

Screening for Wilms Tumor and Hepatoblastoma in Children With Beckwith-Wiedemann Syndromes: A Cost-Effective Model

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Background. We undertook a cost-benefit analysis of screening for Wilms tumor and hepatoblastoma in children with Beckwith-Wiedemann syndrome (BWS), a known cancer predisposition syndrome. The purpose of this analysis was twofold: first, to assess whether screening in children with BWS has the potential to be cost-effective; second, if screening appears to be cost-effective, to determine which parameters would be most important to assess if a screening trial were initiated. **Procedures.** We used data from the BWS registry at the National Cancer Institute, the National Wilms Tumor Study (NWTs), and large published series to model events for two hypothetical cohorts of 1,000 infants born with BWS. One hypothetical cohort was screened for cancer until a predetermined age, representing the base case. The other cohort was unscreened. For our base case, we assumed: (a) sonography examinations three times yearly (triannually) from birth until 7 years of age; (b) screening would result in one stage shift downward at diagnosis for Wilms tumor and hepatoblastoma; (c) 100% sensitivity and 95% specificity for detecting clinical stage I

Wilms tumor and hepatoblastoma; (d) a 3% discount rate; (e) a false positive result cost of \$402. We estimated mortality rates based on published Wilms tumor and hepatoblastoma stage specific survival. **Results.** Using the base case, screening a child with BWS from birth until 4 years of age results in a cost per life year saved of \$9,642 while continuing until 7 years of age results in a cost per life-year saved of \$14,740. When variables such as cost of screening examination, discount rate, and effectiveness of screening were varied based on high and low estimates, the incremental cost per life-year saved for screening up until age four remained comparable to acceptable population based cancer screening ranges (<\$50,000 per life year saved). **Conclusions.** Under our model's assumptions, abdominal sonography examinations in children with BWS represent a reasonable strategy for a cancer screening program. A cancer screening trial is warranted to determine if, when, and how often children with BWS should be screened and to determine cost-effectiveness in clinical practice. Med Pediatr Oncol 2001;37:349–356. Published 2001 Wiley-Liss, Inc.[†]

Key words: Beckwith-Wiedemann syndrome; cost-effectiveness analysis; Wilms tumor; cancer screening

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome characterized by some or all of the following features: gigantism, macroglossia, omphalocele, hemihypertrophy, and neonatal hypoglycemia. One of the most striking features of infants with BWS is the increased frequency of embryonal tumors, particularly Wilms tumor and hepatoblastoma [1].

Consequently, clinicians have struggled with the question of whether children with BWS should receive periodic screening for cancer and if so, how often. Recommendations have varied from no screening to abdominal sonography screening every 3 months from birth to 8 years of age. These recommendations are based on expert opinion [2], case reports [3], and retrospective analysis [4]. We recently demonstrated that screening every 4 months reduced the proportion of late stage Wilms tumor in children with BWS to zero which was statistically significant when compared to the 42% of unscreened children who had late stage disease [5]. To date no formal screening trial has been undertaken.

We used a simulation model of children with BWS to determine whether screening for Wilms tumor and hepatoblastoma is potentially cost-effective and to determine the most important parameters to measure in prospective intervention screening.

METHODS

Analytical Model

The spreadsheet model has two hypothetical cohorts of children with BWS: one undergoes screening; one does

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not undergo screening. The cost-effectiveness of screening is determined by comparing the cost of screening, diagnostic follow-up and treatment, and by comparing the predicted life expectancy of the respective cohorts. Predicted life expectancy and cancer treatment costs are modeled as a function of cancer stage-at-diagnosis (as well as favorable/unfavorable histology for Wilms tumor).

Inputs to the model include the observed stage distribution and 4-year survival of Wilms tumor and hepatoblastoma. In the base case the stage detected by screening is assumed to be one stage lower than the stage observed for clinically detected disease, except for stage I where no benefit from screening is assumed. For purpose of estimating remaining life expectancy, 4-year survival is assumed equivalent to cure. Other inputs to the model are age-specific Wilms tumor and hepatoblastoma incidence, all causes of mortality, average age-specific life expectancy, screening frequency, probability of a confirmatory diagnostic CT scan after positive screening ultrasonography, the cost of screening and diagnostic procedures, stage-specific cancer treatment costs, and the discount rate.

Each cohort is followed in 4-month periods (triannually). At the beginning of each period the population available for screening equals the population from the preceding period minus individuals who have died from overall mortality minus incident Wilms tumor and hepatoblastoma (BWS cancer) cases detected during the previous period. Total screening costs for any 4-month period are equal to the number of individuals available for screening multiplied by the unit cost of screening. For each period the number and stage of BWS cancers are derived from the total population available for screening and the predetermined estimates of age-specific BWS cancer incidence and stage distribution (which are different for the screened and unscreened cohorts).

The estimated life-years lost due to BWS cancers in any given period is equal to the number of stage-specific cases, multiplied by the 4-year cumulative probability of BWS cancer death (i.e., 1–4 year survival), multiplied by age-specific life expectancy for all individuals (–2 years to take into account the average life expectancy already observed during the 4-year survival period). There are three assumptions embodied in this procedure: (a) 4-year survival is equivalent to cure; (b) life expectancy for a cured BWS patient is identical to normal life expectancy; (c) lead time due to screening for BWS cancers is short compared to remaining life expectancy. Total life-years lost to BWS cancers are determined by adding life-years lost for each age and stage of cancer across all BWS stage-specific cancers. Since screening changes the stage distribution and 4-year survival varies by stage, total life-years lost to BWS cancers will be

TABLE I. Base Case Assumptions

Number of patients in cohort at birth	1,000
Discount rate	0.03
False positive rate	0.05
Cost of false positive result	\$402
Percent of cancer shifted one stage downward	100%
Cost of screening examination	\$211
Age that screening is stopped	7 years of age

different (lower) for the screened compared to the unscreened cohort.

All period-specific costs and life-years lost are summed across periods. All costs and life-years lost are also discounted at the specified discount rate of 3% per year in the base case. To obtain cost-effectiveness ratios, total (discounted) costs and total (discounted) life-years lost are compared between the screened and the unscreened cohorts (Table I).

We have presented our calculations in year 2000 dollars using the medical care component of the consumer price index, available at the US Bureau of Labor Statistics web page (<http://stats.bls.gov:80/datahome.htm>).

Determination of Incidence

We used the BWS registry to determine the cumulative incidence and age-specific incidence of hepatoblastoma in children with BWS during the first four years of life [1]. We derived the incidence of hepatoblastoma for the first four years by taking the number of hepatoblastoma cases seen in the registry and dividing by the number of patient years for the first four years. This provided the 4 year average incidence. The proportion of hepatoblastomas for each year of life were based upon population (SEER) reports [6]. We then multiplied the proportion of hepatoblastomas in each year of life up to 4 years by the average 4 year incidence of hepatoblastoma to estimate the average annual incidence of hepatoblastoma. We did not include the development of hepatoblastoma beyond the first four years of life as an event, because 99% of all hepatoblastoma tumors occur prior to 4 years of age [7]. The stage distribution of hepatoblastoma was based on a large series of children with hepatoblastoma (Table IV) [7].

The age-specific incidence of Wilms tumor was calculated in a similar manner as for hepatoblastoma. We used The BWS registry to establish incidence of Wilms tumor in the first ten years of life [1] and the NWTS to determine the age-specific proportion of children with BWS and Wilms tumor during the first ten years of life [8]. The age-specific incidence of Wilms tumor was then determined by multiplying the average 10 year incidence of Wilms tumor by the age-specific proportion of children with Wilms tumor (Table II). The stage distribution, histology, and survival, presented in Tables III and V respectively, were based on the data

TABLE II. Incidence Estimates of Wilms Tumor and Hepatoblastoma Per 100 Children With Beckwith-Wiedemann Syndrome

Age (years)	Incidence of Wilms tumor	Incidence of hepatoblastoma	Cumulative percentage of Wilms tumor and hepatoblastoma occurring by age
0-1	2.01	1.98	28
1-2	2.21	1.2	51
2-3	1.73	0.55	67
3-4	1.28	0.45	79
4-5	1.28	0.07	89
5-6	0.61	0	93
6-7	0.35	0	95
7-8	0.35	0	98
8-9	0.16	0	99
9-10	0.16	0	100

obtained from NWTS III and IV (Personal Communication, Norman Breslow).

Frequency of Abdominal Sonography Examinations

The recommended interval for those who have suggested screening evaluations in children with BWS has varied from 3 to 6 months [3, 9]. In a separate study, we have found sonography examinations done every 4 months were effective in decreasing the proportion of late stage Wilms tumor [5]. In fact, none of the patients who were screened in intervals of 4 months or less had late stage Wilms tumor [5]. Based on these results, we used an interval of every 4 months for sonography examinations. We did not expand the interval to 6 months because our previous results indicated that screening every 6 months did not prevent late stage disease.

Mortality From Wilms Tumor, Hepatoblastoma and Other Causes

Using the simulation model, we predicted the total number of expected deaths in each triannual period. The total number of deaths included the sum of the expected deaths from Wilms tumor, hepatoblastoma and other causes. The expected number of deaths from Wilms tumor was based on histology, stage of diagnosis, and

TABLE III. Stage Distribution for Unscreened and Screened Patients With Wilms Tumor

	Unscreened	Screened
Favorable histology (stage)		
I	0.42	0.62
II	0.20	0.20
III	0.20	0.08
IV	0.08	0.00
Unfavourable histology (stage)		
I-III	0.09	0.11
IV	0.02	0.00

TABLE IV. Stage Distribution for Unscreened and Screened Patients With Hepatoblastoma

	Unscreened	Screened
Stages I and II	0.41	0.8
Stage III	0.39	0.20
Stage IV	0.2	0.0

4 year survival rates (personal communication, Norman Breslow, see Tables III and V). For hepatoblastoma, the expected number of deaths was based on stage and five-year survival rates (Table VI) [10]. For other causes, the expected number of deaths was based on United States Vital Statistics data [11].

Sensitivity and Specificity of Abdominal Sonography

Abdominal sonography examinations can detect 100% of renal tumors that are at least 30 mm in diameter [12]. We assumed abdominal sonography was 100% sensitive and 95% specific to detect clinical stage I Wilms tumor at least 3 cm in diameter and clinical stage I hepatoblastoma. We also used a 95% specificity rate for detection of Stage III Wilms tumor.

Determination of Costs

We assessed treatment costs and the costs associated with screening for each triannual screen. The primary determinant of cost in this cancer screening program is the abdominal screening examination. The direct cost of an abdominal sonography examination was \$155 based on information provided by a large health maintenance organization (personal communication, Bruce Fireman, Department of Research, Kaiser Permanente, Northern California). The total cost for triannual screening examinations was calculated by multiplying the total number of screening examinations (from birth until the year that the screening examinations stopped) by \$155.

In each four-month interval, the total number of sonography examinations was adjusted for the number of expected deaths attributable to Wilms tumor, hepatoblastoma, and other causes. Screening is determined by comparing the cost of screening, diagnostic follow-up

TABLE V. Four-Year Survival Rate for Patients With Wilms Tumor

	Survival rate
Favourable histology (stage)	
I	0.96
II	0.92
III	0.87
IV	0.82
Unfavourable histology (stage)	
I-III	0.68
IV	0.55

and treatment, and by comparing the predicted life-expectancy of the respective cohorts. Predicted life-expectancy and cancer treatment costs are modeled as a function of cancer stage-at-diagnosis as well as favorable/unfavorable histology for Wilms tumor.

The additional cost of confirmatory diagnostic testing for a false positive test was calculated as the number of BWS patients per triannual period multiplied by the false positive rate of 5% multiplied by the unit cost of a CT scan. In addition, as part of our sensitivity analysis, we calculated the cost of sending an additional 5% of CT positive but true negative patients to surgery at a hypothetical cost (not charge, which would vary by provider and region) of \$5,000 per procedure. Cancer treatment costs were determined by multiplying stage-specific treatment costs by stage-specific number of cases. Within each period, screening, diagnostic, and treatment costs were summed for each stage and summed across all stages.

We used the willingness to pay method to calculate the indirect costs of the cancer screening program, the cost associated with time and economic opportunity lost by the family [13]. We mailed 200 questionnaires to parents of patients in the BWS registry and received responses from 124 families (62%). In the questionnaire we asked the following question:

If a new test could be done that is just as good as an ultrasound done at the hospital but only requires you to take a Polaroid picture at home, what is the most you would be willing to pay out of pocket (not paid by insurance) for this new test:

- less than \$50
- \$50-99
- \$100-149
- \$150-199
- more than \$200.

The average response was \$42 (in 1993 dollars) based on the midpoint of range (for the response of more than \$200, we used \$200). In our model, we specified a total screening cost of \$211, reflecting an adjustment to year 2000 dollars.

The cost of treatment for Wilms tumor and hepatoblastoma varies considerably depending on the patient and the treatment regimen. For all patients with Wilms tumor and hepatoblastoma, treatment includes surgical resection of the cancer and usually combination chemotherapy. For patients with advanced Wilms tumor (Stages III and IV) standard treatment includes radiation therapy. While treatment for advanced hepatoblastoma may include liver transplant, transplantation is not considered standard care. The major difference in cost between early and late stage Wilms tumor is the cost associated with radiation therapy. Whereas, for early and

late stage hepatoblastoma there is no clear treatment cost difference since all patients receive surgery and chemotherapy.

We elected to include only the incremental costs associated with medical treatment of early stage when compared to late stage Wilms tumor. The incremental charge difference, found to be \$704, for late stage versus early stage therapy has been systematically reviewed and published [14]. Because the results of the study by Green et al. were based on data obtained in New York, we used the New York statewide average operating cost-to-charge ratio (0.63) for urban hospitals to derive the average incremental cost from this charge data [15]. The average increment cost between late and early stage Wilms tumor was estimated as \$443.

Calculation of Average Cost Per Life-Year Saved

The cost-effectiveness of the cancer screening program was calculated using the following formula:

$$CE = (C_s - C_c) / (LYL_c - LYL_s),$$

C indicates the total costs in the screened (C_s) and unscreened cohorts (C_c), including the aggregate costs of screening up to the age at which screening is stopped in the screened cohort and the incremental therapy costs associated with late stage Wilms tumor. LYL indicates the aggregate number of life-years lost in the screened (LYL_s) and unscreened cohorts (LYL_c). All costs and life-years were discounted at 3% per annum.

Calculation of Incremental Cost Per Life-Year Saved

Incremental costs in this analysis refer to the additional costs per life-year saved when screening is extended by one year. The incremental cost-effectiveness was calculated by comparing the difference between the costs associated with stopping abdominal sonography examinations in two successive years divided by the difference of the life-years saved for the same successive years.

RESULTS

Our base-case analysis held five assumptions:

- (1) abdominal screening was done from birth until 7 years of age;

TABLE VI. Four-Year Survival Rate for Patients With Hepatoblastoma

	Survival rate
Stages I and II	0.91
Stage III	0.67
Stage IV	0.125

- (2) screening is 100% sensitive and 95% specific for detecting early stage Wilms tumor and hepatoblastoma;
- (3) screening results in one downward stage shift of Wilms tumor and hepatoblastoma when compared with no detection;
- (4) the costs and benefits of screening were discounted at 3%;
- (5) a false-positive rate of 5% with a cost of \$402/false-positive result.

Using the base-case analysis, screening for cancer in children with BWS up until 7 years of age costs \$14,740 per life-year saved. If the age that screening is stopped is advanced from 7 to 8, 9 or 10 years of age, the cost per life-year saved increases to \$16,377, \$17,996, and \$19,554, respectively (Table VII). If the age that screening is stopped decreases from 7 to 6, 5 or 4 years of age, the cost per life year saved decreases to \$13,023, \$ 11,272, and \$9,642 respectively (Table VII).

The incremental cost per life-year saved is much higher when compared to the average cost per life-year saved. The discrepancy between the incremental and average cost for each corresponding year occurs because most of the benefit for cancer screening is in the first few years when the annual incidence of cancer is the highest. As the cohort of children with BWS ages, fewer cancers are detected per year; however, approximately, the same number of sonography examinations are done each year. Thus, the incremental cost of cancer screening increases dramatically with each year.

SENSITIVITY ANALYSIS

To determine whether our estimates of key parameters had a significant impact on the results, we modified the parameter of interest while keeping the other parameters unchanged.

Efficacy of Sonography to Detect Early Stage Wilms Tumor/Hepatoblastoma

For the base case, we assumed that screening with abdominal sonography examination would result in one downward shift in diagnosis for every patient with Stages II, III, or IV Wilms tumor or Stages II, III, or IV hepatoblastoma, i.e., 100% effectiveness. We varied the effectiveness of screening from 100 to 50%. The resulting cost per life-year saved increased from the base case of \$14,740 to \$16,703.

Effect of Doubling the Cost of Sonogram Examinations

If the cost of the sonogram is doubled, with no doubling of the indirect cost, the cost per life-year saved for the base case would increase from \$14,740 to \$24,736. If screening stopped at 4, 6, 8 or 10 years, the cost per life-year saved would be \$16,196, \$21,861, \$27,476, and \$32,795 respectively.

Effect of Detecting Wilms Tumor and Not Detecting Hepatoblastoma When Screening

If screening does not affect the stage distribution of hepatoblastoma, the cost per life-year saved with screening until age seven would increase from \$14,740.44 to \$70,290 for the base case. Furthermore, if screening had stopped at 4, 6, 8 or 10 years of age rather than 7 years of age as in the base case, the cost per life-year saved would have been \$54,262, \$62,519, \$76,458, and \$89,763 respectively.

Effect of Treatment Costs

We only included incremental costs of therapy in children with stage III and IV Wilms tumor. We did not add other costs associated with treatment for hepatoblastoma. To determine if the exclusion of these costs had an effect on our primary estimates, we increased the

TABLE VII. Estimates of Cost-Effectiveness of Screening for Cancer in Children With Beckwith-Wiedemann Syndrome, 3% Discount Rate for Both Costs and Health Effects (Numbers are not Exact due to Rounding off)

Year screening stops	Total cost	Life-years saved	Cost per life-years saved	Incremental cost per life-year saved
1	\$656,045	117.91	\$5,503	
2	\$1,226,806	185.62	\$6,535	\$8,330
3	\$1,760,685	218.16	\$7,986	\$16,266
4	\$2,265,579	232.74	\$9,642	\$34,589
5	\$2,745,898	241.45	\$11,272	\$54,884
6	\$3,205,460	244.19	\$13,023	\$166,737
7	\$3,647,889	245.72	\$14,740	\$289,648
8	\$4,074,686	247.18	\$16,377	\$291,037
9	\$4,486,755	247.82	\$17,996	\$643,889
10	\$4,885,239	248.44	\$19,561	\$647,164

incremental cost from \$443 to \$2,640. This change resulted in less than a \$500 difference in the cost per life-year saved when compared to the base case since the major expense is the cost of the screening procedures used.

We evaluated the effect of sending the patients with false positive CT results (5%) to surgery at a cost of \$5,000 (per surgical procedure). If 1,000 persons are screened at a cost of \$211 per test, the resulting screening cost is \$211,000. In an average, test period 0.003% test positive for Wilms tumor but 5% of those are discovered to be false positives during exploratory surgery. For example, the cost of false positive results is equal to the total number of patients (n) testing positive (if 1,000 individuals are screened, n will be equal to 3) multiplied by the number of persons who are falsely positive (0.05) multiplied by the cost of surgery (\$5,000). The product is \$750. Thus the cost of a false positive result, when 1,000 children are screened, is small compared to the overall cost of \$211,000.

Effect of Discount Rate

The discount rate had a marginal impact on the average and incremental cost per life-year saved. In our base case, we discounted life-years saved and cost at 3%. When we changed the discount rate from 3 to 7% and then eliminated discount rate entirely (discount rate equal to zero), the results of the base case changed from \$14,740 to \$16,643 and \$3,224, respectively.

Effect of the Cost of a False Positive Result

When the cost of a false positive result increased from \$402 to \$1,320, the average cost per life-year saved for the base case increased to approximately \$19,000, representing a 25% increase.

Worst-Case Scenario

To determine what would happen if the worst-case scenario were used, we varied several worst estimate assumptions simultaneously: discount rate of 7%; false positive rate of 10%; false positive cost of \$1,320; and a 50% reduction in stage shift. Based on these assumptions, the average cost per life-year for the base case was \$95,294. The incremental cost when the age of screening cessation was increased from 7 to 8 years of age was \$1,894,165. Under this scenario, screening would have to stop at 3 years of age to keep the incremental cost below \$100,000.

DISCUSSION

When determining whether a cancer screening intervention program is worthwhile, two critical questions must be answered. First, does the screening program

decrease morbidity or mortality associated with the cancer, i.e., is the screening program effective? Second, does the cost of the screening program per life-year saved compare favorably with other acceptable cancer screening [16]? Based on previous work indicating that screening is clinically effective [5], we have shown that screening for BWS is potentially cost-effective and warrants prospective evaluation as an intervention trial.

Given the small number of children with BWS, why should a cost-effectiveness analysis even be considered? First, children with BWS represent only one of several cancer predisposition syndromes associated with Wilms tumor or hepatoblastoma. A similar rationale for Wilms tumor screening can be made for children with idiopathic hemihypertrophy, Simpson–Golabi–Behmel, Aniridia and Denys–Drash syndromes. No formal guidelines exist regarding the relative merits or consequences of cancer screening for children with Wilms tumor predisposition syndromes. Thus, our model provides the first step in formulating a decision about whether cancer screening is feasible in these select populations. Second and equally as important, children with BWS have a significant risk of cancer, thus for this small group of patients, screening may decrease the mortality and possibly morbidity.

As the characterization of cancer predisposition genes continues to improve, patients, families, and physicians will be forced to weigh the relative benefit versus cost of cancer screening. If a future trial is to be offered, the key variables that should be measured must be identified. For these reasons a simulation model for cancer screening in this population is a valid and important starting point.

The favorable cost-effectiveness for cancer screening in this population is driven by three factors. First, in children with BWS the incidences of Wilms tumor and hepatoblastoma is extremely high in early infancy and childhood. In a cohort of 183 children with BWS followed from birth through their first 4 years of life, there were 6 patients with Wilms tumor and 5 with hepatoblastoma [1]. Second, the survival of both Wilms tumor and hepatoblastoma is closely related to the clinical stage at the time of diagnosis and the ability to completely resect the tumor. Thus, children who are identified as having early stage cancer have a much better predicted survival when compared to children who have late stage cancer. Finally, the major cost of the screening program is a sonography examination, a simple and inexpensive screening intervention that is readily accepted and tolerated. Though we had a response rate of less than two-thirds to our questionnaire, we did find that there is a willingness to pay for parental peace of mind.

Given the base-case assumptions of the model, screening up to 7 years appears to be favorably cost-effective under all but the worst-case scenario: discount rate of 7%; false positive rate of 10%; false positive cost of \$1,320; and 50% reduction in stage shift effectiveness.

The worst-case scenario is possible, but we have no reason to believe that it is the most likely model. Even with high and low estimates in the hypothetical cohort, our results for cancer screening in children with BWS are comparable to other cancer screening programs. These screening programs include mammography, for women over 50 years of age, at \$46,200 [17] or fecal occult blood tests at \$48,840 [18] per life year saved respectively. However, our results are not directly comparable to these screening trials. We used a hypothetical cohort and the adult screening studies are based upon actual clinical trial data. In children, a cancer screening trial has only been evaluated for infants with neuroblastoma. Recent data suggests that screening for neuroblastoma is not effective in decreasing the morbidity or mortality [19]; hence making a cost-effectiveness analysis unnecessary.

The incremental data suggest that stopping screening in BWS patients at age four would be the most cost-effective approach. The rapidly increasing increment results from the low number of cases of Wilms tumor and hepatoblastoma in children over 4 years of age. Since the number of events in the older age group is very sparse, it is reasonable to take these very large incremental cost-effectiveness ratios with some caution and weigh them against the additional peace of mind that families may get from screening their child beyond 4 years of age. The latter benefit is something that we have not quantitatively evaluated. Further, it is the very small denominator which makes these incremental cost effectiveness ratios large, not the modest incremental cost. A modest willingness to pay value of the extra piece of mind could make a big difference in the decision regarding cessation of screening. In fact, many parents of children with BWS elect to continue ultrasound examinations beyond 8 years of age despite decreasing risks of Wilms tumor for just this reason (DeBaun, personal communication). Further, our model did not include the cost of eliminating late effects of radiation therapy, which would include second malignancy, scoliosis, and congestive heart failure. The inclusion of this late effects cost, if the cost could be quantified, would improve the level of support that screening for Wilms tumor is potentially cost-effective.

Our simulation model has several limitations regarding a potential screening trial with BWS patients. As with all screening trials, lead time and length time biases must be addressed. Lead time refers to the artificial gain in life years attributable to screening. However in this clinical situation, lead time is minimal because of the rapid growth of Wilms tumor. The doubling time of Wilms tumor is reported to be from 1 to 3 weeks [20]. Given the rapid doubling time of Wilms tumor, many patients who were not screened could have clinically apparent tumor within 6 months. This is supported by our previous data demonstrating the clinical benefits of screening at 4 month intervals [5]. Thus, the maximal lead time would

be 6 months, which is only a small proportion of the expected life years gained through screening. Length time bias occurs when cases of a disease detected by screening are not a random sample of cases with preclinical disease. Thus, cases with more prolonged phases of preclinical disease are over represented in the screened population. Once again given the rapid growth of Wilms tumor and the fact that Wilms tumor is uniformly fatal if not treated, the length of time bias is negligible.

An additional limitation of our model is the optimistic assumption that screening is 100% sensitive. With tri-annual screening, a tumor that escaped detection during one screened would probably have grown to detectable size by the next screening cycle. While indeed no screening test is perfect, modern imaging will allow the detection of small tumors prior to the time when they would be detectable by palpation. The average size of Wilms tumor detected by screening is 3.4 cm [5]; while the average size of Wilms tumor detected by without screening in sporadic patients is greater than 10 cm [21]. Another limitation in our analysis is the cost for sonography. This variable is the only one that can truly be assessed through an empirical trial to establish the true cost of performing sonography in a community based screening setting. Nevertheless, in our model, screening for Wilms tumor among BWS patients remains reasonably cost-effective even when the estimated cost of sonography is increased several fold.

Using a simulation model, we have demonstrated that screening for BWS is potentially cost-effective from 4 years of age through 7 or 8 years of age. Although rare, BWS represents only one of several Wilms tumor cancer predisposition syndromes that would be eligible for a screening intervention trial. Only with a prospective trial could the true cost to patients and their families as well as the true effectiveness of screening be determined for this high risk population.

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