Cost-effectiveness Analysis of Screening Extremely Low Birth Weight Children for Hepatoblastoma Using Serum Alpha-fetoprotein

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Objectives To evaluate the cost-effectiveness of screening children born at extremely low birth weight (ELBW) for hepatoblastoma using serial serum alpha-fetoprotein measurements.

Study design We created a decision tree to evaluate the cost effectiveness of screening children born at ELBW between 3 and 48 months of age compared with current standard of care (no screening). Our model used discounted lifetime costs and monetary benefits in 2018 US dollars, based on estimates in the published literature. The effects of uncertainty in model parameters were also assessed using univariate sensitivity analyses, in which we changed the values for one parameter at a time to assess the effect on the estimated incremental cost-effectiveness ratio.

Results For the estimated 55 699 children born at ELBW in the US each year, this screening is associated with 77.7 additional quality-adjusted life-years (QALYs) at a cost of $8.7 million. This results in an incremental cost-effectiveness ratio of about $112 000/QALY, which is considered cost effective from a US societal perspective. For children diagnosed with hepatoblastoma, our model finds that the screening regimen is associated with a 10.1% increase in survival, a 4.18% increase in expected QALYs, and a $245 184 decrease in expected cost.

Conclusions Screening ELBW children for hepatoblastoma between 3 and 48 months of age dominates the alternative and is cost effective from a societal perspective. *(J Pediatr 2020;225:80-9)*.

Hepatoblastoma, the most common malignant hepatic tumor in children, occurs rarely but can have devastating effects. A disease of very young children, the median age at diagnosis is 18 months and more than 90% of cases occur before age 5 years, with an incidence of 10.5 cases per million in children under one year of age and 5.2 cases per million children ages 1-4 years according to Surveillance, Epidemiology, and End Results data for 2002-2008.[1-4] Often, the diagnosis is not made until an advanced stage, which is associated with lower rates of overall and event-free survival.[5]

Tumors are most commonly classified by assignment to a Pre-Treatment Extent of Disease (PRETEXT) group based on the extent of hepatic involvement.[5,6] Although complete surgical resection is required for curative treatment, approximately one-half of tumors are not fully resectable at diagnosis and require neoadjuvant chemotherapy.[7-9] In patients whose disease remains unresectable after chemotherapy, complete hepatectomy with orthotopic liver transplantation is necessary for curative treatment.[3,10] The baseline costs of diagnosis and treatment therefore range from tens of thousands of dollars for chemotherapy admissions to hundreds of thousands of dollars for liver transplant and follow-up care.[11-18]

The overall incidence of hepatoblastoma in the US has been documented as up to 117 cases annually, or 3.8 cases per million children under age 4 years.[19-21] Approximately 15% of cases are associated with inherited syndromes, including familial adenomatous polyposis and Beckwith-Wiedemann syndrome.[22] Children born weighing less than 1500 g (extremely low birth weight [ELBW]) also have a 17-fold increased risk of developing hepatoblastoma compared with children of average birthweight; those who weigh 1500-2500 g at birth have a 2-fold increased risk.[21-23] This increased incidence has been identified internationally, including in the US, Europe, and Asia.[23-26] In the US, approximately 3.9 million live births occur annually, of which an estimated 1.4% are ELBW infants.[27] As survival of ELBW infants increases, so, too, has the incidence of this tumor.[21,26] We therefore evaluated the cost effectiveness of screening all children born at ELBW (<1500 g), in the US for hepatoblastoma during the first 4 years of life.

We selected serum alpha-fetoprotein (AFP) as the initial screening tool, with elevated values to be followed by abdominal ultrasound examination and biopsy when indicated. Although AFP levels during the first year of life are typically much higher than in adulthood, a linear correlation exists between logarithmically trans-

AFP	Alpha-fetoprotein
CHIC	Children's Hepatic tumors International Collaboration
ELBW	Extremely low birth weight
ICER	Incremental cost-effectiveness ratio
PRETEXT	Pre-Treatment Extent of Disease
QALY	Quality-adjusted life-year
SIOPEL	International Society of Pediatric Oncology Epithelial Liver

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formed serum AFP and age of ELWB infants measured in days; values in infants diagnosed with hepatoblastoma fall significantly outside the range measured in those without the disease.[28,29] A case series describing serial AFP measurements in children with Beckwith-Wiedemann syndrome and isolated hemihyperplasia leading to detection of stage I tumors (by postsurgical staging in all 5 children) suggests that AFP may be more sensitive than imaging alone.[28]

A cost-effectiveness analysis of screening children with Beckwith-Wiedemann syndrome for hepatoblastoma and Wilms tumor using triannual abdominal ultrasound examinations from birth until age 7 demonstrated a cost per life-year saved of $14 740 in 2001, suggesting that screening high-risk children is feasible and cost effective.[30] Given the decrease in expected survival with increasing PRETEXT group at diagnosis and the increase in intensity, duration, and cost of therapy for more advanced disease, we hypothesized that earlier diagnosis would be associated with lower treatment-related costs and greater likelihood of overall survival and event-free survival.[3,5,10]

Methods

We constructed a decision tree to examine the cost effectiveness of a screening regimen that uses serial serum AFP measurements obtained at 12 timepoints between the ages of 3 and 48 months to detect hepatoblastoma in children who were born at ELBW. We elected to begin screening at age 3 months because diagnoses rarely occur before that timepoint; congenital hepatoblastoma has been reported in only about 42 cases in the literature and diagnoses at 3 months of age or less were reported in fewer than 33 children in the International Society of Pediatric Oncology Epithelial Liver (SIOPEL) Tumor group 2 and 3 studies, which took place over from 1994 to 2006.[31-33] Furthermore, infants born at extreme prematurity typically undergo repeated abdominal imaging during their initial hospitalization.[34]

We compared this screening regimen with no screening, or standard well-child care with a general pediatrician and, when available, a neonatal follow-up clinic, wherein a serum AFP and abdominal imaging would be obtained only if clinically indicated based on symptoms. From a US societal perspective, we calculated discounted lifetime costs and monetary benefits in 2018 US dollars based on estimates in the published literature. Future costs and benefits were discounted at a rate of 3% per year. We performed univariate sensitivity analyses to assess the effects of uncertainty in model parameters.

Model

We constructed the decision tree model in Excel (Microsoft, Redmond, Washington; **Figure**). Within the model, children are compared across 2 arms: no screening (standard of care) and screening regimen. In each arm, children are either diagnosed with hepatoblastoma or remain hepatoblastoma-free, based on the probability that an ELBW child develops hepatoblastoma. Children who remain hepatoblastoma free may incur screening costs but are expected to progress through a normal life course. Children diagnosed with hepatoblastoma are categorized by PRETEXT group and assigned to a treatment regimen consistent with current standard practice. The PRETEXT system was developed by the SIOPEL Tumor group and is also used by cooperative groups in Germany and Japan.[35] This classification differs from the risk-stratification system used in the most recently completed Children's Oncology Group hepatoblastoma trial, AHBL0731; however, analysis by the Children's Hepatic tumors International Collaboration (CHIC) of 1605 patients enrolled in trials run by the major international cooperative groups over the past decades has demonstrated that PRETEXT group is one of the factors most significantly related to prognosis.[36-40] We therefore used PRETEXT group as a surrogate for expected outcome and constructed our model utilizing a simplified treatment algorithm in which patients with PRETEXT I disease would undergo resection only, those with PRETEXT II disease would receive 2 cycles of chemotherapy and resection, those with PRETEXT III disease would receive 6 cycles of chemotherapy and resection, and those with PRETEXT IV disease would undergo 6 cycles of chemotherapy plus liver transplantation. Through their treatment regimen, patients incur treatment costs and progress toward 1 of 2 short-term outcome states: sustained remission or death. This simplification of staging and treatment into distinct groups was necessary to allow separate, nonoverlapping cost computations.

Standard Care (No Screening). Despite an increased risk of developing hepatoblastoma, ELBW children are not currently screened for the disease.[24] Patients in the standard care arm are assumed to be tested for hepatoblastoma only upon symptomatic presentation. The grouping, treatment protocol, and disease progression for children in this arm align with current published rates and outcomes. In Brown et al, which we used for PRETEXT grouping data, 8% of cases had missing staging data.[5] We scaled the proportion of patients with nonmissing data from 92% to 100% so that children in standard care arm of the model are assumed to have the following probabilities of being diagnosed by PRETEXT group: I (4%), II (37%), III (32%), and IV (27%).

Screening Regimen. The screening regimen tested in this cost-effectiveness model included screening assays at 3, 6, 9, 12, 16, 20, 24, 30, 36, 42, and 48 months performed in the inpatient setting for infants requiring prolonged hospitalization and in a neonatal follow-up clinic, if available, or a general pediatrician's office after discharge. Values would be compared with the normal range for ELBW infants as presented by Maruyama, with elevated values prompting evaluation by abdominal ultrasound examination.[29] The interpretation of these laboratory results and coordination of radiographic imaging would be performed by a patient's primary care provider, with support from a pediatric oncologist if indicated. More frequent screenings are performed at

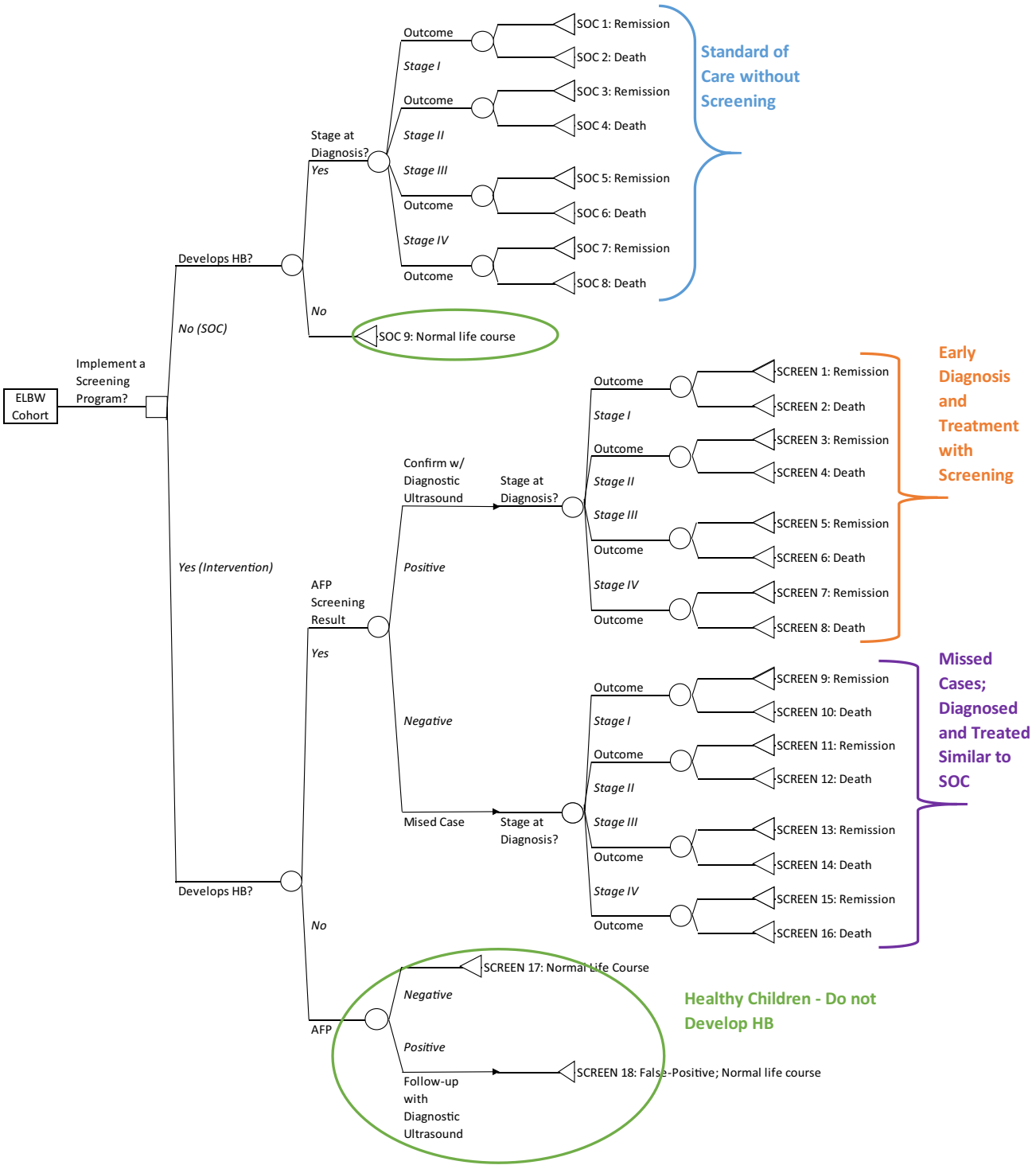

Figure. Decision tree model used with no screening (standard of care) and screening, and all potential end outcomes (normal life course, remission, or death).

younger ages as the likelihood of developing hepatoblastoma is higher among infants.[1,41] The screening regimen incurs additional upfront costs associated with each screening test; however, early detection of hepatoblastoma decreases treatment costs and improves the likelihood of event-free survival.[30] Our model assumed that earlier diagnosis would equate with decreased disease burden and improved outcome, which is represented as the disease being 1 PRETEXT group lower at diagnosis that it would be without screening.[30,42] Under this assumption, the probability of

Table I. Likelihood of model outcomes and sensitivity range

Likelihood parameters	Parameter value: Base case (deterministic)	Parameter value: Lower bound	Parameter value: Upper bound	Parameter value: Range type	ICER: From lower bound	ICER: From upper bound	Author	Year
Developing hepatoblastoma								
General population	0.000023	N/A - did not test alternative values					Linabery and Ross[72]	2008
ELBW	0.000392	0.000333	0.000451	±15%	$148 889	$86 740	Linabery and Ross[72] Spector et al[24]	2008 2009
Screening protocol								
AFP sensitivity	0.96	0.9	1	Literature*	$126 127	$104 584	Clericuzio et al[28]	2003
AFP specificity	0.95	0.8075	1	±15%	$247 914	$92 168	McNeil et al[30]	2001
SOC - group at diagnosis								
PRETEXT group I	0.042	0.036	0.049	±15%	$111 211	$113 931	Brown et al[5]	2000
PRETEXT group II	0.366	0.311	0.421	±15%	$106 343	$118 528	Brown et al[5]	2000
PRETEXT group III	0.317	0.269	0.364	±15%	$114 429	$110 949	Brown et al[5]	2000
PRETEXT group IV	0.275	0.233	0.316	±15%	$118 657	$107 179	Brown et al[5]	2000
Screening protocol - missed case - group at diagnosis								
PRETEXT group I	0.042	0.036	0.049	±15%	$112 656	$112 484	Brown et al[5]	2000
PRETEXT group II	0.366	0.311	0.421	±15%	$113 117	$112 081	Brown et al[5]	2000
PRETEXT group III	0.317	0.269	0.364	±15%	$112 545	$112 591	Brown et al[5]	2000
PRETEXT group IV	0.275	0.233	0.316	±15%	$111 967	$113 127	Brown et al[5]	2000
Screening protocol - group at diagnosis								
PRETEXT group I	0.408	0.347	0.470	±15%	$121 115	$105 734	Brown et al[5] McNeil et al[30]	2000 2001
PRETEXT group II	0.317	0.269	0.364	±15%	$113 799	$111 470	Brown et al[5] McNeil et al[30]	2000 2001
PRETEXT group III	0.275	0.233	0.316	±15%	$103 964	$121 482	Brown et al[5] McNeil et al[30]	2000 2001
PRETEXT group IV	0.000	N/A	0.050	Selected value	N/A	$142 475	Brown et al[5] McNeil et al[30]	2000 2001
Outcomes								
Remission if group I at diagnosis	1	0.95	N/A	Selected value	$112 569	N/A	Brown et al[5]	2000
Remission if group II at diagnosis	0.91	0.82	1	95% CI	$108 961	$116 409	Brown et al[5]	2000
Remission if group III at diagnosis	0.68	0.55	0.82	95% CI	$108 133	$117 744	Brown et al[5]	2000
Remission if group IV at diagnosis	0.57	0.41	0.73	95% CI	$94 157	$142 991	Brown et al[5]	2000

N/A, not applicable; *SOC*, standard of care.
In this table, we report the probabilities used in the main decision tree model. We also provide lower bounds and upper bounds for each probability and test the effect of the varied probabilities on the ICER. The ICER bounds reflect analysis according to the upper and lower bounds of each variable and thus the ICER from the lower bound of the model variable is in some cases larger.
*Range reported in Chung et al (2011).

each PRETEXT group would become: I (41%; probabilities of diagnosis at group I and II without screening combined), II (32%), and III (27%). No tumors would be expected to be group IV at diagnosis.

Measuring Effectiveness

We assumed that children developed hepatoblastoma at 18 months of age, the median age of diagnosis and that all children were healthy until this point.[1] We assumed tumors detected through screening would be one PRETEXT group lower than those diagnosed without active screening.[30] Children diagnosed with hepatoblastoma were expected to progress to either sustained remission or death. The likelihood of each end point varied based upon the PRETEXT group at diagnosis (**Table I**), with children diagnosed earlier being more likely to achieve sustained remission. Children who did not receive a liver transplant and reached the short-term end point of remission were assumed to live a healthy life to the average life US expectancy of 79 years.[27]

Utility was measured using quality-adjusted life-years (QALYs). For children who did not develop hepatoblastoma, these were modeled based on the average QALYs (by age group).[43] While receiving treatment for hepatoblastoma, children were assumed to have lower QALYs owing to the side effects of treatment. Because utility estimates specific to children with hepatoblastoma were not available in the literature, QALYs for similar conditions or symptoms were used. Specifically, we modeled the expected QALYs during treatment as 0.62 per year based on estimates of the QALYs for patients undergoing chemotherapy following breast

cancer resection.[44] These finding were within the range of QALYs noted in the literature for adults undergoing chemotherapy for hepatocellular carcinoma and gastric cancer.[45,46]

For children who underwent transplantation and achieved a sustained remission, the QALYs were slightly lower than for those who did not develop hepatoblastoma, reflecting the disutility associated with long-term immunosuppression. The QALY in the first year after transplantation was 0.62 and in subsequent years was 0.75. Upon reaching adulthood, the expected QALYs decayed at the same rate per year as for individuals who did not receive a transplant. For children who died from hepatoblastoma, we assumed that death occurred 12 months after diagnosis (at 30 months of age). Death is assigned 0.0 QALYs.

Children in our model who did not develop hepatoblastoma were assumed to live a healthy life and were assigned the average QALYs for each year of life.[43] The disutility of a false-positive result in children in the screening arm who did not develop hepatoblastoma was modeled as a 1-time decrease of 0.005 in utility.[47] We discounted QALYs in future years at a rate of 3% a year.

Measuring Costs

We provide full details of the data sources and assumptions for the costs included in the model in **Table II**, including detailed estimates of inpatient and outpatient costs of treatment. Consistent with typical clinical practice based upon the PRETEXT group at diagnosis, our model includes short-term costs for central line placement, hospital admissions for chemotherapy, surgical resection, liver transplantation, and outpatient pediatric oncology visits estimated to occur weekly for 6 months, twice monthly for 3 months, then once monthly for 3 months.[12-15] We also accounted for the long-term costs of care associated with hepatoblastoma, including monitoring and immunosuppression for children who underwent transplantation. Clinical costs were extracted from the 2018 Medicare Fee Schedule when possible and were otherwise based on estimates from the published literature. These cost estimates were inflation adjusted to 2018 US dollars using the Bureau of Labor and Statistics consumer price index inflation calculator.[48] We provide more detail on the process and assumptions associated with identifying estimates in the published literature in **Tables III-V** (available at www.jpeds.com) We also included future earnings and costs, as well as nonmedical costs based on the published population averages.[43] Individuals were expected to incur long-term costs and earnings through the age of 79 years, the average life expectancy.[27]

Sensitivity Analyses

We performed univariate sensitivity analyses to assess the effects of uncertainty in model parameters. These types of sensitivity analyses test the impact that a range of values for one parameter (eg, a cost, probability, or utility) in the model can have on the incremental cost-effectiveness ratio (ICER) estimate. Typically, there are several parameters that could impact the ICER value and overall interpretation of the model. Sensitivity ranges were based on values in the published literature. When no range estimates were available, the point estimates from the base model were varied by ±15%.

Results

Expected Cost and Effectiveness

For the estimated 55 699 children born at ELBW in the US in a given year, the screening protocol is associated with 77.7 additional QALYs, at a cost of $8.7 million.[27] These findings result in an ICER of about $112 000/QALY, which is below the US societal willingness-to-pay threshold of $150 000/QALY. Thus, screening ELBW children for hepatoblastoma between 3 and 48 months of age is cost effective from a societal perspective.

For children diagnosed with hepatoblastoma, our model finds that the screening regimen is associated with 10.1% increase in survival, an increase of 4.18 expected QALYs per child, and a $245 184 decrease in expected cost per child diagnosed with hepatoblastoma. Although children diagnosed with hepatoblastoma have lower treatment costs, overall costs in the model were driven by the repeated testing of children at risk for hepatoblastoma who do not subsequently develop the condition.

Sensitivity Analysis

Results from the univariate sensitivity analysis did not substantively change the conclusion that implementing a screening regimen is cost-effective for ELBW children. In **Table I**, we report the effects of varying the point estimates for the model probabilities and the ICERs. The estimated ICER remained below the threshold of $150 000/QALY when varying all but one parameter. Varying the AFP screening sensitivity by ±15% leads to ICER estimates ranging from $92 168/QALY to $247 914/QALY. McNeil et al provide a point estimate of 0.95 for the specificity of AFP screening to diagnose hepatoblastoma, but do not include a sensitivity range.[30] We did not locate a sensitivity range elsewhere in the literature. Although it is common to vary such point estimates by ±15%, decreasing the estimated sensitivity to 0.8075 is likely too low a value for the sensitivity of this test.

In **Table II**, we report the effects of varying the cost estimates used in the model and the resulting ICERs. The estimated ICER remained below the threshold of $150 000/QALY when varying each of the parameters. The 2 most sensitive cost parameters are the cost of AFP screening and the cost of long-term immunosuppression. Decreasing the cost estimate of AFP screening by 15% (a decrease of $3.52 per screening) decreases the ICER to $86 010/QALY. Conversely, a lower cost of immunosuppression raises the estimated ICER.

The estimated ICER remained in the range of $109 000/QALY to $116 000/QALY when varying each utility parameter, with the exception of the QALYs for children after

Table II. Model costs and sensitivity ranges

Cost parameters	Frequency	Code	Parameter value: Base case (deterministic)	Parameter value: Lower bound	Parameter value: Upper bound	Parameter value: Range type	ICER: From lower bound	ICER: From upper bound	Author	Year
AFP screening	Per assay	CPT 82105	$23	$20	$27	±15%	$86 010	$139 128	CMS	2017
Diagnosis										
Diagnostic ultrasound	Per Study	CPT 76700	$126	$107	$144	±15%	$111 914	$113 225	CMS	2018
Diagnostic biopsy	Per Study	N/A	$4838	$4112	$5563	±15%	$112 569	$112 569	Younossi et al[11]	1998
Treatment										
Resection	Fixed	N/A	$29 253	$12 967	$76 250	Literature*	$111 399	$115 946	Spolverato et al[13]	2015
Chemotherapy	Per Cycle	N/A	$41 557	$35 324	$47 791	±15%	$115 831	$109 307	Price et al[14]	2009
Central venous line	Fixed	N/A	$6098	$5503	$6693	Literature†	$112 626	$112 512	Horattas et al[12]	2001
E&M visit	Fixed	CPT 99215	$148	$125	$170	±15%	$112 569	$112 569	CMS	2018
Transplant	Fixed	N/A	$160 142	$65 051	$330 312	Literature‡	$119 402	$100 342	Minneman et al[15]	2016
Transplant follow-up	Fixed	N/A	$148 082	$53 628	$242 533	Literature§	$117 741	$107 397	Ammori et al[16]	2008
Related long-term medical costs										
Immunosuppression	Annual	N/A	$17 186	$1131	$45 521	Literature¶	$132 909	$76 672	Kasiske et al[18]	2000
									Willoughby et al[17]	2007
Monitoring	Annual	N/A	$776	$509	$1017	Literature*	$112 275	$112 835	Spolverato et al[13]	2015
Other long-term medical costs										
Age <25	Annual	N/A	$500	$390	$610	95% CI	$112 505	$112 633	Neumann et al[43]	2016
Age 25-34	Annual	N/A	$829	$729	$929	95% CI	$112 554	$112 584	Neumann et al[43]	2016
Age 35-44	Annual	N/A	$994	$843	$1146	95% CI	$112 552	$112 586	Neumann et al[43]	2016
Age 45-54	Annual	N/A	$1492	$1347	$1638	95% CI	$112 557	$112 581	Neumann et al[43]	2016
Age 55-64	Annual	N/A	$2210	$2031	$2389	95% CI	$112 558	$112 580	Neumann et al[43]	2016
Age 65-74	Annual	N/A	$2895	$2731	$3059	95% CI	$112 561	$112 577	Neumann et al[43]	2016
Age ≥75	Annual	N/A	$3253	$3037	$3469	95% CI	$112 558	$112 580	Neumann et al[43]	2016
Nonmedical costs										
Age <25	Annual	N/A	$15 598	$14 162	$17 034	95% CI	$111 729	$113 409	Neumann et al[43]	2016
Age 25-34	Annual	N/A	$17 376	$16 179	$18 572	95% CI	$112 385	$112 753	Neumann et al[43]	2016
Age 35-44	Annual	N/A	$17 333	$16 251	$18 416	95% CI	$112 445	$112 693	Neumann et al[43]	2016
Age 45-54	Annual	N/A	$22 270	$20 851	$23 689	95% CI	$112 448	$112 690	Neumann et al[43]	2016
Age 55-64	Annual	N/A	$26 002	$24 533	$27 471	95% CI	$112 476	$112 662	Neumann et al[43]	2016
Age 65-74	Annual	N/A	$23 191	$21 319	$25 063	95% CI	$112 481	$112 657	Neumann et al[43]	2016
Age ≥75	Annual	N/A	$19 525	$17 626	$21 424	95% CI	$112 471	$112 667	Neumann et al[43]	2016
Income										2016
Age 18-25	Annual	N/A	($21 622)	($22 582)	($20 662)	95% CI	$112 436	$112 702	Neumann et al[43]	2016
Age 25-34	Annual	N/A	($42 301)	($43 417)	($41 186)	95% CI	$112 397	$112 741	Neumann et al[43]	2016
Age 35-44	Annual	N/A	($54 448)	($55 971)	($52 925)	95% CI	$112 395	$112 744	Neumann et al[43]	2016
Age 45-54	Annual	N/A	($55 914)	($57 412)	($54 416)	95% CI	$112 453	$112 686	Neumann et al[43]	2016
Age 55-64	Annual	N/A	($56 529)	($58 243)	($54 815)	95% CI	$112 448	$112 691	Neumann et al[43]	2016
Age 65-74	Annual	N/A	($43 796)	($47 054)	($40 538)	95% CI	$112 416	$112 723	Neumann et al[43]	2016
Age ≥75	Annual	N/A	($39 538)	($46 668)	($32 408)	95% CI	$112 201	$112 938	Neumann et al[43]	2016
Death	Fixed	N/A	0	N/A - did not test alternative values						

E&M, evaluation and management.
In this table, we report the cost estimates used in the main decision tree model. We also provide lower bounds and upper bounds for each cost estimate based on published literature and test the effect of the varied costs on the ICER. The ICER bounds reflect analysis according to the upper and lower bounds of each variable and thus the ICER from the lower bound of the model variable is in some cases larger.
*Range reported in Spolverato et al[13] (2015) adjusted to 2018 USD.
†Range reported in Horattas et al[12] (2001) adjusted to 2018 USD.
‡Range reported in Minneman et al[15] (2016) adjusted to 2018 USD.
§Range reported in Ammori et al[16] (2008) adjusted to 2018 USD.
¶Range reported in Kasiske et al[18] (2000) adjusted to 2018 USD.

transplantation. The range of utility values and associated ICERs used in the sensitivity analysis are reported in Table VI. Using a published range of QALYs for more than 1 year after transplantation led to an ICER range of $98 510/QALY to $134 507/QALY.[49] Although the ICER estimate is more sensitive to the long-term quality of life for children who undergo a transplant, the range of values remains below the accepted cost-effectiveness threshold of $150 000/QALY.

Discussion

This study evaluated the cost-effectiveness of the use of serial AFP measurements to screen children born at ELBW for

Table VI. Expected effects (QALYs) and sensitivity ranges

Utility parameters	Frequency	Parameter value: Base case (deterministic)	Parameter value: Lower bound	Parameter value: Upper bound	Parameter value: Range type	ICER: From lower bound	ICER: From upper bound	Author	Year
Screening and diagnosis									
False positive	Fixed	−0.005	−0.00575	−0.00425	±15%	$115 585	$109 707	Ungar et al[47]	2010
Condition/treatment									
Chemotherapy or surgery for HB	Annual	0.62	0.566	0.677	95% CI	$112 461	$112 677	Marguet et al[44]	2016
Transplant									
First year post-transplant	Fixed	0.62	0.57	0.67	Literature*	$112 346	$112 793	Mohammad et al[49]	2012
Second year and beyond	Annual	0.75	0.63	0.89	Literature*	$98 510	$134 507	Mohammad et al[49]	2012
Healthy life									
Childhood	Annual	0.930	0.911	0.949	95% CI	$114 705	$110 512	Feeny et al[73]	2004
Adulthood									
18-29	Annual	0.922	0.918	0.926	95% CI	$112 769	$112 370	Sullivan and Ghushchyan[74]	2006
30-39	Annual	0.901	0.897	0.905	95% CI	$112 701	$112 437	Sullivan and Ghushchyan[74]	2006
40-49	Annual	0.871	0.866	0.876	95% CI	$112 682	$112 457	Sullivan and Ghushchyan[74]	2006
50-59	Annual	0.842	0.837	0.847	95% CI	$112 667	$112 472	Sullivan and Ghushchyan[74]	2006
60-69	Annual	0.823	0.816	0.830	95% CI	$112 657	$112 481	Sullivan and Ghushchyan[74]	2006
70-79	Annual	0.79	0.783	0.797	95% CI	$112 639	$112 500	Sullivan and Ghushchyan[74]	2006
≥80	Annual	0.736	0.724	0.748	95% CI	$112 569	$112 569	Sullivan and Ghushchyan[74]	2006
Adverse outcome									
Death	Fixed	0	N/A - did not test alternative values						

HB, hepatoblastoma.

In this table, we report the utilities used in the main decision tree model. We also provide lower bounds and upper bounds for each utility based on published literature and test the effect of the varied utilities on the ICER. The ICER bounds reflect analysis according to the upper and lower bounds of each variable and thus the ICER from the lower bound of the model variable is in some cases larger.

*Range reported in Mohammad et al[49] (2012).

hepatoblastoma during the first 4 years of life. Our results suggest that the proposed screening regimen would lead to a greater number of life years and QALYs saved among children diagnosed with hepatoblastoma compared with no screening (current standard of care) with a cost that is below the cost-effectiveness threshold of $150 000/QALY.[50,51]

Historically, $50 000 per QALY was used as the threshold of acceptable cost for medical intervention after approximation of the cost-effectiveness ratio for dialysis in patients with chronic renal failure in 1982.[50] Of note, this is equivalent to $131 424.71 in 2018 US dollars. More recent willingness-to-pay thresholds have ranged from $50 000 to $150 000 per QALY and analysis of spending behavior in the US suggests that a range of $183 000 to $264 000 per QALY is a more accurate estimate.[50-52] Although these costs remain high, many physicians and the public express discomfort at idea of denying access to evidence-based care based on cost alone.[50,53] In the pediatric population especially, staggering costs of treatment may lead to considerable gains in life-years and QALYs, which tend to be highly valued.[54] Our results also indicate a gain in life-years as evidenced by a 10.1% increase in overall survival, an increase in expected QALYs of 4.18, and a decrease in expected treatment costs of $245 184.

We believe that our findings support the implementation of a screening program of serial AFP measurements followed by abdominal ultrasound examinations for elevated levels be instituted in ELBW infants from the age of 3 months through 4 years. The tests involved are minimally invasive and do not require special laboratory or imaging services. The frequency of testing, with shorter intervals during the first year, mimics the typical timing of well-child checks; screenings can be linked with appointments in neonatal follow-up clinics where available or with primary care providers. Our proposed screening uses the expected AFP values, including 95% CIs, documented by Maruyama for ELBW infants during the first 800 days of life.[29] After that time period, standard laboratory reference ranges would be expected to apply and could be used to identify elevations. Levels would be ordered and monitored by primary care providers, with support from pediatric hematology/oncology providers if needed.

The acquisition cost of this screening for an individual patient is low; laboratory processing of a single serum AFP measurement costs $23.49 according to the Medicare Clinical Laboratory Fee Schedule 2018, making the estimated cost of the screening regimen $247.03 per child if no values are elevated. This estimation includes only the cost of the test itself, because this screening would be performed during standard well-child or neonatal follow-up visits and could be performed separately from a provider visit if a visit was not otherwise indicated. Labor, time, or equipment costs are not individually factored into our model.

Children with an elevated screening AFP would undergo an abdominal ultrasound examination, which carries an estimated additional cost of $125.64 for the imaging study itself. Although the cost to screen each patient is low, the rarity of this tumor requires screening many children to detect a single case of hepatoblastoma; therefore, the cost of AFP screenings is the largest driver of cost in our model. However, although

the disease is rare, its incidence in the US has increased 4-fold over the past several decades, and the need for liver transplants as part of treatment has increased 20-fold.[19] From an insurer's perspective, the cost savings of diagnosing hepatoblastoma earlier and decreasing the extent of medical care required for treatment, especially avoidance of a liver transplant and years of immunosuppression, are significant. Preventing the need for a single orthotopic liver transplant also allows an organ to be allocated to another patient, a significant gain given that the need for donated organs far exceeds their availability.[55]

Our study has several limitations, most notably the use of estimated costs. The most recent pediatric-specific estimates in the literature were used for this model. However, there is likely significant cost variability between centers. Additionally, these estimates fail to account for the significant costs and complications of treatment with myelosuppressive chemotherapy, including the need for multiple blood product transfusions and growth factor support; admissions for febrile neutropenia and potentially sepsis, for which an average admission to the pediatric intensive care unit costs $248 478; and, in some cases, end-of-life care.[56-59]

The number of ELBW infants expected to undergo screening is likely an overestimate. Although survival outcomes for infants born in extreme prematurity continue to improve, data from 2009 indicates a standardized mortality rate of 12.4% among infants born weighing between 501 and 1500 g.[60] Therefore, the number of screening tests performed to diagnose each case of hepatoblastoma—and the overall cost of screening—would likely be lower than estimated here.

The model also uses the assumption that screening would detect a hepatoblastoma at 1 PRETEXT group lower than it would be diagnosed without screening. This proposed screening model is similar to the one for hepatoblastoma and Wilms tumor among children with Beckwith-Wiedemann syndrome that used a postsurgical staging system but assumed that tumors detected through screening would be 1 stage lower than those diagnosed without screening.[30] It is possible that AFP screening would result in tumors detected by screening being classified in the same PRETEXT group as they would have been with no screening; however, it is equally if not more likely that it would result in detection at more than one group lower (eg, detection at group II for a tumor that would have been diagnosed at group IV without screening) as supported by the detection of group I hepatoblastoma in 5 children with Beckwith-Wiedemann syndrome or isolated hemihyperplasia screened with AFP.[28]

As in all economic models, the clinical pathway for patients is typically an oversimplification of the real-world pathway(s) that clinicians may select in partnership with their patients.[61] This is certainly the case for this patient cohort, where many patients' care pathway and outcomes are determined by factors other than PRETEXT group, including tumor histology and AFP at diagnosis. The decision was made to use PRETEXT group as a surrogate for outcome owing to its demonstrated robustness and its widespread use among international research cooperatives. Although this model does not offer specific outcomes based on these factors, it provides generalizable information on value for the entire patient population. We hope that the tradeoff of a lack of specificity is met with an appreciation for management of screening to improve population health in this cohort of children.

The study lacked QALY values specific to the patient cohort, primarily because patient-reported outcomes of health utilities are difficult, almost impossible, to measure for young infants. As a result, we assumed that the QALY value for breast cancer was an appropriate proxy for the health utility of infants at risk for hepatoblastoma, given that the ranges of utilities for cancer outcomes are somewhat proximal to breast cancer. We used sensitivity analysis to test the uncertainty in this assumption.

Several potential challenges to this screening regimen also must be noted. Families might find it undesirable to undergo all screening blood draws as this represents much more frequent blood work than would normally be performed in otherwise healthy young children.[62] Current recommendations in the literature do not include counseling families of ELBW infants regarding the increased risk of hepatoblastoma. The importance of close follow-up of growth and development, motor function, screening for vision and hearing loss, and administration of vaccinations are well-documented, but the increased risk of, and potential screening for, hepatoblastoma are notably absent.[63,64] Mention of this risk is also lacking in the literature surrounding counseling of families facing periviable births, so introduction of the need for screening may induce additional stress among families.[65,66] In the setting of screening, false-positive results may also be associated with psychological distress, although most studies have reported only low to moderate levels among patients being screened and we account for the disutility of false-positive results in our model.[67]

Unfortunately, not all screening efforts have led to improved clinical outcomes from malignancies; in the past, several national programs evaluating urine for catecholamine metabolites to screen for neuroblastoma yielded no decreases in disease-specific mortality, likely owing to identification through screening of early-stage tumors with favorable characteristics that ultimately regressed without treatment.[68,69] Lessons learned from prior efforts include the necessity of evaluating new screening methods before implementing them en masse, though no similar phenomenon of spontaneous regression exists in hepatoblastoma has been noted. Ultimately, we do suggest performing feasibility studies on our proposed screening regimen considering large-scale implementation.

In summary, we have demonstrated the cost-effectiveness based on a $150 000 willingness-to-pay threshold of serial AFP measurements throughout the first 4 years of life in children born at ELBW to aid earlier detection of hepatoblastoma. Based on our analysis, implementation of such a

screening program would be expected to yield both significant cost savings and decreased rates of morbidity and mortality in this population. Although hepatoblastoma is rare, its incidence is increasing, as are the number of extremely preterm births and rates of survival among ELBW infants internationally.[19,70,71] We therefore recommend a study of the feasibility of our proposed intervention with the hopes of developing an effective method to decrease treatment-related costs and increase survival of children afflicted with this disease. ■

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Table III. Likelihood of model outcomes by model end point

Outcome labels	Description of outcome	Probability				Likelihood (product)
		Node 1	Node 2	Node 3	Node 4	
Outcomes: SOC (no screening protocol)						
SOC-1	SOC: group I → remission	0.00039	0.042	1		0.000017
SOC-2	SOC: group I → death	0.00039	0.042	0		0
SOC-3	SOC: group II → remission	0.00039	0.366	0.91		0.000130
SOC-4	SOC: group II → death	0.00039	0.366	0.09		0.000013
SOC-5	SOC: group III → remission	0.00039	0.317	0.68		0.000084
SOC-6	SOC: group III → death	0.00039	0.317	0.32		0.000040
SOC-7	SOC: group (transplant) → remission	0.00039	0.275	0.57		0.000061
SOC-8	SOC: group (transplant) → death	0.00039	0.275			0.000046
SOC-9	SOC: normal life course	0.99961				0.999608
Outcomes: intervention (screening)						
SCREEN-1	Screen positive: group I → remission	0.00039	0.96	0.408	1	0.000154
SCREEN-2	Screen positive: group I → death	0.00039	0.96	0.408	0	0
SCREEN-3	Screen positive: group II → remission	0.00039	0.96	0.317	0.91	0.000108
SCREEN-4	Screen positive: group II → death	0.00039	0.96	0.317	0.09	0.000011
SCREEN-5	Screen positive: group III → remission	0.00039	0.96	0.275	0.68	0.000070
SCREEN-6	Screen positive: group III → death	0.00039	0.96	0.275	0.32	0.000033
SCREEN-7	Screen positive: group IV (transplant) → remission	0.00039	0.96	0	0.57	0
SCREEN-8	Screen positive: group IV (transplant) → death	0.00039	0.96	0	0.43	0
SCREEN-9	Missed case: group I → remission	0.00039	0.04	0.042	1	0.000001
SCREEN-10	Missed case: group I → death	0.00039	0.04	0.042	0	0
SCREEN-11	Missed case: group II → remission	0.00039	0.04	0.366	0.91	0.000005
SCREEN-12	Missed case: group II → death	0.00039	0.04	0.366	0.09	0.000001
SCREEN-13	Missed case: group III → remission	0.00039	0.04	0.317	0.68	0.000003
SCREEN-14	Missed case: group III → death	0.00039	0.04	0.317	0.32	0.000002
SCREEN-15	Missed case: group IV (transplant) → remission	0.00039	0.04	0.275	0.57	0.000002
SCREEN-16	Missed case: group IV (transplant) → death	0.00039	0.04	0.275	0.43	0.000002
SCREEN-17	Screen negative: normal life course	0.99961	0.95			0.949628
SCREEN-18	False positive: normal life course	0.99961	0.05			0.049980

SOC, standard of care.

In this table, we report the probabilities for each node of the decision tree. In the final column, we report the overall probability of an individual in the model being included in the specific arm (outcome) of the decision tree. This is calculated by multiplying the probabilities from each node of the decision tree.

Table IV. Discounted costs by model end point

		Screening		Diagnosis		Treatment								Long-term costs					
Outcome labels	Description of outcome	AFP screening protocol (HB)	AFP screening protocol (healthy)	Diagnostic follow-up (ultrasound)	Diagnostic follow-up (biopsy)	Resection	2 Admissions for chemotherapy	6 Admissions for chemotherapy	Clinic visits for 6 months active treatment + 6 months monitoring following initial treatment	Central venous line	Transplant	Treatment following transplant (first year)	Treatment following transplant (6 mo)	Monitoring following remission	Immuno-suppression	Medical costs	Nonmedical costs	Income	Total cost
		$139	$247	$122	$4697	$28 401	$83 374	$246 968	$4961	$5920	$155 478	$139 580	$69 790	$23295	$516 113	$30 168	$530 097	–$768 853	
Costs: SOC (no screening protocol)																			
SOC-1	SOC: group I → remission			•	•	•			•					•		•	•	•	–$147 112
SOC-2	SOC: group I → death			•	•	•			•										$38 181
SOC-3	SOC: group II → remission			•	•	•	•		•	•				•		•	•	•	–$57 818
SOC-4	SOC: group II → death			•	•	•	•		•	•									$127 475
SOC-5	SOC: group II → remission			•	•	•		•	•	•				•		•	•	•	$105 776
SOC-6	SOC: group III → death			•	•	•		•	•	•									$291 070
SOC-7	SOC: group IV (transplant) → remission			•	•			•	•	•	•	•		•	•	•	•	•	$888 546
SOC-8	SOC: group IV (transplant) → death			•	•			•	•	•	•		•						$487 936
SOC-9	SOC: normal life course															•	•	•	–$208 588
Costs: intervention (screening)																			
SCREEN-1	Screen positive: group I → remission	•		•	•	•			•					•		•	•	•	–$146 973
SCREEN-2	Screen positive: group I → death	•		•	•	•			•										$38 320
SCREEN-3	Screen positive: group II → remission	•		•	•	•	•		•	•				•		•	•	•	–$57 679
SCREEN-4	Screen positive: group II → death	•		•	•	•	•		•	•									$127 614
SCREEN-5	Screen positive: group III → remission	•		•	•	•		•	•	•				•		•	•	•	$105 915
SCREEN-6	Screen positive: group III → death	•		•	•	•		•	•	•									$291 209
SCREEN-7	Screen positive: group IV (transplant) → remission	•		•	•			•	•	•	•	•		•	•	•	•	•	$888 685

(*continued*)

Table IV. Continued

		Screening		Diagnosis		Treatment								Long-term costs					
Outcome labels	Description of outcome	AFP screening protocol (HB)	AFP screening protocol (healthy)	Diagnostic follow-up (ultrasound)	Diagnostic follow-up (biopsy)	Resection	2 Admissions for chemotherapy	6 Admissions for chemotherapy	Clinic visits for 6 months active treatment + 6 months monitoring following initial treatment	Central venous line	Transplant	Treatment following transplant (first year)	Treatment following transplant (6 mo)	Monitoring following remission	Immuno-suppression	Medical costs	Nonmedical costs	Income	Total cost
		$139	$247	$122	$4697	$28 401	$83 374	$246 968	$4961	$5920	$155 478	$139 580	$69 790	$23295	$516 113	$30 168	$530 097	–$768 853	
SCREEN-8	Screen positive: group IV (transplant) → death	•		•	•			•	•	•	•		•						$488 075
SCREEN-9	Missed case: group I → remission	•		•	•	•			•					•		•	•	•	–$146 973
SCREEN-10	Missed case: group I → death	•		•	•	•			•										$38 320
SCREEN-11	Missed case: group II → remission	•		•	•	•	•		•	•				•		•	•	•	–$57 679
SCREEN-12	Missed case: group II → death	•		•	•	•	•		•	•									$127 614
SCREEN-13	Missed case: group III → remission	•		•	•	•		•	•	•				•		•	•	•	$105 915
SCREEN-14	Missed case: group III → death	•		•	•	•		•	•	•									$291 209
SCREEN-15	Missed case: group IV (transplant) → remission	•		•	•			•	•	•	•	•		•	•	•	•	•	$888 685
SCREEN-16	Missed case: group IV (transplant) → death	•		•	•			•	•	•	•		•						$488 075
SCREEN-17	Screen negative: normal life course		•													•	•	•	–$208 341
SCREEN-18	False positive: normal life course		•	•												•	•	•	–$208 219

In this table, we report the estimated costs for diagnosis and treatment of hepatoblastoma, as well as other long-term medical and nonmedical costs. We show what costs are included for each arm (outcome) of the decision tree. In contrast to the other parameters in the table, we assign income a negative value, because it is a benefit rather than a cost.

Table V. Discounted utilities by model end point

Outcome labels	Description of outcome	False positive	Healthy child - before 18 months	Healthy child - 18 to 24 months	Hepatoblastoma - 18 to 24 months	Healthy child - after 2 years	Hepatoblastoma (nontransplant) - 18 to 30 months	Adult life w/o HB sequelae	Transplant (year 1) - 24 to 36 months	Transplant (>1 year post-transplant) - 3 years to 79 years	Death	Total QALYs
		−0.0049	1.38	0.45	0.30	11.34	0.59	14.95	0.584	20.48	0	
Utilities: standard of care (no screening protocol)												
SOC-1	SOC: group I → remission		•		•	•		•				27.98
SOC-2	SOC: group I → death		•				•				•	1.98
SOC-3	SOC: group II → remission		•		•	•		•				27.98
SOC-4	SOC: group II → death		•				•				•	1.98
SOC-5	SOC: group III → remission		•		•	•		•				27.98
SOC-6	SOC: group III → death		•				•				•	1.98
SOC-7	SOC: group IV (transplant) → remission		•		•				•	•		22.74
SOC-8	SOC: group IV (transplant) → death		•				•				•	1.98
SOC-9	SOC: normal life course		•	•		•		•				28.13
Utilities: intervention (screening)												
SCREEN-1	Screen positive: group I → remission		•		•	•		•				27.98
SCREEN-2	Screen positive: group I → death		•				•				•	1.98
SCREEN-3	Screen positive: group II → remission		•		•	•		•				27.98
SCREEN-4	Screen positive: group II → death		•				•				•	1.98
SCREEN-5	Screen positive: group III → remission		•		•	•		•				27.98
SCREEN-6	Screen positive: group III → death		•				•				•	1.98
SCREEN-7	Screen positive: group IV (transplant) → remission		•		•				•	•		22.74
SCREEN-8	Screen positive: group IV (transplant) → death		•				•				•	1.98
SCREEN-9	Missed case: group I → remission		•		•	•		•				27.98
SCREEN-10	Missed case: group I → death		•				•				•	1.98
SCREEN-11	Missed case: group II → remission		•		•	•		•				27.98
SCREEN-12	Missed case: group II → death		•				•				•	1.98
SCREEN-13	Missed case: group III → remission		•		•	•		•				27.98
SCREEN-14	Missed case: group III → death		•				•				•	1.98
SCREEN-15	Missed case: group IV (transplant) → remission		•		•				•	•		22.74
SCREEN-16	Missed case: group IV (transplant) → death		•				•				•	1.98
SCREEN-17	Screen negative: normal life course		•	•		•		•				28.13
SCREEN-18	False positive: normal life course	•	•	•		•		•				28.12

HB, hepatoblastoma.

In this table, we report the estimated utilities for diagnosis and treatment of hepatoblastoma, as well as long-term utilities following treatment for hepatoblastoma. We show what utilities are included for each arm (outcome) of the decision tree.