Appendix

The IMAGINE (**I**AEA **M**edical **imAGI**ng and **N**uclear m**E**dicine global resources database[1]

Sources of data for the IMAGINE database:

The data collection for IMAGINE first started in 2015, and the database was publicly launched by the IAEA in 2019. Sources of information are listed in Figure 1. Information on imaging equipment and workforce numbers was obtained from country delegates at regional IAEA meetings, from official reports from IAEA fact-finding missions like imPACT reviews, and from reports from Ministries of Health and Regulatory Authorities of individual countries. Data was also obtained through extensive reviews of reports from WHO, UNSCEAR, OECD, and EUROSTAT. In addition, individual country leaders of Radiology and Nuclear Medicine as well as professional societies were approached to provide information on equipment and workforce in their countries.

Data Sharing:

The IAEA is a U.N. agency, and its database IMAGINE is intended as a tool towards improving health for all. IMAGINE is therefore an open access source. IMAGINE can be accessed using the internet search terms "IAEA IMAGINE" or via the IAEA Human Health Campus at https://humanhealth.iaea.org/HHW/DBStatistics/IMAGINE.html.

Access to deidentified data in the IMAGINE database is available to researchers, and any requests for data related to IMAGINE can be submitted to imagine@iaea.org.

Model Overview

We briefly describe here a previously developed microsimulation (individual-level) model of global cancer survival - see references 2 and 3 by Ward ZJ, et al. for more details.[2,3] The model simulates survival for 11 cancers in 200 countries/territories. The cancer sites were selected based on which comparable topography codes from the International Classification of Diseases for Oncology (3rd edition) were available in both GLOBOCAN 2018 and CONCORD-3: oesophagus (C15), stomach (C16), colon (C18), rectum (C19–20), anus (C21), liver (C22), pancreas (C25), lung (C33–34), breast (C50), cervix uteri (C53), and prostate (C61). The model simulates the number of incident (diagnosed) cancer cases in each country/territory and models the individual-level cancer treatment cascade and survival outcome for each patient with cancer.

Model Inputs

Population Projections

We obtained country-specific population projections from the 2019 UN World Population Prospects.[4] To project forward to 2030 we used the probabilistic population projections (PPP) to estimate the number of individuals in the population from 2020 onwards. In each iteration we sampled a population trajectory from 2020-2030.

Cancer Incidence

Estimated cancer incidence was obtained from GLOBOCAN 2018, and was available for 166-78 countries, depending on cancer site. Estimates were not available for countries with small populations, so we imputed incidence rates from similar countries (ie, similar region and income group). Due to the paucity of data on cancer stage distribution at diagnosis, we performed a literature review to obtain estimates of country-specific and cancer-specific stage distribution, which yielded 485 final estimates. We used a Bayesian hierarchical modelling approach to regularise the stage distribution estimates, and to make estimates for countries with no data, and used raking to estimate the joint probabilities of age and stage at diagnosis in the model.

For simplicity, we assumed that cancer incidence rates would remain constant during the period 2020-2030. In each iteration we sampled an incident number of cases in 2020 and scaled this number by the (sampled) projected population size. The number of diagnosed cases was sampled from the GLOBOCAN 2018 uncertainty intervals for each cancer within a country independently. For each simulated patient with cancer we then sampled their cancer stage and age at diagnosis from the estimated cancer-specific joint distribution.

Maximum Achievable Survival

To account for variation in the curability of different cancers, we estimated maximum achievable survival probabilities using 2010–16 data on 5-year net survival from the Surveillance, Epidemiology, and End Results (SEER) Program by cancer type and stage.[5] We inflated the SEER estimates to account for the possibility of non-optimal service delivery in the

USA. This model parameter is used to estimate relative differences in survival by cancer site and stage, and represents the highest possible survival given current knowledge and medical technology.

Cancer Survival Curves

To estimate longer-term cancer survival for our economic evaluation analyses we estimated 10-year annual relative survival curves by stage for SEER cases diagnosed in 2000-2016. For each country/cancer, we re-scaled the estimated survival curve from SEER so that 5-year survival matched the calibrated 5-year net survival in the model (see Model Calibration below). Using the re-scaled survival curves we then drew a year of death for each cancer case in the model. We assumed that if the patient survived 10 years they would not die from the cancer. Due to lack of observed declining survival in SEER, we used the shape of stage II breast cancer for stage I breast cancer, and stage I prostate cancer for stages II and III prostate cancer.

Lifetables

We obtained country-specific estimated lifetables (annual mortality rates) for 1950-2100 from the UN World Population Prospects 2019. Lifetables were available by 5-year age group and 5-year intervals. We used linear interpolation to interpolate mortality rates between ages and years. Annual mortality rates were converted to annual probabilities for use in the model. Lifetables were not available for 14 countries, so we imputed lifetables from similar countries. Lifetables by age and calendar year were used to simulate competing mortality risks.

Modality Efficacy

To set prior probability distributions for the impact of treatment and imaging modalities on stage-specific cancer survival, we used a two-stage survey to elicit expert opinion. A sample of actively practising physicians (33 imaging experts and 22 therapy experts) was selected, based on expertise in their field, both in high-income and low-income settings. Respondents were asked to indicate the impact of each treatment/imaging modality on 5-year net survival for each cancer/stage using a four-point scale, ranging from necessary for 5-year survival to no impact on 5-year survival. We used these responses to estimate priors for the probability that the modality was necessary to achieve 5-year survival, given diagnosis and stage.

We also estimated the proportion of cancer cases expected to benefit from modern modalities (i.e. targeted therapy, CT, MRI, PET, and SPECT). Because these modalities were generally not available until the late 1970s or early 1980s, we analysed trends in stage-specific survival using SEER data between 1973 and 2014 to estimate the level of survival achievable before the introduction of modern modalities.

Treatment Availability

To estimate the availability of traditional treatment modalities (chemotherapy, radiotherapy, and surgery), we relied on previously published estimates. We estimated priors of the availability of chemotherapy using data from a published global survey of oncologists.[6] Estimates of radiotherapy coverage were based on the Lancet Oncology Commission on

Expanding Global Access to Radiotherapy.[7] Surgery estimates were based on a modelling study of the Lancet Commission on Global Surgery.[8]

Data on the global availability of targeted therapy are scarce, but available estimates suggest that patients in many countries have poor access to targeted therapy, usually because of the high cost. We therefore set priors by income group for targeted therapy availability, and ensured that the calibrated probabilities of targeted therapy availability were lower than for chemotherapy in each country.

Imaging Availability

We obtained coverage estimates for each imaging modality (i.e. equipment per million population) from the International Atomic Energy Agency IMAGINE database. To estimate probabilities of availability, we set thresholds of minimum coverage density needed to ensure availability. Because there are no general guidelines regarding the ideal number of imaging units per population, we set thresholds based on observed data in high-income countries with relatively low coverage so as not to overestimate the thresholds needed to ensure availability.

Quality of Care

We also included a parameter for quality of care, defined by the Institute of Medicine as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[9] This parameter captures health-system and facility-level factors that account for residual differences in survival not explained by cancer stage or treatment and imaging availability.

Cancer Treatment Costs

We undertook a literature review to estimate the direct costs of adult cancer treatment around the world. We obtained 108 cost estimates for 17 cancers in 30 countries (see reference 3, Ward et al., for more details).[3] Most costs were already reported in $US, but for any costs reported in local currency the year-specific conversion rate to $US was used. We then calculated the ratio of reported costs to the country's estimated per capita GDP for the same year.

We estimated the relationship between cancer treatment costs and estimated per capita GDP in 2020 using a linear regression model: $\text{Ratio} = \beta_0 + \beta_1 * \log(\text{GDP}) + \beta_2 * \log(\text{GDP})^2$. In each iteration of the simulation model we sampled from the fitted regression coefficients to predict cancer treatment costs for each country by year.

Imaging and Non-Procedure Costs

We used the national dataset of Medicare Fee-for-Service (FFS) 100% Research Identifiable Files: inpatient, outpatient, carrier, DME, hospice, home health, SNF, vital status, and master beneficiary summary files from 2010 through 2014. To determine inclusion in the analysis cohort, all Medicare beneficiaries were considered who appeared to be beginning cancer treatment or management of recurrent disease in 2011-2013. Each case had new claims for cancer care after a year (or more) without a claim for a cancer diagnosis. Based on these data,

we find that radiology/nuclear medicine costs account for 7% of total cancer treatment in the US, with small variations by diagnosis, ranging from 5.8% for colon cancer to 8.9% for lung cancer and liver cancer.

Estimates of the proportion of cancer treatment costs due to imaging from other countries are similar. We obtained estimates from the following studies which estimated the breakdown of costs of cancer treatment among patients with cancer. An analysis in Belgium of incoming cancer patients in 2006 and followed for 5 years (or until death) finds that radiology and nuclear medicine accounted for 11% of costs (Storme 2016).[10] Estimates of the cost of treating invasive cervical cancer find that imaging studies accounted for only 2.5% of treatment costs in Brazil,[11] and that laboratory and image tests accounted for 6.32% of cervical cancer costs in Mexico.[12]

An analysis of lung cancer management costs in Australia finds that staging (imaging and pathology) accounted for 10.1% of costs, treatment (surgery, radiotherapy, chemotherapy) accounted for 41.2% of costs, and hospitalization and follow-up accounted for 48.7% of costs.[13] A study of pancreatic cancer costs in the US found that inpatient and hospice accounted for 40% of costs.[14] We therefore assume that non-procedure costs account for 50% of total cancer management costs.

GDP Projections

We obtained per capita GDP data and projections ($US 2018) from the IMF for the period 1980-2023.[15] Data were not available for 14 countries. We imputed per capita GDP for these countries based on the mean of their Region/Income group (see reference 3, Ward et al., for details).[3] To continue projections to 2030 we calculated the average growth percentage per year (2015-2023) and used these estimates to project per capita GDP forward. We enforced bounds of +/- 8% growth to keep the projections within historical and anticipated trends.

Model Calibration

We used Bayesian hierarchical models with four levels (income group, geographical area, geographical region, and country) to synthesise all available estimates and generate prior probability distributions, allowing us to regularise the reported estimates and estimate priors for countries for which no data were available. We used these priors as initial sampling distributions for model calibration and enforced non-decreasing income group intercepts when sampling from the hierarchical models.

We calibrated the model to country-specific 5-year net survival estimates from CONCORD-3, reserving a set of 50 randomly sampled estimates as a validation test set. Comparing our model results with the CONCORD-3 estimates, our posterior predictive checks of our training set found that our 95% UIs overlapped with the CONCORD 95% CIs 94·2% of the time and contained the reported point estimate 80·9% of the time. Our validation checks of our test set found that 96·0% of our 95% UIs overlapped the CONCORD 95% CIs, with a coverage probability of 82·0%.

We incorporated the uncertainty around model parameters when calibrating the model, so our estimated 95% UIs, reported for all model outcomes, indicate the sensitivity of our results to different parameter values and account for their joint distribution.

Web Appendix References

1. International Atomic Energy Agency. Human Health Campus. IMAGINE - IAEA Medical Imaging and Nuclear Medicine Global Resources Database; Oct 2019. Available from: https://humanhealth.iaea.org/HHW/DBStatistics/IMAGINE.html. Accessed November 20, 2020.
2. Ward ZJ, Scott AM, Hricak H, et al. Estimating the impact of treatment and imaging modalities on 5-year net survival of 11 cancers in 200 countries: a simulation-based analysis. Lancet Oncol 2020; 21: 1077-88.
3. Ward ZJ, Scott AM, Hricak H, Atun R. Global costs, health, and economic benefits of scaling up treatment and imaging modalities for survival of 11 cancers: a simulation-based analysis. Under review.
4. United Nations, Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019, Online Edition. https://population.un.org/wpp/Download/Standard/CSV/
5. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat database. Incidence -SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (2000–2016) - Linked to county attributes - Total US, 1969–2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission. https://seer.cancer.gov/datasoftware (accessed July 2, 2020).
6. Cohen P, Friedrich P, Lam C, et al. Global access to essential medicines for childhood cancer: a cross-sectional survey. J Glob Oncol 2018; 4: 1–11.
7. Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. Lancet Oncol 2015; 16: 1153–86.
8. Alkire BC, Raykar NP, Shrime MG, et al. Global access to surgical care: a modelling study. Lancet Glob Health 2015; 3: e316–23.
9. Institute of Medicine. Medicare: a strategy for quality assurance. Washington, DC: National Academy Press, 1990.
10. Storme G, Dhaese S, Corens D, De Ridder M. The cost of cancer care is not related to its outcomes. Ecancermedicalscience 2016; 10: 687.
11. Santos CL, Souza AI, Figueiroa JN, Vidal SA. Estimation of the Costs of Invasive Cervical Cancer Treatment in Brazil: A Micro-Costing Study. Rev Bras Ginecol Obstet 2019; 41(6): 387-393.
12. Granados-García V, Piña-Sánchez P, Reynoso-Noveron N, et al. Medical Cost to Treat Cervical Cancer Patients at a Social Security Third Level Oncology Hospital in Mexico City. Asian Pac J Cancer Prev 2019; 20(5): 1547-1554.
13. Kang S, Koh ES, Vinod SK, Jalaludin B. Cost analysis of lung cancer management in South Western Sydney. J Med Imaging Radiat Oncol 2012; 56(2): 235-41.
14. O'Neill CB, Atoria CL, O'Reilly EM, LaFemina J, Henman MC, Elkin EB. Costs and trends in pancreatic cancer treatment. Cancer 2012; 118(20): 5132-9.

15. IMF - World Economic Outlook (April 2018). Available at: https://www.imf.org/external/pubs/ft/weo/2018/01/weodata/index.aspx

Web Appendix

Table: Sensitivity Analysis using Human Capital Approach

	Incremental cancer treatment costs (2020-2030), $ billion (95% uncertainty interval)		Lifetime return on investment: Human capital [1x GDP, ages 18-64], (95% uncertainty interval)		
	Difference	Percent increase	Productivity gains, $ billion	Net benefit, $ billion	Return per $ invested
Global					
Imaging only	6.84 (1.77-15.86)	0.2% (0.1-0.3)	216.30 (100.12-402.12)	209.46 (94.96-394.72)	31.61 (15.09-110.14)
Treatment only	50.72 (14.92-111.88)	1.5% (0.8-2.4)	251.35 (112.65-439.49)	200.62 (83.24-359.12)	4.96 (2.61-13.03)
Treatment + quality	225.50 (83.87-408.34)	6.7% (5.7-7.8)	295.53 (157.74-468.59)	70.03 (-136.07-283.70)	1.31 (0.59-3.63)
Comprehensive	232.88 (85.92-421.97)	6.9% (6.0-8.0)	573.30 (361.08-775.28)	340.42 (99.37-592.59)	2.46 (1.29-6.52)
Africa					
Imaging only	0.46 (0.23-0.79)	1.9% (1.2-3.0)	6.39 (2.27-16.25)	5.94 (1.93-15.82)	14.00 (4.90-30.98)
Treatment only	6.85 (3.82-11.22)	29.4% (17.6-42.2)	31.28 (12.96-54.08)	24.43 (7.15-45.84)	4.57 (2.11-8.93)
Treatment + quality	11.14 (6.64-16.98)	47.8% (34.1-63.1)	42.42 (21.99-60.72)	31.28 (12.99-49.81)	3.81 (2.07-6.60)
Comprehensive	11.67 (7.01-17.70)	50.1% (36.2-66.4)	63.84 (48.20-77.63)	52.16 (36.62-66.56)	5.47 (3.62-8.73)
Asia					
Imaging only	3.42 (0.66-9.37)	0.4% (0.1-0.6)	126.19 (18.94-285.44)	122.78 (18.07-279.28)	36.92 (14.81-148.4)
Treatment only	24.58 (4.35-69.42)	2.7% (0.5-6.2)	145.09 (25.54-329.24)	120.50 (18.69-265.79)	5.90 (2.76-14.88)
Treatment + quality	37.98 (13.16-86.15)	4.4% (1.9-8.5)	166.27 (40.65-331.89)	128.29 (21.12-270.23)	4.38 (1.82-10.57)
Comprehensive	41.59 (14.76-91.25)	4.7% (2.3-8.9)	328.98 (167.92-474.42)	287.39 (141.77-431.71)	7.91 (3.72-19.94)
Europe					
Imaging only	1.95 (0.23-5.52)	0.2% (0.0-0.4)	47.81 (13.63-107.96)	45.86 (12.75-100.67)	24.54 (11.91-114.23)
Treatment only	14.73 (1.88-38.95)	1.2% (0.2-2.6)	50.27 (14.23-101.45)	35.54 (8.15-79.18)	3.41 (1.61-13.09)
Treatment + quality	171.39 (59.50-314.06)	14.5% (13.3-16.0)	58.00 (20.17-115.30)	-113.39 (-260.53-13.26)	-0.34 (0.09-1.18)
Comprehensive	173.59 (59.79-315.94)	14.7% (13.6-16.1)	111.98 (65.39-159.67)	-61.61 (-206.73-59.75)	-0.65 (0.29-1.91)
Latin America and the Caribbean					
Imaging only	0.52 (0.03-1.31)	0.6% (0.0-1.1)	22.30 (1.53-42.06)	21.78 (1.50-41.54)	42.78 (17.53-215.06)
Treatment only	2.21 (0.20-7.03)	2.9% (0.3-7.4)	14.84 (1.87-44.23)	12.63 (1.60-41.24)	6.73 (2.55-28.97)
Treatment + quality	2.56 (0.45-7.42)	3.4% (0.7-8.0)	16.26 (2.05-45.77)	13.70 (1.47-42.99)	6.36 (2.28-23.43)
Comprehensive	3.08 (0.61-8.04)	4.1% (1.3-8.7)	41.85 (20.24-70.79)	38.77 (18.46-65.78)	13.57 (5.20-63.60)
Northern America					
Imaging only	0.37 (0.00-3.26)	0.0% (0.0-0.2)	10.07 (0.00-74.14)	9.70 (0.00-70.96)	27.35 (13.16-96.38)
Treatment only	1.22 (0.00-11.54)	0.1% (0.0-0.8)	5.28 (0.00-46.86)	4.06 (0.00-34.22)	4.32 (1.66-17.11)
Treatment + quality	1.22 (0.00-11.54)	0.1% (0.0-0.8)	6.87 (0.00-46.86)	5.65 (0.00-36.29)	5.62 (1.77-264.17)
Comprehensive	1.59 (0.00-11.58)	0.1% (0.0-0.8)	16.95 (0.00-78.91)	15.36 (0.00-76.24)	10.66 (1.93-183.45)
Oceania					
Imaging only	0.13 (0.00-0.59)	0.1% (0.0-0.6)	3.54 (0.03-15.56)	3.40 (0.02-15.21)	27.04 (5.91-70.67)
Treatment only	1.14 (0.02-4.59)	1.2% (0.0-4.4)	4.60 (0.03-17.69)	3.46 (0.01-14.55)	4.05 (1.19-11.89)
Treatment + quality	1.21 (0.09-4.68)	1.3% (0.1-4.5)	5.70 (0.18-18.88)	4.49 (0.06-16.49)	4.70 (1.47-38.39)
Comprehensive	1.35 (0.13-4.83)	1.4% (0.2-4.5)	9.70 (2.04-22.84)	8.36 (1.84-19.72)	7.21 (2.59-49.89)