Supplementary Material to the manuscript:

An inverse stage-shift model to estimate the excess mortality and health economic impact of delayed access to cancer services due to the COVID-19 pandemic

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Supplementary Material 1: Details on approximation of stage-specific healthcare costs

The modelling framework uses disease stage-specific healthcare costs to estimate the overall economic impact of a shift in disease stage at treatment initiation. It does so by comparing the expected costs on patient or population level according to the baseline scenario, which represents our best belief about how the distribution of disease stages at treatment initiation without a stage shift, to those of the stage shift scenario, which represents the distribution of disease stages following the stage shift. For each scenario, the expected costs are obtained by weighting the stage-specific costs by the respective distribution of disease stages at treatment initiation. This appendix details how stage-specific healthcare costs were obtained for the illustration of the modelling framework.

The illustration included estimates of the economic impact of stage shifts following COVID-19 induced delays in the time to treatment initiation for breast cancer, colorectal cancer, lung cancer and melanoma from an Australian healthcare payer perspective. The study by Goldsbury et al. (2018) [1] was preferred as a single source of evidence for Australian costing data for all considered cancer, because costing estimates from different costing studies are often incomparable due to differences in healthcare system context or study design. However, Goldsbury et al. do not present stage-specific costing data, which are required as inputs for the modelling. Hence, stage-specific cost estimates were obtained by synthesizing data presented by Goldsbury et al. with information of the distribution of costs over disease stages from other publications in three steps:

1. the total expected costs over the 5 years after diagnosis were estimated based on the year-specific costs presented by Goldsbury et al. and the combined survival probabilities over all disease stages;
2. the distribution of costs between disease stages were approximated using information from other studies;
3. the stage-specific costs were estimated so that the combined costs weighted according to the distribution of disease stages at treatment initiation in the baseline scenario result in the total expected costs (Step 1), while matching the distribution of costs between stages (Step 2).

Step 1: estimating the total costs over the 5 years after diagnosis

Goldsbury et al. present year-specific excess costs for the 5 years after diagnosis per patient that received care in that year. To calculate the total expected costs over this period, it would be wrong to sum these year-specific costs, because not every patient will be alive throughout the 5 years after diagnosis. Hence, the expected value of the
total 5-year healthcare costs $TC$ is calculated by taking into consideration the survival probabilities, using the following formula:

$$TC = \sum_{t=0}^{4}(S(t) \times c_t)$$  \hspace{1cm} \text{Equation 1}

where $t$ represents the year after diagnosis, $S(t)$ is the survival probability, and $c_t$ represents the year-specific costs per patient who is receiving care. Note that $t = 0$ represents the first year after diagnosis, where all patients are assumed to receive care, i.e. $S(0) = 1$. The stage-specific survival probabilities are reported in the main manuscript and were weighted according to the baseline scenario to obtain the combined survival $S(t)$ for each cancer separately. Note that for melanoma this was based on tumour (T) stage rather than overall disease stage (TNM). Based on these data and the data from Goldsbury et al, the total expected excess healthcare costs over the first 5 years after diagnosis presented in Table A1 were calculated.

**Table A1. Year-specific costs per patient receiving care presented in Goldsbury et al. (2018) and expected total excess healthcare costs over the first 5 years after diagnosis in 2013 Australian dollars ($).**

| Cancer Type     | Year 0 - 1 | Year 1 - 2 | Year 2 - 3 | Year 3 - 4 | Year 4 - 5 | Expected Total Costs |
|-----------------|------------|------------|------------|------------|------------|---------------------|
| Breast Cancer   | $36,948    | $7,619     | $3,038     | $3,132     | $2,473     | $52,526             |
| Colorectal Cancer| $48,570    | $10,926    | $7,381     | $6,509     | $4,525     | $71,829             |
| Lung Cancer     | $28,059    | $17,863    | $12,903    | $6,563     | $4,021     | $51,435             |
| Melanoma        | $7,110     | $2,260     | $2,792     | $2,506     | $1,784     | $15,828             |

**Step 2: defining the distribution of costs between disease stages**

To approximate the stage-specific costs based on the reported overall costs by Goldsbury et al, the relation between costs across the different stages were based on other studies (Table A2). For breast cancer, a global systematic review reporting stage-specific costs was used [2], since this was the only study to distinguish between stage I and stage II disease. An Australian costing study was used for colorectal cancer [3]. No studies that distinguish between stage I and stage II lung cancer were found, so a recent study from the United States (US) was used [4]. A US study was also used for melanoma, assuming the relation between disease stage-specific costs for T-stage to be equivalent to the distribution of costs according to TNM classification [5]. These stage-specific costs were used solely to define the relationship between healthcare costs for different stages.
Table A2. Disease stage-specific costs extracted from literature (currency not of relevance).

| Cancer Type     | Stage I  | Stage II | Stage III | Stage IV | Reference                  |
|-----------------|----------|----------|-----------|----------|----------------------------|
| Breast Cancer   | 29,724   | 39,322   | 57,827    | 62,108   | Sun et al. (2019)           |
| Colorectal Cancer| 34,952   | 45,108   | 82,449    | 81,403   | Ananda et al. (2016)        |
| Lung Cancer     | 2,636    | 2,636    | 6,196     | 7,303    | Sheehan et al. (2019)       |
| Melanoma        | 14,499   | 26,667   | 31,778    | 39,631   | Seidl et al. (2010)         |

Since the studies did not report on healthcare costs for patient with an unknown stage, this needed to be estimated, which was done by assuming the “stage unknown” category is a mix of stage III and stage IV patients for breast cancer, colorectal cancer and lung cancer, and a potential mix of T1, T2, T3 and T4 patients for melanoma. The weight of each stage was determined through a least-squares regression matching the weighted stage-specific survival to the survival for the “stage unknown” category. The results of this analysis are presented in Table A3.

Table A3. Contributions of disease stages to the “unknown stage” category used to define the relation between costs for this category relative to the other categories.

| Cancer Type     | Stage I | Stage II | Stage III | Stage IV |
|-----------------|---------|----------|-----------|----------|
| Breast Cancer   | -       | -        | 69%       | 31%      |
| Colorectal Cancer| -      | -        | 69%       | 31%      |
| Lung Cancer     | -       | -        | 70%       | 30%      |
| Melanoma        | 22%     | 0%       | 0%        | 78%      |

Step 3: estimating the stage-specific healthcare costs

The final step to approximate the stage-specific costs was to estimate them in such a way that the combined costs weighted according to the distribution of disease stages at treatment initiation in the baseline scenario were equivalent to the expected total costs (Step 1), while matching the distribution of costs between stages (Step 2).

This can be done, for example, through the “Goal Seek” function in Microsoft Excel, a least-squares regression or other optimization algorithm. More specifically, by setting the costs for stage I, for example, the costs for the other stages were defined through the relations defined in Step 2, which then defined the combined costs according to the distribution of stages. The value for the costs of stage I was optimized such that the weighted combined costs matched the expected total costs estimated in Step 1. The results of this step are presented in Table A4.
Table A4. Approximated stage-specific excess healthcare costs in 2013 Australian dollars.

| Cancer Type       | Stage I  | Stage II | Stage III | Stage IV | Stage Unknown |
|-------------------|----------|----------|-----------|----------|---------------|
| Breast Cancer     | $39,433  | $52,166  | $76,716   | $82,395  | $78,449       |
| Colorectal Cancer | $40,081  | $51,727  | $94,547   | $93,348  | $84,174       |
| Lung Cancer       | $22,192  | $22,192  | $52,163   | $61,481  | $54,973       |
| Melanoma          | $10,875  | $20,001  | $23,835   | $29,725  | $25,636       |

Finally, since the costs presented by Goldsbury et al. were reported in 2013 Australian dollars, the stage-specific costs were indexed to 2020 Australian dollars using the Australian Health Index [6], which resulted in the final estimates that were used in the analysis (Table A5).

Table A5. Approximated stage-specific excess healthcare costs in 2020 Australian dollars.

| Cancer Type       | Stage I  | Stage II | Stage III | Stage IV | Stage Unknown |
|-------------------|----------|----------|-----------|----------|---------------|
| Breast Cancer     | $50,699  | $67,069  | $98,632   | $105,934 | $100,860      |
| Colorectal Cancer | $51,531  | $66,504  | $121,558  | $120,015 | $121,077      |
| Lung Cancer       | $28,532  | $28,532  | $67,065   | $79,045  | $70,678       |
| Melanoma          | $13,981  | $25,715  | $30,644   | $38,216  | $32,960       |
Supplementary Material 2: Details on estimating the stage-shifts following delays

The stage-shift modelling framework considers up to 5 disease stage categories to define the *baseline* and *stage shift scenario*. Although these are classified as stage I, stage II, stage III, stage IV and unknown stage (TNM stages) in the online tool, they can also be used for other classifications, for example according to T stage as in the illustration for melanoma. The illustration here used data on the distribution of disease stage published by the AIHW [7] to define the *baseline scenario* for breast, colorectal and lung cancer, and data published by Cancer Council Victoria for the distribution of T stage for melanoma [8].

In the absence of empirical evidence on the distribution of disease stage at treatment initiation during the COVID-19 pandemic, 2 approaches were explored and compared to approximate this distribution through estimating time to stage progression. The first approach was based on the relation between time to treatment initiation (TTI) and survival, whereas the second approach was based on the tumor growth rate. The first approach was applied for breast, colorectal and lung cancer, and the second approach was applied for melanoma. To be conservative in these exploratory analyses and reduce the complexity of the illustration, only shifts from stage I to stage II were modelled for breast, colorectal and lung cancer, and from stage T1 to T2 for melanoma. Two realistic delay periods were considered: 3 months and 6 months.

**Stage progression based on the relation between TTI and survival**

The *treatment delay approach* was based on the relation between TTI and survival, estimating how long a delay in TTI needs to be such that the mortality rate for stage I patients matches the rate for stage II patients. For each cancer type separately, stage-specific excess mortality rates, denoted here by \( rate_j^{mortality} \), were calculated from 5-year relative survival probabilities reported by the AIHW [7]. Here, \( j = \text{stage I, stage II} \), but this also generalizes to more stage categories. The required hazard ratio \( HR_j^{mortality} \) for a \( rate_j^{mortality} \) to match the rate of the subsequent stage \( j + 1 \) was calculated as the ratio between the two rates:

\[
HR_j^{mortality} = \frac{rate_{j+1}^{mortality}}{rate_j^{mortality}}
\]  

*Equation 1*

Subsequently, using a stage-specific hazard ratio of a delay in TTI on overall survival \( HR_j^{delay} \) and corresponding delay in \( t_j^{delay} \) reported in literature, the expected delay \( t_j^{TSP} \) required for a stage shift was determined by assuming a linear relationship between the delays and hazard ratios on logarithmic scale (Equation 2). This
resembles a continuous variable in a Cox-proportional hazards model, assuming an exponential relation between a delay in TTI and overall survival.

\[ \ln(HR_{j}^{\text{mortality}}) = (\ln(HR_{j}^{\text{delay}})/t_{j}^{\text{delay}}) \times t_{j}^{\text{TTPS}} \]  \hspace{1cm} \text{Equation 2} 

Since \( t_{j}^{\text{TTPS}} \) represents the expected value of the delay in TTI required for a stage shift to occur, the corresponding event rate for TTSP can be calculated as follows:

\[ \text{rate}_{j}^{\text{TTPS}} = 1/t_{j}^{\text{TTPS}} \]  \hspace{1cm} \text{Equation 3} 

This event rate can be used to define an exponential distribution to calculate the probability that a patient will progress given a certain delay. Since the 100% relative 5-year survival for stage I breast cancer in Australia reported by the AIHW does not allow this approach to be applied, because it suggests an excess mortality rate of zero, 5-year relative survival was assumed to be 99.9% in calculating \( HR_{\text{stage I}}^{\text{mortality}} \) for breast cancer. Hazard ratios for 1-week TTI delays on overall survival for stage I patients extracted from a large population study were 1.018 (breast cancer), 1.005 (colorectal cancer) and 1.032 (lung cancer) [9], yielding time to stage progression estimates of 4.3 years, 8.3 and 2.9 years, respectively. This study used data from the National Cancer Database (NCDB) (breast cancer: \( n = 1,368,024 \); colorectal cancer: \( n = 662,094 \); lung cancer: \( n = 363,863 \)) to estimate the impact of time between clinical or histologically confirmed diagnosis and the start of any cancer-directed treatment on survival, considering time beyond 6 weeks as delays. The time to stage progression estimates were used to calculate the proportion of patients that would experience a stage progression in each month in which services were disrupted, assuming incident cases are diagnosed evenly throughout the year. These proportions were then applied to the baseline scenario to define the stage shift scenario for the 3 and 6 month delays separately.

**Stage progression based on tumor growth**

The tumor growth approach estimated the proportion of patients that will progress to a more advanced stage based on the tumor growth rate. This approach was illustrated for melanoma, where the T stage is directly linked to the thickness of the tumor (Breslow thickness) and evidence on the monthly increase of tumor thickness is available. Liu et al (2006) have reported an average growth in tumor thickness of 0.08 mm per month for tumors that are up to 1 mm in thickness based on individual patient reports of times from first change in a lesion to a pathological diagnosis [10]. Based on this growth rate and by assuming a Uniform distribution for tumor thickness for T1 tumors at treatment initiation, it was simulated how many patients would have progression to a T2 tumor (i.e., with a thickness between 1 and 2 mm) following a 3 or 6-month delay. This Uniform distribution was defined with a minimum and maximum of 0.25 and 1 mm, respectively, based on inspection of empirical T1 tumor
thickness data from the Melanoma Research Victoria (MRV) registry (n = 710). The resulting simulated mean thickness without a delay of 0.63 mm matched the observed mean of 0.64 mm well. The estimated proportions were applied to the baseline scenario to define the stage shift scenarios.
**Supplementary Material 3: References**

The following references were cited throughout this appendix:

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