Economic Evaluation of Pediatric Cancer Treatment: A Systematic Literature Review

OBJECTIVE: Although there is a growing national focus on health care cost containment and accountability in resource utilization, childhood cancer therapy costs continue to increase without proportionate survival improvements. Economic evaluations (EEs) such as cost and/or cost effectiveness analysis may identify areas to improve resource efficiency. This review aims to identify and characterize the EE studies performed in this field.

METHODS: We performed a structured literature search of the Medline, PubMed, and the National Health Service EE databases from 2000 to 2011. Concepts for the search included “cost analyses,” “child,” and “cancer.” Studies were limited to original research, comparison of 2 or more treatments using monetary units, English language, and originating from economically developed countries. Identified studies were assessed by the Drummond checklist and characterized by the therapy studied, data sources, and research perspectives.

RESULTS: Forty studies met inclusion criteria. Eleven studied chemotherapy, surgery, or radiation. Twenty-nine studied supportive measures such as growth factor support or treatment of infection. The median Drummond score was 6 of 10 (range, 2–9). Only 15 (36%) included treatment outcomes when comparing costs. Methodological limitations were common.

CONCLUSIONS: A wide variety of topics and methodological limitations made comparisons between studies difficult. Strategies for increasing the generalizability of future EE studies are presented. Substantial opportunity exists for EE research in childhood cancer. Pediatrics 2013;131:e273–e287
Dramatic increases in overall childhood cancer survival since the 1970s are due, in part, to collaborative, prospective research. However, childhood cancer represents a mixture of cancer types with varying survival. Children with acute lymphocytic leukemia (ALL), germ cell tumors, or nephroblastoma are most likely to benefit from current medical technologies. Consistently curative treatment of other types of cancers such as bone-based malignancies or central nervous system tumors remains elusive. Mortality rates for these types of tumors were unchanged from 1996 to 2006.1

Treating a child with cancer is an expensive and resource-intense proposition for the health care system and the families involved. Therapies for childhood cancer have mirrored or outstripped the rapid growth seen in the overall health care system. According to the Healthcare Cost and Utilization Project, the average charge of an admissions for pediatric cancer therapy increased by 36%, from $29 700 in 2000 to $40 400 in 2009 (2009 US dollar [USD]), greater than the 30% increase in other pediatric admissions during that same time.2 Total inpatient and outpatient medical costs averaged ~$19 000 per year per patient in a 1985 study3 and closer to $51 000 per patient in the first year of treatment in a 1992 single institution review.4 Analysis of total medical costs of treatment of children with leukemia or central nervous system tumors in 2004 estimated average costs of $89 000 for children who survived and $236 000 for those who died.5 Families of children with cancer face out-of-pocket medical expenses, expenses for travel, and loss of income from time off of work; expenses that may exceed a family’s income.6,7

Increasing health care resource utilization and varied survival gains suggest that a portion of the increased utilization is not associated with improved outcomes. Economic evaluation (EE), or comparing treatments on the basis of monetary units, may provide decisionmakers with additional data to supplement medical-based outcomes. EE can estimate the monetary values only (cost analysis [CA]) or relate the costs to an outcome such as survival or infection (cost effectiveness analysis [CEA]), a user preference (cost utility analysis [CUA]), or a willingness to pay for the treatment (cost benefit analysis [CBA]). Such evaluations require resources to perform properly and can have limited generalizability across time, geographic borders, and health care systems.8 These later limitations can be lessened by robust EE methodology. EEs consider the perspective of the decision-maker (medical system, patient, society) when deciding which components of treatment to include in the costs.9 A treatment that is more cost effective for the hospital or third party payer is not necessarily more cost effective for the family, or may have significant late effects that affects the patient’s long-term productivity.10 The object of this study was to identify and describe existing EE applied to childhood cancer therapies via a systematic review of the literature with hopes to instruct future research.

METHODS

Study Selection

Inclusion criteria for our systematic review required reports of original research using monetary units to comparing 2 or more tumor-directed or supportive measures for the treatment of childhood cancer. This review was limited to articles in the English language and originating from nations associated with the Organization for Economic Cooperation and Development. If an article included reports on both adults and children, it was included only if a child-specific EE was evident. A structured literature search was performed of the Medline (Ovid), PubMed (National Library of Medicine), and the National Health Service EE databases from January 1, 2000, to December 31, 2011. Concepts that made up the search included “cost analyses,” “child,” and “cancer.” A complete list of search strategies can be found in Supplemental Appendix 1. The resulting abstracts were evaluated by the predefined inclusion and exclusion criteria first in abstract form and then in full-text format by a single reviewer (Dr Russell). When the reviewer questioned inclusion of an article, the research group decided via consensus. Two reviewers (Drs Russell and Panchal) abstracted data from each article into an extraction spreadsheet according to their field of expertise. Information collected included patient population, outcomes, treatments under comparison, and whether these were tumor-directed therapies (component of direct antitumor interventions with chemotherapy, radiation therapy, surgical procedures, or a combination) or supportive therapies (medications, surgical intervention, or processes designed to abrogate complications from tumor-directed therapies). The type of EE was captured and categorized as CA if it measured or valued treatments in monetary units without comparison with an outcome, a CEA if the monetary units were compared with a health outcome consequence, a CUA if the monetary units were compared with a patient/caregiver utility or value-based consequence, or CBA if results were presented as a willingness to pay for the therapy. Incremental cost effectiveness ratios, a measure of the additional cost for an additional successful outcome, were identified if included in the report. All monetary units were converted to 2012 USD by using the Consumer Price Index.11 The exchange rate on June 30 of
the original year was used to convert other currencies to USD. If the article did not state the monetary unit’s original year, the year before the year of publication was assumed. If a range of dates was presented, the midpoint year was chosen as the original year. Descriptive features of the investigators were captured by identifying the country (or countries) of origin and research setting (single institution, multiple institution, or cooperative group). The perspective of the EE was captured according to the authors’ stated definition or as “not stated.” Data sources were categorized as retrospective or prospective medical and/or research charts, hospital database for institution-based administrative database, and regional-national database for reimbursement or health care databases available to more than 1 institution. Descriptive statistics were performed by using Stata version 11 (Stata Corp, College Station, TX).

**Qualitative Assessment of EEs**

A quality assessment of the methodology was executed on included studies by utilizing the criteria provided by Drummond et al., entitled “A check-list for assessing economic evaluations.” This previously validated checklist identifies 10 key elements and methodological characteristics users may expect to find in well-executed studies (Table 1). Each item is scored as “yes,” “no,” or “can’t tell,” and a point is given for each “yes.” A higher quality study was defined as a score ≥7. A single reviewer (Dr. Panchal), experienced in applying this tool, scored all the articles.

**RESULTS**

**Search Results**

Of the 854 citations identified, 40 met our inclusion criteria (Fig 1). Most studies (24; 60%) were published in 2005 or earlier. European investigators performed the majority of the studies \((n = 22, 55\%)\) followed by investigators in the United States \((n = 10, 25\%)\) and Canada \((n = 7, 17\%)\). The intervention studies were varied but concentrated toward a few topics. Eleven studies addressed costs of tumor-directed therapies (Table 2); 5 of these compared or described costs associated with hematopoietic stem cell transplantation.Twenty-nine articles compared costs of supportive therapies (Table 3). Nine (31%) of these studies investigated costs associated with treatment of infections, 7 articles questioned the cost and/or benefits of adding granulocyte colony stimulating factor [G-CSF] to myelosuppressive chemotherapy, 3 articles studied the
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<tr>
<td>Madero et al</td>
<td>Allogeneic SCT for leukemia with PBPC or BM graft</td>
<td>Survival at +100 d</td>
<td>CEA</td>
<td>Single institution, Spain</td>
<td>Not stated</td>
<td>1999 USD; direct medical costs from product collection to +100 d</td>
<td>Patient (R); n = 25; hospital DB; regional-national DB</td>
<td>6</td>
<td>No difference in survival. The average cost of PBPC SCT was $19,514. The average cost of BM SCT was $27,368 ($P = .047).</td>
</tr>
<tr>
<td>Vicent et al</td>
<td>Autologous SCT with PBPC or BM graft</td>
<td>LYG</td>
<td>CEA</td>
<td>Single institution, Spain</td>
<td>Hospital</td>
<td>1999 USD; direct medical costs of stem cell collection and transplant admission</td>
<td>Patient (R); n = 124; hospital DB; regional-national DB</td>
<td>7</td>
<td>The average cost of PBPC was $10,891. Average cost of BM SCT was $16,305. Incremental cost of PBPC per LYG for acute myeloid leukemia was $96,304 and for ALL was $55,242.</td>
</tr>
<tr>
<td>Yeoh et al</td>
<td>PBPC mobilization in medulloblastoma with filgrastim alone or combined with topotecan</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, United States</td>
<td>Hospital</td>
<td>1999 USD; direct medical costs of mobilization and collection</td>
<td>Patient (P); n = 24; hospital DB; literature</td>
<td>7</td>
<td>Filgrastim + topotecan resulted in an overall savings of $5470 per patient over filgrastim alone.</td>
</tr>
<tr>
<td>Lin et al</td>
<td>Allogeneic SCT for leukemia with PBPC or BM graft</td>
<td>Disease-free survival at 1 y after SCT</td>
<td>CEA</td>
<td>Single institution, United States</td>
<td>Health care providers and policy makers</td>
<td>2008 USD; direct medical costs from preparative regimen to 1 y after SCT</td>
<td>Patient (R); n = 140; hospital DB</td>
<td>9</td>
<td>Average cost per patient was $402,748 for PBPC SCT and $487,886 in BM SCT ($P = NS). ICER for BM SCT - $733,421 for standard risk patient and $1.8 million for patients with high-risk features.</td>
</tr>
<tr>
<td>Majhail et al</td>
<td>Allogeneic SCT with matched-related donors, matched-unrelated donors, or unrelated umbilical cord blood grafts</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, United States</td>
<td>Not stated</td>
<td>2004–2006 USD; direct medical costs of graft acquisition and from day −30 until +100, excluding physician costs and home services</td>
<td>Patient (R); N = 148; hospital DB</td>
<td>6</td>
<td>Average cost for acquisition: matched-related donor, $10,462; matched-unrelated donor, $6,731; umbilical cord, $69,321; average cost per day survived: matched-related donor, $40,55; matched-unrelated donor, $47,86; umbilical cord, $5,321 ($P &lt; .01).</td>
</tr>
</tbody>
</table>

Leukemia

Kurre et al | Randomly assigned patients with leukemia to Pegaspargase versus native Escherichia coli L-asparaginase | NA | CA | Cooperative group, United States | Payer; societal | 1988 USD; direct and indirect costs associated with all phases of treatment including asparaginase | Patient (P); N = 42; diaries; hospital DB | 7 | Total medical costs of Pegaspargase arm was $48,083; E coli asparaginase arm was $47,143. |
### TABLE 2 Continued

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<tr>
<td>Van Litsenburg et al&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Consecutive upfront ALL regimens ALL9 (1997–2004) and ALL10 (2004–contemporary)</td>
<td>National 5y EFS</td>
<td>CEA</td>
<td>Single institution, Netherlands</td>
<td>Hospital</td>
<td>2008 USD; direct medical costs for entire treatment excluding recurrence, follow-up, or late effects</td>
<td>Patient (R); N = 50; hospital DB</td>
<td>9</td>
<td>Cost per LYG for ALL9 was $2094, for ALL10 was $2834. Cost effectiveness ratio for treatment according to ALL10 was $8739 with ALL9 as reference.</td>
</tr>
<tr>
<td>Hall et al&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Brain tumor resection in the conventional operating room or interventional magnetic resonance suite</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, United States</td>
<td>Not stated</td>
<td>2001 USD&lt;sup&gt;a&lt;/sup&gt;; total hospital costs for surgical admission</td>
<td>Patient (R); N = 47; hospital DB</td>
<td>6</td>
<td>Total hospital costs for interventional surgery was lower than conventional surgery by 44.7 to 46.4%.</td>
</tr>
<tr>
<td>Lundkvist et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Proton radiation therapy versus conventional radiation therapy for medulloblastoma</td>
<td>Life years and Quality adjusted life-years</td>
<td>CEA</td>
<td>Single institution, Sweden</td>
<td>Societal</td>
<td>2002 Euros; costs and all potential long-term consequences of radiation therapy</td>
<td>Literature</td>
<td>9</td>
<td>The total cost of proton radiation was estimated at -$38 150 with conventional radiation as base case.</td>
</tr>
<tr>
<td>Stanford, et al&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Open versus laparoscopic adrenalectomy</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, United States</td>
<td>Hospital</td>
<td>2001 USD&lt;sup&gt;a&lt;/sup&gt;; operative charges and costs of hospital stay</td>
<td>Patient (R); N = 64; source of unit costs not stated</td>
<td>4</td>
<td>Mean operative charge for laparoscopic procedure was $16 793 versus $8117 for open adrenalectomy. Total hospital costs similar for both procedures. The overall mean cost per patient treatment with rituximab was $1005 less than treatment without. The addition of rituximab was associated with a mean 0.18 LYG.</td>
</tr>
<tr>
<td>Ferrara and Ravasio&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Chemotherapy with or without rituximab for lymphoma</td>
<td>LYG</td>
<td>CEA</td>
<td>Single institution, Italy</td>
<td>Italian National Health Service</td>
<td>2007 Euro; direct medical costs involved in administration of chemotherapy and rescue therapy</td>
<td>Model literature; regional - national DB</td>
<td>9</td>
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<sup>a</sup> Currency not stated in year, assumed year before publication.
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<tr>
<td>Klaassen et al(^\text{18})</td>
<td>Randomly assigned patients with low risk F+N to early discharge with continued oral cloxacillin + ceftaxime or placebo</td>
<td>Readmit for fever or bacterial infection</td>
<td>CEA</td>
<td>Single institution, Canada</td>
<td>Health care system</td>
<td>1998 CD; all medical costs from presentation with fever until neutropenic resolution</td>
<td>Patient (P); N = 54; hospital DB; regional-national DB</td>
<td>7</td>
<td>Total cost for placebo arm was $87,142; and for treatment arm it was $96,273. Fewer readmissions occurred in placebo arm; incremental cost of placebo was $18,905/100 patients</td>
</tr>
<tr>
<td>Agaoglu et al(^\text{16})</td>
<td>Randomly assigned patients with F+N to 1 of 3 regimens for F+N: Cefepime + netilmicin; ceftazidime + amikacin; or meropenem.</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Turkey</td>
<td>Not stated</td>
<td>2000 USD(^\text{a}); not stated</td>
<td>Patient (P); N = 82; source of unit costs not stated</td>
<td>4</td>
<td>Cost per day Cefepime + netilmicin = $71.80; ceftazidime + amikacin, $61.66; or meropenem, $162.</td>
</tr>
<tr>
<td>Santolaya et al(^\text{19})</td>
<td>Randomly assigned patients with low risk F+N to receive early discharge with home antibiotics or continued hospitalization</td>
<td>NA</td>
<td>CA</td>
<td>Multiple institutions, Chile</td>
<td>Health care system and patient</td>
<td>2003 USD; direct medical costs for F+N episode, family transportation costs</td>
<td>Patient (P); N = 161; regional-national DB</td>
<td>5</td>
<td>The average cost for ambulatory treatment was $797, and for hospital treatment it was $1128.</td>
</tr>
<tr>
<td>Corapcioglu et al(^\text{20})</td>
<td>Compared regimens used for treatment of F+N.</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Turkey</td>
<td>Not stated</td>
<td>2003 USD(^\text{a}); hospitalization, antibiotics, growth factors</td>
<td>Patient (R); N = 50; source of unit costs not stated</td>
<td>4</td>
<td>Average cost of episode was $873.</td>
</tr>
<tr>
<td>Corapcioglu et al(^\text{21})</td>
<td>Randomly assigned patients with F+N to Cefepime or Ceftazidime + Amikacin</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Turkey</td>
<td>Not stated</td>
<td>2004 USD(^\text{a}); hospitalization, antibiotics, growth factors, transfusions</td>
<td>Patient (P); N = 29; source of unit costs not stated</td>
<td>4</td>
<td>Average cost per episode for Cefepime was $1,480, and for Ceftazidime + Amikacin it was $661.8.</td>
</tr>
<tr>
<td>Corapcioglu et al(^\text{22})</td>
<td>Randomly assigned patients with F+N to cefepime or Piperacillin/tazobactam</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Turkey</td>
<td>Not stated</td>
<td>2005 USD(^\text{a}); hospitalization, antibiotics, growth factors, transfusions</td>
<td>Patient (P); N = 28; source of unit costs not stated</td>
<td>5</td>
<td>Average cost per episode for cefepime was $1,453, and for Piperacillin/tazobactam it was $1,490.</td>
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<td>Simon et al(^\text{17})</td>
<td>Compared changing indwelling catheter access every 72 h or every 7 d.</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Germany</td>
<td>Hospital</td>
<td>2005 USD(^\text{a}); not stated</td>
<td>Patient (P); N = 175; hospital DB</td>
<td>2</td>
<td>Estimated costs for changing access every 72 h was $4,186,81, and for every 7 d it was $3,031.</td>
</tr>
<tr>
<td>Truffel et al(^\text{15})</td>
<td>Compared 4 treatment strategies for inpatient or outpatient treatment of F+N.</td>
<td>Quality adjusted F+N episodes</td>
<td>CEA(^\text{a})</td>
<td>Single institution, Canada</td>
<td>Health care payer</td>
<td>2009 CD; all direct medical costs associated with the F+N episode</td>
<td>Model; hospital DB; regional-national DB</td>
<td>9</td>
<td>IV Antibiotics at home served as base case, $286 per episode. Early hospital discharge with home antibiotics was $3582 per episode. Although slightly more effective, it had an ICER of $1,42814 per quality adjusted F+N episodes. Home oral and hospital IV were dominated.</td>
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**Growth Factors**

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<tr>
<td>Bennett et al(^\text{24})</td>
<td>Randomly assigned patients with leukemia to induction and maintenance chemotherapy with or without G-CSF</td>
<td>NA</td>
<td>CA</td>
<td>Cooperative group, United States</td>
<td>Not stated</td>
<td>1999 USD(^\text{a}); direct medical costs from start of treatment until end of maintenance therapy. Excluded physician, imaging and, laboratory fees</td>
<td>Patient (P); N = 88; regional-national DB</td>
<td>8</td>
<td>Median cost for treatment with G-CSF was $48,257; without G-CSF, $40,420.</td>
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<tr>
<td>Little et al(^{25})</td>
<td>Randomly assigned patients with leukemia or lymphoma to receive 1 course of intensive chemotherapy with or without G-CSF. Cross over design.</td>
<td>NA</td>
<td>CA</td>
<td>Multiple institutions, United Kingdom</td>
<td>Not stated</td>
<td>2001 USD(^{6}), costs of G-CSF administration, total bed cost and antibiotic cost</td>
<td>Patient (P); N = 48; source of unit costs not stated</td>
<td>6</td>
<td>Total costs (for all patients) with G-CSF was $287,034, and for chemotherapy alone it was $311,538.</td>
</tr>
<tr>
<td>Gonzalez-Vicent et al(^{27})</td>
<td>Patients received G-CSF or not after autologous SCT at provider discretion</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Spain</td>
<td>Not stated</td>
<td>2001 USD(^{6}), hospitalization, transfusion, antibiotics, G-CSF</td>
<td>Patient (R); N = 123; source of unit costs not stated</td>
<td>3</td>
<td>Supportive costs were similar, but G-CSF added median of $908.</td>
</tr>
<tr>
<td>Ammann et al(^{23})</td>
<td>Randomly assigned patients to G-CSF dosing on &quot;individualized&quot; versus &quot;standardized&quot; schedule</td>
<td>NA</td>
<td>CA</td>
<td>Multiple institutions, Switzerland</td>
<td>Not stated</td>
<td>USD 2000; costs of G-CSF, administration, blood counts</td>
<td>Patient (P); N = 17</td>
<td>5</td>
<td>Individualized schedule reduced costs by median of $205 per cycle.</td>
</tr>
<tr>
<td>Delorme et al(^{26})</td>
<td>Randomly assigned patients with leukemia to chemotherapy with or without G-CSF</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, France</td>
<td>Hospital</td>
<td>1998 USD; direct medical costs for hospital stay, transfusions, and drugs</td>
<td>Patient (R); N = 67; medical records; hospital DB; national/regional DB</td>
<td>7</td>
<td>Average costs per patient receiving G-CSF was $45,553, and for without G-CSF it was $44,545.</td>
</tr>
<tr>
<td>Gonzalez-Vicent, M et al(^{28})</td>
<td>Randomly assigned patients to receive G-CSF or not after autologous SCT</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Spain</td>
<td>Not stated</td>
<td>2003 Euros(^{5}), regression model of clinical determinants to predict total costs</td>
<td>Patient (R); N = 117; source of unit costs not stated</td>
<td>4</td>
<td>Costs were similar in both groups. Median cost for SCT with G-CSF was $12,850, and for SCT without G-CSF it was $12,419 (P = .1).</td>
</tr>
<tr>
<td>Valteau-Couanet et al(^{29})</td>
<td>Randomly assigned patients to no G-CSF, G-CSF starting day +1, or G-CSF starting day +3 after autologous SCT</td>
<td>NA</td>
<td>CA</td>
<td>Cooperative group, France</td>
<td>Hospital</td>
<td>1998 Euros; direct medical costs including hospitalization, transfusions, G-CSF, antibiotics, and IV nutrition</td>
<td>Patient (P); N = 52; hospital DB; regional-national DB</td>
<td>6</td>
<td>Total costs were not different between the 3 groups.</td>
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**Genotyping**

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<tr>
<td>Van den Akker-van Marle et al(^{30})</td>
<td>Screening patients with leukemia with TPMT genotyping</td>
<td>LYG</td>
<td>CEA</td>
<td>Multiple institutions, European</td>
<td>Societal</td>
<td>2004 Euros; costs of genetic testing and toxicities</td>
<td>Model; literature; expert opinion</td>
<td>7</td>
<td>Genetic testing resulted in cost-effectiveness ratio of $89,201 per LYG</td>
</tr>
<tr>
<td>Donnan et al(^{31})</td>
<td>Compared leukemia chemotherapy dosing by weight, screening with TPMT genotyping or enzyme</td>
<td>Myelo-suppression within 3 mo</td>
<td>CEA</td>
<td>Single institution, Canada</td>
<td>Health care system</td>
<td>2008 CD; direct medical costs including chemotherapy, laboratories, and hospital admissions</td>
<td>Model; literature; regional-national DB</td>
<td>8</td>
<td>Total expected costs per patient for weight based dosing was $683 and $1065 for enzymatic testing, $1159 for genotyping with no difference in events at 3 mo.</td>
</tr>
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<td>Costs Included</td>
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<td>Drummond Scoring</td>
<td>Results (in 2012 USD)</td>
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<tr>
<td>Dionne et al</td>
<td>Screening for genetic predisposition to hearing loss from cisplatin</td>
<td>Incidence of ototoxicity</td>
<td>CEA</td>
<td>Single institution, Canada</td>
<td>Not stated</td>
<td>2010 CD; costs of genetic testing, costs of ototoxicity treatment, and limitations imposed by hearing impairment</td>
<td>Model; literature; hospital DB</td>
<td>4</td>
<td>If genetic testing prevented all ototoxicity and had same cure rate, each test would save $73,448.</td>
</tr>
<tr>
<td>Miano et al</td>
<td>Delivered IV supportive therapies (antibiotics, laboratories, parenteral nutrition) through home-based delivery program</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Italy</td>
<td>Not stated</td>
<td>2001 Euro; direct medical cost of therapy delivered including physician or nurse time</td>
<td>Patient (R); N = 45; hospital DB</td>
<td>5</td>
<td>The average cost per patient in home program was $48,124 and would have been $16,036 if delivered in hospital.</td>
</tr>
<tr>
<td>Stevens et al</td>
<td>Patients with leukemia randomly assigned to chemotherapy at home or in clinic/hospital</td>
<td>NA</td>
<td>CA</td>
<td>Multiple institutions, Canada, Perspective</td>
<td>Not stated</td>
<td>2004 CD; parental survey reporting visits, direct and indirect costs</td>
<td>Patient (P); N = 28; regional-national DB</td>
<td>6</td>
<td>Median family cost was $38,724. The difference between family costs based on treatment location was not significant.</td>
</tr>
<tr>
<td>Mahadeo et al</td>
<td>Compared methotrexate and hydration in the hospital versus hydration at home in osteosarcoma</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, United States</td>
<td>Hospital</td>
<td>2008 USD; direct medical costs of delivering the hydration, excluded chemotherapy, laboratory and physicians</td>
<td>Patient (R12); Hospital DB; regional/national DB</td>
<td>5</td>
<td>Average cost per cycle of inpatient was $25,444, of outpatient was $10,374.</td>
</tr>
<tr>
<td>Annemans et al</td>
<td>Compared historic controls to addition of rasburicase for treatment or preventive measure</td>
<td>LYG</td>
<td>CEA</td>
<td>Multiple institutions, European</td>
<td>Not stated</td>
<td>2002 Euro; direct medical costs of treatment or prevention of tumor lysis syndrome including drugs, physicians, laboratories, diagnostic imaging hospitalization</td>
<td>Patient (R); N = 348; regional-national DB</td>
<td>8</td>
<td>Treatment with rasburicase was cost saving, average $15,577 to $59,13; ICER of prevention of tumor lysis syndrome was $1,226 to $4,927.</td>
</tr>
<tr>
<td>Eaddy et al</td>
<td>Compared treatment with rasburicase or allopurinol</td>
<td>NA</td>
<td>CA</td>
<td>Corporate United States</td>
<td>Not stated</td>
<td>2008 USD; total costs of hospitalization</td>
<td>Premier Perspective Database; N = 126</td>
<td>6</td>
<td>Average cost for rasburicase hospitalization was $32,640, for allopurinol hospitalization was $37,689, P = .427.</td>
</tr>
<tr>
<td>Walker et al</td>
<td>Hospital guideline change from IV to oral antiemetics</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, United States</td>
<td>Not stated</td>
<td>1997 USD; institutional purchase of IV ondansetron</td>
<td>Patient (P); N = 184; hospital DB</td>
<td>3</td>
<td>The oral regimen resulted in $53,986 saved during the study year.</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Outcome</td>
<td>EE</td>
<td>Investigators</td>
<td>Perspective</td>
<td>Costs Included</td>
<td>Data Sources</td>
<td>Drummond Scoring</td>
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<tr>
<td>Corapcioglu et al</td>
<td>Randomly assigned patients to IV or orally disintegrating preparations of ondansetron</td>
<td>Degree of emesis control per course</td>
<td>CEA</td>
<td>Single institution, Turkey</td>
<td>Not stated</td>
<td>2005 USD; pharmaceutical costs</td>
<td>Patient (P); N = 22; source of unit costs not stated</td>
<td>4</td>
<td>The average costs for successfully controlled days were $61.90 for IV and $33.30 for oral formulation.</td>
</tr>
<tr>
<td>Iannalı et al</td>
<td>Randomly assigned patients to moderate sedation or general anesthesia for procedures</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Italy</td>
<td>Not stated</td>
<td>2004 USD, direct costs of pharmaceuticals and professional resources including training</td>
<td>Patient (P); N = 31; source of unit costs not stated</td>
<td>4</td>
<td>Average cost of moderate sedation was $92.24 per patient, and for general anesthesia it was $122 per patient.</td>
</tr>
<tr>
<td>Stolarska et al</td>
<td>Compared chemotherapy with or without amifostine</td>
<td>NA</td>
<td>CA</td>
<td>Single institution, Poland</td>
<td>Not stated</td>
<td>2005 PLN; Amifostine, IV antibiotics, G-CSF, blood products, immunoglobulins, days in hospital</td>
<td>Patient (R); N = 57; source of unit costs not stated</td>
<td>3</td>
<td>Total costs of chemotherapy cycle with or without amifostine were similar ($3042 vs $3157).</td>
</tr>
<tr>
<td>Abbott et al</td>
<td>Compare fresh-frozen plasma and cryoprecipitate infusions to prevent or treat CNS thrombosis in patients with leukemia</td>
<td>NA</td>
<td>CA</td>
<td>Multiple institutions, Canada</td>
<td>Not stated</td>
<td>2008 CD; costs of blood products, laboratory test, hospitalization, and imaging</td>
<td>Patient (R); N = 719; hospital DB</td>
<td>3</td>
<td>Mean cost of managing a CNS thrombosis was $20,684 per patient. The median cost of prophylaxis for all high risk patients was $355 per patient.</td>
</tr>
<tr>
<td>Hancock-Howard et al</td>
<td>Placement of central venous access device by using interventional radiologic versus conventional methods</td>
<td>No. of placement-related complications within 30 d of insertion</td>
<td>CEA</td>
<td>Single institution, Canada</td>
<td>Not stated</td>
<td>2004 CD; direct medical costs of placement of device, parental out-of-pocket and productivity losses</td>
<td>Patient (R); N = 60; hospital DB; regional/national DB</td>
<td>9</td>
<td>Median cost per patient for interventional radiology placement was $18,800, and for conventional it was $14,428. Interventional radiology was associated with fewer complications; ICER $11,655 per complication averted.</td>
</tr>
</tbody>
</table>

CD, Canadian dollar; CNS, central nervous system; DB, database; LYG, life years gained; NA, not applicable; Patient (P), study included prospectively gathered patient data; Patient (R), study included retrospective patient data; TPMT, thiorurine methyltransferase.

* Currency not stated in year, assumed year before publication.

* Evaluation included both CUA and CBA.
the “hospital” perspective. Six described the perspective as including the family or societal costs. Twenty-one articles did not state the perspective of their EE.

The inputs and sources of data were captured for each analysis (Tables 2 and 3). Two articles did not state the inputs considered in their EE.16,17 The majority of studies (n = 34, 85%) included data from a median of 55.5 (range, 12–719) patients’ medical or research charts. Twenty-four (69%) of these studies used patient data from a single institution. Because patient medical or research records rarely contain the costs or charges of medical therapy, additional sources are required to identify monetary units to assign to each input. The most common additional sources used for single institution studies were the hospital administrative databases (n = 16, 67%) and regional or national databases (n = 9, 38%). The additional sources were not identified in 10 of the single institution studies (42%). Six studies modeled hypothetical patients from a combination of sources. Once inputs are identified in terms of monetary units, the “time” of the monetary unit provides a reference point for decision-makers when comparing across studies. The currency (USD, Canadian dollar, Euro, etc) was stated in all articles, but the time reference of that currency was only stated in 21 (53%) of the articles (n = 21).

Infection

Eight articles considered treatment (n = 7) or prevention (n = 1) of infection. Three of these articles stated the health care system as the perspective of their EE,15,17,18 and 1 stated both the health care system and the patient.19 The 4 remaining articles did not state their perspective, input, or cost sources16,20–22 and were excluded from further comparison. Teuffel et al15 modeled options for delivering antibiotics in the inpatient and outpatient setting for children with low-risk fever and neutropenia (F+N). They used repeat F+N episodes adjusted for family preference as a clinical end point. They estimated the costs of home intravenous (IV) antibiotics as $2866 per episode, and although brief admissions for IV antibiotics followed by home antibiotics was more effective, it was also more expensive ($5852 per episode) costing an additional $142 to $14 per repeat F+N episode prevented. Klaassen et al18 estimated the costs of a brief hospitalization for F+N followed by discharge after randomization to antibiotics or placebo; their CEA analysis used readmission for infection as a clinical end point. Fewer readmissions occurred for patients receiving placebo resulting in an incremental saving of $189 per patient.18 Santolaya et al19 also compared the costs of continuing antibiotics at home or in the hospital, options similar to 2 of the 4 considered by Teuffel et al.15 They estimated early discharge with antibiotics at home to cost less than continuing in the hospital ($797 vs $1128 per episode). This more cost effective option was similar to the option estimated to cost $5852 by Teuffel et al.15 The sevenfold difference in total costs may reflect the health care systems performing the studies, Canadian versus Chilean.

Granulocyte Colony Stimulating Factor

Seven articles studied the incorporation of G-CSF into therapy. All EEs were cost analyses rather than CEA. Although only 2 articles expressly stated from the health care decision-maker’s perspective in their EE, all 7 included direct medical costs of treatment consistent with that perspective. Ammann et al23 compared schedules for repeating laboratories and discontinuing G-CSF and revealed individualized schedule saved $203 per patient over a standardized schedule. Three articles presented results of trials randomly assigning patients with leukemia to chemotherapy with or without G-CSF although the phase of leukemia treatment is different in each study limiting comparison of total costs between the studies.24–26 Three additional studies compared the costs of including G-CSF after autologous hematopoietic stem cell transplant (SCT), 1 at the investigator’s discretion27 and the others via randomization.28,29 There was no statistically significant difference between total costs in any of these 6 studies although G-CSF made a substantial contribution to costs if patients received it, whereas hospital costs were greater if G-CSF was not given (Table 4). Gonzalez-Vincent

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<tr>
<td>Bennett et al24</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>67</td>
<td>91</td>
<td>-24</td>
<td>5</td>
<td>1.9</td>
<td>3.1</td>
<td>1.9</td>
<td>2.7</td>
<td>-0.8</td>
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<tr>
<td>Little et al26</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>59</td>
<td>80</td>
<td>-21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.6</td>
<td>7.5</td>
<td>-0.9</td>
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<tr>
<td>Delorme et al26</td>
<td>12</td>
<td>0.8</td>
<td>11</td>
<td>68</td>
<td>82</td>
<td>-14</td>
<td>8.9</td>
<td>6.2</td>
<td>2.7</td>
<td>4.9</td>
<td>5.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>Gonzalez-Vicent et al27</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>60</td>
<td>72</td>
<td>-12</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>6.4</td>
<td>8.8</td>
<td>-2.4</td>
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<tr>
<td>Valtue-Couanet et al29</td>
<td>D+1</td>
<td>D+5</td>
<td>0.3</td>
<td>5.3</td>
<td>3.9</td>
<td>2.9</td>
<td>9.2</td>
<td>6.7</td>
<td>2.5</td>
<td>6.6</td>
<td>9.7</td>
<td>-3.1</td>
</tr>
</tbody>
</table>

D+1: Day +1 after stem cell infusion; D+5: Day +5 after stem cell infusion.
et al 38 was excluded from this table because they did not present final components in monetary units.

Hematopoietic Stem Cell Transplant

Five articles compared SCT regimens at single institutions. Although only 3 expressly stated the health care decision-maker’s perspective in their EE, all 5 included direct medical costs of treatment consistent with that perspective. Yoeh et al 30 compared costs of 2 methods of stem cell mobilization for medulloblastoma. The other 4 retrospectively reviewed mixed populations of patients with cancer receiving transplants. 31–34 The difference in total costs reported on these studies reflect, in part, the time horizon after transplant captured. Three articles included costs of graft acquisition and direct medical costs from admission to discharge from the transplant admission 32 or +100 days. 31,34 Average costs of a peripheral blood SCT on these studies are estimated as $10,891 32 and $19,514. 31 Majhail et al 34 reported costs in costs per day survived, which limits comparison with the other studies. Lin et al 33 excluded costs of graft acquisition in the final total costs but included direct medical costs for 1 year after transplant and estimated the total average cost of a PBSC transplant as $402,798 on this study. Costs associated with SCT are likely concentrated early in the process, but even if the +100-day cost estimate by Madero et al 31 was assumed to continue throughout the entire first year after transplant, Lin et al’s 33 estimate is 6.9-fold higher. Although these studies take a similar perspective and capture similar costs, they were performed a decade apart in different health care systems (Spain and United States).

Societal/Family Costs

Six articles stated a perspective other than the health care system, and 1 additional article included cost inputs consistent with this perspective. Three of these considered the societal perspective by including long-term medical and productivity costs of treatments. Lundkvist et al 35 modeled proton beam versus conventional radiation therapy for treatment of medulloblastoma. This group used literature to estimated frequency and lifetime costs of cognitive loss, hearing loss, hypothyroidism, osteoporosis, growth hormone deficiency, second malignancies, and fatalities. Their model predicts a lifetime societal savings of $38,150 per proton patient, based on the assumption that toxicities occur less frequently and tumor-free survival is at least equivalent to that of conventional radiation therapy. Van den Akker-van Marle et al 36 developed a model to evaluate the value of thiopurine methyltransferase genotyping all patients with leukemia allowing dosing of 6-mercaptopurine according to toxicity risk. Although the authors described their EE as from the societal perspective, they limited their input to direct medical costs of genotyping and acute and long-term toxicities and excluded family indirect costs and patient productivity, a perspective more consistent with a health system and a long time horizon. Genotyping in this model would cost $213,000 for 1000 patients, but if 1 patient was saved and that patient lived an additional 67 years, genotyping everyone would cost $3,180 per year of life gained by that 1 patient. 56 Similarly Dionne et al 57 modeled genotyping patients for susceptibility to cisplatin-induced otoxicity and included lifetime medical costs and productivity losses based on severity of hearing loss. Their model assumed that genotyping a patient would allow a treatment that maintained the same cure rate and reduced ototoxicity by 100% and would thus save the society $73,448 per test administered. 57 Each of these 3 models demonstrates a cost savings effect of their new intervention based on long-term assumptions. The other 4 articles performing EE from a societal perspective included costs the family incurred as a result of treatments. Stevens et al 58 randomly assigned patients with leukemia from a single institution in Canada to receive chemotherapy in the clinic or delivered at home. Their EE focused entirely on the families’ perspective capturing inputs by using the Health Service Utilization and Costs of Care Inventory 38 and then estimating the costs of these inputs from a regional database. They found that the median family cost was not significantly different between treatment locations, ~$3,970 per family. Kurre et al 39 Santolaya et al 19 and Hancock-Howard et al 40 included both direct medical costs and family costs in their societal perspective. Kurre et al 39 used family diaries to collect expenses of patients with leukemia randomly assigned to pegaspargase or Escherichia coli asparaginase through induction and delayed intensification phases of chemotherapy. Travel, productivity, and lodging costs were ~$3,725 to $4,648, <10% of the total direct medical costs ($47,143–$48,084). 39 The treatment arm with higher family costs had lower total costs. Only 38% of patients were compliant with diaries by the end of the study. Santolaya et al 19 included family travel costs in their study comparing costs of early hospital discharge after F+N. Although estimated total costs were lower than other contemporary F+N reports as noted above, travel costs were <5% of these costs. Finally, Hancock-Howard et al 40 estimated costs of venous access placement in a conventional operating room or interventional radiology. Productivity losses contributed 6.8% to 7.5% of total costs, and travel costs only 0.7% to 1.5%. 40 When family and direct medical costs are analyzed together, family costs were consistently a minor component of total costs.
DISCUSSION
We identified only 40 original research works applying comparative EE methods on childhood cancer treatments. A review of the state of economic methods applied to childhood cancer up to 2004 by Barr et al identified 1 article that was included in our analysis and another that was published in 1997. Barr et al’s review focused on demonstrating the potential of utility measures into economic comparisons and may have not identified all of the published EEs. A structured review of publications on health-related quality of life and economic outcomes in ALL before 2000 failed to identify any comprehensive EE of treatment. The increase in publications over the past decade suggests in increased application of EE methods. The predominance of single-institution studies and broad spectrum of treatment questions, especially supportive measures, found in our review suggests an individualist approach to EE research in this field. The relative logistical ease of single institutional research over collaborative work and supportive therapy questions (ie, a short time line, a well-defined treatment and outcome) over more complicated cooperative group treatment regimens make such a direction more appealing to the researcher with limited resources.

We reviewed literature representative of medical management in the contemporary, economically developed health care systems. Our time frame of 2000 forward accounts for contemporary treatments, outcomes, and supportive decisions. Nations affiliated with the Organization for Economic Cooperation and Development are all considered high-income nations by the World Bank. Health care systems from these nations could be expected to give technologically similar therapies. But differences in organization and funding pose challenges when applying treatment costs from 1 system to another or across time. Using a qualitative scoring system such as the Drummond Scale is 1 way to gauge the transferability of a study and its results. It is limited to the EE and does not address other aspects of the study such as medical merit or applicability in the new location. Other tools to assess all aspects of generalizability are under development and all determine the quality of the EE. Scoring systems are limited by bias of the reviewer although interreviewer variability seems minimal.

This review helps to demonstrate the challenges associated with comparing results of EE studies when the quality of the EE is low. Our distribution of individual categorical scoring is consistent with previous validation of this tool. Items 1, 2, 3, and 10 are almost always present, and item 7 (costs adjusted for differential timing) is almost never present. Only half of the studies we reviewed stated a time reference for their costs estimates. Our use of the value the year before publication, which assumes that the authors adjusted all their costs within the study, may have resulted in an erroneous estimate of current value because inflation and exchange rates change with time. Studies that did not clarify the perspective of the EE prevented a clear assessment of whether all the costs were included, but studies that did not clarify what costs were included or where they derived their unit costs cannot be compared with other studies nor generalized outside of their institution. Correction of these reporting limitations in future EE would add significantly to the usefulness of the results to decision-makers.

EEs determine an estimate of cost around which there remains uncertainty because the design of the study and the parameters used within the study are not completely accurate. Assessment of the impact of uncertainty, referred to as sensitivity analysis, is an important component of an EE but was included in only 37% of the studies. Very few studies identified a statistically significant difference between treatments under comparison. EE may require larger samples sizes than those needed to detect clinical difference, so the low number of patients on the studies reviewed limited the success. Studies from multiple institutions or use of models may help produce more reliable results, although each of these solutions has its own limitations.

Four of our articles included family costs of transportation, productivity losses, and/or living expenses associated with the treatments being compared. When the EE included these costs in the total costs, the costs incurred by the families was <10% of total costs and were unlikely to impact the overall cost differential. But if considered only from the perspective of the family, the costs could be substantial. In addition, the family costs estimated on these studies represents only a portion of all the family costs incurred during treatment of a child with cancer. A 2011 systematic literature review focusing on studies of family-incurred costs revealed that costs could reach >200% of annual income. Similar to the EEs identified our study, methodological issues and limited research were significant limitations to understanding family costs. When comparing treatments by family costs or health care costs, the treatments are not necessarily cost effective by both perspectives as seen in the study by Kurre et al. Because of the enormous disparity between the impacts on a family versus the health care system, consideration should be given to consistent inclusion of family costs in EE but evaluating the results separately from direct medical costs.

CONCLUSIONS
The results of this review demonstrate the significant opportunities for EE of treatments of childhood cancer.
Incorporating indirect cost estimations and cost-utility evaluation may balance the health care and family perspectives if methodological issues are overcome. This review demonstrates an imbalance of tumor-directed therapy and supportive therapy evaluations. Tumor-directed treatments predict the toxicities encountered and needs for supportive therapies and likely have the largest economic impact. Pediatric oncology has made survival improvements through prospective clinical trials performed in collaborative networks. Applying EE tools to tumor-directed therapies in a systematic and objective manner in collaboration within these networks could lead to more efficient use of limited resources.

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(Continued from first page)

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Economic Evaluation of Pediatric Cancer Treatment: A Systematic Literature Review
Heidi V. Russell, Janki Panchal, Helena VonVille, Luisa Franzini and J. Michael Swint

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