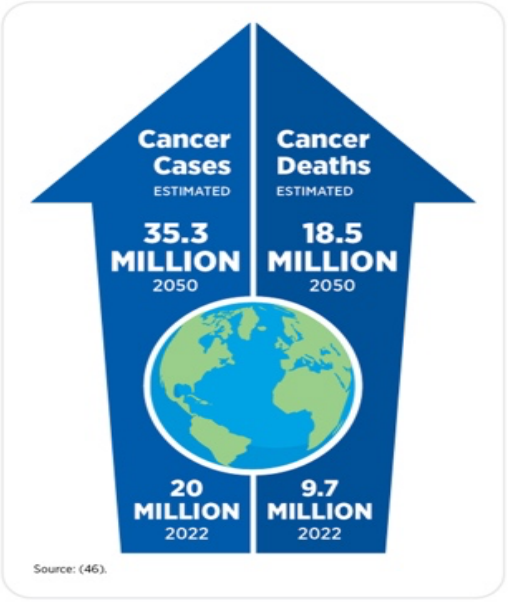
Summary of Findings

Initiative on Access to Oncology Medicines in Resource-Challenged Countries
- A Burgeoning Business Opportunity -

Executive Summary:

Cancer is the second leading cause of death globally. According to multiple sources (WHO, American Cancer Society, FP Analytics), in 2022, there were 20 million new cancer cases diagnosed and nearly 10 million cancer-related deaths worldwide. The total number of cancer diagnoses is expected to rise to 35 million by 2050, with estimates that 1 in 5 people will develop cancer in their lifetime. Out of nearly 10 million cancer-related deaths worldwide in 2022, 70% were in low- and middle-income countries. According to sources such as those listed above, the cancer survival rate in high-income countries is 80%. In Africa, the cancer survival rate is 12%. While RCCs account for the vast majority of disease burden, they account for only 5% of cancer spending. While 90% of people in high-income countries have access to comprehensive cancer care, fewer than 15% have access in RCCs, and 75% lack access to any diagnosis and treatment. Among numerous factors, growth in smoking and obesity in resource-challenged countries (RCCs) is contributing to a marked increase in cancer cases, and low survival rates are significantly due to the fact that people in these regions often receive cancer diagnoses at later stages of the disease and have limited access to treatment options compared to their counterparts in developed countries.



This initiative was launched to better understand whether and how oncology medicines are reaching those in RCCs, and what other factors are contributing to the poor oncology outcomes. It is led by experts from Harvard Medical School and Massachusetts General Hospital Cancer Center, partnered with former pharmaceutical executives (names and affiliations are listed below). The project team has decades of experience focused on reaching patients in need worldwide. This effort was highly targeted, comprising confidential discussions with innovator pharmaceutical companies to understand how they

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are approaching access to their oncology medicines in resource-challenged countries and drawing on the project team's past experiences and research into factors that could maximize the impact of breakthrough oncology medicines reaching patients in RCCs.

The Challenge: A Perfect Storm:

In the book "The Road Less Traveled" by M. Scott Peck, the first sentence begins with the assertion that "life is difficult". What follows is that once this simple truth is acknowledged, it can be transcended and permit us to focus on solutions. This equation can also very aptly apply to the complex challenges and multiple variables involved in making innovative oncology medicines accessible to cancer patients in resource-challenged countries. The data are clear. Patient oncological needs in RCCs are not being met for the vast majority of people in such countries who are afflicted with cancer, and the number of those afflicted is sizeable and growing. It is also clear that the reasons are multifactorial. The poor outcomes for patients in RCCs are the result of a "perfect storm" of factors, including poor health systems, insufficient screening and diagnosis, and lack of medicines. Poverty, political will, and business priorities all contribute, as well.

Our discussions with the innovator pharma companies indicated that they are pursuing various strategies to make their oncology treatments available in RCCs, but for the most part they are limited efforts, hampered by the "perfect storm" of difficulties referred to above – as well as crucial economic factors (countries' and patients' willingness and ability to afford/pay), regulatory hurdles, diagnostic limitations, and concerns about intellectual property protection. Several of these factors also contribute to the general hesitancy of most pharma companies to increase their commitment to expanding access to their medicines in RCCs. These factors are even more challenging to overcome for some of the most novel and sophisticated therapies that are being introduced, since the production and administration of many of the newest medicines demand even more expertise, training, and equipment.

The "access to medicines" strategies of the companies we interviewed covered a wide range of actions, including: donations, producing alternate brands, and using normal marketing channels for their branded medicines. We found little to no interest in or utilization of licensing (often referred to as "voluntary licensing"), mainly due to fears of leakage to higher-income commercial markets not intended for the licensed product (also referred to as "parallel trade") and the desire of the innovator companies to maintain

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control of platform technologies (and their resulting medicines) that could be adapted in the future to address multiple additional diseases or indications. We observed a general tendency among pharma companies to focus their attention and RCC access strategies primarily on medicines with expiring patents, rather than on their latest innovations. This was due to a combination of the factors cited above, in addition to concern about blowback from higher-income country payers if a lower-priced version is offered in RCCs (also referred to as "reference pricing") and the inability of health systems to administer new, more complicated treatments. None of the companies seemed satisfied that their efforts were having as substantial an impact on public health as they would have preferred.

It appears that a vicious cycle exists, wherein the challenges (ranging from the dearth of health capacity and financial resources in RCCs to the difficulty of doing business there) lead to limited expectations, which then lead to limited efforts and limited outcomes.

Many companies are not allocating substantial resources to these access initiatives. Some have scaled back their efforts due to the difficulties of operating in resource-challenged countries and the financial pressures they encounter. RCCs' inability to pay results in a weak revenue incentive for pharmaceutical companies. As a result, pharma companies tend to view RCCs as charity cases, perceiving minimal benefits and considerable risks to their financial performance. Many of the challenges and lessons relevant to access to oncology medicines in RCCs overlap with those spelled out in a separate report on Voluntary Licensing and Access to Medicines (VLAM) co-authored by some of the team members involved in this initiative. These can be found at this link: https://globalaccessaction.org/vlam/.

While it is easy to point the finger at pharmaceutical companies for not finding ways to deliver more medicines at more affordable prices in RCCs – through lower pricing on their medicines, or through strategies such as donations, alternate brands, or voluntary licensing – it is clear that any solution that results in significantly improved outcomes for cancer patients, will require a holistic and collaborative approach. New thinking is needed on the part of all stakeholders in the system. This is particularly true in oncology, where prevention and early diagnosis are the biggest factors in improved patient outcomes.

Findings of this oncology initiative comport with those of the VLAM project: the solution will only come from all stakeholders being called on to make contributions to the effort, including the global donor and advocacy community, donor governments, multi-lateral

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organizations, governments of RCCs, innovator pharmaceutical companies, and local manufacturers in RCCs.

Challenges and Opportunities

- ***Challenges****: health systems capacity; too little awareness, prevention, and diagnosis; insufficient funding; regulatory hurdles; inadequate IP protection; and pharma companies' perception of risks (financial and IP).*

  Current Pharma Actions*: small-scale experimentation; drug donations; NGO partnerships; access to medicine organizations; voluntary licensing; and alternate brands.*

- ***Opportunities****: new coordination mechanisms; new low-margin, high-volume business models; and assurances and incentives by RCC governments that facilitate and streamline innovators' ability to do business when they implement adaptive access models, such as voluntary licensing.*

A Model for Collaboration to Advance Patient Cancer Outcomes and Access to Medicines in RCCs:

Though not a perfect model – the global response to HIV offers important lessons about how success can be achieved through a multi-stakeholder response to a worldwide public health challenge. In the HIV response, the principal actors shifted into a collaborative problem-solving mode. Albeit, the billions of dollars committed by donor countries and philanthropic organizations provided an important fillip. Yet, it was also evident that RCCs, multi-lateral organizations, pharma companies, and NGOs all adapted to meet the moment – including mobilizing action, raising disease awareness, and improving health capacity. As part of the HIV response, Gilead Sciences entered into voluntary licensing agreements with generic manufacturers in RCCs to make available the latest, patent-protected HIV treatments at prices that were a fraction of the cost in high-income countries. The combined effect of all actors' efforts was to transform a disease afflicting over 30 million people from a death sentence to a chronic condition.

The global response to HIV was characterized by its humanitarian purpose, and the significant donor grant funding allocated to the task. The world appears to be reluctant to provide that level of donor funding for other public health challenges. Thus, for cancer, the equation would need to be different. That said, several key lessons from the HIV response are relevant:

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(1) Advocates, activists, donor governments, multilateral organizations, and RCCs all changed behaviors (adaptation) to facilitate and expedite the HIV response. For cancer, it thus should be possible for the same actors to find ways to make policy and regulatory changes to remove roadblocks to cancer prevention, diagnosis and treatment. Specifically, regarding the latter, which is the most relevant to this initiative, a concerted effort could be made to smooth the path for pharma companies seeking to bring their novel cancer treatments to RCCs (whether expediting regulatory processes, ensuring the availability of diagnostic tools, or protecting intellectual property).

(2) Pharma companies adapted their business models to meet the HIV challenge. The most successful models need to be sustainable, which means that they cannot be giveaways or money-losing propositions for the companies. The voluntary licensing model used extensively by Gilead generated revenues. The approach emphasized low-margin/high-volume strategies, which kept the company's access to medicines business unit net balance in the black. Similarly, for cancer, companies will need to innovate to find models that stay in the black, whether through licensing, alternate brands/branded generics, or tiered pricing strategies, while still meeting patient needs.

It is also important to look at ways to update the mechanisms put in place for HIV, to build on their success in a way that brings greater public health benefit. For instance, the infrastructure established over the last two-plus decades that transformed HIV/AIDS into a chronic disease could evolve to more effectively provide broader healthcare – avoiding a scenario where HIV treatments are provided to patients for years only to have them die of a cancer that went undiagnosed. Let's seek to expand and adapt the efforts of global donors and implementers to address this by utilizing existing resources and efforts to maximize the public health benefits.

For HIV, all actors came together to mobilize a transformation in the way drug access was improved. Like a symphony, a similar approach could be taken to bring all actors together to create a significantly improved outcome for cancer. Effective coordinating mechanisms should be established towards this end.

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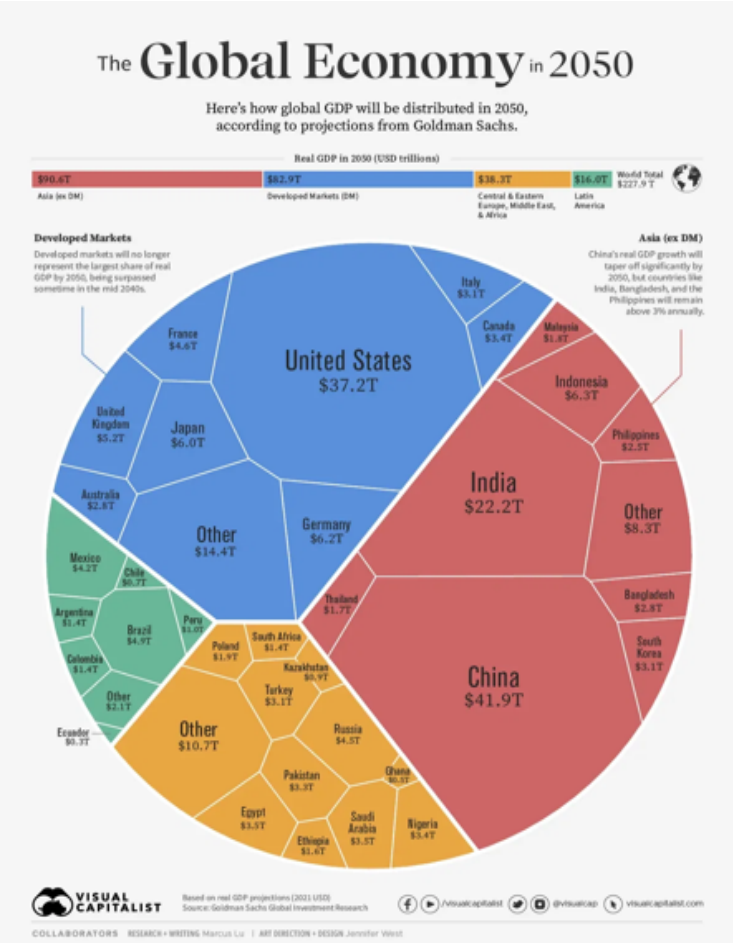
Economic Growth in RCCs Creates Business Opportunities:

As challenging as the environment is in RCCs today (see "perfect storm" above), this bloc of nations, home to over 4 billion people, is not monolithic; significant economic opportunity exists for businesses that can adapt and capitalize on these regions' burgeoning economies. RCCs are composed of many countries that have experienced staggering population and economic growth over the past 2-3 decades, with others anticipated to follow this trend through 2050. The combined GDP of the "Emerging 7" economies (E7) may double the G7's combined GDP by 2050. There are economic opportunities for pharma companies in seeking ways to tap into these markets, even if it means adopting new business models.

Strategies such as voluntary licensing and creating alternate brands have successfully generated revenues in RCCs for pharma innovators. Even with smaller margins, companies can and do make money.



There is also ample evidence that fears of parallel trade (or leakage) are exaggerated. We heard this from at least one of the pharma companies we interviewed, and we have seen that Gilead has managed extensive licensing for almost 20 years while earning revenues and without impacting its core businesses in high-income markets. Furthermore, tiered or variable pricing strategies that adapt to individual RCCs' disease burden and GNI per capita (a better indicator than GDP, since GNI measures actual income while GDP measures economic output) are highly effective mechanisms for finding an equilibrium that maximizes both access and revenues.

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For decades, technology and consumer products companies have innovated to meet the needs of consumers at the base of the economic pyramid (from Bata and Coca Cola to Heineken and Unilever). Additionally, the perspective of developed nations was that it was virtually impossible to establish formal banking and lending systems in RCCs, until companies like Grameen Bank and MPESA transformed both industries with banking and money transfer via mobile phones in Asia and Africa, respectively.

New business models should likewise be a part of the global health toolkit in order for innovator pharma companies to engage with and expand their footprints in the rapidly growing RCCs (economies and populations), all while also contributing to solving the challenge of access to medicines.

It's a Business – It's not a Pact with the Devil:

Lastly, because access to oncology medicines and improved outcomes for patients in RCCs cannot be substantially addressed without the collaboration among diverse stakeholders, we believe that the likelihood that pharma innovators will unilaterally make significant changes based on the information outlined above will remain low in the absence of any actions taken by other stakeholders. This has been borne out by the current state of affairs.

Recognizing the profit motive is step one. It isn't just innovator pharma companies from the US, Europe, and Japan that seek profits (typically leading to accusations that their being profit-seeking is the main barrier to access to novel therapies). Another key stakeholder group consists of the local companies in RCCs, many of which are generics manufacturers. In many cases, the introduction of breakthrough medicines by innovator companies based in high-income countries is blocked or delayed by governments of RCCs, often in response to pressure from (profit-oriented) local companies lobbying to protect their domination of the domestic market. This is simply another fact – a "difficulty" in the parlance of M. Scott Peck – and an endemic issue in global public health that must be acknowledged in order for effective solutions to be found. Local companies are stakeholders whose influence and interests must be accounted for.

Ultimately, whether we are addressing pharma companies that aim to import new medicines into RCCs or local companies operating in those same RCCs, all will seek to

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maximize their revenues. Both needs must be addressed in order to find a sustainable access to medicines solution. Consequently, it is imperative for the global stakeholder community to advocate for both adaptive business models and the policies that support their implementation. These are two sides of the same access to medicines coin. It will be important to solve for the business case that supports the economic engine that propels the pharma/biotech world to be full partners, but that also recognizes that there are downstream actors who have a financial stake (including local companies, in addition to RCC governments and healthcare providers).

Conclusion:

Overcoming impediments to access to medicines in RCCs is a significant challenge. Solving this has been a perennial difficulty. Yet, the problem is set to grow dramatically in the coming years as the incidence of non-communicable diseases (NCDs) such as cancer escalates.

Some past initiatives offer valuable lessons to draw from – as mentioned above, for example, we could benefit from adopting elements of the HIV response from the last two decades. But prior models are insufficient. What we learned in this initiative comports with our diverse professional experiences, including in: the practice of medicine on the ground; global public health, aid, and trade policy; academic research; and the pharmaceutical industry. Our conclusion is that a change in mindsets is necessary to move all stakeholders (not just the pharma industry) to a cooperative and collaborative team approach, where all are asked to make changes in order to achieve an optimal outcome for patients in RCCs. Major adaptations are needed in global public health mechanisms, the role of multilateral agencies, donors, RCC governments, NGOs, and how pharma companies and other businesses approach doing business in RCCs.

Dramatically enhancing access to medicines and patient outcomes in RCCs (for oncology and beyond) requires a matrix mindset, where every stakeholder views itself as part of a diverse team, and each must not only view itself as a critical actor but also see the other stakeholders as equal partners. To this end, it is vital to not only be motivated by idealism (e.g., humanitarianism, access to medicines, and collaboration) but also by pragmatism, where the self-interest of all actors is acknowledged and accepted as elements of any

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solutions. Pharmaceutical innovator companies (and the governments supporting them) are the perennial villains, accused of naked self-interest operating to the detriment of access to medicines for those who are resource-challenged. But, as we have cited above, other self-interested parties play a vital role in access to medicines in RCCs, including the generic pharma industry and the governments of RCCs where those companies are domiciled.

The challenge of access to and affordability of oncology medicines in RCCs calls for the acknowledgment from all stakeholders that a key part of the equation is that pharma companies (innovators and manufacturers of generics) are businesses—businesses driven by commercial interests, needing financial incentives (even moderate ones) to operate sustainably. This should not be considered a value-laden observation. It is simply a fact that cannot be wished away. Demonization, naming and shaming, have already proven to be a failing tactic (since a vast improvement in access to medicines remains only a dream). The status quo is not attaining the desired results.

By embracing innovative collaborative approaches, it should be possible to reach compromises that offer sufficient incentives to core players (e.g., innovator pharma companies, manufacturers of generics, and RCC governments) while simultaneously ensuring the broadest possible access to affordable medicines—a true win-win-win-win for cancer patients, pharma companies, governments, and the global public health community.

A universal social contract that is subscribed to by all stakeholders could help upend the status quo and address the rapidly growing challenge of access to cancer treatment (and access to medicines, more broadly) in RCCs. Such an approach to global public health has been needed all along. And, it is even more important today, as medicines - especially cancer therapeutics - become harder to reverse engineer and even more complicated to administer and manage. To provide more specific recommendations along these lines, the Appendix below offers a menu of suggested actions that could be taken by a wide spectrum of stakeholders who are all part of the access to medicines equation.

In the complex (M. Scott Peck's "difficult") environment that affects access to oncology medicines in RCCs, all stakeholders have a vital role to play: healthcare capacity building, regulatory reform, supply chain & logistical allocations, policies and policy advocacy, and existing pharma business models all need to adapt to stem the rising tide of cancer in RCCs.

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Appendix

The following outlines potential actions the various stakeholders can adopt to influence the ecosystem impacting access to medicines in RCCs:

Innovator Pharma Companies:

- Develop strategies for doing business in RCCs that incorporate lower-margin business models, such as voluntary licensing, contract manufacturing, and alternate brands.
- Create a tiered-pricing model based on countries' GNI per capita and disease burden.
- Work with RCC governments to implement hybrid models that allow for higher pricing for the country's top economic echelons while implementing dramatically lower pricing or volume-based pricing for disadvantaged populations.

Governments of Higher-Income Countries:

- Put in place policies and programs to incentivize innovator pharma companies to adopt lower-margin business models for RCCs, including via programs such as "patents for humanity".
- Use international aid financing/grants to incentivize change among other actors in the system, to encourage the actions listed elsewhere in this Appendix.
- Focus policy advocacy and diplomacy on creating a more shared burden on all stakeholders to take action to help overcome the challenge of access to medicines.

Generic Pharma Manufacturers:

- Expand partnerships and incorporate new business models (such as via voluntary licensing or contract manufacturing) with innovator pharma companies that allow for mutual financial benefit while expanding access in RCCs.
- Encourage local governments in RCCs to facilitate the use of innovative pharma companies' new access-friendly business models and partnerships with local companies.

Governments of Resource-Challenged Countries:

- Use laws and policies to incentivize innovator pharma access to medicines business models: (a) streamline, expedite, and bring predictability to regulatory processes; (b) in the countries where applicable, streamline patent review.
- Employ government actions on policies and regulations (incentives) to encourage partnerships between innovator pharma companies and local manufacturers.

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Multilateral Agencies:

- Advocacy should be directed at encouraging all the actions recommended in this Appendix (by RCC governments, generic manufacturers, innovator pharma, high-income countries, et al) to reshape the environment and create the opportunity for innovator pharma to implement new business models and strategies in RCCs.
- Programs and funding should be used to ease the implementation of the recommendations made here, including supporting regulatory reform efforts, capacity building, and incentivizing new business models.
- Global public health should evolve from a siloed focus on a few diseases (e.g., HIV, TB, Malaria) to a more holistic approach to patient care that would address all major health issues, such as NCDs (cancer, diabetes, and cardiovascular disease, which are seeing skyrocketing growth in RCCs).
- Take the lead in bringing all stakeholders together to create new coordinating mechanisms and articulate a new Access to Medicines Social Contract subscribed to (and implemented) by all stakeholders, including RCC governments, generic pharma companies, innovator pharma companies, donor governments, civil society, and the multilateral agencies.
- The Access to Medicines Social Contract should require all actors to commit to taking actions, such as those outlined in this Appendix, to dramatically upend the status quo. A timeline should be established for stakeholders to implement their obligations.

NGOs/Civil Society:

- Advocacy and funding should be directed at reshaping mindsets among all stakeholders, in parallel with the efforts of multilateral agencies. Advocacy should also seek the earliest implementation of the recommendations herein.

Donors:

- Advocacy should prioritize implementing the Access to Medicines Social Contract and the actions recommended herein.
- Funding should be conditioned on implementation/action.
- Donor aid should move away from a narrow focus on a few infectious diseases (e.g., HIV, TB, Malaria) to a more holistic approach to health that would address a broader swath of diseases, including NCDs.

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