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	National Health Insurance (NHI) list
	New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)	Pharmaceutical Management Agency (PHARMAC) list
	Singapore	Health Sciences Authority (HSA)	Standard Drug List (SDL), Medication Assistance Fund (MAF)
	South Korea	Ministry of Food and Drug Safety (MFDS)	National Health Insurance (NHI) list
	Taiwan	Food and Drug Administration (FDA)	National Health Insurance (NHI) list
MIDDLE-INCOME MARKETS	China	National Medical Products Administration (NMPA)	National Reimbursement Drug List (NRDL)
	India	Central Drugs Standard Control Organisation (CDSCO)	(no scheme for entire population)*
	Indonesia	National Agency of Drug and Food Control (BPOM)	National Formulary (Fornas)
	Malaysia	National Pharmaceutical Regulatory Agency (NPRA)	Ministry of Health Medicines Formulary (MOHMF)
	Philippines	Food and Drug Administration (FDA)	Philippine National Formulary (PNF)
	Thailand	Food and Drug Administration (FDA)	National List of Essential Medicines (NLEM)
	Vietnam	Drug Administration of Vietnam (DAV)	Reimbursement Drug List (RDL)

Notes: * In the analysis, inclusion in the National List of Essential Medicines (NLEM) in its latest version from 2015 was used as a proxy for inferring reimbursement status.

Table A3: Level of granularity available in public databases of regulatory agencies and reimbursement schemes

	MARKET	REGULATORY APPROVAL		REIMBURSEMENT APPROVAL	
		Current status	Exact date	Current status	Exact date
HIGH-INCOME MARKETS	Australia	I	I	I	I
	Hong Kong	D (except IO)	D (except most innovative indications in CCF)	I (CCF+SF) D (HADF)	I (CCF+SF partly) X (HADF)
	Japan	I (after 2004)	I (after 2004)	I (after 2004)	I (after 2004 partly)
	New Zealand	I	I	I	I
	Singapore	I	I (after 2016)	I	X
	South Korea	I	I	I	I
	Taiwan	I	D (except IO and most innovative indications)	I	I
MIDDLE-INCOME MARKETS	China	I	D (except IO and most innovative indications)	I	I
	India	I	I	D	X
	Indonesia	I	D (except some indications)	I	I
	Malaysia	I	I	I	I
	Philippines	D (except IO)	D	I	I
	Thailand	I	D (except some indications)	I	I
	Vietnam	I	D	D*	D

Notes: I = by indication; D = by drug only; X = no information. IO = immunotherapy drugs information provided by MSD or retrieved through company press releases. CCF = Community Care Fund; SF = Samaritan Fund; HADF = Hospital Authority Drug Fund. * All approved indications are usually reimbursed when a drug is on the Reimbursement Drug List.

Table A4: Sample of innovative drug-indications analyzed in calculations of delay between regulatory approval and reimbursement

AUS	HKG	JPN	NZL	KOR	TWN
Afatinib	Alectinib	Abemaciclib	Alectinib (x2)	Abemaciclib	Afatinib
Alectinib	Ceritinib	Afatinib	Palbociclib	Afatinib	Alectinib (x2)
Atezolizumab	Durvalumab	Alectinib (x2)	Pertuzumab	Alectinib (x2)	Atezolizumab
Ceritinib	Lenvatinib	Atezolizumab	Trastuzumab emtansine	Atezolizumab	Ceritinib
Crizotinib	Osimertinib	Ceritinib		Ceritinib	Crizotinib
Durvalumab	Pembrolizumab	Crizotinib		Crizotinib	Lenvatinib
Lenvatinib	Pertuzumab	Durvalumab		Durvalumab	Nivolumab (x2)
Nivolumab (x2)	Ribociclib	Lenvatinib		Lenvatinib	Osimertinib (x2)
Osimertinib (x2)	Trastuzumab emtansine	Nivolumab (x3)		Nivolumab	Pembrolizumab (x3)
Pembrolizumab (x3)		Olaparib		Osimertinib	Pertuzumab
Pertuzumab		Osimertinib (x2)		Palbociclib	Regorafenib
Ribociclib		Palbociclib		Pembrolizumab	Ribociclib
Trastuzumab emtansine		Pembrolizumab (x7)		Pertuzumab	
		Pertuzumab (x2)		Regorafenib	
		Regorafenib		Trastuzumab emtansine	
		Trastuzumab emtansine			

CHN	IDN	MYS	VNM
Afatinib	Afatinib	Afatinib	Afatinib
Alectinib (x2)			
Ceritinib			
Crizotinib			
Osimertinib			
Pertuzumab			
Regorafenib			

HEALTH SPENDING ON CANCER DRUGS AND UNMET PATIENT NEEDS IN ASIA-PACIFIC

Sub-report 4 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

Thomas Hofmarcher
George Keel
Peter Lindgren

IHE - The Swedish Institute for Health Economics

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Report summary

Cancer drugs are an integral part of modern cancer care. The availability of targeted therapies and immunotherapies has changed the standard of care in many cancer types during the last two decades. While such clinical innovation helps address the growing burden of cancer, this poses challenges to health care systems and policy makers with finite health resources available.

Linking resource use in cancer care to patient outcomes is vital to inform funding decisions that strive to maximize value-for-money for patients, the health care system, and society. Expenditure on cancer drugs are a strong indicator of expenditure on cancer care services overall, due to their close links with diagnostics services and other physical infrastructure and manpower required to administer drugs. There is a clear positive relationship between the level of cancer drug expenditure and cancer patient survival across markets in Asia-Pacific. This suggests that patient outcomes are indeed associated with the amount of investment on cancer drugs and other cancer care services in general.

High-income markets in Asia-Pacific spent around 10-20% of total pharmaceutical expenditure – financed via public and private sources – on cancer drugs in 2019, whereas middle-income markets spent around 1-9%. These proportions directed to cancer are comparatively low in relation to the size of the disease burden of cancer. For example, the proportion of cancer deaths amounted to around 30% of all deaths in high-income markets and 9-25% of all deaths in middle-income markets in 2019.

In Asia-Pacific, Japan spent the most on cancer drugs per capita with over $90 in 2019, compared to around $110–$130 per capita in top-spending countries in Europe (Austria, Germany, Switzerland). South Korea spent the least on cancer drugs among high-income markets with around $30 per capita, which puts the market at the same level as European countries with lower GDP per capita than South Korea. In middle-income markets, per capita spending levels ranged from a mere $0.2 in India to $6.6 in Thailand. Higher list prices of drugs and higher numbers of cancer patients in high-income markets might explain some of the vast differences across Asia-Pacific. However, cancer drug expenditure per cancer case still ranged from less than $600 in India and Indonesia to $17,500 in Singapore.

Public spending on cancer drugs exhibits the same vast discrepancies between high-income markets and middle-income markets as observed with total spending. The differences in public spending were particularly pronounced among innovative cancer drugs (i.e., drugs with substantial clinical benefit according to ESMO-MCBS), with average spending of $7,300 per cancer case in high-income markets compared to $370 per cancer case in middle-income markets. Higher use of innovative drugs with much better patient accessibility via reimbursement might explain some of the differences.

Despite securing national reimbursement, patient access to the specific treatment might not necessarily be guaranteed. This could potentially be due to reasons such as the presence of high patient co-payments without a sufficient safety net for disadvantaged groups, sub-optimal level of health infrastructure and manpower, and government budget constraints that might limit accessibility.

Based on a case study of the cancer drug pemetrexed in non-small cell lung cancer, patient needs and actual access were compared (quantified by a comparison of the drug volume needed to treat all eligible patients with the actual drug volume administered). The analysis based on local data in markets such as Australia and Japan that reimburse the newer combination of pemetrexed with immunotherapy (pembrolizumab) seems to suggest that only about half of the patient needs were addressed despite reimbursement. Rigid clinical processes and narrow reimbursement criteria might explain this. Other markets that only reimburse the older combination of pemetrexed with cisplatin, were generally able to meet patient needs. The availability of generic versions of these drugs might have helped in this process, yet immunotherapy (without or in combination with chemotherapy) has now become standard of care, replacing platinum-based chemotherapy regimens. In middle-income markets with no reimbursement of pemetrexed, less than 10% of patient needs are met. This means that many patient life years have already been lost due to limited access and will continue to be so unless there is improved patient access to more effective treatment via reimbursement in a timely manner.

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1. Cancer drugs and unmet patient needs

Cancer drugs are an integral part of modern cancer care (1). Chemotherapy drugs and hormone therapy drugs were introduced in the 1940s-1970s and are still today a standard-of-care treatment modality during the treatment course of many cancer types (2). Chemotherapy can cause toxic side effects as it may damage normal healthy cells alongside malignant cells in the body (3). Targeted therapy drugs, introduced at the end of the 1990s, use a different mode of action and act on specific molecules (e.g., genes, proteins) that are involved in the growth and survival of cancer cells (4, 5). They have now become one of the main treatment options for some tumors. Since 2011, immunotherapy drugs, such as checkpoint inhibitor therapies and more recently CAR T-cell therapies that help the body's immune system to recognize and attack cancer cells, have been added to the therapeutic arsenal and they too have started to replace or complement chemotherapies (6).

As shown in sub-report 3, almost 100 new cancer drugs have been launched over the last decade alone, with many offering substantial clinical benefits to patients. While such clinical innovation helps address the growing burden of cancer, this poses challenges to health care systems and policy makers with finite health resources available.

Many new cancer drugs are given in combination with already existing drugs, and some new cancer drugs allow patient groups to be treated for which there was no drug treatment before. These circumstances render it difficult to maintain a constant level of spending on cancer drugs per patient over time. In fact, evidence from Europe shows that health expenditure on cancer drugs (based on list prices) tripled between 2005 and 2018, yet health expenditure on cancer care remained virtually constant in relation to total health expenditure (around 6%) during this period (7). What seems to have happened in Europe is that increasing expenditure on cancer drugs were largely offset by reductions in expenditure on inpatient care. These reductions stem from a transformation of cancer care from an inpatient to an outpatient setting, partly enabled by new cancer drugs that might lead to reductions in hospitalization due to better efficacy, easier management of side effects with reduced toxicity, or more convenient mode of administration. Importantly, patient outcomes have improved during this period in Europe (8), highlighting the importance of incorporating clinical innovation in clinical practice (6).

The availability and accessibility of cancer drugs differs substantially across Asia-Pacific (9). Sub-report 3 shows that high-income markets achieve much higher regulatory approval and

reimbursement approval rates of innovative[1] cancer drugs (91% and 59%, respectively) than middle-income markets (68% and 17%, respectively). Without reimbursement and insurance coverage, patients have to pay out-of-pocket for cancer drugs, which in practice severely limits accessibility (9). Limited accessibility because of delayed reimbursement results in almost 1 million patient life years lost across Asia-Pacific for each year of delay, based on a sample of only 10 innovative cancer drugs, as shown in sub-report 3. A prioritization of reimbursement of innovative drugs that provide the greatest benefits to patients is thus vital and could also help to accommodate these drugs in constrained health care budgets.

Access to drugs is a multi-dimensional issue that involves multiple stakeholders and sectors over the entire product life cycle, from research and development to quality assurance, supply chain management and use (10). Despite securing national reimbursement, patient access to the specific treatment might not necessarily be guaranteed. This could potentially be due to reasons such as the presence of high patient co-payments without a sufficient safety net for disadvantaged groups, sub-optimal level of health infrastructure and manpower, and government budget constraints that might limit accessibility. As emphasized in sub-report 2, all of these dimensions need to be addressed jointly to ensure adequate coverage of the provided services to meet patient needs.

1.1 Aim of the sub-report

The aim of this sub-report is to describe the extent of health spending on cancer drugs in Asia-Pacific[2].

- Section 2 describes total health spending on cancer drugs.
- Section 3 describes public health spending on cancer drugs.
- Section 4 examines the level of cancer drug spending in relation to patient needs.

[1] In this report, drug-indications with a “substantial clinical benefit” are called “innovative”. This follows the ESMO-MCBS scoring system. Drug-indications used in a curative setting receive a score of A, B, or C. A is the highest score and C is the lowest score. Drug-indications used in a non-curative setting receive a score of 5, 4, 3, 2, or 1. 5 is the highest score and 1 is the lowest score. An indication is said to have a “substantial magnitude of clinical benefit” if it receives a score of A or B in the curative setting or a score of 5 or 4 in the non-curative setting.

[2] Asia-Pacific consists in this report of 7 high-income markets – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 middle-income markets – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

2. Total health spending on cancer drugs

This section explores the relative and absolute level of total health spending – public and private expenditure – on cancer drugs across all markets in Asia-Pacific. It aims to answer the following questions: What is the proportion of total health spending on cancer drugs in relation to all pharmaceuticals? What is the total health spending on cancer drugs per capita and per cancer patient?

2.1 Method and data

Information on drug expenditure for the treatment of different diseases are not routinely reported by most public authorities in the region. In some cases where such data is available, only the cost that was borne by the public payer would typically be reported and not drug expenditure through other financing mechanisms such as private insurance and out-of-pocket expenses. Data that include both public and private expenditure on cancer drugs were sourced from IQVIA, a global provider of pharmaceutical sales data, for 13 markets and from IPMG for Indonesia. Cancer drugs in groups L01 and L02 of the Anatomical Therapeutic Chemical (ATC) Classification System were included. This includes drugs of all different types of cancer therapy: chemotherapy, hormonal therapy, immunotherapy, and targeted therapy.

To put the size of the expenditure on cancer drugs into perspective, additional information on the total health expenditure (see sub-report 2) and total pharmaceutical expenditure were sourced from the WHO and IQVIA, respectively. Furthermore, cancer drug expenditure are compared across markets in Asia-Pacific in terms of per capita and per cancer incidence (i.e., number of newly diagnosed cases). The latter comparison is made due to differences between population demographics and the cancer incidence across markets (see sub-report 1). The lower reliability of cancer incidence data in middle-income markets and some high-income markets due to the absence of a nationwide high-quality cancer registries should be recalled here. Finally, cancer drug expenditure (serving as a proxy for total health expenditure on cancer care) are related to cancer patient outcomes in a similar manner as in sub-report 2. Linear regression analysis is used to examine the strength of the correlation between the two measures.

Sales data come with certain limitations. IQVIA sales data are based on list prices (i.e., ex-manufacturer prices), which means that they typically do not fully capture confidential rebates and arrangements between payers and drug manufacturers. The numbers reported in this section are thus upper bound estimates. Sales data for cancer drugs (but not for total pharmaceutical sales) for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer

drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs (but not for total pharmaceutical sales) from IPMG for Indonesia lack most sales of generics/biosimilars.

2.2 Results

Pharmaceuticals are a cornerstone in the treatment of many diseases, including cancer. Figure 1 shows the proportion of total health expenditure spent on all pharmaceuticals (financed by public and private sources) across the 14 markets in Asia-Pacific in 2018. High-income markets tended to spend a lower proportion (average of 11%) on pharmaceuticals than middle-income markets (average of 22%). New Zealand spent the lowest proportion on pharmaceuticals which has partly been attributed to the single public payer (PHARMAC) operating on a capped budget (11, 12). The same general pattern as in Figure 1 has also been observed among wealthier and poorer countries of the OECD (13). One reason for this pattern are greater differences in relative prices of staff-based health care services (e.g., salaries of physicians, nurses) and pharmaceuticals in poorer countries. Staff-based health care services reflect domestic labor cost levels, whereas the prices of pharmaceuticals tend to lie within an international price corridor.

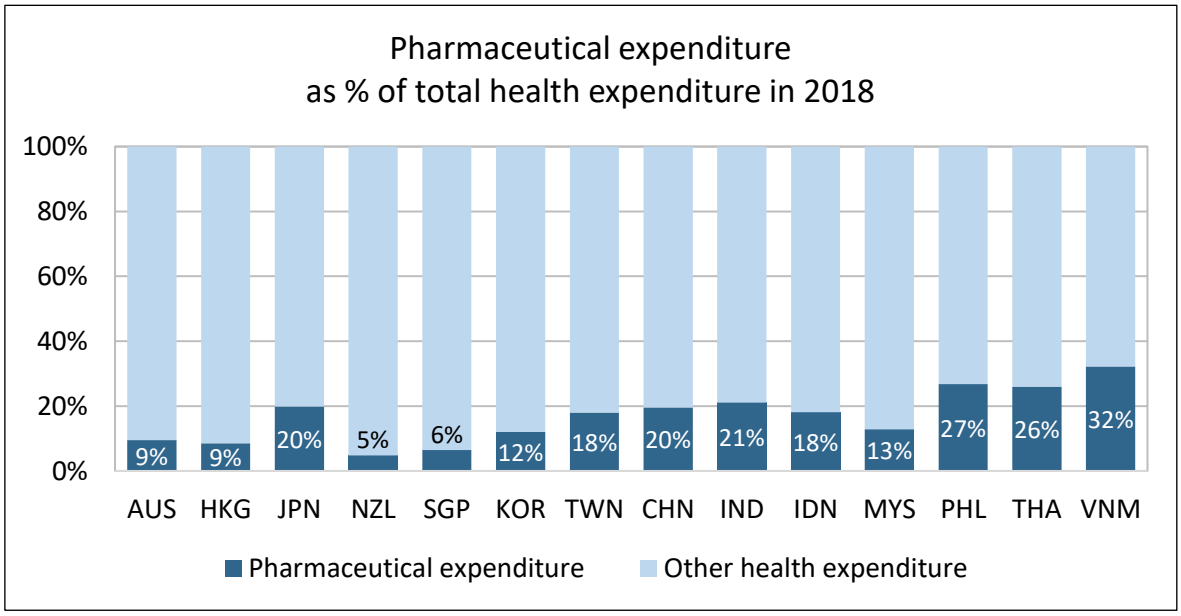

Figure 1: Expenditure on pharmaceuticals as % of total health expenditure, 2018

Notes: Expenditure include financing from public and private sources. Pharmaceutical expenditure were based on sales data based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The proportions for pharmaceuticals reported here are thus upper bound estimates.
Source: WHO (14), Department of Health for HKG (15), and Ministry of Health and Welfare for TWN (16) for total health expenditure. IQVIA Market Prognosis Reports and OECD for NZL (17) for pharmaceutical expenditure.

Looking at cancer drugs specifically, Figure 2 shows that high-income markets in Asia-Pacific spent around 10-20% of total pharmaceutical expenditure on cancer drugs in 2019, whereas middle-income

markets spent around 1-9%. The proportions observed in high-income markets resemble the proportions in France, Germany, and the UK (6).

If we recall the burden of cancer mortality across respective markets, the analysis in sub-report 1 illustrated that around 30% of deaths in high-income markets are due to cancer. In comparison to the cancer burden observed, only 10-20% of total pharmaceutical spending has been directed to cancer to address this health issue. Similarly, in middle-income markets where 9-25% of deaths were attributed to cancer, only 1-9% of drug expenditure was on cancer.

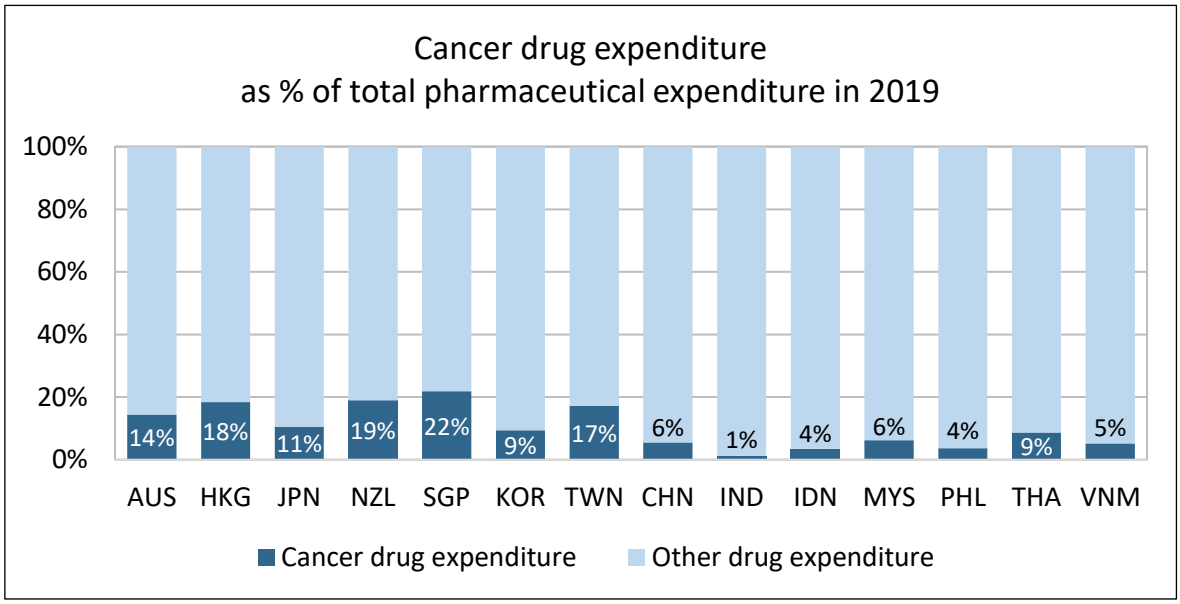

Figure 2: Expenditure on cancer drugs as % of total pharmaceutical expenditure, 2019

Notes: Expenditure include financing from public and private sources. Underlying sales data do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers, which would overestimate the proportion of cancer drug expenditure if the size of rebates for cancer drugs is greater than for other pharmaceuticals. Sales data for cancer drugs for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs for Indonesia lack most sales of generics/biosimilars. Sales of cancer drugs in ATC groups L01 and L02 are included.
Source: IQVIA Market Prognosis Reports and OECD for NZL (17) for total pharmaceutical expenditure. IQVIA MIDAS database for sales data of cancer drugs (18) and IPMG sales data of cancer drugs in IDN.

Cancer drug expenditure (based on list prices) in absolute terms are shown in Figure 3. Per capita spending levels on cancer drugs differ considerably across the region in 2019. Among high-income markets, Japan spent the most on cancer drugs per capita with over $90 while South Korea spent the least with around $30. Compared to the situation in Europe, Japan spent around as much as France on cancer drugs but not as much as the three top-spending countries (Austria, Germany, Switzerland) which spent around $110–$130 per capita in 2018 (6, 7). Cancer drug spending in South Korea was similar to that of poorer countries in Europe, such as Croatia, Hungary, and Portugal with lower GDP per capita than South Korea (6, 7).

Per capita spending levels on cancer drugs in middle-income markets range from a mere $0.2 in India to $6.6 in Thailand. These levels are exceptionally low compared to high-income markets in Asia-Pacific or countries in Europe. A potential explanation for lower national spending levels is the lower cancer incidence due to their relatively younger populations (see sub-report 1).

We then analyzed cancer drug expenditure per cancer incidence, which ranged from around $230 to $17,500 in the region as shown in Figure 3. While the cancer incidence might be underreported due to inadequate registration of patients in the national cancer registry (see also Box 2 in sub-report 1) and hence our estimates could be overstated, Singapore had the highest cancer drug expenditure per cancer incidence. Drug prices in Singapore are mainly driven by market forces with its free pricing policy even for generics, although tendering is practiced at public hospitals and government clinics (19). New Zealand and South Korea spent around 50% less on cancer drugs per cancer case compared to Australia, Hong Kong, and Japan. Strict price control due to PHARMAC's capped budgeting (20), along with the distinctly lower reimbursement rates of cancer drugs observed in sub-report 3, might explain the finding for New Zealand.

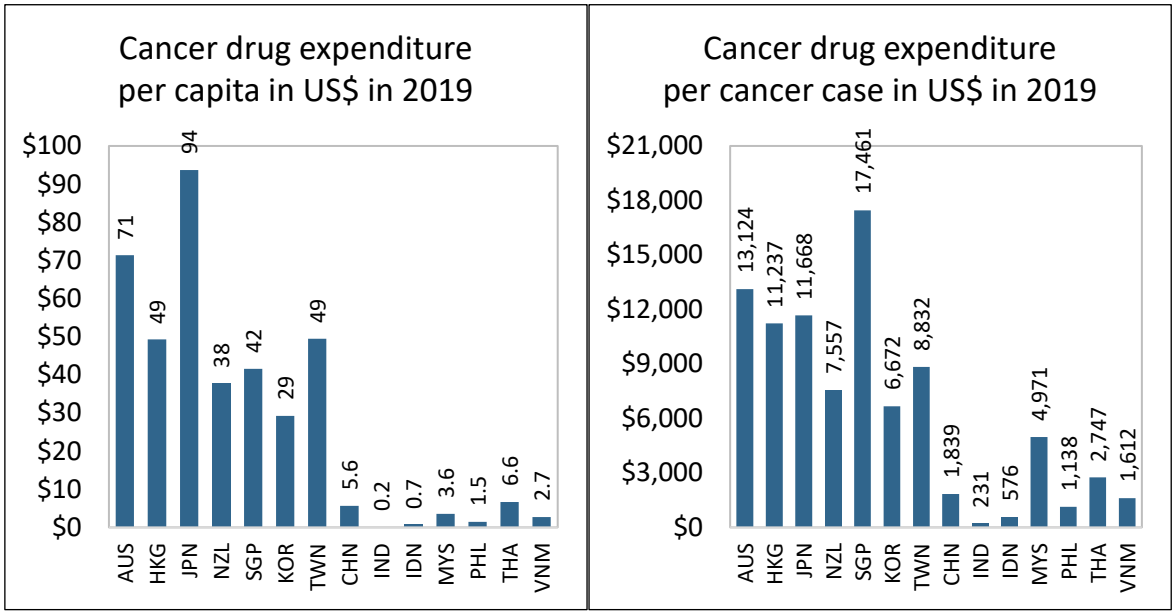

Figure 3: Cancer drug expenditure per capita and per cancer case in US$, 2019

Notes: Cancer drug expenditure include financing from public and private sources. They show current prices and are not adjusted for differences in purchasing power parity. Cancer drug expenditure are based on sales data based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates. Sales data for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total sales in China and <1% of total sales in Taiwan). Sales data for Indonesia do not contain most sales of generics/biosimilars. Sales of cancer drugs in ATC groups L01 and L02 are included. Cancer case is defined as cancer incidence (newly diagnosed cases) in 2018 in absence of data for 2019.
Source: IQVIA MIDAS database for sales data of cancer drugs (18) and IPMG sales data of cancer drugs in IDN, and national cancer registries and GLOBOCAN for cancer cases (see Table A1 in sub-report 1).

Among the middle-income markets, India and Indonesia spent the least with only $231 and $576 per cancer incidence respectively. In comparison, Malaysia spent almost $5,000 per cancer case but this number might be inflated as there could be an underestimation of patient numbers in Malaysia due to inadequate registration of patients in the national cancer registry (see also Box 1 in sub-report 1). However, previous studies have pointed to the free pricing policy in Malaysia's private healthcare sector as a reason for high drug prices and consequently high drug expenditure (20).

As emphasized in sub-report 2, linking resource use in cancer care to patient outcomes is vital to inform funding decisions that strive to maximize value-for-money for patients. Data on (public and private) expenditure on the universe of health care services used in cancer care are not systematically available markets across Asia-Pacific. However, overall spending on cancer care services is typically closely linked to spending on cancer drugs. Using cancer drug expenditure per capita as a proxy for total health expenditure on cancer care (resources use), Figure 4 shows how this correlates with the complement of the mortality-to-incidence ratio (1–MIR) (patient outcomes).

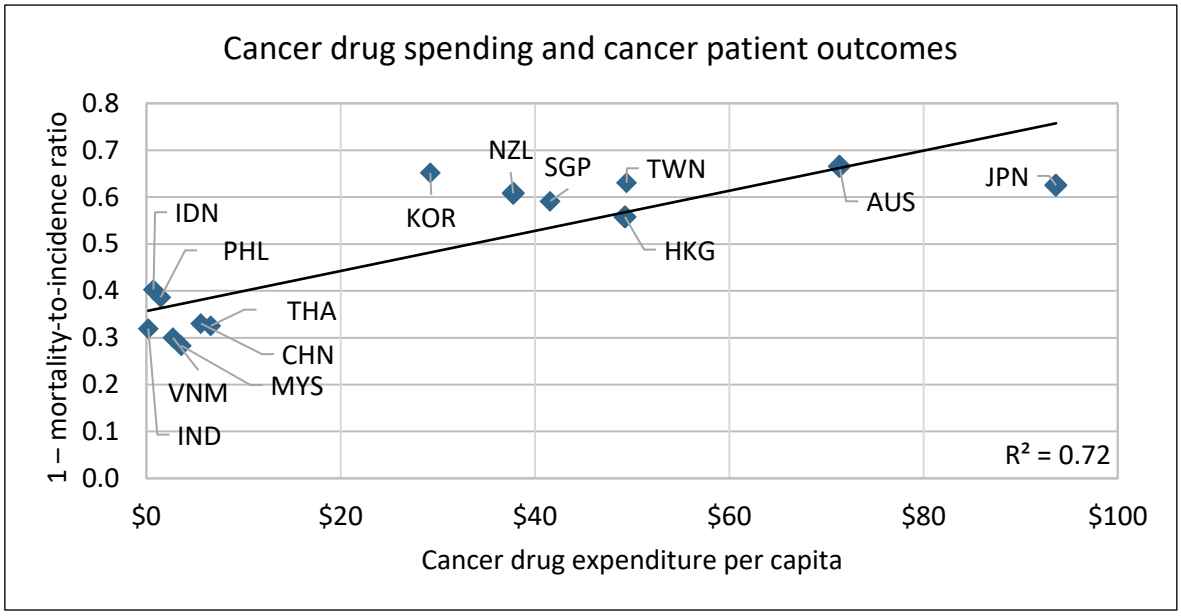

Figure 4: Total cancer drug expenditure per capita and complement of the mortality-to-incidence ratio of cancer, 2018

Notes: Cancer drug expenditure include financing from public and private sources. They are not adjusted for differences in purchasing power parity and refer to 2019 in absence of data for 2018. Cancer drug expenditure for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total sales in China and <1% of total sales in Taiwan). Cancer drug expenditure for Indonesia do not contain most sales of generics/biosimilars.
Source: National cancer registries and GLOBOCAN for mortality-to-incidence ratio (see sub-report 1) and IQVIA/IPMG sales data for cancer drug expenditure (see Figure 3).

Each dot in Figure 4 represents a market and the drawn (unweighted) line represents the relationship between resource use and outcomes inferred based on the 14 markets in Asia-Pacific. A strong positive correlation can be observed (correlation coefficient of 0.72; 0 is no correlation and 1 is

perfect correlation), which suggests that markets with higher spending on cancer drugs achieve better patient outcomes. A relationship of this kind does not need to be causal, but it suggests that the level of cancer drug spending (which should be closely related to spending on other cancer care services as well) might be a stronger driver of cancer patient outcomes. A similar analysis drawing on a set of countries in Europe has found a comparable association (21).

3. Public health spending on cancer drugs

This section explores the level of public health spending on innovative cancer drugs used in the treatment of five major cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer – in Asia-Pacific. Innovation status was defined according to the ESMO-MCBS score (drug indications with a "substantial clinical benefit") (22), analogously to sub-report 3. The section aims to answer the following question: What is the level of public health spending on innovative cancer drugs?

3.1 Method and data

As described in section 2.1, public authorities typically do not report drug expenditure on the disease level. In this report, the following method was used to estimate cancer drug expenditure covered by public sources (i.e., the government) in 2019. The starting point was IQVIA quarterly sales data (and IPMG data for Indonesia) on drugs in 2019, covering both private and public sales. As in sub-report 3, cancer drugs used in the treatment of five cancer types – breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, non-small cell lung cancer – were included in the analysis; see Table A1 in the Appendix for the full list of 141 drug-indications.

In the first step, the reimbursement status of all indications of every drug in all quarters of 2019 was deduced from the date of inclusion in the respective national formularies (see Table A2 in the Appendix for an overview of the reimbursement schemes used).[3] Secondly, sales of drugs with multiple indications were split into different indications based on a proxy for potential patient numbers (incidence; see Table A1 in the Appendix of sub-report 1 for sources used), due to the limitation that IQVIA data do not capture sales by indication.[4] This allowed us to estimate the total public cancer drug expenditure on reimbursed indications only. A limitation of the sole consideration of the five cancer types is that some drugs may still have some reimbursed indications in other cancer

[3] India's health system is relatively fragmented and does not have a comprehensive national reimbursement scheme as yet; the National List of Essential Medicines (NLEM) was used as a proxy for inferring reimbursement status instead. In Singapore, two schemes, Standard Drug List (SDL) and Medication Assistance Fund (MAF), were used to infer reimbursement status, but in reality three additional public health insurance schemes (MediShield Life, MediSave, MediFund) can be used to cover treatment costs of approved cancer drugs. In Thailand, the National List of Essential Medicines (NLEM) was used as all three main public health insurance schemes (CSMBS, SSS, UCS) provide drugs on this list.

[4] In case a drug had only received regulatory approval for several indications, sales were split among those indications, whereas in case a drug had received reimbursement status for one or several indications, sales were only split among the reimbursed indications. This means that for drugs with multiple approved indications and where not all indications are reimbursed, sales in non-reimbursed indications cannot be discerned from remaining sales and are counted as reimbursed. The same applies to drugs with multiple approved indications within the same cancer type.

types, e.g., cetuximab and regorafenib may also be reimbursed for use in colorectal cancer. It was not possible to separate these sales from the ones included in the analysis. The estimates derived here for public drug expenditure on the five cancer types thus represent upper bounds of the true size of expenditure.

Thirdly, the total public expenditure were categorized under sales of innovative drug-indications and other drug-indications (see Table A1 in the Appendix). Innovation status was defined according to ESMO-MCBS score with a "substantial magnitude of clinical benefit", i.e. a score of A or B in the curative setting and 5 or 4 in the non-curative setting (22).

Another limitation of the IQVIA/IPMG data is that sales are based on the published list prices and volume of drugs sold. Thus, they do not capture confidential rebates and arrangements between public payers and pharmaceutical manufacturers, which leads to an overestimation of spending levels reported in this section. In addition, we are unable to separate any patient co-payments from the estimated public drug expenditure. Despite reimbursement status of a drug, patient co-payments (prescription fees) exist across markets in Asia-Pacific; see Appendix for examples. The amount of co-payment varies between markets and also depending on the specific drug within a specific market (e.g., higher co-payments on patent-protected drugs than on older drugs for which generic versions are available). Therefore, the estimates derived here for public drug expenditure are upper bounds.

3.2 Results

Public expenditure on cancer drugs used in the treatment of breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, and non-small cell lung cancer differ widely across markets in Asia-Pacific in 2019. Figure 5 shows that public spending (based on list prices) on the basket of 141 drug-indications in middle income markets was in the range of $0.1 to $2.9 per capita. By contrast, public spending ranged from $9 per capita in New Zealand to $58 in Japan in the high-income markets. As already observed in section 2, New Zealand's spending level is comparatively

Box 1: Public coverage of cancer drug expenditure in Singapore

In Singapore, cancer drug expenditure of patients are covered in several ways. At public health care institutions, older drugs with generic availability are often covered by the Standard Drug List (SDL) with 50% subsidies for all Singaporeans and the Medication Assistance Fund (MAF) with up to 75% subsidies for means-tested Singaporeans from lower to middle income households. There are also three public health insurance schemes, known as the "3M", MediShield Life (MSL), MediSave, and MediFund, for use at both public and private health care institutions that build on the already subsidized health care in public healthcare institutions (23). For cancer drug therapy, patients can draw up to SGD 3,000 per month under MSL, and up to SGD 1,200 per month under MediSave. MediFund is in place for low-income citizens who require further financial assistance (24).

low, and this might be partly due to the strict price control imposed via PHARMAC's capped budgeting (20).

Out of the 141 drug-indications, there were 38 classified as innovative according to the ESMO-MCBS scoring system. Figure 5 shows that public drug spending across these innovative drugs-indications was less than $1 per capita in all middle-income markets in 2019. Across high-income markets, this ranged from $7 in New Zealand to $34 in Japan. The relative difference in average spending between high-income and middle-income markets is thus larger for innovative drug-indications ($16 and $0.4, respectively) than for all drug-indications ($24 and $1.1, respectively).

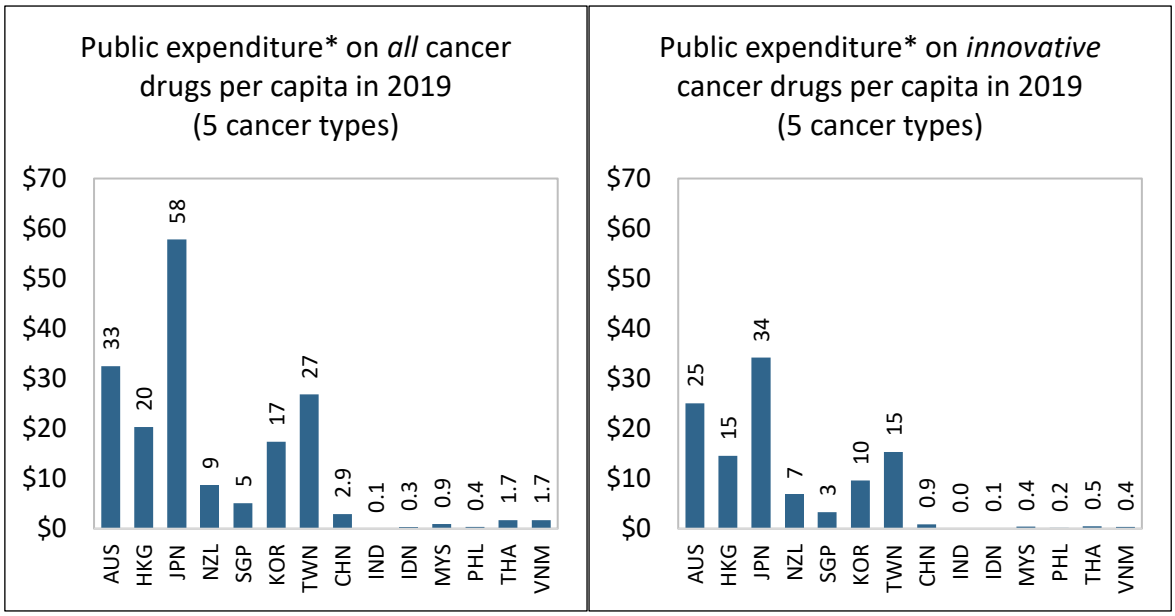

Figure 5: Public expenditure on cancer drugs of five selected cancer types per capita in US$, 2019

Notes: All cancer drugs refer to 141 indications and innovative cancer drugs to a subset of 38 indications used in the treatment of breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, and lung cancer; see Table A1 in the Appendix. * Including any OOP prescription fees for reimbursed drugs. Cancer drug expenditure are in current prices and are not adjusted for differences in purchasing power parity. Underlying sales data are based on list prices and do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates, except for Singapore where expenditure covered by the public health insurance scheme MediShield Life (MSL) are not included. Sales data for cancer drugs for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs for Indonesia do not contain most sales of generics/biosimilars. Source: IQVIA MIDAS database (18) and IPMG sales data in IDN.

In Singapore, public expenditure on cancer drugs were based on the limited drugs and indications that have been listed on the SDL and MAF (see Box 1). Therefore, the current analysis indicated relatively low public expenditure on cancer drugs per capita at around $3-5. However, public health insurance schemes known as the "3M" (see Box 1) are available for patients to access cancer drugs beyond those listed on the SDL and MAF. For example, the government had spent SG$ 156.5 million in 2018 to provide financial assistance to low-income citizens via the MediFund (25). Such public

investment in cancer care in Singapore have not been captured in this analysis, as we are unable to distinguish between the different financing sources with IQVIA sales and other available data.

The relatively higher public spending on – both innovative and other – cancer drugs in high-income markets might be partly related to higher list prices in these markets compared to middle-income markets. Another reason are vast differences in reimbursement rates of drugs. Indeed, the analysis in sub-report 3 shows that the average reimbursement rate of the sample of innovative drug-indications was 59% in high-income markets and 17% in middle-income markets; in the sample of all drug-indications the rates were 53% and 30% respectively.

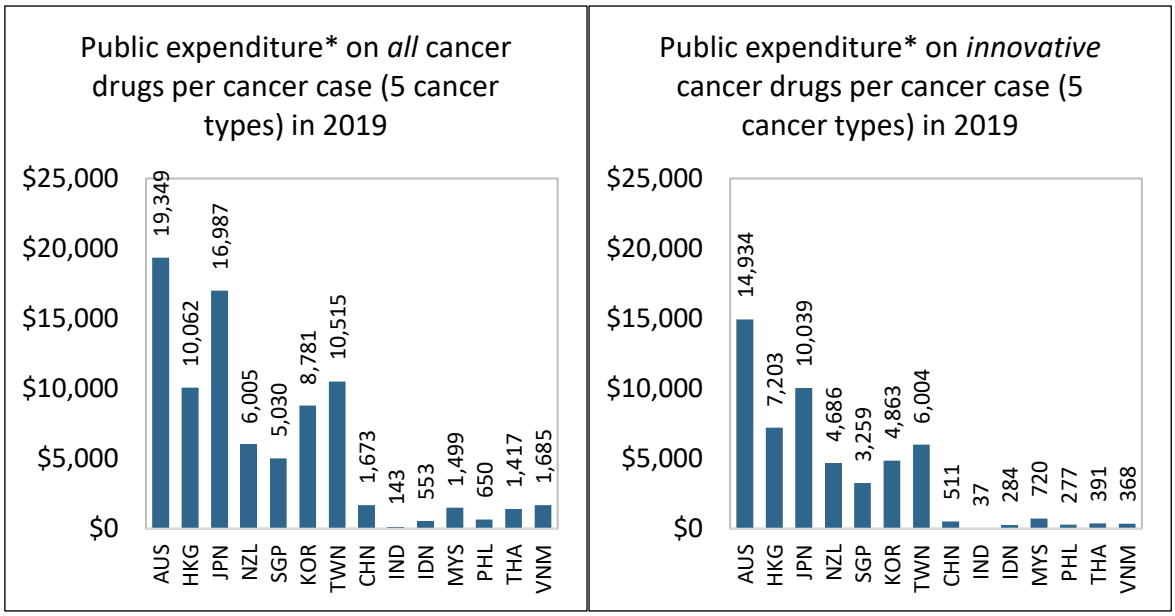

Figure 6: Public expenditure on (all and innovative) cancer drugs of five selected cancer types per cancer case in US$, 2019

Notes: * Including any OOP prescription fees for reimbursed drugs. Cancer drug expenditure are in current prices and are not adjusted for differences in purchasing power parity. Underlying sales data are based on list prices and do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers. The absolute numbers reported here are thus upper bound estimates, except for Singapore where expenditure covered by the public health insurance scheme MediShield Life (MSL) are not included. Sales data for cancer drugs for China and Taiwan do not include sales in the retail sector, yet they are small (around 5% of total cancer drug sales in China and <1% of total cancer drug sales in Taiwan). Sales data for cancer drugs for Indonesia do not contain most sales of generics/biosimilars. Cancer drugs used in the treatment of breast cancer, gastro-esophageal cancer, head and neck cancer, liver cancer, and lung cancer are included; see Table A1 in the Appendix of sub-report 1 for the full list. Cancer case is defined as cancer incidence (newly diagnosed cases) of the five included cancer types in 2018 in absence of data for 2019.
Source: IQVIA MIDAS database for sales data of cancer drugs (18), and national cancer registries and GLOBOCAN for cancer cases (see sub-report 1).

The higher number of cancer patients also contributes to the relatively higher public spending on cancer drugs in high-income markets. Therefore, Figure 6 shows spending levels per cancer case, defined as the sum of newly diagnosed cases of the five specific cancer types included. Public spending on all cancer drugs (based on list prices) ranged from $6,000 per cancer case in New Zealand to around $20,000 in Australia in the high-income markets (excluding Singapore; see Box

1). In middle-income markets public spending ranged from just above $140 per cancer case in India to around $1,700 in China and Vietnam.

Public spending on innovative drugs in high-income markets was on average $7,300 compared to $370 in middle-income markets. For all drugs, the corresponding averages were $11,000 and $1,100, respectively. The greater differences for innovative drugs might be related to the lower numbers of innovative cancer drugs being reimbursed in middle-income markets as noted above.

4. Patient needs in relation to cancer drug spending

The previous sections have established that spending on cancer drugs differs widely across markets in Asia-Pacific, even after considering differences in patient numbers. Reimbursement plays an important role here. Yet, despite securing national reimbursement, patient access to the specific treatment might not necessarily be guaranteed, e.g., due to the presence of high patient co-payments. This section quantifies to what extent the level of cancer drug spending meets patient needs. It aims to answer the following question: Is health spending on cancer drugs sufficient to meet patient needs?

4.1 Method and data

A case study of the cancer drug pemetrexed was conducted to illustrate how well spending on cancer drugs meets patient needs. The period of analysis was the third quarter of 2020 (Q3, July to September).

Pemetrexed is a chemotherapy drug and has been in use globally since 2004. It was available in all 14 markets across Asia-Pacific in 2020. Other than Japan, it had already lost its patent protection and faced generic competition (see sub-report 5). It is predominantly[5] used in the treatment of non-small cell lung cancer (NSCLC) and had received the following approved indications by the US FDA:

- August 2004: Second line after prior chemotherapy, as monotherapy, in locally advanced or metastatic disease. The approval was based on clinical trial data showing non-inferiority to docetaxel (26).
- September 2008: First line, in combination with cisplatin, in locally advanced or metastatic non-squamous disease. The approval was based on clinical trial data showing superiority to gemcitabine + cisplatin in patients with non-squamous disease but not with squamous disease (27).
- July 2009: Second line after four cycles of platinum-based chemotherapy (maintenance treatment in non-progressing disease), as monotherapy, in locally advanced or metastatic non-squamous disease. The approval was based on clinical trial data showing superiority to placebo (28).

[5] It is also used together with cisplatin in the treatment of mesothelioma, a relatively rare cancer type.

- May 2017: First line, in combination with pembrolizumab and carboplatin (or cisplatin since August 2018), in metastatic non-squamous disease with no EGFR or ALK genomic tumor aberrations. The approval was based on clinical trial data showing superiority to pemetrexed + carboplatin (later also to pemetrexed + cisplatin) (29).

The initial second-line indication, approved in 2004, was later limited to the treatment of patients with non-squamous disease by the US FDA. The bottom three indications of pemetrexed for first-line treatment and second-line maintenance are all innovative indications, each with an ESMO-MCBS score of 4 (22).

Analysis of drug volume needed

Several steps were taken to assess the drug volume of pemetrexed required to meet patient needs. First, the patient target population was defined as "*first-line therapy for non-squamous disease in stage IIIB+IIIC+IV NSCLC*". With advancement in research, pemetrexed in combination with cisplatin is no longer standard of care (SoC) in some patient segments. This concerns EGFR+ and ALK+ patients where tyrosine kinase inhibitors are SoC, EGFR/ALK wild type patients with high PD-L1 expression where immunotherapy drugs as monotherapy are SoC, and EGFR/ALK wild type patients without strong PD-L1 expression where the combination of immunotherapy and chemotherapy drugs is SoC, based on NCCN guidelines (30).

Table 1: Reimbursement status of first-line treatment options in advanced non-squamous NSCLC in the third quarter of 2020 across Asia-Pacific

		Pemetrexed	EGFR-TKI	ALK-TKI	IO mono for PD-L1 TPS≥50	IO chemo combo
High-income markets	Australia	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	Hong Kong	**Yes**	**Yes**	**Yes**	**Yes**	No
	Japan	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	New Zealand	**Yes**	**Yes**	**Yes**	No	No
	Singapore	*	*	*	*	*
	South Korea	**Yes**	**Yes**	**Yes**	No	No
	Taiwan	**Yes**	**Yes**	**Yes**	**Yes**	No
Middle-income markets	China	**Yes**	**Yes**	**Yes**	No	No
	India	No	No	No	No	No
	Indonesia	**Yes**	**Yes**	No	No	No
	Malaysia	No (2L only)	**Yes**	No	No	No
	Philippines	No	No	No	No	No
	Thailand	No	No	No	No	No
	Vietnam	**Yes**	**Yes**	No	No	No

Notes: * In Singapore, pemetrexed is not on the SDL or MAF but patients are covered through the 3M schemes (see Box 1). In Thailand, the information here is based on the NLEM. TKI = tyrosine kinase inhibitor, IO = immunotherapy, TPS = tumor proportion score, mono = monotherapy, chemo combo = in combination with chemotherapy, 2L = second line.
Source: Retrieved from sources listed in Table A2 in the Appendix.

Therefore, the estimated addressable population for pemetrexed would reduce in size when (i) an EGFR inhibitor, (ii) an ALK inhibitor, and/or (iii) immunotherapy in monotherapy for PD-L1 TPS≥50% was reimbursed in first-line therapy in the local market in Q3 2020; see Table 1. This was based on the assumption that these three types of treatment would replace pemetrexed in their respective patient segments. The final patient target population in each market is shown in Table 2.

Second, the average drug volume needed per patient was calculated for pemetrexed. The general dosage schedule for pemetrexed (both if given as monotherapy or in combination) is 500 mg/m^2 on day 1 of each 21-day cycle. A body surface area of 1.8 m^2 was assumed. In markets where the combination of pemetrexed and pembrolizumab was reimbursed, this combination was assumed to be the SoC, based on NCCN guidelines (30). The following average treatment duration with pemetrexed was assumed:

- If pemetrexed is given in combination with cisplatin, it is administered for up to 6 cycles in the absence of disease progression or unacceptable toxicity. The average treatment duration in the pivotal clinical trial (H3E-MC-JMDB) was 3.0 months (27).
- If pemetrexed is given in combination with pembrolizumab and carboplatin/cisplatin, it is administered until disease progression or unacceptable toxicity. The average treatment duration in the pivotal clinical trial (KEYNOTE-189) was 8.1 months (31).

Third, the total volume of pemetrexed needed (in milligram) was derived by combining the number of patients in the target population with the average drug volume needed per patient.

Analysis of drug volume administered

The drug volume of pemetrexed administered to patients was defined as the drug volume sold in Q3 2020.[6] Data on volume sold (in milligrams) was obtained from the IQVIA MIDAS database for each market in Asia-Pacific (18). For Indonesia, IPMG data did not contain sales of generic versions and sales of the originator drugs were zero, which is why this market was excluded from the analysis. The IQVIA data available do not provide a split by public and private channels across all markets, and neither by indication nor by line of therapy.[7] However, the latter issues are less problematic for pemetrexed than for most other cancer drugs because of its narrow use in clinical practice for NSCLC only.

[6] Despite the COVID-19 pandemic, sales volumes of pemetrexed do not show any noticeable increases or decreases in Q3 2020 compared to quarters throughout 2019 in all markets in the IQVIA MIDAS database.
[7] Use of pemetrexed in the treatment of mesothelioma was assumed to be negligible. Note that pemetrexed is typically not used in second-line or later-line therapy if it is already used in first-line therapy.

*Table 2: Estimation of eligible patients for first-line treatment of advanced non-squamous NSCLC with pemetrexed in 2020**

		Lung cancer incidence	NSCLC in lung cancer	Non-squamous in NSCLC	EGFR+ in non-squamous	ALK+ in non-squamous	PD-L1 TPS≥50% in EGFR- ALK-	Disease stage IIIB+IIIC+IV	Eligible patients
		[a]	[b]	[c]	[d]	[e]	[f]	[g]	[h]
High-income markets	Australia	12,712	85%	74%	19%	3%	25%	70%	3,266
	Hong Kong	5,252	85%	74%	48%	3%	30%	70%	795
	Japan	125,100	85%	74%	48%	3%	30%	70%	18,932
	New Zealand	2,255	85%	74%	19%	3%	25%	70%	772
	Singapore ^	1,556	85%	74%	48%	3%	30%	70%	235
	South Korea	26,985	85%	74%	48%	3%	30%	70%	5,834
	Taiwan	16,023	85%	74%	48%	3%	30%	70%	2,425
Middle-income markets	China	774,323	85%	74%	48%	3%	30%	70%	167,399
	India	67,795	85%	74%	31%	3%	25%	75%	31,982
	Indonesia	30,023	85%	74%	48%	3%	30%	70%	6,887
	Malaysia	4,686	85%	74%	48%	3%	30%	70%	1,075
	Philippines	17,255	85%	74%	48%	3%	30%	70%	7,597
	Thailand	23,957	85%	74%	48%	3%	30%	70%	10,548
	Vietnam	23,667	85%	74%	48%	3%	30%	70%	5,429

Notes: Eligible patients [h] are obtained by multiplying column [a] with [b], [c], [g] and – depending on information provided in Table 1– with (1-[d]), (1-[e]), (1-[f]).
* Eligible patient numbers are later divided by 4 in the actual calculations to match sales in Q3 2020.
^ For Singapore it was assumed that patients have access to EGFR/ALK and IO mono for PD-L1 TPS≥50%.
Sources: [a] national cancer registries and GLOBOCAN cited in sub-report 1, with numbers for 2018 used as a proxy for 2020. [b] (32, 33). [c] (34). [d] (32, 35, 36). [e] (37). [f] (37). [g] (32, 33).

4.2 Results

Medical treatment of many cancer types has changed radically during the last two decades with the availability of targeted therapy and immunotherapy. Yet unmet patient needs are still high in most cancer types. Non-small cell lung cancer is a cancer type characterized by high unmet needs, as evidenced by a 5-year survival rate of around 20% (see sub-report 1). The chemotherapy drug pemetrexed together with cisplatin has offered the subset of patients with non-squamous disease the prospect of prolonged survival compared to previous first-line therapy since 2009. With US FDA approval in 2017, the addition of the immunotherapy drug pembrolizumab to pemetrexed and cisplatin/carboplatin has further improved survival prospects in EGFR/ALK wild type patients.

Table 3 shows to what extent patient needs for treatment with pemetrexed was met based on information on the volume of pemetrexed sold in Q3 2020 and the patient segment addressed by pemetrexed. For Australia, Japan, and Singapore, the volume needed was based on use in EGFR/ALK wild type patients without high PD-L1 expression and the combination therapy with pembrolizumab and cisplatin/carboplatin for on average 8.1 months per patient. In all other markets, the volume needed was based on use in the combination therapy with cisplatin only for on average 3.0 months per patient in the respective patient population, see Table 1 and Table 2.

In Australia and Japan, around half (47% and 48%, respectively) of the patient needs of pemetrexed was met compared to over 80% in Singapore. For Japan, previous studies on drug use in advanced NSCLC have also pointed to a large proportion of patients (around 32%) not receiving any first-line systemic treatment, as well as suboptimal testing for genomic alterations required to administer targeted therapies (38, 39). For Australia, an explanation of the gap in unmet patient needs might be the limitation of reimbursement of the combination of pemetrexed and pembrolizumab to patients with ECOG performance status (PS) 0 and 1, thus denying patients with PS 2-4 this treatment (40, 41). Treatment guidelines by the European Society for Medical Oncology (ESMO) recommend systemic treatment to metastatic NSCLC patients with PS 0-2 (42). Previous studies indicated that around one third of lung cancer patients might have PS 2-4 in Australia (43).

In the other high-income markets, patient needs seem to be fully met in Hong Kong, South Korea, and Taiwan. In fact, the achievement of 100% patient need is unrealistic, as there are patients with poor performance status who cannot receive systemic treatment. An explanation for the high numbers in these three markets might be the use of pemetrexed for longer than the average treatment duration observed in the pivotal clinical trial, which was 3.0 months and capped at six cycles (27), due to

ensuing maintenance therapy. In the control arm of the pivotal clinical trial of pemetrexed and pembrolizumab, the average treatment duration of pemetrexed was 5.7 months without capping (31).

Table 3: Drug volume needed vs. drug volume administered of pemetrexed in the third quarter of 2020

		Reimbursement status of pemetrexed in first-line non-squamous NSCLC	Addressable patient group	Proportion of pemetrexed volume sold relative to estimated patient needs
High-income markets	Australia	Yes (combo with pembrolizumab)	EGFR/ALK wild type TPS<50%	47%
	Hong Kong	Yes (combo with cisplatin)	EGFR/ALK wild type TPS<50%	100%
	Japan	Yes (combo with pembrolizumab)	EGFR/ALK wild type TPS<50%	48%
	New Zealand	Yes (combo with cisplatin)	EGFR/ALK wild type	51%
	Singapore	Yes* (combo with pembrolizumab)	EGFR/ALK wild type TPS<50%	81%
	South Korea	Yes (combo with cisplatin)	EGFR/ALK wild type	100%
	Taiwan	Yes (combo with cisplatin)	EGFR/ALK wild type TPS<50%	100%
Middle-income markets	China	Yes (combo with cisplatin)	EGFR/ALK wild type	84%
	India	No	All non-squamous	7%
	Indonesia	Yes (combo with cisplatin)	EGFR wild type	n/a
	Malaysia	No (second line only)	EGFR wild type	28%
	Philippines	No	All non-squamous	2%
	Thailand	No	All non-squamous	5%
	Vietnam	Yes (combo with cisplatin)	EGFR wild type	75%

Notes: * In Singapore, pemetrexed is not on the SDL or MAF but it is assumed patients have access through the 3M schemes (see Box 1). n/a = no sales of the originator drug or generic versions recorded in the IQVIA MIDAS database.

Unmet patient needs are high in most middle-income markets. China and Vietnam are the only markets that seem to be able to meet patient needs. They are also the only markets (except for Indonesia with missing data) where pemetrexed is reimbursed. Co-payments apply in both China and Vietnam, see Appendix. In Vietnam, a 50% patient co-payment applies to pemetrexed, which might explain the higher proportion of unmet need compared to China where co-payments tend to be a bit lower but might vary across the country. In Malaysia, pemetrexed is only reimbursed as a second-line treatment and the total sales recorded (which include private sales) would have only been sufficient to meet the needs of less than a third of patients. In India, the Philippines, and Thailand there was no national reimbursement of pemetrexed in any line of therapy. Sales are thus predominantly financed by private sources. Limited access via self-pay in these markets means that fewer than 5% of eligible patients see their clinical needs being met.

Even though the analysis in this section is only based on the case of pemetrexed, several conclusions can be drawn. First, reimbursement of drugs is vital for the vast majority of patients to gain access. Without reimbursement, patients are forced to pay the full price out-of-pocket. This exceeds the financial means of most patients even if there might already by generic versions available, such as for pemetrexed. Second, high-income markets may struggle to meet patient needs in the initial years after a new medical treatment is introduced. In Australia and Japan, the combination therapy of pemetrexed and pembrolizumab had been approved for 7 months and 18 months, respectively, before Q3 2020. Slow uptake of new treatments can either be caused by factors within the health system (such as rigid clinical processes) or outside the health system (such as restrictions in use imposed by narrow reimbursement criteria). Lastly, markets that do not yet reimburse the combination of pemetrexed with immunotherapy (let alone markets that do not yet reimburse pemetrexed with cisplatin only) continue to amass staggering numbers of patient life years lost until reimbursement, as shown in sub-report 3 due to significant delays or the lack of reimbursement of innovative cancer treatment.

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Appendix

Table A1: List of US FDA-approved indications and ESMO-MCBS score (Sep 30, 2020)

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Abemaciclib	BC	2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	28-Sep-2017	4	Innovative
Abemaciclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	26-Feb-2018	3	Others
Abemaciclib	BC	2L, mono, HR+ HER2-, advanced or metastatic	28-Sep-2017		Others
Afatinib	LUC	1L, mono, EGFR+, metastatic	12-Jan-2018 (12-Jul-2013)	4	Innovative
Afatinib	LUC	2L, mono, SQ, metastatic	15-Apr-2016	2	Others
Alectinib	LUC	1L, mono, ALK+, metastatic	6-Nov-2017	4	Innovative
Alectinib	LUC	2L, mono, ALK+, metastatic	11-Dec-2015	4	Innovative
Alpelisib	BC	2L, combo with fulvestrant, HR+ HER2- PIK3CA+, advanced or metastatic	24-May-2019	3	Others
Anastrozole	BC	2L, mono, advanced	27-Dec-1995		Others
Anastrozole	BC	1L, mono, HR+, advanced or metastatic	1-Sep-2000		Others
Anastrozole	BC	Adjuvant, HR+	5-Sep-2002		Others
Atezolizumab	LUC	2L, mono, metastatic	18-Oct-2016	5	Innovative
Atezolizumab	BC	1L, combo with nab-paclitaxel, triple-negative, PD-L1+, advanced or metastatic	8-Mar-2019	3	Others
Atezolizumab	LIC	1L, combo with bevacizumab, HCC, metastatic	29-May-2020		Others
Atezolizumab	LUC	1L, combo with bevacizumab + paclitaxel + carboplatin, NSQ, EGFR- ALK-, metastatic	6-Dec-2018	3	Others
Atezolizumab	LUC	1L, combo with nab-paclitaxel + carboplatin, NSQ, EGFR- ALK-, metastatic	3-Dec-2019	3	Others
Atezolizumab	LUC	1L, mono, PD-L1+ EGFR- ALK-, metastatic	18-May-2020		Others
Bevacizumab	LIC	1L, combo with atezolizumab, HCC, metastatic	29-May-2020		Others
Bevacizumab	LUC	1L, combo with carboplatin + paclitaxel, NSQ, metastatic	11-Oct-2006	2	Others
Bleomycin	HNC	1L, mono, SCCHN, metastatic	31-Jul-1973		Others
Brigatinib	LUC	1L, mono, ALK+, metastatic	22-May-2020 (2-Oct-2017)	3	Others
Cabozantinib	LIC	2L, mono, HCC, metastatic	14-Jan-2019	3	Others
Capecitabine	BC	2L/3L, mono, metastatic	30-Apr-1998		Others
Capecitabine	BC	2L, combo with docetaxel, metastatic	7-Sep-2001		Others
Capmatinib	LUC	1L, mono, MET+, metastatic	6-May-2020		Others
Ceritinib	LUC	1L, mono, ALK+, metastatic	26-May-2017 (29-Apr-2014)	4	Innovative
Cetuximab	HNC	1L, combo with radiation therapy, SCCHN, advanced	1-Mar-2006		Others
Cetuximab	HNC	2L, mono, SCCHN, metastatic	1-Mar-2006		Others
Cetuximab	HNC	1L, combo with platinum + fluorouracil, SCCHN, metastatic	7-Nov-2011	3	Others
Crizotinib	LUC	1L, mono, ALK+ or ROS1+, metastatic	21-Jul-2017 (26-Aug-2011)	4 / 3	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Cyclophosphamide	BC	1L, mono	[16-Nov-1959]		Others
Dabrafenib	LUC	1L, combo with dabrafenib, BRAF V600E+, metastatic	22-Jun-2017	2	Others
Dacomitinib	LUC	1L, mono, EGFR+, metastatic	27-Sep-2018	3	Others
Docetaxel	GEC	1L, combo with cisplatin + fluorouracil, gastric or GEJ AC, advanced	22-Mar-2006	A	Innovative
Docetaxel	BC	2L, mono, advanced or metastatic	22-Jun-1996 (14-May-1996)		Others
Docetaxel	BC	Adjuvant, combo with doxorubicin and cyclophosphamide, node-positive	18-Aug-2004		Others
Docetaxel	HNC	1L, combo with cisplatin + fluorouracil, SCCHN, advanced	28-Sep-2007 (17-Nov-2006)		Others
Docetaxel	LUC	2L, mono, advanced or metastatic	23-Dec-1998		Others
Docetaxel	LUC	1L, combo with cisplatin, advanced or metastatic	27-Nov-2002		Others
Doxorubicin	BC	1L, mono, metastatic	[7-Aug-1974]		Others
Doxorubicin	BC	Adjuvant, combo	8-May-2003		Others
Doxorubicin	GEC	1L, mono, gastric, metastatic	[7-Aug-1974]		Others
Durvalumab	LUC	2L, mono, stage III	16-Feb-2018	4	Innovative
Entrectinib	LUC	1L, mono, ROS1+, metastatic	15-Aug-2019	3	Others
Epirubicin	BC	Adjuvant, combo	15-Sep-1999		Others
Eribulin	BC	3L, mono, metastatic	15-Aug-2010	2	Others
Erlotinib	LUC	1L or laterL, mono, EGFR+, metastatic	18-Oct-2016 (18-Nov-2004)	4	Innovative
Everolimus	BC	2L, combo with exemestane, HR+ HER2-, advanced	20-Jul-2012	2	Others
Exemestane	BC	2L, mono, advanced	21-Oct-1999		Others
Exemestane	BC	Adjuvant after tamoxifen, ER+	5-Oct-2005		Others
Fluorouracil	GEC	Perioperative, combo with cisplatin, gastric or GEJ or esophageal AC, resectable	[25-Apr-1962]	A	Innovative
Fluorouracil	BC	1L, mono, AC	[25-Apr-1962]		Others
Fulvestrant	BC	2L, mono, HR+, advanced	25-Aug-2017 (25-Apr-2002)	2	Others
Fulvestrant	BC	2L, combo with palbociclib or abemaciclib, HR+ HER2-, advanced or metastatic	14-Nov-2018 (2-Mar-2016)		Others
Fulvestrant	BC	1L, mono, HR+ HER2-, advanced	25-Aug-2017	2	Others
Fulvestrant	BC	1L/2L, combo with ribociclib, HR+ HER2-, advanced or metastatic	11-Mar-2019		Others
Gefitinib	LUC	1L, mono, EGFR+, metastatic	13-Jul-2015 (3-May-2003)	4	Innovative
Gemcitabine	BC	1L, combo with paclitaxel, metastatic	19-Mar-2010 (19-May-2004)		Others
Gemcitabine	LUC	1L, combo with cisplatin, metastatic	19-Mar-2010 (25-Aug-1998)		Others
Goserelin	BC	1L, mono, advanced	31-Aug-2009 (1989)		Others
Hydroxyurea	HNC	1L, combo with chemoradiation, SCCHN, advanced	[7-Dec-1967]		Others
Ipilimumab	LIC	2L, combo with nivolumab, HCC, metastatic	10-Mar-2020		Others
Ipilimumab	LUC	1L, combo with nivolumab, PD-L1+ EGFR- ALK-, metastatic	15-May-2020		Others
Ipilimumab	LUC	1L, combo with nivolumab + Pt-based chemo, EGFR- ALK-, metastatic	26-May-2020		Others

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Ixabepilone	BC	3L, combo with capecitabine, metastatic	16-Oct-2007		Others
Ixabepilone	BC	4L, mono, metastatic	16-Oct-2007		Others
Lapatinib	BC	2L, combo with capecitabine, HER2+, advanced or metastatic	13-Mar-2007	3	Others
Lapatinib	BC	1L, combo with letrozole, HR+ HER2+, metastatic	29-Jan-2010		Others
Larotrectinib	LUC	1L, mono, NTRK+, metastatic	26-Nov-2018	3	Others
Lenvatinib	LIC	1L, mono, HCC, unresectable	15-Aug-2018	4	Innovative
Letrozole	BC	1L/2L, mono, HR+, advanced	2-Mar-2010 (25-Jul-1997)		Others
Letrozole	BC	Adjuvant after tamoxifen	29-Oct-2004		Others
Letrozole	BC	Adjuvant, HR+	28-Dec-2005		Others
Lorlatinib	LUC	2L/3L, mono, ALK+, metastatic	2-Nov-2018	3	Others
Methotrexate	BC	1L, mono	[10-Aug-1959]		Others
Methotrexate	HNC	1L, mono, epidermoid	[10-Aug-1959]		Others
Methotrexate	LUC	1L, mono, SQ	[10-Aug-1959]		Others
Mitomycin	GEC	1L, combo with chemo, gastric AC, metastatic	1-Jan-1974		Others
Necitumumab	LUC	1L, combo with gemcitabine + cisplatin, SQ, metastatic	24-Nov-2015	1	Others
Neratinib	BC	Adjuvant-extended, mono, HER2+	1-Oct-2018 (17-Jul-2017)	A	Innovative
Neratinib	BC	3L, combo with capecitabine, HER2+, metastatic	25-Feb-2020		Others
Nivolumab	HNC	2L, mono, SCCHN, metastatic	10-Nov-2016	4 / 5	Innovative
Nivolumab	LUC	2L, mono, metastatic	9-Oct-2015 (4-Mar-2015)	5	Innovative
Nivolumab	LIC	2L, mono or combo with ipilimumab, HCC, metastatic	10-Mar-2020 (22-Sep-2017)		Others
Nivolumab	LUC	1L, combo with ipilimumab, PD-L1+ EGFR- ALK-, metastatic	15-May-2020		Others
Nivolumab	LUC	1L, combo with ipilimumab + Pt-based chemo, EGFR- ALK-, metastatic	26-May-2020		Others
Nivolumab	GEC	2L, mono, ESCC, metastatic	10-Jun-2020	4	Innovative
Olaparib	BC	2L, mono, gBRCAm+ HER2-, metastatic	12-Jan-2018	4	Innovative
Osimertinib	LUC	2L, mono, EGFR-T790M+, metastatic	13-Nov-2015	4	Innovative
Osimertinib	LUC	1L, mono, EGFR+, metastatic	18-Apr-2018	4	Innovative
Paclitaxel	BC	2L, mono, metastatic	13-Apr-1994		Others
Paclitaxel	BC	Adjuvant, combo with doxorubicin-based chemo, node-positive	25-Oct-1999		Others
Paclitaxel	LUC	1L, combo with cisplatin, metastatic	30-Jun-1998		Others
Paclitaxel-nab	BC	2L, mono, metastatic	7-Jan-2005		Others
Paclitaxel-nab	LUC	1L, combo with carboplatin, advanced or metastatic	11-Oct-2012		Others
Palbociclib	BC	2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	19-Feb-2016	4	Innovative
Palbociclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	31-Mar-2017 (3-Feb-2015)	3	Others
Pembrolizumab	HNC	1L, mono, SCCHN, PD-L1+, metastatic	17-Jun-2019	4 / 5	Innovative
Pembrolizumab	HNC	1L, combo with platinum + fluorouracil, SCCHN, metastatic	17-Jun-2019	4	Innovative
Pembrolizumab	HNC	2L, mono, SCCHN, metastatic	5-Aug-2016	4	Innovative
Pembrolizumab	LUC	2L, mono, PD-L1+, metastatic	24-Oct-2016 (2-Oct-2015)	5	Innovative
Pembrolizumab	LUC	1L, mono, PD-L1+ EGFR- ALK-, stage III or metastatic	11-Apr-2019 (24-Oct-2016)	5	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Pembrolizumab	LUC	1L, combo with pemetrexed + carboplatin, NSQ, EGFR- ALK-, metastatic	30-Oct-2018 (17-May-2017)	4	Innovative
Pembrolizumab	LUC	1L, combo with carboplatin + (nab-)paclitaxel, SQ, metastatic	30-Oct-2018	4	Innovative
Pembrolizumab	LIC	2L, mono, HCC, metastatic	9-Nov-2018		Others
Pembrolizumab	GEC	3L, mono, gastric or GEJ AC, PD-L1+, metastatic	22-Sep-2017		Others
Pembrolizumab	GEC	2L, mono, ESCC, PD-L1+, metastatic	30-Jul-2019		Others
Pemetrexed	LUC	2L maintenance, NSQ, advanced or metastatic	2-Jul-2009	4	Innovative
Pemetrexed	LUC	1L, como with cisplatin, NSQ, advanced or metastatic	11-Oct-2017 (26-Sep-2008)	4	Innovative
Pemetrexed	LUC	2L, mono, NSQ, metastatic	11-Oct-2017 (19-Aug-2004)		Others
Pemetrexed	LUC	1L, combo with pembrolizumab + carboplatin, NSQ, EGFR- ALK-, metastatic	30-Jan-2019 (4-Jun-2018)		Others
Pertuzumab	BC	1L, combo with trastuzumab + docetaxel, HER2+, metastatic	8-Jun-2012	4	Innovative
Pertuzumab	BC	Adjuvant, combo with trastuzumab + chemotherapy, HER2+	20-Dec-2017	B	Innovative
Pertuzumab	BC	Neoadjuvant, combo with trastuzumab + chemotherapy, HER2+	20-Dec-2017 (30-Sep-2013)	C	Others
Pralsetinib	LUC	1L, mono, RET+, metastatic	4-Sep-2020		Others
Ramucirumab	LIC	2L, mono, HCC, metastatic	10-May-2019	1	Others
Ramucirumab	LUC	2L, combo with docetaxel, metastatic	12-Dec-2014	1	Others
Ramucirumab	LUC	1L, combo with erlotinib, EGFR+, metastatic	29-May-2020	3	Others
Ramucirumab	GEC	2L, mono or combo with paclitaxel, gastric or GEJ AC, metastatic	12-Dec-2014 (21-Apr-2014)	2	Others
Regorafenib	LIC	2L, mono, HCC, metastatic	27-Apr-2017	4	Innovative
Ribociclib	BC	1L, combo with aromatase inhibitor, HR+ HER2-, advanced or metastatic	18-Jul-2018 (13-Mar-2017)	3 / 5	Innovative
Ribociclib	BC	1L or 2L, combo with fulvestrant, HR+ HER2-, advanced or metastatic	18-Jul-2018	4	Innovative
Sacituzumab govitecan	BC	3L, mono, triple-negative, metastatic	22-Apr-2020		Others
Selpercatinib	LUC	1L, mono, RET+, metastatic	8-May-2020		Others
Sorafenib	LIC	1L, mono, HCC, metastatic	16-Nov-2007		Others
Talazoparib	BC	1L, mono, gBRCAm+ HER2-, advanced or metastatic	16-Oct-2018	4	Innovative
Tamoxifen	BC	1L, mono, metastatic	29-Oct-1998 (30-Dec-1977)		Others
Tamoxifen	BC	Adjuvant, mono	29-Oct-1998 (30-Dec-1977)		Others
Thiotepa	BC	1L, mono, metastatic	9-Mar-1959		Others
Toremifene	BC	1L, mono, ER+, metastatic	20-Nov-1997		Others
Trametinib	LUC	1L, combo with dabrafenib, BRAF V600E+, metastatic	22-Jun-2017		Others
Trastuzumab	BC	Adjuvant / 1L / laterL, mono/combo, HER2+, all stages	18-Jan-2008 (25-Sep-1998)	A	Innovative
Trastuzumab	GEC	1L, mono, gastric or GEJ AC, metastatic	20-Oct-2010		Others
Trastuzumab deruxtecan	BC	3L, mono, HER2+, metastatic	20-Dec-2019	2	Others
Trastuzumab emtansine	BC	2L, mono, HER2+, metastatic	19-Aug-2013	4	Innovative

Molecule	Cancer type	Indication	FDA approval	ESMO - MCBS	Innovation status
Trastuzumab emtansine	BC	Adjuvant, mono, HER2+	3-May-2019		Others
Trifluridine & tipiracil	GEC	3L, mono, gastric or GEJ AC, metastatic	22-Feb-2019	3	Others
Tucatinib	BC	2L, combo with trastuzumab and capecitabine, HER2+, advanced or metastatic	17-Apr-2020	3	Others
Vinblastine	BC	2L, metastatic	[25-Nov-1965]		Others
Vinorelbine	LUC	1L, mono, metastatic	14-Mar-2014 (23-Dec-1994)		Others
Vinorelbine	LUC	1L, combo with cisplatin, advanced or metastatic	14-Mar-2014 (23-Dec-1994)		Others

Notes: BC = breast cancer, GEC = gastro-esophageal cancer, HNC = head and neck cancer, LIC = liver cancer, LUC = non-small cell lung cancer. AC = adenocarcinoma, ESCC = esophageal squamous cell carcinoma, GEJ = gastroesophageal junction, HCC = hepatocellular carcinoma, NSQ = non-squamous, SCCHN = squamous cell carcinoma of the head and neck, SQ = squamous. FDA approval dates in parenthesis () indicate original date of approved indication that has been replaced by the current one, and brackets [] indicate drug approval date in absence of information on indication approval date.

Table A2: National regulatory drug agencies and national drug reimbursement schemes

	MARKET	REGULATORY AGENCY	REIMBURSEMENT SCHEME
HIGH-INCOME MARKETS	Australia	Therapeutic Goods Administration (TGA)	Pharmaceutical Benefits Scheme (PBS) list
	Hong Kong	Drug Office (DO)	Hospital Authority Drug Formulary (HADF), Samaritan Fund (SF), Community Care Fund (CCF)
	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	National Health Insurance (NHI) list
	New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)	Pharmaceutical Management Agency (PHARMAC) list
	Singapore	Health Sciences Authority (HSA)	Standard Drug List (SDL), Medication Assistance Fund (MAF)
	South Korea	Ministry of Food and Drug Safety (MFDS)	National Health Insurance (NHI) list
	Taiwan	Food and Drug Administration (FDA)	National Health Insurance (NHI) list
MIDDLE-INCOME MARKETS	China	National Medical Products Administration (NMPA)	National Reimbursement Drug List (NRDL)
	India	Central Drugs Standard Control Organisation (CDSCO)	(no scheme for entire population)*
	Indonesia	National Agency of Drug and Food Control (BPOM)	National Formulary (Fornas)
	Malaysia	National Pharmaceutical Regulatory Agency (NPRA)	Ministry of Health Medicines Formulary (MOHMF)
	Philippines	Food and Drug Administration (FDA)	Philippine National Formulary (PNF)
	Thailand	Food and Drug Administration (FDA)	National List of Essential Medicines (NLEM)
	Vietnam	Drug Administration of Vietnam (DAV)	Reimbursement Drug List (RDL)

Notes: * In the analysis, inclusion in the National List of Essential Medicines (NLEM) in its latest version from 2015 was used as a proxy for inferring reimbursement status.

Out-of-pocket payments on reimbursed cancer drugs

Co-payments for prescribed cancer drugs are common across Asia-Pacific; see below for a list of examples. Different sizes in co-payment need to be taken into consideration when interpreting the size of public expenditure on cancer drugs shown in Figure 5 and Figure 6 in this report, as co-payments are included in the presented numbers.

High-income markets:

- **Australia**: Most drugs on the Pharmaceutical Benefits Scheme (PBS) require a co-payment of AUD 41.30 per prescription (or AUD 6.60 for special groups with a concession card) (44). Notably, the number of treatment cycles with patent-protected cancer drugs is typically restricted on the PBS. For example, the number packs of osimertinib is restricted to five (45), enough for five months of treatment, which can be compared to over 20 months of treatment in the key clinical trial of osimertinib in first-line EGFR-positive non-small cell lung cancer (46). After the co-payment of AUD 41.30 for each of the five packs paid via the PBS, patients would face a dispense price of AUD 7,971.16 per pack.
- **Japan**: Co-payments of 10% to 30% (depending on income level and age) apply to prescription drugs on the National Health Insurance (NHI) list. Two safety nets, Tokutei Shikkan Iryo Hojo and Kogaku Ryoyohi Seido, exists to protect from excessive amounts of co-payments (47).
- **New Zealand**: There is a NZD 5 co-payment per prescription drug listed with PHARMAC, yet drugs administered directly in hospitals come with no co-payment (48).
- **Singapore**: As described in Box 1 above, several public schemes exist to cover costs of cancer drugs. According to the Ministry of Health, the coverage they provided every month was enough to fully cover drug treatment costs for 9 out of 10 patients in 2017 (23).

Middle-income markets:

- **China**: Drug co-payments and deductibles vary by insurance scheme, by province/city and by drug (49). Drugs included on A List of the National Reimbursement Drug List (NRDL) are free of co-payment nationwide for insured persons of the UEBMI or URBMI scheme. The level of reimbursement for drugs on the B list of the NRDL is set by local authorities and varies across the country. Previous studies noted that patients might not be able to afford the high co-payment rates in order to access targeted therapies on the B list of the NRDL (50). For instance, the average co-payment rate in tertiary hospitals for patients enrolled in urban and rural medical insurance systems was 40.7% for trastuzumab. The absolute size of

the co-payment for annual treatment with trastuzumab (around $6,600) exceeded the average disposable income per capita (around $4,300) in 2018 (50).

- **Vietnam**: For most targeted therapies (including tyrosine kinase inhibitors like Afatinib, Gefitinib, Sorafenib and monoclonal antibodies such as Bevacizumab, Cetuximab, Trastuzumab) on the latest Reimbursement Drug List (RDL) issued in 2018, health insurance will pay 50% of the costs (51). Co-payment might also differ depending on the indication of a specific drug (e.g., trastuzumab has a coverage ratio of 60% in breast cancer and 50% in gastric cancer). For most chemotherapies, health insurance will cover all costs.

PRICING POLICIES FOR OFF-PATENT DRUGS IN ASIA-PACIFIC

Sub-report 5 of the main report "Cancer care and access to cancer drugs in Asia-Pacific"

Thomas Hofmarcher
George Keel
Peter Lindgren

IHE - The Swedish Institute for Health Economics

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www.ihe.se | ihe@ihe.se

Report summary

In general, most payers and authorities adopt cost-containment policies to increase market uptake of generics and biosimilars, and thus curb pharmaceutical spending. As such, generics and biosimilars have become fundamental to pharmaceutical cost control, but many markets could better leverage such policies to control pharmaceutical expenditure more effectively, freeing up resources to improve patient access to more advanced cancer treatment options.

One such policy lies within the pricing of off-patent drugs. Once a patent expires, market exclusivity is lost, and generic copies of the originator can enter the market. This stimulates competition between manufacturers and should cause the price of the originator drug to fall. Pricing policies for off-patent medicines affect the magnitude of price decreases following patent expiry of originator drugs, and larger price drops could generate substantial savings particularly for widely prescribed drugs.

In general, markets in Asia-Pacific react as anticipated with prices of originator drugs overwhelmingly falling after patent expiry (or loss of exclusivity), but the magnitudes of price drops vary substantially across drugs and markets. Drawing on a limited sample of 11 major cancer drugs with patent loss between 2010 and 2020, the analysis in this report indicates that all markets could save from 3% to 20% of total cancer drug expenditure, if more effective off-patent pricing mechanisms are adopted. In middle-income markets where access to originator drugs is low, price drops associated with effective pricing mechanisms on off-patent drugs would likely trigger increased sales volumes, thus compounding the savings.

While there may not be a one-size-fits-all approach, markets in Asia-Pacific should invest in learning from each other to develop policies on off-patent drugs that are effective in their local market. This could play a crucial role in increasing access to innovative drugs for the growing population of cancer patients. Ensuring effective pricing policies for off-patent drugs and stimulating availability of and competition between generics/biosimilars, which provide “equal” clinical value as originators can lead to substantive savings. An effective reduction of prices creates budget headroom for reimbursing new innovative drugs. Ultimately, an effective re-channeling of resources from off-patent drugs to new innovative drugs could offer a more sustainable financing model of innovative drugs.

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1. Pricing mechanisms and off-patent cancer drugs

In general, across most countries, payers and authorities adopt cost-containment policies to increase market uptake of generics and biosimilars, and thus curb pharmaceutical spending (1-3). As such, generics and biosimilars have become fundamental to pharmaceutical cost control, but many markets could better exploit such policies to more effectively control pharmaceutical expenditure, freeing up resources to improve patient access to cancer drugs (1-3).

One such policy lies within the pricing of off-patent drugs. Once a patent expires, market exclusivity is lost, and generic copies of the branded drug enter the market, causing the price to fall. The introduction of generics to the market following patent expiry of originator cancer drugs is a key means of savings for healthcare budgets (4). Healthy off-patent pricing mechanisms allow for cost containment (5), and thus for markets to off-set the financial cost of granting patients access to new originator products (6). While patent expiration is generally associated with price drops in originator products, the magnitudes of these drops vary between drugs and markets (6). Policies surrounding off-patent pricing mechanisms likely have a direct influence on the magnitude of price decreases following patent expiry of originator drugs, and larger price drops could generate substantial savings for widely prescribed drugs.

1.1 Aim of the sub-report

The aim of this sub-report is to present current patterns in market price reactions to patent expiry of cancer drugs in Asia-Pacific[1], and to estimate the potential savings associated with effective off-patent pricing mechanisms adopted for cancer drugs.

- Section 2 presents the price control mechanisms across markets and explores the impact of patent expiry on the price of branded cancer drugs within these markets.
- Section 3 presents the savings opportunities associated with effective off-patent pricing mechanisms.

[1] Asia-Pacific consists in this report of 7 high-income markets – Australia, Hong Kong, Japan, New Zealand, Singapore, South Korea, Taiwan – and 7 middle-income markets – China, India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

2. Price response to patent expiry across markets

2.1 Method and data

Changes in price of originator drugs following patent expiry were explored across 13 markets across Asia-Pacific. The analysis primarily focused on drugs used for the same five cancer types as discussed in previous sub-reports (breast cancer, gastro-esophageal cancer, head & neck cancer, liver cancer, lung cancer), but drugs for the treatment of other cancer types were also selected in order to create a representative sample of biologics and small-molecule drugs. 11 drugs (bevacizumab (Avastin), capecitabine (Xeloda), erlotinib (Tarceva), fulvestrant (Faslodex), gefitinib (Iressa), imatinib (Glivec/Gleevec), letrozole (Femara), pemetrexed (Alimta), rituximab (Mabthera/Rituxan), sorafenib (Nexavar), and trastuzumab (Herceptin)) with patent loss between 2010 and 2020 were selected. Data on sales volumes of these drugs across 13 markets from Q1 2010 to Q3 2020 were obtained from the MIDAS® database, an international database containing comparable pharmaceutical sales data (7). For Indonesia, data were only available from Q1 2014 to Q3 2020 from the International Pharmaceuticals Manufacturer's Group (IPMG) (8). The largest 40 pharmaceutical companies share data with IPMG, and these companies contribute to around 70% of the market. India was excluded from this analysis due to data limitations associated with both sales data and information on patent expiry.

Quarterly sales data were obtained in both local currencies and ex-manufacturer US dollars, and corresponding sales volumes were obtained in what IQVIA refers to as "counting units". Counting units were converted to milligrams (mg) using methods described in Appendix 3. The price per mg was calculated per market, per drug, per quarter.

Data on patent expiry dates were available from local industry contacts in Australia, New Zealand,and Taiwan (9-11). For all other markets, no local public source on patent expiry dates was identified. Instead, the date of the first generic/biosimilar approved was obtained from national regulatory agencies (see Table A2 in sub-report 3). In Japan, where the latter information was not available, the date of first sales of generics/biosimilars within the MIDAS® database was used (7). Patent expiry dates (or their proxies) for each drug and market are presented in Appendix 1.

For each market-drug, the data were normalized around date of patent expiry, with the quarter of patent expiry serving as quarter-zero (Q_0). The price per mg the quarter before patent expiry (Q_{-1})

served as a benchmark against which quarterly prices were indexed for each market-drug. Prices were analyzed 1 year pre- and 2 years post-patent expiry.

It should be noted that IQVIA data does not capture the impact of confidential price negotiations between manufacturers and governments and other payers. In cases where confidential price negotiations were made, the associated price decreases are not detected in the MIDAS data. The database may have other limitations; however, we based our analysis on best available data, which in this case, is the MIDAS database.

2.2 Results

In general, the selected Asia-Pacific markets reacted as anticipated with prices overwhelmingly falling after patent expiry. The magnitude of price drops varied substantially across drugs and markets, and while it is difficult to tease out a perfect mechanism, markets could invest in learning from one another to develop effective policies for their local context.

It is important to note how differences between biologics and small-molecule drugs impact post-expiry prices of originators and their predecessors. Biologics are more complicated and expensive to produce, and they are therefore more difficult to reverse engineer, including generic forms (called “biosimilars”). Biosimilars are typically developed at a cost of $10-40 million, while generics usually cost $1-2 million to develop (12). Additionally, the fixed costs associated with building manufacturing facilities for the production of biologics lies in the range of $100-200 million (12). Therefore, off-patent biologics, facing fewer and higher-cost competitors as compared to small molecules, experience smaller price drops (12, 13). Figure 1 presents the mean price drop of all small-molecule branded drugs for each high-income market, and Figure 2 presents the same for biologics. Consideration should be taken to approach cost-containment policies for handling off-patent competition separately for biosimilars and small molecules, including pricing (14).

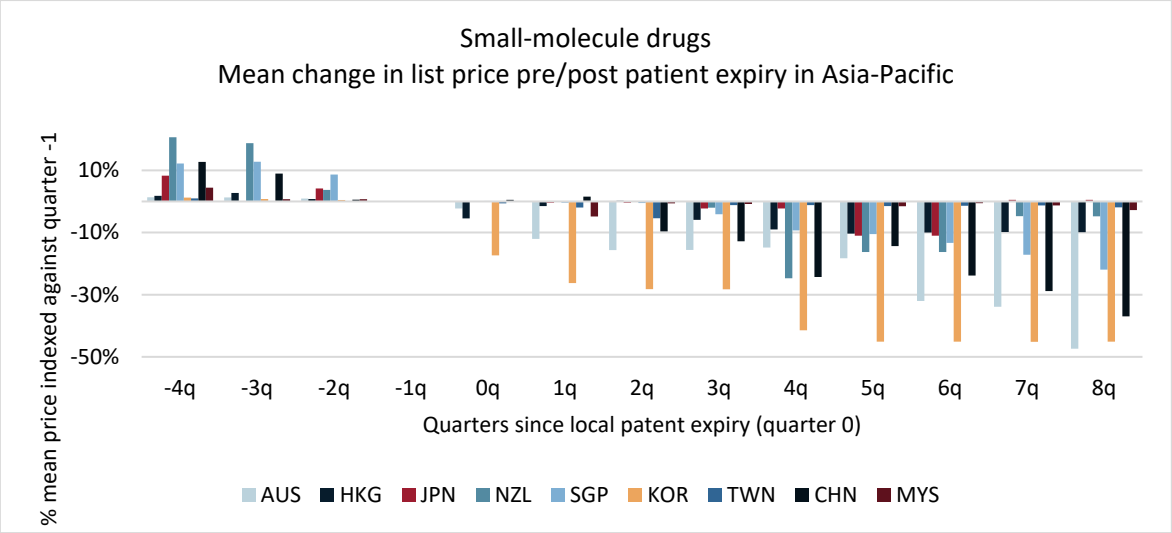


Figure 1: Indexed price per mg changes in list price pre/post patent expiry for small molecule drugs

Notes: Eight major small-molecule cancer drugs with patent loss between 2010 and 2020 were included in the analysis. Quarter 0 refers to the quarter during which a drug's patent expired or (if the former information was not available) to the quarter during which the first generic version received regulatory approval or started being sold.

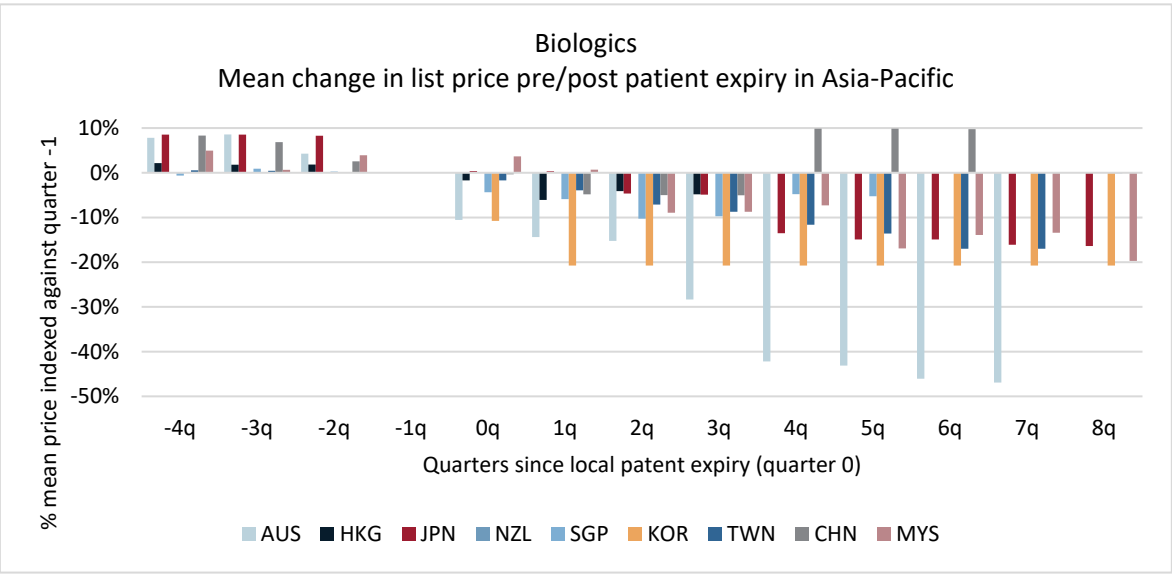


Figure 2: Indexed price per mg changes in list price pre/post patent expiry for biologics

Notes: Three major biologics with patent loss between 2010 and 2020 were included in the analysis. Quarter 0 refers to the quarter during which a drug's patent expired or (if the former information was not available) to the quarter during which the first generic version received regulatory approval or started being sold.

Australia

Australia implements mandatory price cuts combined with price-disclosure policies on off-patent drugs (15-17). In 2007, two separate formularies were created for PBS drugs, and price disclosure and statutory price reductions were introduced, which have been accelerated and expanded since. There is currently a mandatory price reduction of 25% (16% until September 2018) when the first generic was added to the PBS, and the originator went off patent (18, 19). The price of the first generic would be 25% cheaper than the originators' original price. Subsequent price reductions are based on a price-disclosure policy for off-patent originator drugs. Avastin, Mabthera, Herceptin, and Glivec all experienced the expected 25% mandatory price drops expected with post-2016 patent expiry, and Xeloda and Femara experienced the expected pre-2016 16% price drops.

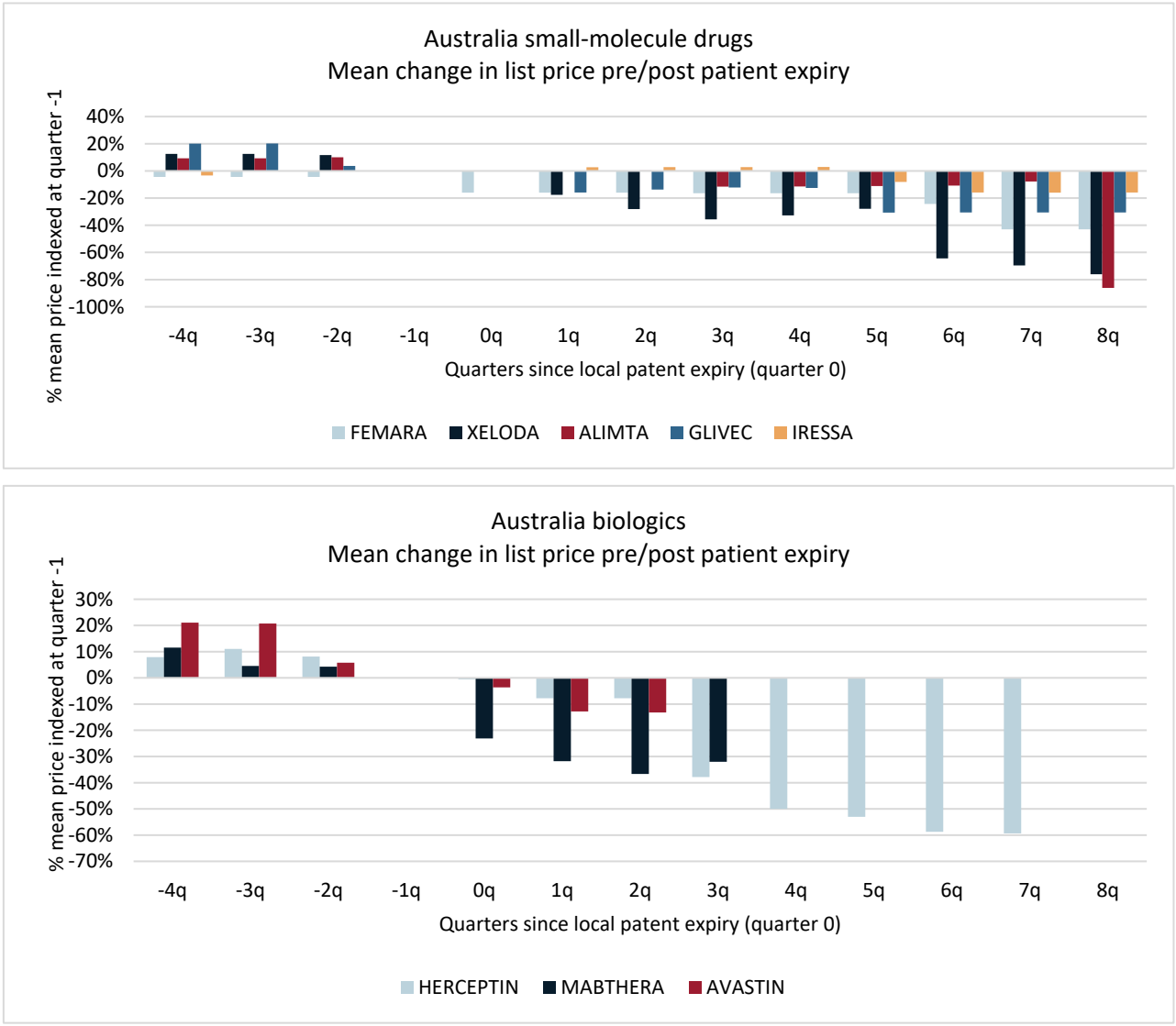


Figure 3: Australia, price changes pre- and post-patent expiry

Hong Kong

Price negotiations and tendering lie at the core of drug pricing policy in Hong Kong, and prices go free of direct regulatory control to allow for competition within the market. In the public sector, tender-based procurement of multi-source drugs (including non-originator drugs) limits public physician choice and increases prescription of generics and biosimilars. However, in the private sector, original brand drugs and biologics are continuing to be widely prescribed even after generics and biosimilars enter the market (20). In Hong Kong, the data did not allow for differentiation in sales data between the public and private sector. Among high-income markets, Hong Kong has a relatively high share of private spending (see Figure 3 in sub-report 2). Prescribers and citizens in Hong Kong are reported to be brand conscious due to lingering historical safety concerns associated with the bioequivalence of generic products, and prices of branded drugs could thus be more resistant to entry of generics into the market (20). The Hospital Authority places strong focus on drug safety with generic purchasing, which could also hinder the entry of generics into the public market. Specifically, it was mandated that generics undergo good manufacturing practice certification and delivered with bioequivalence/bioavailability data and a sample for testing. This could explain why several drugs did not see expected price drops following patent expiry. These policies were loosened in 2016 when Hong Kong joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and began purchasing generics from PIC/S member markets in 2017. Prior to joining PIC/S, Hong Kong purchased generics from manufacturers stationed in member markets of the International Conference of Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. Generics from markets affiliated with the ICH were treated with caution, as compared to suppliers based in PIC/S affiliated markets. Expected expansion of tender-based purchasing contracts for generics are yet to take hold, but low-cost generics are expected to step up competition in coming years (20).

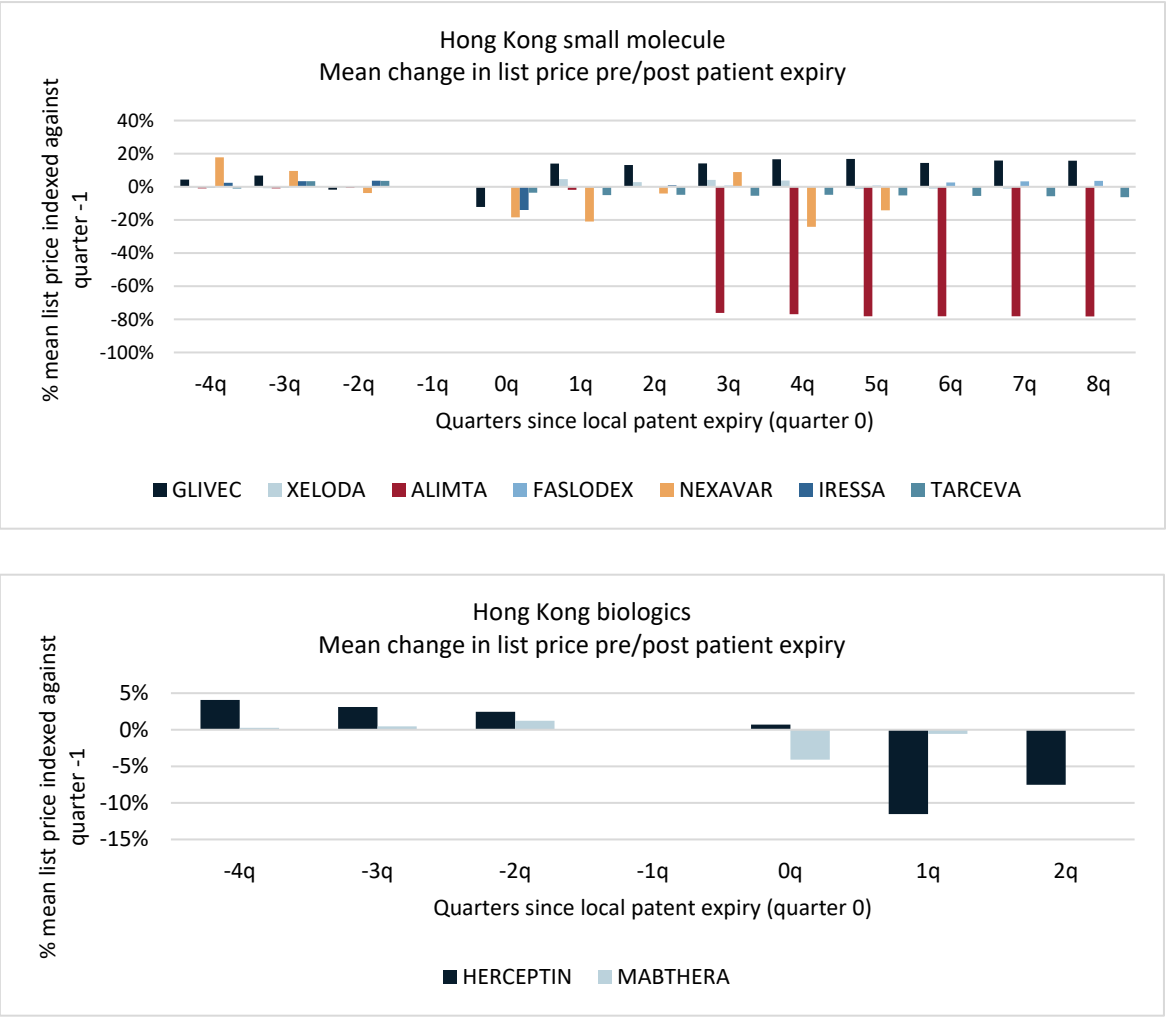


Figure 4: Hong Kong, price changes pre- and post-patent expiry

Japan

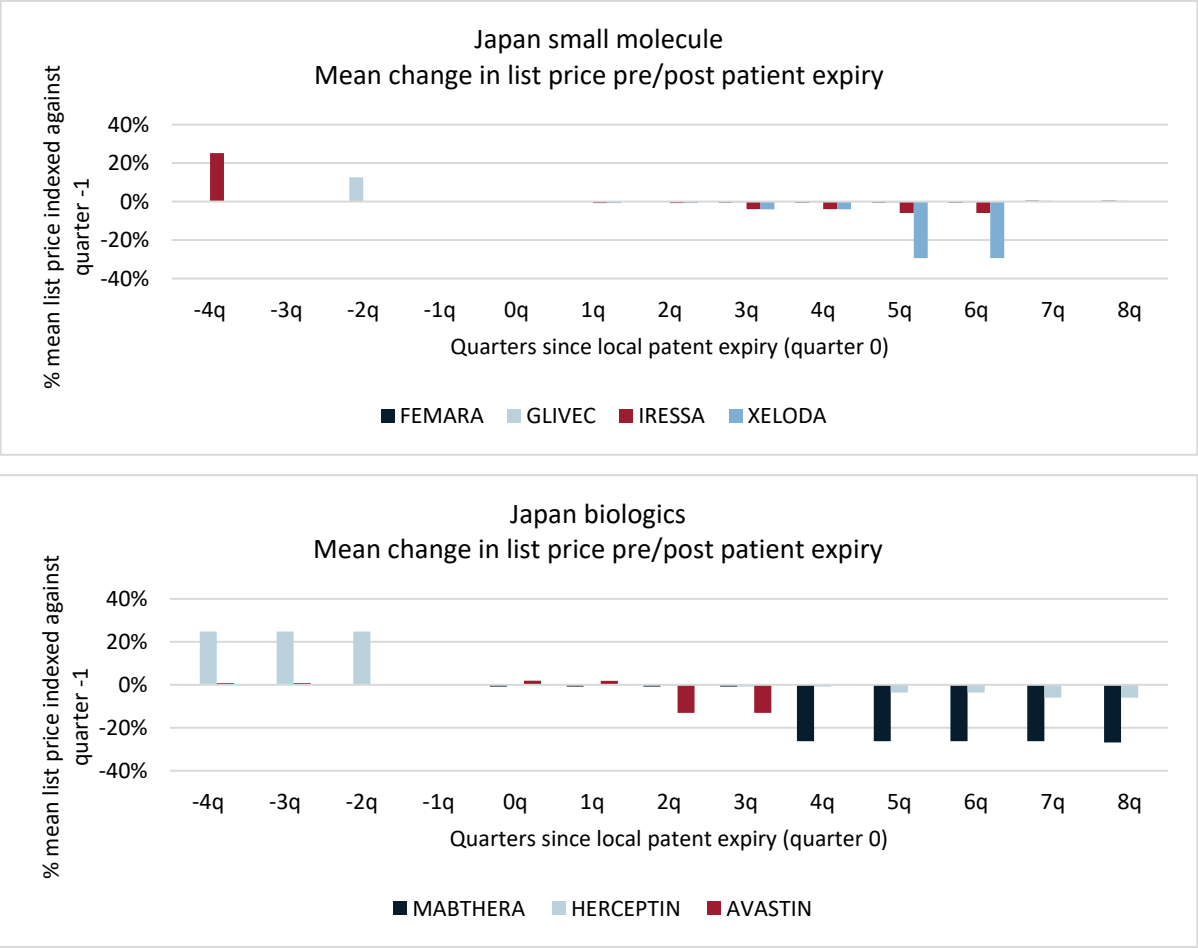
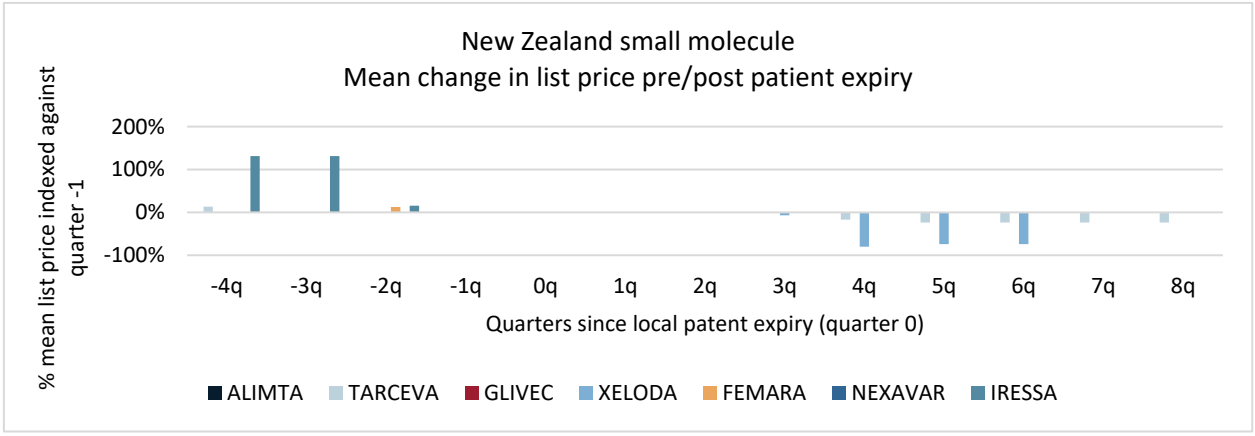


Figure 5: Japan, price changes pre- and post-patent expiry

Of the markets included in this report, Japan has the highest share of public spending, and employs a range of pricing policies to control costs and to support pharmaceutical innovation. The price of generics is set to 50% of the original product, and 40% if the number of already approved brands exceeds ten generic products. The price of new biosimilars is set to 70% of the original product (60% if the number of already approved brands exceeds ten). Twice a year (June and December), generic drugs have the opportunity to be included in the Japan's National Health Insurance reimbursement list. To help free up resources from spending on pharmaceuticals, a national volume target of 80% generics was set to be met by September 2020 by the MHLW (it was 40% in September 2011) (21). The largest insurer had reached 79% by 2019, and of the 47 prefectures, 20 had reached 80% by the end of 2020 (22). As a larger percentage of generics and biosimilars have been incorporated into the market, originators experiencing patent expiry more recently also experience larger price drops. More recent cancer drugs, like Iressa, Herceptin, and Mabthera, experienced expected price cuts after patent expiry. Older drugs like Femara did not experience a price fall for several years after generics entered the market.

New Zealand



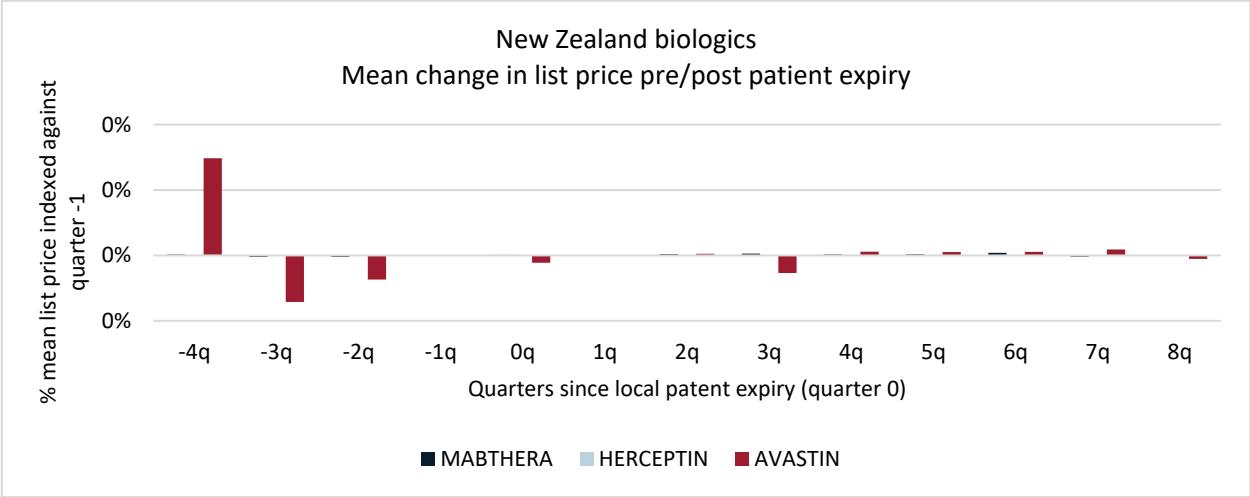


Figure 6: New Zealand, price changes pre- and post-patent expiry

New Zealand uses a competitive tender across therapeutic areas to decide on brands that will be subsidized, and historically effective price negotiations with manufactures have led to significant reductions in brand prices well before patent expiry (16). Since 1997, the Pharmaceutical Management Agency of New Zealand (PHARMAC) has been tendering out sole supply contracts for generic drugs, for a limited period, to encourage the development of cheaper generic versions of off-patent drugs (15, 23). Effective negotiating prior to listing originator products has led to significant price reductions in New Zealand, and is reflected in the price for Tarceva, Mabthera, and Iressa. However, the expected price drops because of generic entry into the market are not seen in the results. This is most likely a limitation of data availability. IQVIA sales data is unable to capture the price impact of confidential agreements across markets. PHARMAC keeps the specifics of price negotiations confidential from other buyers, and thus the rest of the world, introducing a lack of transparency to the actual price of drugs in New Zealand's Pharmaceutical Schedule (23, 24). This may be why price drops are not always detected in the dataset, and New Zealand almost certainly achieves lower prices than those presented in this analysis.

Singapore

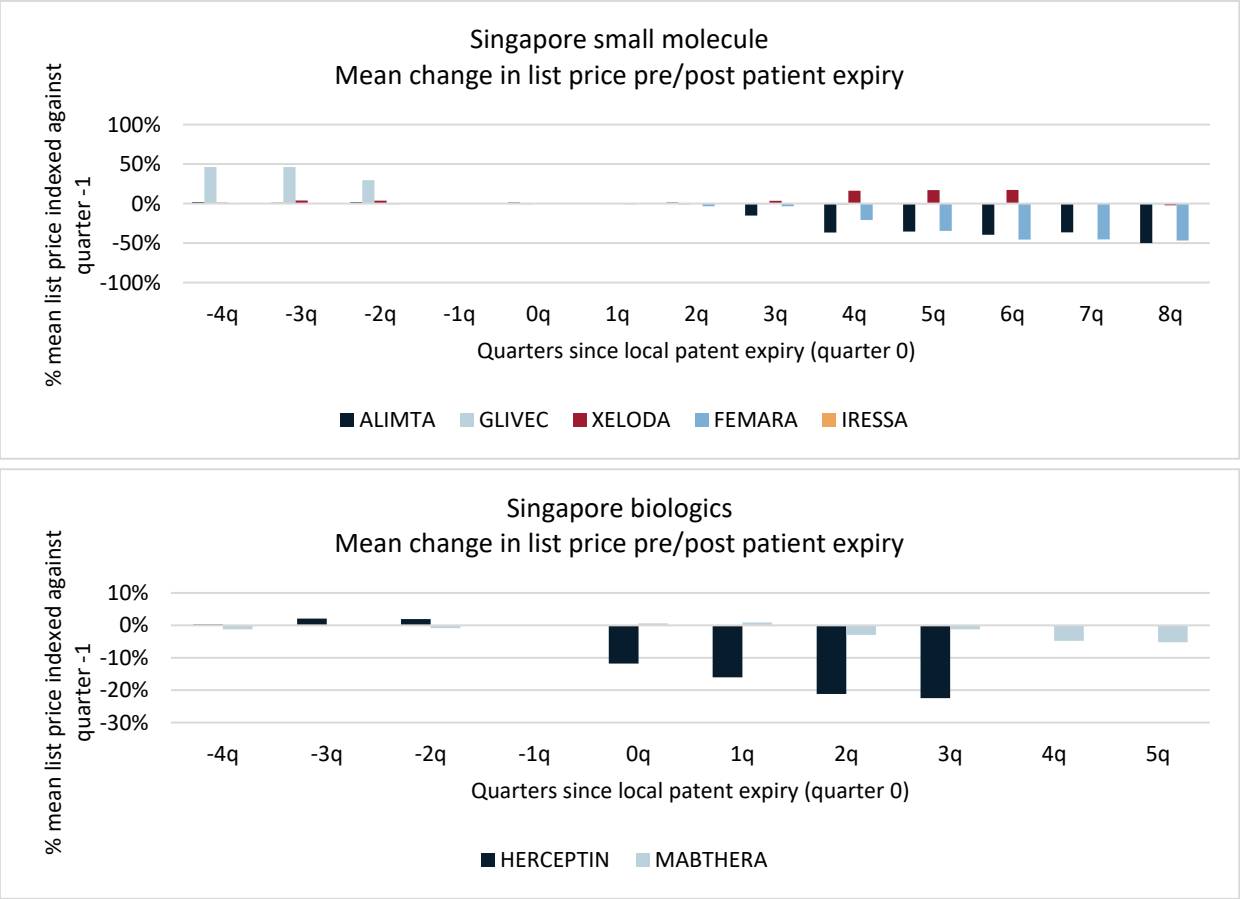
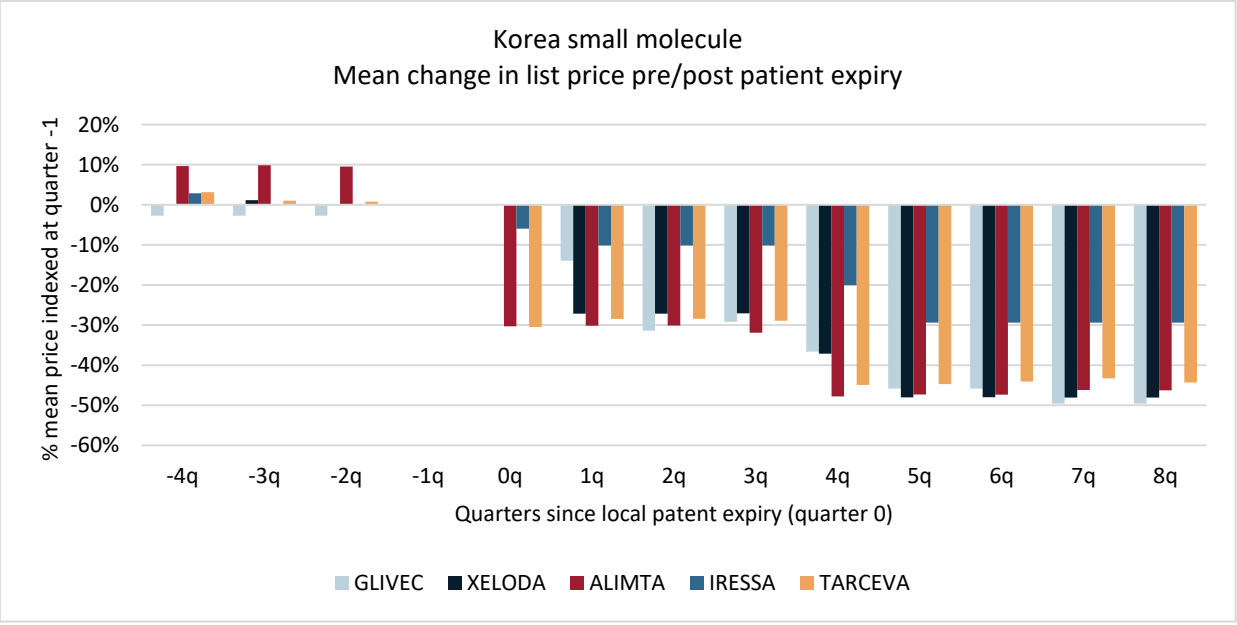


Figure 7: Singapore, price changes pre- and post-patent expiry

In Singapore, prices are set by manufacturers, and are controlled for public providers through a tendering process, which has been shown to reduce prices in both public and private markets after generic entry (16). Private providers also engage in bulk purchasing practices, which has successfully kept private sector prices comparable to, if not slightly higher than, publicly tendered products in the public sector (25). The prices set through negotiations in the public and private sector are heavily impacted by the availability of generics on the market, thus recently off-patent drugs should experience reductions in price. Historically, general practitioners and private providers have adhered to prescribing originator products even after generic entry, but this trend has shifted, and continues to shift in recent years (25). In Singapore, prices consistently drop following patent expiry, but not as dramatically as what is seen in other markets. This could be because of brand-conscious prescribing practices, and also that tendering and bulk purchasing practices in Singapore successfully set the prices of originator drugs at a low level from the outset.

South Korea



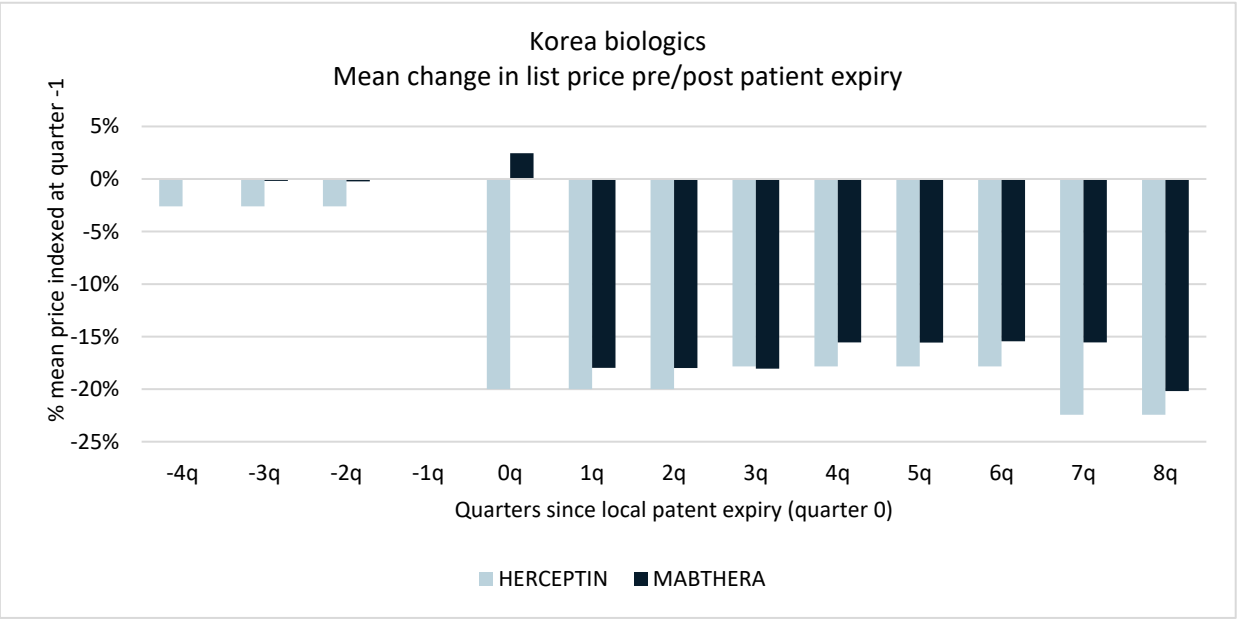


Figure 8: Korea, price changes pre- and post-patent expiry

South Korea exercises mandatory price discounts internally referenced to the originator product when generics enter the market, and a subsequent percentage reduction two years after generic entry (16). As a result, prices can be expected to experience reductions of around 30% and 10% in the first and second years following generic entry, respectively (16). The results align well with the expected first- and second-year price drops (16)

Taiwan

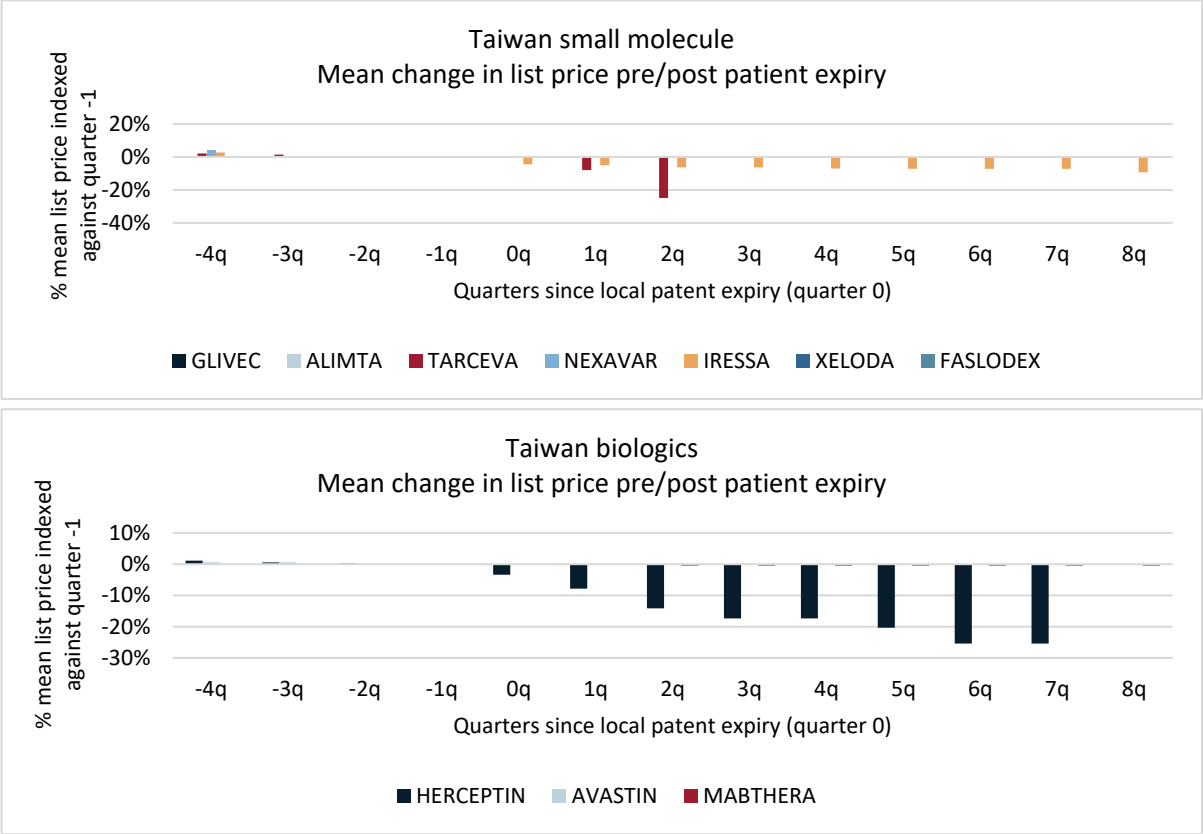


Figure 9: Taiwan, price changes pre- and post-patent expiry

Taiwan uses reference pricing, drawing on a basket of ten reference markets: the United States, the United Kingdom, Canada, France, Belgium, Germany, Japan, Sweden, Australia, and Switzerland (26). The designated reference price is set in accordance with the level of evidence and efficacy of the treatment. However, many manufactures often apply with prices lower than the required reference prices in order to secure a place on the approval list, and to reduce review time (26). The National Health Insurance Administration monitors differences in procurement and reimbursement prices and makes price adjustments in cases where the prices differ by more than 30%. Further, prices are monitored and adjusted every two years. Since 1999, the price of brand drugs with bioequivalent generic alternatives must not exceed 85% of the designated reference price (27). Originators that went off patent within one year are set equal to the minimum price of the 10 reference markets. After one year, prices are set to a weighted average price of all generic competitors plus 15%. Expected substantial price drops are seen in Tarceva, Nexavar, Iressa, and Herceptin, but the other six drugs facing patent expiry – Avastin, Xeloda, Faslodex, Glivec, Alimta, and Mabthera – see no change in price in subsequent quarters. Given the clear policies in place in Taiwan that go beyond the downward pressure of market competition, it can be assumed that this is due to limitations surrounding data availability.

China

In 2009, China began to explore policies to close the gap between the price of originator drugs that go off patent and their generic counterparts. In 2010, the State council decided that prices of recently off-patent drugs will be revisited every two to three years, which result in price reductions of generally no less than 15% (28). In 2015, China began piloting price negotiations with manufactures pre-patent. Iressa was selected as one of these drugs, all of which experienced price drops greater than 50% pre-patent expiry (28). Iressa was followed by Tarceva, Avastin, Mabthera, Nexavar, and Herceptin, all experiencing price drops of 40 to 60%, all before patent expiry. Further drops were also seen in quarters immediately following patent expiry in all drugs but Mabthera.

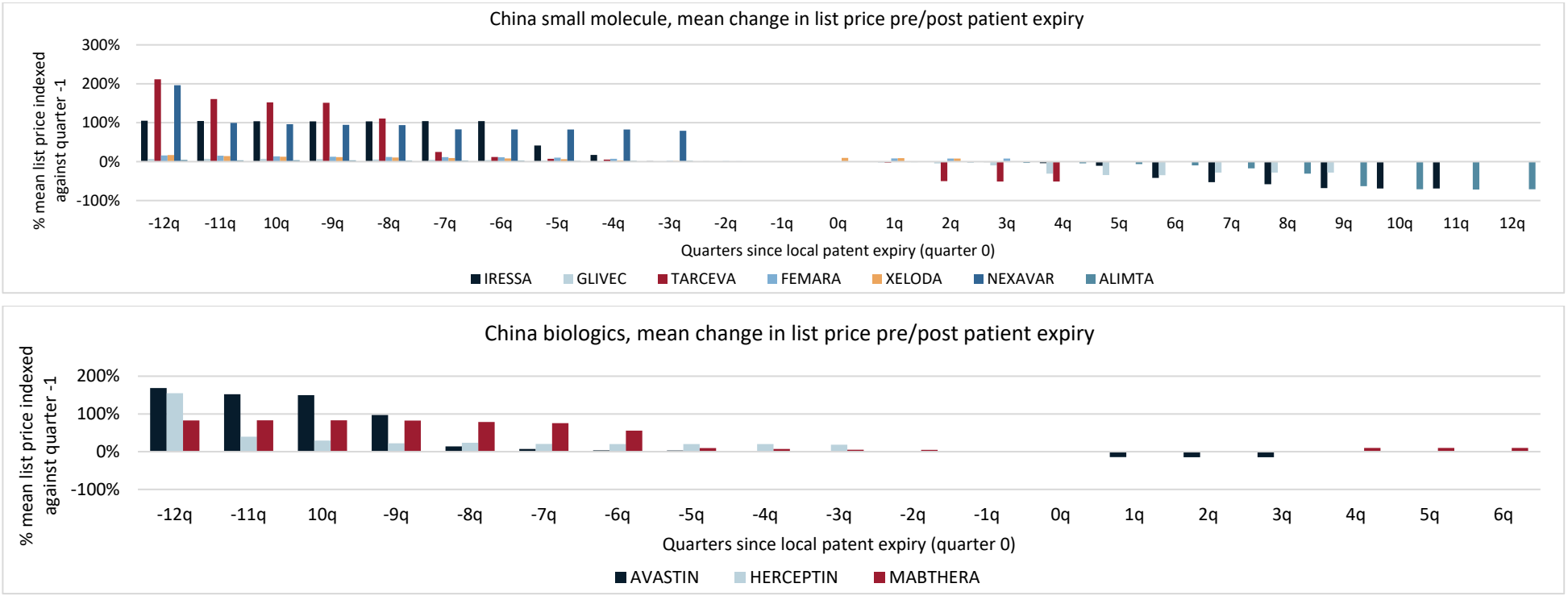


Figure 10: China, price changes pre- and post-patent expiry

Malaysia

In Malaysia, the Ministry of Health (MOH) procures drugs to public providers. To gain listing status in the national formulary, manufactures must present evidence of efficacy and reasonable price, and are selected through a tendering process (29). Prices are then monitored to maintain affordability for the MOH. Drug prices within the private sector are not regulated and there are no mechanisms in place to control prices within private pharmacies at the retail level (30). The private sector has a markets share of around 60% (31), and limited price controls paired with brand-conscious prescribing mean that drug prices in Malaysia remain comparatively high (30). The MOH is discussing the implementation of international reference pricing, setting a ceiling price at the median level of the average of the lowest of three reference prices. However, the basket of markets is yet to be specified, and this along with other price control policies are still under discussion. It is unclear when they will come into effect, but are expected to hit the public sector first (29).

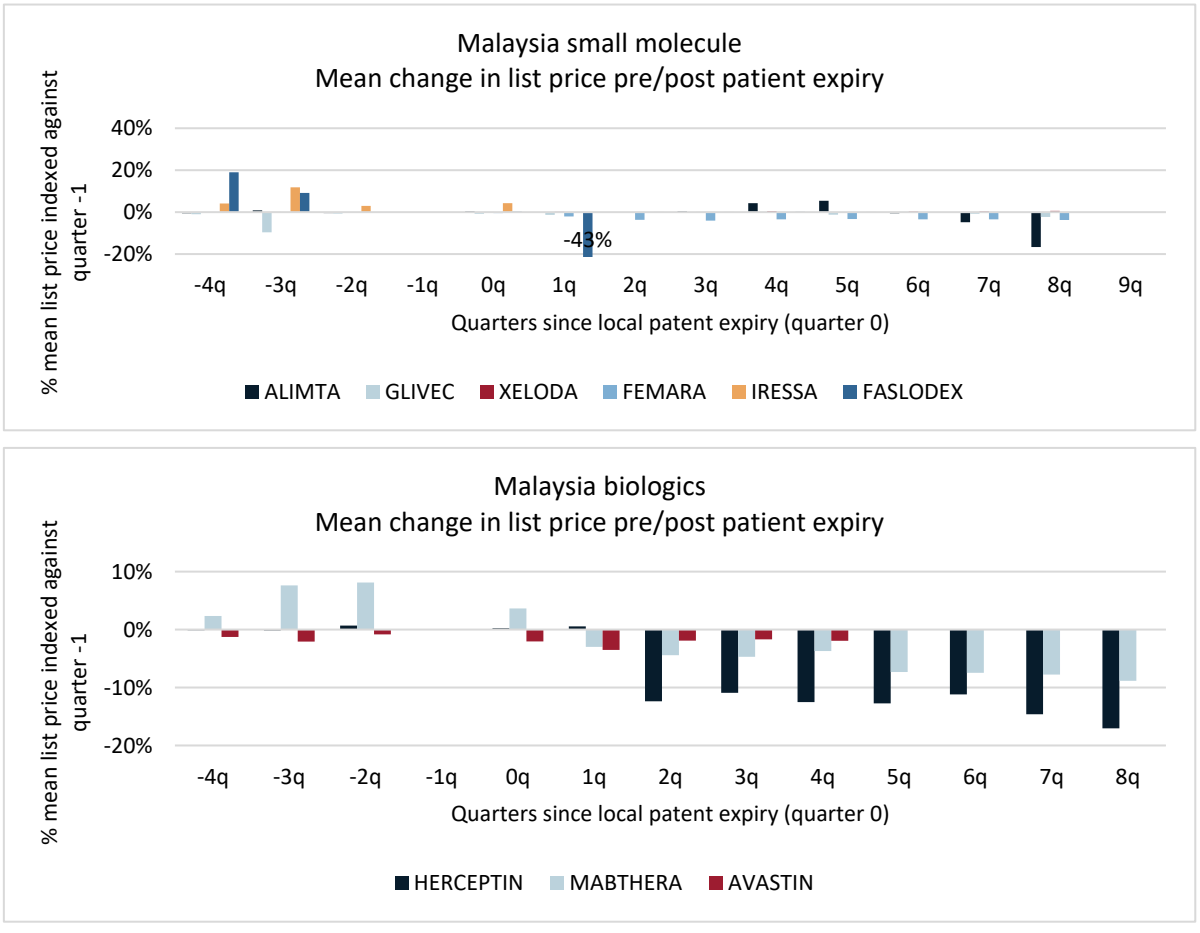


Figure 11:Malaysia, price changes pre- and post-patent expiry

For Malaysia, the MIDAS dataset allowed for differentiation between public and private sales. For most drugs, following patent expiry, the price of branded products falls in the public sector following patent expiry, and returns to original price levels in the quarters that follow, indicated generic takeover of the market – see the example of Alimta in Figure 12. This is also the case for Avastin,

Faslodex, Glivec, Alimta, and Mabthera. Public sector prices of Femara and Herceptin drop and stay down after the entry of generics, and sales of Iressa cease after patent expiry. The lack of changes in private sector prices could be in part due to brand-conscious prescribing behavior in the private market. The quality of data coming out of the private sector is also reported as less reliable, although, the MOH is taking steps to collect data more accurately and broadly from the private sector in coming years (29). Finally, in Malaysia, it can take time for the government to put tenders into place after generic approval, which may explain some of the delay seen in price drops.

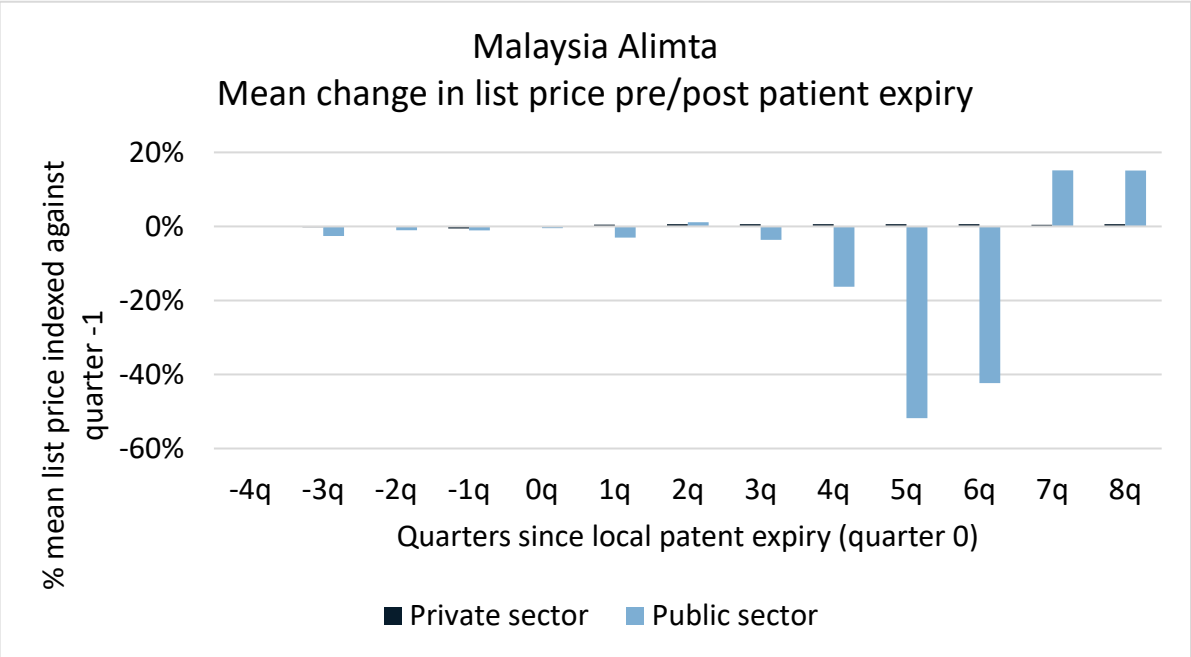


Figure 12: Case example of Alimta price changes in Malaysia

Thailand, the Philippines, Indonesia, and Vietnam

In all four of these markets, increased price control policies are expected in the coming few years. In Indonesia, the Philippines, and Vietnam, the private sector accounts for a large proportion of the market and goes largely unregulated. In Thailand, median pricing and other strict pricing negotiations limit the successful entry of originator drugs into the market (32). For off-patent drugs facing competition from generics and biosimilars, median pricing obtained from the average price of all versions of the drug (generic and original). The median pricing leads to cuts ranging from 10%-90% and averaging on 50% (32). Post patent expiry, in this analysis Thailand experiences no price change in originator products in the quarters following patent expiry. Among middle-income markets, Thailand has the largest share of public financing (see sub-report 2, Figure 3), and under these policies generic competition should bring originator prices down considerably. The current policy environment surrounding off-patent drugs is inconsistent with unaffected prices of originator products, so we must conclude that the IQVIA data is not capturing pricing events that likely have happened.

In Indonesia, after drugs are listed on the national formulary, they are most often purchased through the e-catalogue and priced using a cost-plus approach. These prices serve as the basis of a price ceiling system (33). This ceiling process is multi-source and also involves locally produced generic products, and resulting competition drives prices very low. For single-source products, prices are set through negotiations between MOH and manufacturers. These negotiations often involve budget impact analysis, and resources available to spend on high priced products, allowing limited room for negotiation. As a result, many single-source products are not available in the e-catalogue, and prices in Indonesia remain relatively low (33). Vietnam, Thailand, and the Philippines all experience relatively high drug prices, comparable to those seen in European markets.

In all cases, generic entry into an unregulated private sector should lead to price drops in originator products. Within the outputs of the analysis of MIDAS and IPMG data, however, prices in all four markets remain essentially unchanged before and after patent expiry. Some possible exceptions are Femara in Indonesia, Mabthera in the Philippines, and Faslodex, Femara, Iressa, Nexavar, and Mabthera in Vietnam. However, in all of these cases the trends are unstable, distorted, and generally uninterpretable. As was the case with Thailand, these results are inconsistent with expected price drops of originator products associated with generic entry into the market. We therefore assume that the IQVIA data is not capturing pricing events associated with generic entry to markets.

However, in each of these markets (Indonesia, Thailand, Vietnam, and the Philippines), price levels are consistent with those seen in other markets, and sales volumes appear to respond as expected, as seen in the following analysis.

3. Potential savings from efficient pricing mechanisms

3.1 Method and data

Focusing on the same 11 drugs, the prices of the originator drugs were analyzed across markets to estimate the savings associated with effective off-patent pricing mechanisms. Effectiveness is here defined as achieving the lowest possible price.

For the year following patent expiry, total currency sales were divided by the total mg sales for each market to estimate the annual price per mg of originator drugs the year following patent expiry. For each drug, market specific annual prices were benchmarked against the market with the absolute lowest price per mg. Candidates for benchmarking included both the 13 markets excluding India in Asia-Pacific and a set of OECD markets for which MIDAS data were also available (Belgium, Canada, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, and the UK). For each drug, the price difference between the benchmark price and each market's off-patent price was multiplied by the volume sold (mg) in the respective market the year after patent expiry to estimate potential savings.

3.2 Results

The estimated savings per drug per market are presented in Appendix 2. Estimated total savings per newly diagnosed cancer case in the respective markets are presented in US dollars in Figure 13. All markets included in this analysis could theoretically achieve considerable amounts of savings. Compared to total cancer drug expenditure (see Figure 3 in sub-report 4), potential savings range from 3% to 20% of cancer drug expenditure across the markets; see Figure 14.

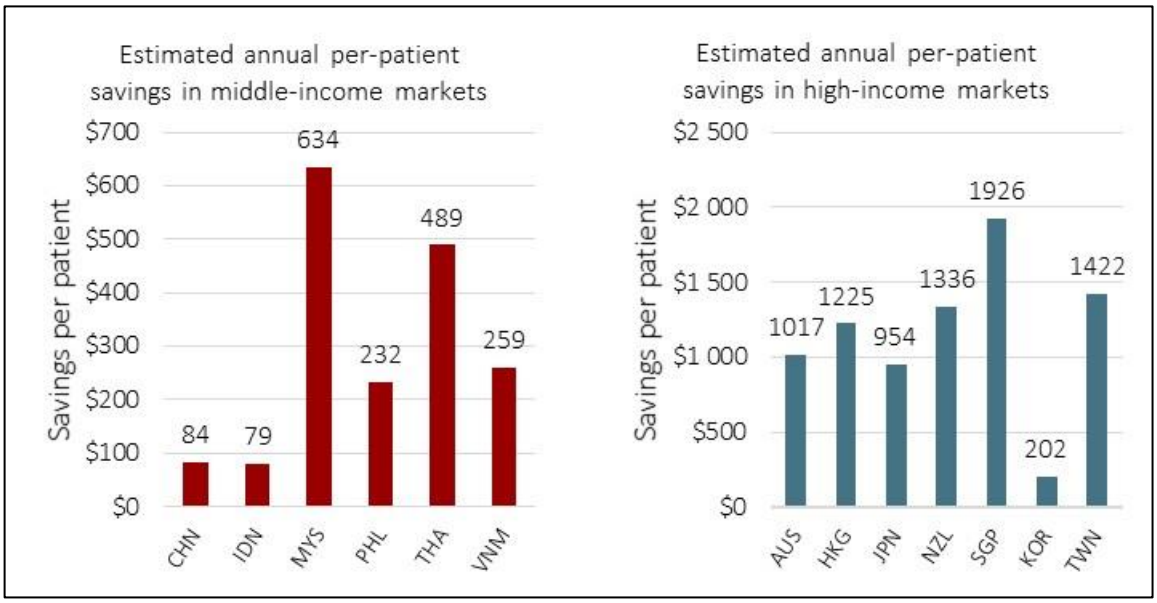


Figure 13: Estimated savings per newly diagnosed cancer case (US$) from more effective off-patent pricing outcomes of 11 cancer drugs

Notes: No data available for India. Effectiveness is here defined as achieving the lowest possible price for the originator drug after patent expiry or loss of exclusivity. The analysis is based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers.

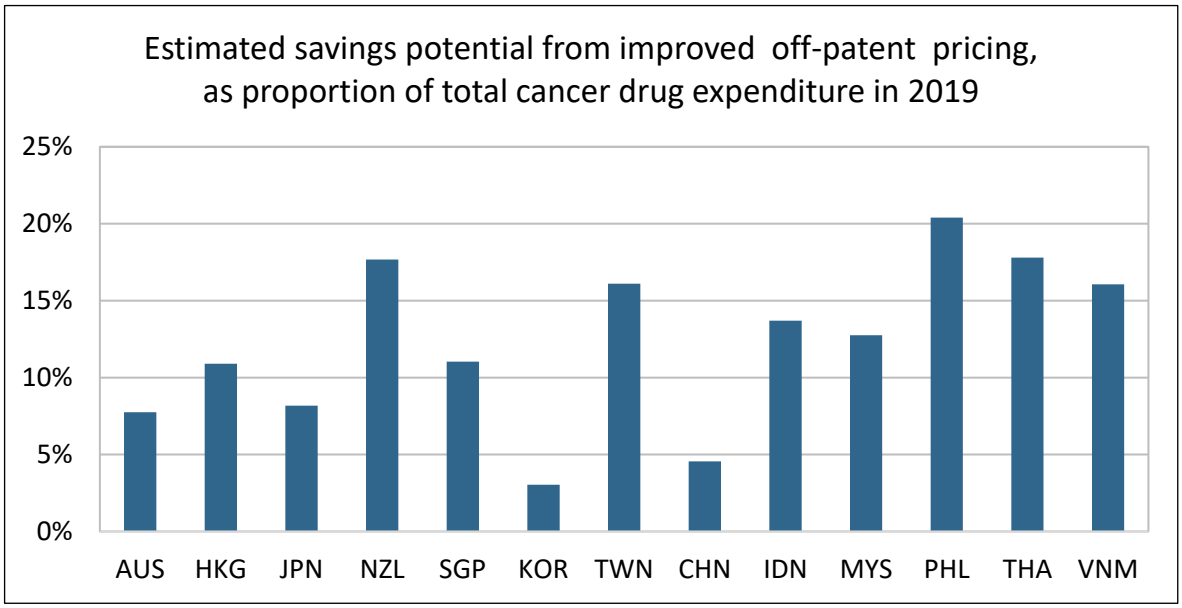


Figure 14: Estimated savings from more effective off-patent pricing outcomes of 11 cancer drugs as a proportion of total expenditure on all cancer drugs

Notes: No data available for India. Effectiveness is here defined as achieving the lowest possible price for the originator drug after patent expiry or loss of exclusivity. The analysis is based on list prices, which typically do not fully capture confidential rebates and arrangements granted by drug manufacturers to payers.

The analysis in section 2 concluded that the IQVIA data likely did not capture price reductions following patent expiry in Indonesia, Thailand, Vietnam, and The Philippines. Prices during the year following patent expiry in these markets would likely be overestimated, and thus savings may be overestimated as well. In these same middle-income markets, however, where originator drugs are often unaffordable, price reductions associated with effective off-patent pricing mechanisms would likely trigger increases in sales volumes, thus compounding the savings and improving access to drugs. Therefore, savings estimates in middle-income markets are likely underestimated. Under current market conditions, sales volumes in these markets already increase post-patent expiry; see Figure 15 where Australia, New Zealand, and South Korea are also included as reference markets where these drugs are reimbursed. Thus, sales volumes are already maximized at patent expiry. The observed increase in sales volumes implies that an expansion of patient access to these drugs in middle-income markets. The possibility that these increases were due to either confidential agreements or reimbursement pricing actions following self-payment across all these markets is unlikely. Thus, it can be assumed that there were actions in the self-pay sector that were not captured by the MIDAS database.

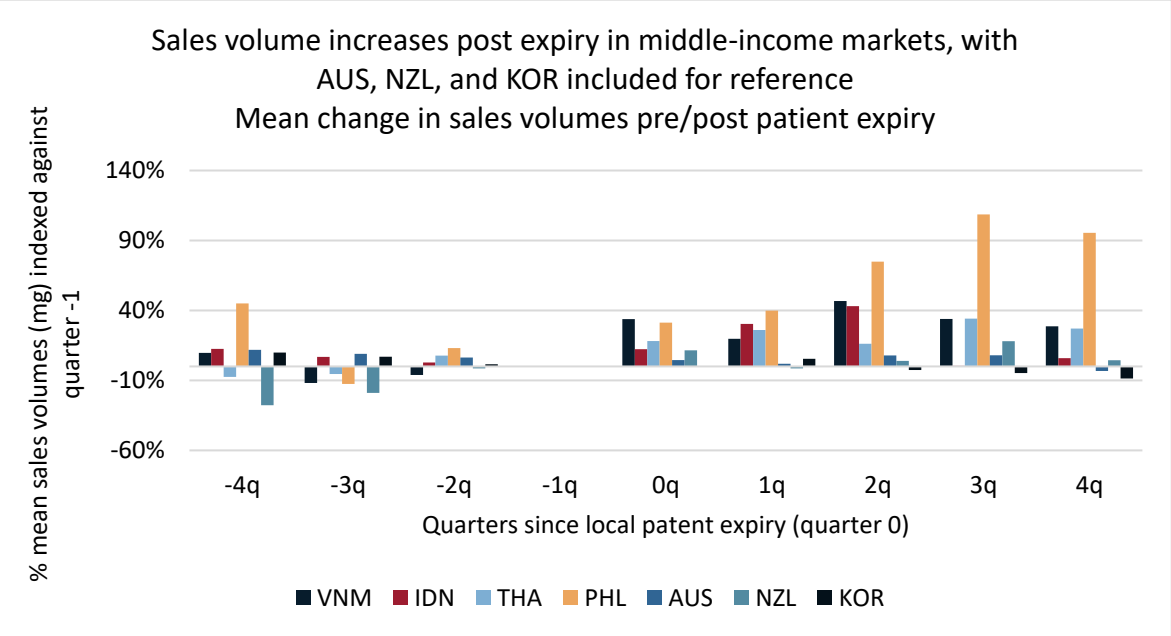


Figure 15: Sales volumes in select middle-income markets, with high-income markets as reference

Notes: Middle-income markets where IQVIA data did not detect off-patent originator price changes.
AUS, NZL, and KOR included for reference.

In New Zealand, price changes that likely occur were not present in the dataset. Many price discounts remain confidential in New Zealand, and if they were truly reflected in the dataset, the potential savings in New Zealand would be proportionally decreased.

While there is likely no one-size-fits-all approach, governments and policy makers across the Asia-Pacific should aim to maximize potential from pricing policies on off-patent drugs and adopt those that are effective in their individual market. This analysis involves only a sample of 11 drugs, and more savings can be expected if a broader scope of drugs were included. Finally, the savings estimated from this analysis are theoretical estimates, and do not represent empirical findings. The analysis highlights the potential to free up limited health resources to better address the unmet needs of cancer patients.

A recent study in South Korea found that patent loss could save 20% of expenditure on cancer drugs over five years, freeing up resources for innovative treatments and to treat more patients (4). Affordable access to off-patent treatments is one of the most valuable assets for patients in market when achieved (34), and should be a priority in these middle-income markets where there is potential for expansion. Ensuring effective pricing policies for off-patent drugs stimulates the availability of and competition between generics/biosimilars, which provide “equal” clinical value to originator drugs and can lead to substantive savings. Patent expiry should be viewed as an opportunity where effective policy can improve access to drugs and free up resources to re-invest in more effective and innovative treatments for patients (4, 6, 35).

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Appendix 1. Patent expiry dates by drug and market

	AUS (10)	HKG	JPN (7)	NZL (10)	SGP	KOR	TWN (9)	CHN	IND	IDN	MYS	PHL	THA	VNM
Bevacizumab	Q1 2020	n/a	Q4 2019	Q2 2018	n/a	n/a	Q4 2019	Q4 2019	Q1 2016	n/a	Q3 2019	n/a	Q1 2019	n/a
Capecitabine	Q2 2014	Q2 2014	Q1 2019	Q4 2013	Q3 2014	Q1 2012	Q4 2013	Q1 2020	X	Q1 2017	Q4 2017	Q4 2012	Q3 2014	Q1 2012
Erlotinib	n/a	Q3 2017	n/a	Q1 2016	n/a	Q1 2013	Q1 2020	Q3 2019	Q3 2010	Q2 2019	n/a	Q4 2013	Q3 2018	Q4 2013
Fulvestrant	n/a	Q3 2018	n/a	n/a	n/a	n/a	Q3 2019	n/a	X	n/a	Q1 2019	n/a	Q2 2020	Q3 2019
Gefitinib	Q4 2017	Q3 2019	Q1 2019	Q1 2013	Q3 2020	Q2 2015	Q2 2017	Q4 2017	X	Q2 2019	Q3 2020	Q1 2017	Q1 2020	Q4 2015
Imatinib	Q3 2016	Q4 2013	Q3 2010	Q1 2013	Q4 2016	Q1 2013	Q1 2013	Q2 2018	X	Q2 2019	Q3 2013	Q1 2016	Q3 2014	Q4 2015
Letrozole	Q2 2012	n/a	Q3 2010	Q3 2010	Q1 2011	n/a	n/a	Q4 2019	X	Q2 2016	Q3 2010	Q3 2011	n/a	Q1 2013
Pemetrexed	Q2 2015	Q3 2016	n/a	Q1 2013	Q2 2014	Q2 2012	Q1 2011	Q3 2017	X	Q2 2019	Q3 2017	Q2 2016	Q2 2019	Q4 2012
Rituximab	Q4 2019	Q4 2019	Q2 2017	Q4 2013	Q2 2019	Q3 2015	Q4 2013	Q1 2019	Q3 2012	Q4 2018	Q3 2018	Q1 2019	Q2 2018	Q4 2012
Sorafenib	n/a	Q2 2019	n/a	Q1 2020	n/a	n/a	Q2 2020	Q3 2020	Q2 2010	n/a	n/a	n/a	n/a	Q4 2019
Trastuzumab	Q4 2018	Q1 2020	Q3 2018	Q3 2014	Q4 2019	Q1 2014	Q4 2018	Q3 2020	Q3 2012	Q2 2018	Q3 2018	Q1 2017	Q2 2018	Q3 2019

Source: Patent expiry date obtained from government sources where available. If the latter was not available, date of first generic/biosimilar approved was obtained from regulatory agencies. If the latter was not available, date of first sales of generic/biosimilar in IQVIA MIDAS database was used.
Data and data period for analysis of price patterns: IQVIA MIDAS data Q1 2010 to Q3 2020
n/a = still on patent at the end of Q3 2020 or patent expiry/first generic version approved/sold before Q1 2010
X = no patent expiry date or date of first generics approved/sold identified

Appendix 2. Estimated savings per drug per market

Table 1: Estimated savings in million US$ per drug per market

	Reference	AUS	HKG	JPN	NZL	SGP	KOR	TWN	CHN	IDN	MYS	PHL	THA	VNM
Bevacizumab	CHN	14	on patent	270	1	on patent	on patent	18	reference	on patent	2	on patent	11	on patent
Capecitabine	KOR	3	1	33	1	1	reference	5	60	4	0	1	2	2
Erlotinib	CHN	on patent	4	on patent	0	on patent	3	10	reference	3	on patent	2	3	6
Fulvestrant	NWY	on patent	1	on patent	on patent	on patent	on patent	2	on patent	on patent	0	on patent	1	0
Gefitinib	MYS	2	6	18	1	2	11	16	52	12	0	2	15	4
Imatinib	IDN	31	8	341	14	4	32	42	93	reference	7	9	14	17
Letrozole	BEL	7	on patent	80	0	1	on patent	on patent	38	0	1	1	on patent	0
Pemetrexed	KOR	9	1	on patent	0	2	reference	17	24	no sales	1	2	2	no sales
Rituximab	KOR	26	6	143	4	6	0	10	73	6	0	3	12	3
Sorafenib	CHN	on patent	1	on patent	0	on patent	on patent	22	reference	on patent	on patent	on patent	on patent	2
Trastuzumab	KOR	49	13	81	12	11	reference	45	17	2	3	12	22	10
Total Savings		140	40	967	33	26	46	188	357	27	15	33	82	42

"no sales" indicates that no sales occurred in the respective market during the year following patent expiry.
"reference" indicates that this is the reference market specific to the corresponding drug.
"on patent" indicates that the drug is still on patent at the end of Q3 2020 or patent expiry/first generic version approved/sold occurred before Q1 2010.

Appendix 3. Handling of data unit variables

Within the extracted MIDAS dataset used in this analysis, there were some hurdles to overcome associated with the unit of analysis surrounding sales volumes. Sales volumes were provided both in terms of counting units (CU) and standard units (SU). Depending on the dosage form, CUs were defined as either the number of tablets in a package, the number of mL in a vial, or the number of mg in a vial. The CUs were then divided by a "standard unit factor" to obtain SUs.

The standard unit factor was equal to 1 for all solid dosage forms; one SU was equal to one CU. Across quarters within the same drug/market, the unit count changed in intervals equal to the pack size, and it was therefore suspected and later confirmed by IQVIA that one unit (SU or CU) was equal to the standard unit factor, or one tablet. The mg per tablet remained unchanged for each drug, so the counting units for solid dosage forms were acceptable for our analytical purposes.

For liquid forms where concentration and volume were defined, the CU was total volume in mL, the standard unit factor was the volume of the vial in mL, and the resulting SU was the number of vials of the specified volume. For vial dosage mediums where the volume and concentration were not specified, the CU was total mg, the standard unit factor was the number of mg in the vial, and the resulting SU was one vial.

This information was used to convert all units into milligrams for the purposes of our analysis. In some cases, the price per mg can vary substantially. For example, sub cutaneous vials are generally priced lower than infusion vials due to added administration and production costs associated with infusion treatments. To account for these differences in our analysis, thresholds were set up to detect cases where the price per mg deviates substantially, and in these cases, comparisons were made as if they were separate drugs.

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