World Bank definitions based on per capita gross domestic product (GDP).

A "model" package is provided as a guide for countries to consider when tailoring a package to national needs. An important point is that, even for the poorest countries, some treatment of early-stage cancers that involves surgery, drug therapy (chemotherapy and/or endocrine therapy) and radiotherapy, should be included along with preventive interventions, even if initially at only a single centre of excellence in a major city. Palliative care with a foundation of pain control using opioid drugs (the most basic being oral morphine) should be made widely available, at least to those with end-stage cancer pain, down to village level, as a near-term priority.

In developing the essential package, cost-effectiveness estimates were compiled for each cancer and each intervention, from studies in or including low- and middle-income countries (LMICs), published in 2003–2013 (3), when possible. Such literature is scarce, however, and the literature was supplemented with studies from high-income countries.

All analyses were stratified by World Bank country group classifications as defined by 2013 per capita gross national income: 34 low-income countries (less than US$ 1,045), 50
lower-middle-income countries (US$ 1,046 to US$ 4,125), and 55 upper-middle-income countries (US$ 4,126 to US$ 12,745) (4).

Interventions were defined as “very cost-effective,” “cost-effective,” and “cost-ineffective” using the scale developed by the Commission on Macroeconomics and Health (2001) costing, respectively, <1, 1–3, and >3 times per capita income per QALY (or other measure) (5). The essential package includes interventions rated as very cost-effective and cost-effective and considered potentially affordable and feasible in resource-constrained environments.

The essential package is offered as a starting point for countries to consider what would be most useful within their borders. A country-specific package should respond not only to disease burden and resources, but also to the societal norms of the population as regards cancer. Whether or not a programme can be implemented is modulated by social, ethnic and cultural factors and beliefs, as well as the population’s education level, gender attitudes, and other factors. These considerations are left to individual country health-care policymakers.

**Key messages**

Cancer is already a major cause of death in low- and middle-income countries (LMICs), particularly in middle-income countries, and will increase as a percentage of deaths in all LMICs, driven by population ageing and faster declines in other causes of death.

In most populations, helping current tobacco users to quit and young people not to start smoking are the most urgent priorities in cancer prevention (and also to control other noncommunicable diseases), along with vaccination against hepatitis B (HBV) and the human papillomavirus (HPV). Higher tobacco taxes and accompanying interventions will reduce cancer incidence and generate substantial extra revenues for governments.

Other than tobacco- and virus-related cancers, however, most of the increase in cancer incidence is not currently preventable, but many cases of cancer can be effectively treated. Early breast cancer and cervical cancer are common, and often curable; precancerous cervical lesions are even more curable. Childhood cancers are relatively rare, but many are highly curable.

In most LMICs, it will take years or decades to develop a workforce capable of treating the cancer patients who can be helped. Even with state-of-the-art treatment (as in many high-income countries today), a large proportion of treated patients will die painful deaths from cancer. A final recommendation of Cancer is widespread availability of opioid drugs, at least for end-of-life cancer pain. Currently, opioid access is absent in nearly all LMICs.

The DCP3 Cancer essential package of cost-effective and feasible interventions (Table 1) would, if fully implemented worldwide in LMICs, cost an additional US$ 20 billion per year, or 3% of total public spending on health in LMICs; 2.6% in upper-middle-income countries (UMICs); and 5% in lower-middle-income countries; but 13% in low-income countries (LICs). In per capita terms, this would cost US$ 5.70, US$ 1.70, and US$ 1.70 annually in UMICs, lower-middle-income, and LICs, respectively. Such increases are potentially feasible without external support in all but the LICs.

Cancer services that are considered appropriate for a national cancer strategy should be covered through universal health coverage as soon as countries are able to do so.

Global initiatives for cancer control in LMICs are needed to lower the costs of key inputs for the essential package, including large-scale commodity purchases; to expand technical assistance; and to promote cancer research.

**Box 1: The Disease Control Priorities series**

In 1993, the World Bank published Disease Control Priorities in Developing Countries (DCP1), the first systematic assessment of the cost-effectiveness (value for money) of interventions that would address the major sources of disease burden in low- and middle-income countries (19). The World Bank’s 1993 World Development Report drew heavily on DCP1 to conclude that specific interventions against noncommunicable diseases were cost-effective, even in environments in which substantial burdens of infection and undernutrition persisted.

DCP2, published in 2006, updated and extended DCP1 in several respects, including explicit consideration of the implications for health systems of expanded intervention coverage (20).

DCP3, which consists of nine topic-related volumes, extends and consolidates the concepts of platforms and packages, introduced in DCP2. It gives explicit consideration to the financial risk protection objective of health systems, including the distribution across income groups of the financial and health outcomes resulting from specific policies. The broad aim of DCP3 is to offer, for consideration and adaptation, essential intervention packages – such as the essential cancer package in this volume – and their related delivery platforms.

**The DCP3 Model Essential Cancer Package**

The World Health Organization (WHO) produced a list of noncommunicable disease (NCD) best buys for LMICs in 2011, which were limited to services considered feasible at...
those most relevant to cancer, which are included in the DCP3 Cancer package, are three preventive measures:

- a set of tobacco control interventions;
- hepatitis B vaccination to prevent liver cancer; and
- some form of screening and treatment for precancerous cervical lesions (6).

The DCP3 Cancer essential package adds:

- HPV vaccination to prevent cervical cancer;
- treatment of early-stage cervical cancer; and
- diagnosis and treatment for early breast cancer;
- diagnosis and treatment for selected, highly curable childhood cancers; and
- palliative care, including, at a minimum, opioid drugs for severe pain control.

Treating early-stage breast and cervical cancer includes quality surgery, which could also be available for many other early-stage resectable cancers.

Each component of the essential package implies a range of interventions, the specifics of which may vary depending

Table 1: Essential Cancer Intervention Package^a

<table>
<thead>
<tr>
<th>Cancer type/Number of deaths, ages 0–69 years, 2012 (thousands)</th>
<th>Platform for intervention delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nationwide policies, regulation, or community information</td>
</tr>
<tr>
<td>All cancers 3,230</td>
<td>Education on tobacco hazards, value of HPV and HBV vaccination, and importance of seeking early treatment for common cancers</td>
</tr>
<tr>
<td>Selected tobacco related cancers (oral, lung and esophagus) 900</td>
<td>Taxation; warning labels or plain packaging; bans on public smoking, advertising, and promotion; and monitoring</td>
</tr>
<tr>
<td>Breast cancer 280</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer 180</td>
<td>School-based HPV vaccination</td>
</tr>
<tr>
<td>Colorectal cancer 210</td>
<td></td>
</tr>
<tr>
<td>Liver cancer 380</td>
<td></td>
</tr>
<tr>
<td>Childhood cancers 80^f</td>
<td></td>
</tr>
</tbody>
</table>

Source: Cancer, Disease Control Priorities, 3rd edition, Volume 3

Notes: Cancer totals are rounded to nearest 10,000. Education and basic palliative care are relevant for cancers at all ages. HBV = hepatitis B virus; HPV = human papillomavirus.

a. Red type denotes emergency care.
b. First-level hospitals are referred to as district hospitals in some countries.
c. Some interventions may take place at first-level hospitals, by a specialized surgeon visiting once per month, for example.
d. Palliative care should be available at all levels specified in the table and in the home.
e. Early-stage cancer generally refers to stages I and II.
f. Palliative care should be available at all levels specified in the table and in the home.
g. Screening is opportunistic when a test is requested by a patient or offered by a practitioner to a patient attending for another reason. Organized screening is a well-defined process including formal invitations to participate, recalls, reminders, tracking results, ensuring follow-up, monitoring, and reporting programme performance results.
h. Early-stage cancer generally refers to stages I and II.

Platform for intervention delivery: Education on tobacco hazards, value of HPV and HBV vaccination, and importance of seeking early treatment for common cancers.

Palliative care, including, at a minimum, opioids for pain relief.

First-level hospital:

- Treat early-stage cancer with curative intent^e

Specialized cancer centre/unit:

- Treat early-stage cancer

- Treat selected early-stage cancer with curative intent in paediatric cancer units/hospitals

- Including some solid tumours.
The cost of cancer interventions is seldom discussed on the resources and infrastructure of each country. Resource-level appropriateness is a useful concept for deciding at a country level what will and will not be supported. The idea has been developed by the Breast Global Health Initiative, which has developed and refined it specifically for breast cancer over the last decade (7). It is grounded in the fact that several generations of effective breast cancer treatments exist, which differ not only in cost, but in the infrastructure needed to support them and the skill level of practitioners to apply them (see Box 2). The resource-level appropriate concept has gained adherents and groups have begun to apply it to a number of other common cancers with a range of effective treatments.

**Costs of interventions**

The cost of cancer interventions is seldom discussed explicitly, and actual costs is almost nonexistent in the literature from LMICs. DCP3 Cancer reports a best estimate of per capita and global costs for the elements of the model essential package, for low-income, lower-middle-income, and upper-middle-income countries. We stacked the direct costs of each intervention, then added a multiplier equal to 50% of the total to account for system costs (e.g., pathology, administration), as has been done in studies costing other health interventions, such as nutrition (8) and health systems (9).

In low-income and lower-middle-income countries, the package cost comes to less than US$ 2 per capita, and for upper-middle-income countries, US$ 5–6 per capita. Globally, the annual cost for LMICs is about US$ 20 billion in 2013 dollars. These must be taken as very rough estimates only, and countries must examine costs in their own systems before committing to provide these or other services. To the extent that such data are collected, both the data and the methods used would make valuable contributions to the global literature.

A useful metric is the cost of the package as a proportion of current total public spending on health. This is 2.6% in upper-middle-income countries, 5% in lower-middle-income countries, and 13% in LICs. By comparison, high-income countries devote 3–7% of their total health spending to cancer control (10). Most LMICs allocate far less; cancer currently accounts for about 1% of health spending (public and private) in Brazil and India, and 2% in China and Mexico (11–13).

**Cost-effectiveness of interventions**

The very scarce evidence for both effectiveness and costs
signals a weak ability to estimate the cost-effectiveness (CE) of interventions. Using all available cost-effectiveness studies from LMICs and some from high-income countries, DCP3 Cancer offers a starting point for considering the cost-effectiveness of tobacco taxation; breast cancer treatment; liver cancer prevention; and cervical cancer prevention (with the HPV vaccine), screening and treatment. The remaining elements are not represented in this literature. The results are summarized in Table 2.

### Affordability and financing
Financing for cancer control will have to come mainly from national health-care budgets, particularly in middle-income countries, where incomes are expected to continue rising. These are also countries that are beginning or expanding public financing for health (14,15). South Africa, for example, has assessed which interventions it might include in an expanded national health insurance package (16) and similar work is underway in India (9,17). In LICs, shifting enough health-care spending to fully fund expanded cancer control will take longer, but can proceed at a reasonable pace with some added support from global sources.

### Global community
Finally, global initiatives might well help to lower the cost of cancer drugs and other commodities, and develop and disseminate standardized resource-appropriate treatment protocols, such as those developed by the Breast Health Global Initiative. Gavi, the Vaccine Alliance is a good example of how this has worked to increase vaccine coverage and reduce the cost of vaccines. Programmes to lower the cost of commodities for HIV/AIDS is another (18).

In addition to policy inputs by governments and international organizations, many cancer centres – mainly in high-income countries, but including some in LMICs – run global programmes that maintain ongoing relationships with hospitals and centres in one or more LMICs. For example, the main global activity of the Fred Hutchinson Cancer Center in Seattle, Washington, is a close 20-year long relationship with the Uganda Cancer Institute (UCI) in Kampala. As a result of this collaboration, the UCI-Fred Hutch Cancer Center opened in May 2015. The center is a new US$ 10 million facility to serve Uganda and neighbouring countries in East Africa, where almost no cancer facilities exist. This and similar relationships can involve staff exchanges, training, telemedicine and other services, in addition to subsidizing buildings and equipment. These substantial contributions should be aligned with national needs.

### Conclusion
The burden that cancer places on LMICs is increasing and will continue to do so throughout this century. Developing the infrastructure and workforce to meet the cancer challenge has been neglected by much of the global community – including the LMICs themselves, international organizations and the global health donor community. DCP3 Cancer provides a guide for LMICs that uses the best available evidence to develop cancer services beginning immediately and expanding over the next several decades.

Hellen Gelband is Associate Director for Policy at the Center for Disease Dynamics, Economics & Policy. Her work spans infectious disease, particularly malaria and antibiotic resistance and noncommunicable disease policy, mainly in low- and middle-income countries. Before joining CDDEP, then part of Resources for the Future, she conducted policy studies at the (former) Congressional Office of Technology Assessment, the Institute of Medicine of the US National Academies, and at a number of international organizations.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost/DALY averted (2012 US$)</th>
<th>Cost-effectiveness in LMICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco excise taxes</td>
<td>1–150</td>
<td>Very CE in all LMICs</td>
</tr>
<tr>
<td>HBV vaccination to prevent liver cancer</td>
<td>&lt;100</td>
<td>Very CE in all LMICs</td>
</tr>
<tr>
<td>Opportunistic cervical cancer screen and treat precancerous lesions</td>
<td>NA</td>
<td>Very CE in all LMICs</td>
</tr>
<tr>
<td>HPV vaccination to prevent cervical cancer</td>
<td>~150</td>
<td>Likely very CE in all LMICs (at US$ 15/dose)</td>
</tr>
<tr>
<td>Early breast cancer treatment</td>
<td>&lt;150</td>
<td>CE where high-quality surgery is available, mainly MICs</td>
</tr>
</tbody>
</table>

Source: Cancer, Disease Control Priorities, 3rd edition, Volume 3
Professor Susan Horton is Professor at the University of Waterloo and holds the Centre for International Governance Innovation Chair in Global Health Economics in the Balsillie School of International Affairs there. She has consulted for the World Bank, the Asian Development Bank, several United Nations agencies, and the International Development Research Centre, among others in work carried out in over 20 low- and middle-income countries. She led the work on nutrition for the Agency for Research on Cancer in 1993, where he is Special Copenhagen Consensus in 2008, when micro-nutrients were ranked as the top development priority.

Dr Rengaswamy Sankaranarayanan, after working in clinical oncology and cancer control in India, joined the International Agency for Research on Cancer in 1993, where he is Special Adviser on Cancer Control and Head of the Screening Group. His focus is research, training, programme development and technical assistance in early detection and cancer control, particularly in low- and medium-resourced countries. Dr Sankaranarayanan has taught in over 50 international courses on cervical cancer screening, colposcopy, diagnosis and treatment, cancer registry epidemiology and cancer control; and provided technical support to more than 30 national cancer programmes.

Professor Prabhat Jha OC, MD, DPhil, FCAHS is an Endowed Professor in Global Health and Epidemiology, University of Toronto; Canada Research Chair, Dalla Lana School of Public Health; and founding Director, Centre for Global Health Research. He leads the Million Death Study in India, quantifying causes of mortality in over 2 million homes. His studies on tobacco control have enabled a global treaty signed by over 180 countries. He founded the Statistical Alliance for Vital Events, which focuses on reliable measurement of premature mortality worldwide. Jha is Officer of the Order of Canada (2012) and earned degrees from the University of Manitoba and Oxford University.

References

SUCCESS IN FIGHTING THE TOUGHEST CANCERS DEMANDS INNOVATION

Over the last half-century, cancer survival rates have increased. But for the toughest cancers today, successful treatment remains elusive. The toughest cancers have seen minimal therapeutic advances, limited improvement in prognosis, and pose the most difficult challenges for patients and clinicians. Researchers at Amgen are invested in gaining a better understanding of the underlying characteristics of tumor cells that historically have been difficult to treat. These efforts have inspired new thinking in our research labs to address the lack of successful treatment options for some of these cancers.

THERAPEUTIC CHALLENGES AND NEW OPPORTUNITIES

The toughest cancers are commonly characterized as being refractory and resistant, rapidly progressing, diagnosed in advanced stages, invasive and metastatic, limited in therapeutic options, and heterogeneous with multiple subtypes. These cancers present many barriers to treatment and are the focus of the most robust and exciting research today.

<table>
<thead>
<tr>
<th>CANCER TYPE</th>
<th>CHALLENGES/BARRIERS</th>
<th>THERAPEUTIC OPPORTUNITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory and resistant</td>
<td>• Intrinsically unresponsive to therapy</td>
<td>• Identifying mechanisms or mutations of resistance</td>
</tr>
<tr>
<td></td>
<td>• Acquired resistance</td>
<td>• Mutations include: KRAS, BRAF, MDR1</td>
</tr>
<tr>
<td>Rapidly progressing</td>
<td>• Rapid growth</td>
<td>• Identifying targets for molecular therapy</td>
</tr>
<tr>
<td></td>
<td>• Adaptive therapy</td>
<td>• Research into microRNA and cancer stem cells</td>
</tr>
<tr>
<td>Commonly diagnosed in advanced stages</td>
<td>• Regional/distant metastasis</td>
<td>• Increased screening</td>
</tr>
<tr>
<td></td>
<td>• Can seem to suddenly appear</td>
<td>• Detection in earlier stages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• More effective therapies at advanced stages of disease</td>
</tr>
<tr>
<td>Invasive and metastatic</td>
<td>• Spread from primary tumor to regional and distant organs</td>
<td>• Improve understanding of metastatic process at cellular and molecular level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Interrupting interactions of metastatic cells and host homeostatic mechanisms</td>
</tr>
<tr>
<td>Limited lines of therapy</td>
<td>• Cancers have escaped effectiveness of surgery or radiation therapy</td>
<td>• Discovering new signaling pathways using microarray testing for intervention</td>
</tr>
<tr>
<td>Heterogeneity with multiple subtypes</td>
<td>• Tumors with subpopulation of cancer cells that are drug resistant and highly metastatic</td>
<td>• Development of innovative strategies to control these subtypes</td>
</tr>
<tr>
<td></td>
<td>• Cancer cells differ from primary tumor cells in terms of treatment and prognosis</td>
<td>• Stimulating human immune system to destroy cancer cells</td>
</tr>
</tbody>
</table>

Attempts to treat these advanced and difficult cancers can often exceed the capabilities of traditional cornerstones of cancer therapy. Conventional therapeutic options such as surgery, hormonal and radiation therapy, and chemotherapy have the most impact during early stages of the disease or in tumors highly unresponsive to drug therapy. Once cancer cells adapt and mutate in late stages of the disease, traditional treatment options lack effectiveness and patients experience relapse and require re-treatment.
LOOKING FORWARD TO THE FUTURE

As the toughest cancers adapt and evolve, our approach in turn must be innovative and agile in the fight against cancer. Amgen continues to take on some of the toughest cancers, and this effort requires a greater understanding of the pathophysiology of cancer cells and the identification of new targets and signaling pathways so that novel oncologic therapies may be developed.

Our researchers are investigating a number of targeted agents to take on the toughest cancers.

The last two decades have seen remarkable progress, with scientific breakthroughs in genetics, molecular biology, and biotechnology. These advances have led to the emergence of biologic therapies and immunotherapies, which have now become important components of cancer therapy. More recently, a greater appreciation of the human immune system has inspired the development of therapies that use the body’s immune response. In fact, immuno-oncology may herald the beginning of an era that holds great promise for the long-term control of many cancer types.

References: