A Structured Review of Studies on Health-Related Quality of Life and Economic Evaluation in Pediatric Acute Lymphoblastic Leukemia

A. Simon Pickard, Leigh-Ann Topfer, David H. Feeny

Background: A comprehensive review was made of the literature on the health-related quality of life (HRQL) and economic outcomes of children with acute lymphoblastic leukemia (ALL), the most common of all cancers in childhood. Objectives: The primary objectives of the review were to locate and describe measures of HRQL used in pediatrics and in pediatric oncology that might be applicable to ALL, to summarize studies that have applied HRQL measures to ALL, to identify and summarize economic evaluations of the costs and consequences of care for pediatric ALL, and to identify areas requiring further research. Data sources: To identify the HRQL literature in pediatric ALL, searches were run on the major biomedical and social science bibliographic databases. Search terms included a variety of MeSH and other thesaurus terms, text words, names of HRQL instruments, and the names of key authors in the field. The economic literature searches included most of the same databases, with the addition of the National Health Service Economic Evaluation Database and EconLit. Searches on specific authors and instruments and hand searches were also conducted. Study selection: Only English language studies published from 1975 through 2000 were included. Data extraction: Standardized data extraction forms were used to abstract information from HRQL and economic evaluation studies. Two reviewers independently screened the search results, and differences were resolved by consensus. Data synthesis: A number of generic HRQL measures, both adult and pediatric, have been applied in pediatric ALL. In addition, a number of pediatric oncology-specific instruments and pediatric oncology disease-specific instruments have been developed. Most of these instruments have been used to measure the health status of patients undergoing therapy. Despite the limited numbers of patients and resources available to assess HRQL measures in children with cancer, a fairly substantial body of literature has been published. Economic studies of pediatric ALL have only recently been undertaken. Most studies focus on a particular, narrow aspect of costs associated with the disease. There are relatively few cost-effectiveness studies that compare the costs and consequences of two or more treatment options. There are no published, comprehensive economic evaluations of pediatric ALL. Conclusions: HRQL measures provide not only important information on the improvements offered by new therapies but also an outcome measure for economic evaluations. Recently developed HRQL measures and applications that include the direct assessments of children are important contributions. By the age of 7 or 8 years, children can generally provide reliable responses. Furthermore, children often provide information that is not available from parental reports (e.g., in the more subjective areas of pain and emotion). However, the use of multiple viewpoints, such as the patient, parent, and health professional perspectives, can provide valid and important complementary information. Expertise in HRQL measurement should be included in the design of most future trials. Funds for HRQL research should be made available to enhance the scope of HRQL activities by organizations such as the Children’s Oncology Group. In the near future, further work to generate evidence of validity for available HRQL measures for use in children with ALL will be a high priority. Continuation of inquiries into the methods for HRQL assessment of younger children (i.e., preschoolers) is also a priority. [J Natl Cancer Inst Monogr 2004;33:102–25]

BACKGROUND

Acute lymphoblastic leukemia is the most common of all childhood cancers. Survival rates have improved dramatically over the latter course of the 20th century for most forms of childhood cancers, including ALL. The overall survival rate for children with acute lymphocytic leukemia (ALL accounts for the vast majority of cases in that category) in the United States has improved from 53.8% in 1974–1976 to 86.8% for the period 1992–1997 (3).

The tremendous progress in cure rates is attributable, in part, to the cooperative trial program among centers of excellence in pediatric cancer (4). Children who receive treatment according to well-defined protocols in specialized children’s centers have improved survival when compared with that of children who received treatment outside these centers for ALL, lymphoma, Wilms tumor, medulloblastoma, rhabdomyosarcoma, and Ewing’s sarcoma (4). Now that the majority of pediatric patients survive their cancer, quality-of-life measurement is increasingly recognized as an important method of evaluating the impact of treatment interventions and understanding the short- and long-term morbidity (5–15). The two key issues are the burden of morbidity during the treatment process and the long-term effects of the disease and its treatment on the health status and health-related quality of life (HRQL) of childhood cancer survivors (16). Given the current focus of many pediatric oncology trials on toxicity and sequelae-sparring therapies, the assessment of HRQL is becoming increasingly important.

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See “Notes” following “References.”

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A substantial literature has accumulated on the measurement of HRQL in cancer; however, until recently, relatively little of this research focused on pediatric oncology. Health status and HRQL instruments have been developed specifically for use in cancer patients, such as the Functional Living Index—Cancer (FLIC) (17) and the Functional Assessment of Cancer Therapy (FACT) (18), but these instruments do not consider HRQL issues in the context of pediatric oncology.

As for any HRQL measure, an instrument for use in pediatric cancer should possess evidence of content/construct validity and reliability in the patient population of interest. One of the challenges in the development of childhood cancer-specific HRQL measures is to identify the primary HRQL domains of importance. The domains of importance may differ according to the type of cancer and the treatment regimens used. Although many survivors of cancer in childhood enjoy normal health, chronically poor health and specific deficits in cognitive and emotional status have been identified in some children who have had cancer (14). Other aspects of HRQL are cancer-specific concerns such as alopecia, mucositis, and gonadal damage leading to infertility. In some cases, patients experience acute reversible toxic effects; in other cases, the toxic effects persist or are irreversible. The assessment of HRQL provides a mechanism to measure and analyze these complex issues.

Further to the challenge of developing valid and reliable HRQL measures for use in pediatric cancer is the fact that the cognitive capacity of children for self-evaluation changes with the normal process of maturation (16,19). Thus, measures that deal with the problems specific to HRQL measurement in children by age group are needed. Longitudinal assessments of HRQL are complicated by the developmental stages that pediatric subjects undergo during treatment and follow-up (8). Proxy respondents are frequently used, and an understanding of the relationship between parent and child/adolescent assessment of HRQL is important.

One of the first scales developed specifically for use in children with cancer was the Play Performance Scale for Children (PPSC) (20), designed as a measure of a child’s ability to perform day-to-day activities as an indication of health status (20). Since the emergence of the PPSC, a number of generic and cancer-specific HRQL measures have been developed. Trudel et al. (21) identified the following quality-of-life measures available for pediatric cancer patients: the PPSC (20), the Quality of WellBeing Scale (QWB) (22), the Perceived Illness Experience (PIE) Scale (23), the Pediatric Oncology Quality of Life Scale (POQOLS) (24), and the Health Utilities Index (HUI) Mark 2 system (25).

This review includes the following three types of published studies (available up to April 2001): 1) HRQL measures that potentially could be used in pediatric cancer, 2) studies that have applied HRQL measures in populations that include children with ALL, and 3) economic studies involving treatments for children with ALL. The first objective of this review was to identify and describe generic, specific, and disease-specific HRQL measures developed or applied in childhood ALL. The second objective was to identify and describe economic evaluation studies dealing with pediatric ALL.

METHODS

Literature Search

HRQL and health status in pediatric ALL. Literature searches were run on several databases by using various search strategies as shown below. More than 1800 references were identified. A review of the titles and abstracts revealed that most studies were not specific to HRQL in children with leukemia. For example, many studies focused on the quality of life of the parents and on the neurological/cognitive impacts of cancer therapies on adult survivors of leukemia in childhood. The search was restricted to studies published since 1975. Only studies published in English were selected for review. An appendix providing details on the search strategies, keywords, and databases consulted is available from the authors. Search strategies will be described briefly here. Standard databases including PubMed (MEDLINE), EMBASE, Web of Science, and CancerLit were consulted. Given previous knowledge of important studies and measures, specific searches for papers by the authors or for particular HRQL measures were also conducted. Key journal supplements and relevant sources from the personal collection of one of the authors (D. H. Feeny) were also used.

Economic evaluations and costing studies. For the economic component of the review, literature searches were run on biomedical databases used in the HRQL searches and also on economic literature databases, such as EconLit and the National Health Service Economic Evaluation Database. (More details on the search strategies are recorded in an appendix, available upon request.) More than 250 references were identified. However, upon examination of the abstracts, most were not specifically relevant to the costs of ALL in children. This review was also restricted to English language studies published since 1975.

Data Extraction and Presentation

Citations identified by the literature search were independently screened by two reviewers (A. S. Pickard and L.-A. Topfer). Papers that appeared to be relevant were retrieved and were included or rejected on the basis of a review of the entire paper. Disagreements were resolved by consensus. Information was abstracted from each study by using standardized data collection forms (see “Appendix 1”). Three data collection forms were developed, and the information from these forms is summarized in Tables 1–3.

Form I was structured to describe HRQL instruments that have been used or may find application in pediatric ALL in North America in terms of the following: domains (dimensions of health status) included on each measure, intended respondent and age group, number of items, application format, country of origin, and availability of translations in other languages.

Form II was used to extract evidence from studies that have applied HRQL instruments to pediatric ALL. This form included aspects such as the following: sample characteristics, data collection, respondents, study design, phase of care, medication regimen, and additional evidence on the measurement properties of each HRQL instrument generated by the study. This information is summarized in Table 2, which reports the actual activity or applications of the HRQL measures identified as having potential for application in Table 1.

A taxonomy of HRQL measures and explanations of psychometric properties and issues related to HRQL measurement are available elsewhere (16,26,27). Evidence on reliability and validity reported in Table 2 pertains only to studies involving one or more children with ALL. The characteristics in column 13 of Table 2 (i.e., confidence intervals and power calculations) were added in a recent update for this article and were not available (had not been abstracted) for studies identified in an earlier
phase of this project. Only results related to the HRQL measure
of interest are reported in Table 2. A number of studies aggre-
gated ALL patients with other types of cancer patients and did
not report disaggregated results based on type of cancer. The
same patient cohort may have been studied in more than one
paper. Papers that explored single domains of HRQL, such as
anxiety, were excluded. Studies investigating the late effects of
childhood cancer on the HRQL of adults were also excluded.

Form III was used for the economic evaluation and costing
studies. The results from economic evaluations and costing stu-
dies on patient samples or subsamples that include children with
ALL (Table 2) are reported on the basis of criteria that constitute
guidelines for the performance of economic evaluations in
health care (28,29). Our tables are intended to convey a brief
summary of the contents of each study or instrument and are not
a substitute for reading the papers.

RESULTS

The HRQL measures were subdivided into health profiles,
preference-based measures, and childhood cancer-specific pedi-
atriac HRQL instruments (Table 1). A number of pediatric on-
cology-specific instruments have been developed, such as the
Miami Pediatric Quality of Life Questionnaire, the Pediatric
Cancer Quality of Life Inventory (PCQL-32), and the POQOLS.
Finally, several pediatric oncology disease-specific instruments
have been developed. For instance, the Disease Specific Impair-
ment Inventories—Bone Marrow Transplantation (DSII-BMT)
focuses on HRQL in patients undergoing bone marrow trans-
plantation. These instruments have been used in studies of sev-
eral childhood cancers, including ALL. No HRQL measure spe-
cific to ALL was identified.

A number of generic HRQL measures (e.g., the QWB and the
HUI Mark 2 [HUI2] and Mark 3 [HUI3] systems) and generic
pediatric HRQL measures (e.g., the Child Health Questionnaire
[CHQ]) have been applied in pediatric ALL (Table 2). These
instruments have been used both to assess health status and
HRQL during treatment and to assess outcomes.

Most of the literature on the cancer-specific pediatric mea-
sures focused on evidence of validity and reliability. Studies that
describe a specific treatment regimen were more likely to have
a primary objective of evaluation of therapy, with information
on the psychometric properties more likely to have been a sec-
ondary objective.

Sawyer et al. (30) provided evidence on interrater agreement
(generally moderate to high but seldom perfect) for the CHQ
(Table 2). This study also provides similar evidence for func-
tional status measures. Comparable results for interrater reliabil-
ity are reported by Parsons et al. (31) for the Child Health Rating
Inventories (Table 2). Evidence on interrater reliability is also
reported by Barr et al. (32). Test–retest results for HUI2 are
reported by Trudel et al. (21).

Internal consistency results for the QWB are reported by
Bradlyn et al. (22). Phipps et al. (33) reported estimates of in-
ternal consistency for the Behavioral, Affective, and Somatic
Experiences Scale (BASES) (Table 2). Eiser et al. (23) reported
results on internal consistency and test–retest reliability (Table
2). Varni et al. (34,35) reported on internal consistency and
interrater reliability for the PCQL-32 (Table 2). Goodwin et al.
(24) reported high levels of internal consistency and interrater
reliability for POQOLS (Table 2). In general, internal consist-
tency and test–retest reliability have been acceptable for most
instruments.

There are a number of areas of application for cancer out-
come measures. These include the following categories: 1) stu-
dies to provide evidence on the efficacy or effectiveness of an
intervention, 2) studies to provide evidence on the cost-
effectiveness of an intervention, 3) studies to describe the pat-
terns of care, 4) studies to monitor or measure quality of care,
and 5) cost of illness studies. With respect to the HRQL litera-
ture on pediatric ALL (Table 2) summarized in Table 2, approxi-
mately 9.4% of the studies fell into category 1 (establish effective-
ness), 46.9% fell into category 3 (patterns of care), and 43.8% fell into
category 4 (monitor quality of care). Most of the latter group
were late-effects studies that have played an important role in
documenting the sequelae of therapy and disease in childhood
cancer. Results from late-effects studies have been important in
generating interest in new treatments that are toxicity and se-
quelea sparing.

Generic profile measures, such as the CHQ, and generic pref-
ference-based measures, such as the HUI, have been applied in a
number of late-effects studies that monitor the quality of care in
terms of the health status and HRQL in a cohort of survivors.
The use of broad comprehensive measures to examine late
effects is appropriate.

Many of the studies of HRQL in pediatric ALL have been
done in the context of assessing late effects: the quality of sur-
vivorship. The overwhelming majority of these studies are cross-
sectional. These studies have provided important evidence on
construct validity (and in some cases internal consistency reli-
ability); however, given their cross-sectional nature, they have
not provided information on responsiveness or sensitivity to
change.

In pediatric ALL, there are a number of standard phases of
treatment specified within widely used treatment protocols.
These phases typically involve diagnosis, induction of remis-
sion, consolidation of remission, maintenance therapy, and dis-
charge to long-term follow-up. In less successful cases, addi-
tional phases, such as reinduction of remission, intensification of
therapy, salvage therapy, or palliative care, may be relevant. The
bulk of available evidence on HRQL is related to the quality of
survivorship.

Speechley et al. (36) provided evidence on the construct va-

dility of the CHQ and HUI2 (Table 2). Both measure captured
burdens expected on the basis of known groups. Correlations
among similar constructs included in both measures were mod-
e rate to high.

Barr et al. (37) provided evidence on the construct validity of
HUI2 (Table 2). The burden of morbidity among survivors of
high-risk ALL exceeded that among survivors of standard-risk
ALL. Feeny et al. (38) provided evidence on the construct va-
dility of HUI2 in a cohort of survivors of high-risk ALL. Bur-
dens were found in cognition and emotion. Bradlyn et al. (22)
found that QWB scores and performance status ratings were
significantly correlated. Trudel et al. (21) reported on results of
expected correlations between POQOLS and HUI2.

There is less evidence on the responsiveness (sensitivity to
change) of these generic instruments to monitor changes over
time during therapy. In some cases these generic measures have
been responsive. For instance, Barr et al. (32) and Furlong et al.
(39) provided evidence on the responsiveness of HUI2 and
Table 1. Pediatric oncology health-related quality-of-life (HRQL) measures

<table>
<thead>
<tr>
<th>Instrument (reference)</th>
<th>Domains</th>
<th>Respondent</th>
<th>Age, y</th>
<th>Items</th>
<th>Format</th>
<th>Country (language)</th>
<th>Translations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Health and Illness Profile—Adolescent Edition (CHIP-AE) [Starfield et al. 1995 (52)]*</td>
<td>Discomfort, disorders, satisfaction with health, achievement, risks, resilience</td>
<td>Child</td>
<td>11–17</td>
<td>153</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Child Health Questionnaire (CHQ-PF50, -PF28, -CF87) [Landgraf et al., 1998 (53)]*</td>
<td>General health, change in health, physical functioning, bodily pain/discomfort, limitations in school work and social activities, behavior, mental health, self-esteem, emotional/time impact on parents, limitations in family activities, family cohesion</td>
<td>Parent and child</td>
<td>PF: 5–15; CF: 10–15</td>
<td>PF: 50 or 28; CF: 87</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>American-Spanish, Canadian-French, Finnish, French, German, Dutch, Italian, Greek, Honduran, Mexican, Norwegian, Portuguese, Swedish</td>
</tr>
<tr>
<td>DUCA TQOL [Koopman et al., 1997 (54)]*</td>
<td>Physical, emotional, social cognitive/school/home functioning</td>
<td>Child</td>
<td>School aged</td>
<td>32</td>
<td>Self-report</td>
<td>The Netherlands (not stated)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Functional Status II(R); [FS II(R) and FSQ-S] [Stein et al., 1990 (55); Lewis et al., 1989 (56)]*</td>
<td>Physical, psychological, social</td>
<td>Parent</td>
<td>0–16</td>
<td>FS II(R): 43 (long), 14 and 7 (short); FSQ-S: 14</td>
<td>FS II(R): interview; FSQ-S: self-report</td>
<td>United States (English)</td>
<td>FS II(R): Spanish, Dutch (others: not reported)</td>
</tr>
<tr>
<td>How Are You? (HAY) [Bruil et al., 1997 (57)]</td>
<td>Physical, cognitive, and social functioning, physical complaints, happiness and disease specific</td>
<td>Child (parent version for validation)</td>
<td>8–13</td>
<td>—</td>
<td>Self-report</td>
<td>The Netherlands (not stated)</td>
<td>Not reported</td>
</tr>
<tr>
<td>KINDL [Ravens-Sieberer et al., 1998 (58)]*</td>
<td>Psychological well-being, social relationships, physical function, everyday life activities</td>
<td>Child and parent</td>
<td>8–16</td>
<td>40</td>
<td>Self-report</td>
<td>Germany (German)</td>
<td>English (under way: Italian, Dutch, French)</td>
</tr>
<tr>
<td>Sixteen-dimensional health-related measure (16D) [Apajasalo et al., 1996 (59)]*</td>
<td>Mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, friends, physical appearance, mental function, discomfort/symptoms, depression, distress, vitality</td>
<td>Child</td>
<td>12–15</td>
<td>16</td>
<td>Self-report</td>
<td>Finland (not stated)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Seventeen-dimensional health-related measure (17D) [Apajasalo et al., 1996 (60)]*</td>
<td>Mobility, vision, hearing, speech, breathing, sleeping, eating, elimination, discomfort/symptoms, school/hobbies, friends, physical appearance, depression, anxiety, vitality, ability to concentrate, learning ability/memory</td>
<td>Child</td>
<td>8–11</td>
<td>17 (with pictures)</td>
<td>Interview</td>
<td>Finland (not stated)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Health Utilities Index (HUI)—Mark 2 and 3 (2 and 3 have also been tested in general populations) [Feeny et al., 1996 (61); Barr et al., 1994 (62)]*</td>
<td>Mark 2—sensation, mobility, emotion, cognition, self-care, pain, fertility (left out for kids); Mark 3—vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain</td>
<td>Parent, child, physician, other</td>
<td>≥6</td>
<td>—</td>
<td>Self-complete: 15 interviewer: 40</td>
<td>2 and 3: Canada (English and French)</td>
<td>French, Dutch, German, Spanish, Japanese, Swedish, Danish, Norwegian, Italian, Finnish, Mandarin, Chinese, French, Malay; in progress: Polish</td>
</tr>
<tr>
<td>Quality of Well-Being Scale (QWB) (has also been tested in general populations) [Bradlyn et al., 1993 (22)]*</td>
<td>Mobility, physical activity, social activity</td>
<td>Parent with child, adolescent (≥12 y old) and parent separately</td>
<td>Usually &lt;18</td>
<td>40 possible</td>
<td>Interview</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

(Table continues)
<table>
<thead>
<tr>
<th>Instrument (reference)</th>
<th>Domains</th>
<th>Respondent</th>
<th>Age, y</th>
<th>Items</th>
<th>Format</th>
<th>Country (language)</th>
<th>Translations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral, Affective, and Somatic Experiences Scale (BASES; -C, -P) [Phipps et al., 1994 (63)]</td>
<td>Somatic distress, mood/behavior, activity, compliance, interactions</td>
<td>Nurse (BASES), child (BASES-C), parent (BASES-P)</td>
<td>2–20</td>
<td>38 (BASES); 14 (BASES-C); 38 (BASES-P)</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>PIE [Eiser et al., 1995 (23)]</td>
<td>Physical functioning (symptoms, functional disability, and restrictions) and psychological functioning (symptoms)</td>
<td>Child</td>
<td>Adolescents (though tested in children from ages 8 y and up)</td>
<td>34</td>
<td>Self-report</td>
<td>United Kingdom (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Play Performance Scale for Children (PPSC) [Lansky et al., 1987 (20)]</td>
<td>Level of activity</td>
<td>Parent</td>
<td>1–16</td>
<td>1</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pediatric Cancer Quality of Life Inventory (PCQL) [Varni et al., 1998 (35); Seid et al., 1999 (64)]</td>
<td>Disease- and treatment-related symptoms, physical, psychological, social, and cognitive functioning</td>
<td>Child and parent</td>
<td>8–12 (child form), 13–18 (adolescent form)</td>
<td>84 (child form), 87 (adolescent form)</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Spanish</td>
</tr>
<tr>
<td>Pediatric Cancer Quality of Life Inventory (PCQL-32) [Varni et al., 1998a (34); Varni et al., 1999 (65)]</td>
<td>Disease- and treatment-related symptoms, physical, psychological and cognitive functioning</td>
<td>Child and parent</td>
<td>8–12 (child form), 13–18 (adolescent form)</td>
<td>32 (short form)</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>PEDQOL®: quality of life in children and adolescents with cancer [Calaminus et al., 2000 (66)]</td>
<td>Physical functioning, autonomy, emotional functioning, cognition, social functioning/friends, social functioning/family, body image</td>
<td>Child</td>
<td>8–18</td>
<td>34</td>
<td>Self-report</td>
<td>Germany (German)</td>
<td>Plan to publish instrument into other European languages</td>
</tr>
<tr>
<td>PedsQL: Measurement Model for the Pediatric Quality of Life Inventory [Varni et al., 1999 (67)]</td>
<td>Physical, psychological, and social functioning, disease- and treatment-related symptoms</td>
<td>Child and parent</td>
<td>8–12 (child form), 13–18 (adolescent form)</td>
<td>15 core items, plus 8 supplemental modules = 45 items</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Spanish</td>
</tr>
<tr>
<td>Miami Pediatric Quality of Life Questionnaire [Armstrong et al., 1999 (68)]</td>
<td>Social competence, emotional stability, self-competence</td>
<td>Parent</td>
<td>1–18</td>
<td>40</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pediatric Oncology Quality of Life Scale (POQOLS) [Goodwin et al., 1994 (24)]</td>
<td>Physical functions and role restriction, emotional distress, reaction to current medical treatment</td>
<td>Parent</td>
<td>Not stated</td>
<td>21</td>
<td>Self-report</td>
<td>United States (English)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Royal Marsden Hospital Pedriatric Quality of Life Questionnaire (RMH-PQLQ) [Watson et al., 1999 (69)]</td>
<td>Functional status, global quality of life, physical symptoms, emotional status, social functioning, cognitive functioning, behavioral problems, school/educational progress</td>
<td>Parent</td>
<td>Not stated</td>
<td>78</td>
<td>Interview plus self-report</td>
<td>United Kingdom (English)</td>
<td>Swedish, Dutch</td>
</tr>
</tbody>
</table>

*Information excerpted from Connolly and Johnson, 1998 (1).
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Author, y (reference No.)</th>
<th>Data collection period</th>
<th>Site of data collection</th>
<th>Sample demographics</th>
<th>ALL sample</th>
<th>Respondent(s)</th>
<th>Study design</th>
<th>Phase of care</th>
<th>Medication regimen</th>
<th>Reliability</th>
<th>Validity</th>
<th>Confidence intervals for point estimates?</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Health Questionnaire (CHQ-PF50, -PF28, -CF87)</td>
<td>Sawyer et al., 1999 (30)</td>
<td>1997 Adelaide, South Australia</td>
<td>70 adolescent patients aged 10–18 y; 24 active treatment, 46 off treatment</td>
<td>31 (44%)</td>
<td>Patient (child), parent</td>
<td>Cross-sectional</td>
<td>3 wk to 14 y since diagnosis</td>
<td>ALL: induction, consolidation, maintenance</td>
<td>Interrater (parent–child) ICC &gt;0.50 on most scales</td>
<td>Construct: convergent, discriminant</td>
<td>—</td>
<td>Generally good agreement between parent and adolescent HUI Mark 2 and 3 scores</td>
<td></td>
</tr>
<tr>
<td>Speechley et al., 1999 (36)</td>
<td>1997 Multicenter, Canada</td>
<td>244 children aged 7–16 y, mean age 12 y; 35% male</td>
<td>34% had leukemia</td>
<td>Not stated</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>&gt;5 y after cancer diagnosis</td>
<td>Not stated</td>
<td>No original evidence reported</td>
<td>Construct; convergent</td>
<td>—</td>
<td>CHQ and appeared to capture similar constructs in childhood cancer survivors</td>
<td></td>
</tr>
<tr>
<td>Child Health Rating Inventories (CHRIs)</td>
<td>Parsons et al., 1999 (31)</td>
<td>Boston, MA, United States</td>
<td>61 children aged 5–12 y</td>
<td>Not stated</td>
<td>Patient, parent, doctor</td>
<td>2-part cross-sectional</td>
<td>After BMT</td>
<td>Not stated</td>
<td>Internal consistency: alpha &gt;0.60 excepting energy (0.47); fragmentary interrater reliability</td>
<td>Responsiveness: effect size on DII-BMT 1.21; CHRI effect size 0.50</td>
<td>—</td>
<td>Responses of all raters were reliable; parental reports lower than children’s scores</td>
<td></td>
</tr>
<tr>
<td>Functional Status (FSS) [FS-IJR] and FSQ-S</td>
<td>Sawyer et al., 1997 (30)</td>
<td>1997 Adelaide, South Australia</td>
<td>70 adolescent patients aged 10–18 y; 24 active treatment, 46 off treatment</td>
<td>31 (44%)</td>
<td>Patient (child), parent</td>
<td>Cross-sectional</td>
<td>3 wk to 14 y since diagnosis</td>
<td>ALL: induction, consolidation, maintenance</td>
<td>Interrater (parent–child) ICC &gt;0.50 on most scales</td>
<td>Construct: convergent, discriminant</td>
<td>—</td>
<td>Generally good agreement between parent and adolescent scores</td>
<td></td>
</tr>
<tr>
<td>15D (the adult version of the 16D/17D was applied)</td>
<td>Apajalahti et al., 1996 (71)</td>
<td>1961–1993 Helsinki, Finland</td>
<td>106 males, 62 females aged 16–35 y</td>
<td>68</td>
<td>Patient</td>
<td>Cross-sectional</td>
<td>Off therapy at least 1 y</td>
<td>Not stated</td>
<td>None reported</td>
<td>Construct: discriminant</td>
<td>Yes (mean 15D scores for survivors and controls); no difference in dimension weights of 15D assigned by cancer survivors and controls; higher HRQL scores in cancer survivors (P&lt;.001)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

(Table continues)
**Table 2 (continued). Applications of health-related quality-of-life (HRQL) measures to acute lymphoblastic leukemia (ALL)**

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<th>Confidence intervals for point estimates?</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Health Utilities Index (HUI)—Mark 2 and 3</td>
<td>Barr et al., 1993 (37)</td>
<td>Since 1980</td>
<td>Hamilton, Canada</td>
<td>44 patients aged 15–21 4 mo at treatment</td>
<td>25 standard risk, 30 high risk (11 excluded)</td>
<td>Nurse and 4 physicians reached consensus</td>
<td>Cross-sectional</td>
<td>Interval between treatment and assessment 29–145 mo</td>
<td>Various protocols cited</td>
<td>None</td>
<td>Construct: discriminant</td>
<td>Yes (re: odds ratio comparing emotional deficit at different radiation dosages); no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Barr et al., 1997 (32)</td>
<td>Not stated</td>
<td>Hamilton, Canada</td>
<td>18 patients aged 1–14 y</td>
<td>9 standard and 9 high-risk ALL</td>
<td>Patient or parent, doctor, nurse (primary assessor)</td>
<td>Prospective</td>
<td>Continuing chemotherapy following successful remission induction</td>
<td>First 5 days oral corticosteroid during maintenance phase</td>
<td>Interrater: no significant effect due to type of ater</td>
<td>Construct: convergent, discriminant, responsiveness: between week 1 and 2; effect size = 2.00</td>
<td>Provides evidence of construct validity of HUI Mark 2 instrument</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilson and Walker, 1994 (72)</td>
<td>1993</td>
<td>Nottingham, United Kingdom</td>
<td>48 children up to age 17 y</td>
<td>17</td>
<td>Patient or parent, doctor</td>
<td>Cross-sectional</td>
<td>Off treatment for 1 mo to 12 y</td>
<td>Not stated</td>
<td>Doctors identified fewer deficits than patient/parent (not significant)</td>
<td>Not stated</td>
<td>—</td>
<td>Good overall agreement between doctors and patient/parents</td>
</tr>
<tr>
<td></td>
<td>Feeny et al., 1993 (38)</td>
<td>1970–1979</td>
<td>London, United Kingdom</td>
<td>69 children aged 0.5–14 y at treatment, 8–25 y at assessment</td>
<td>Entire sample</td>
<td>Proxy (clinician)</td>
<td>Retrospective cross-sectional</td>
<td>Off treatment 3-drug remission induction</td>
<td>Not stated</td>
<td>None</td>
<td>Construct: convergent and discriminant</td>
<td>No, yes (comparing health status of Canadian population with ALL)</td>
<td>Results underscore the cognitive and emotional burdens of morbidity affecting survivors</td>
</tr>
<tr>
<td></td>
<td>Kanabar et al., 1995 (73)</td>
<td>1980–1993</td>
<td>London, United Kingdom</td>
<td>13 children &lt;14 y old, 15 children &gt;14 y old</td>
<td>4</td>
<td>Patient (if &gt;14 y old); otherwise parent</td>
<td>Cross-sectional</td>
<td>Mean time since treatment 4 y (&lt;14 y old) and 7 y (&gt;14 y old)</td>
<td>Megatherapy followed by autologous bone marrow rescue</td>
<td>None</td>
<td>Not stated</td>
<td>—</td>
<td>A mailout cohort of childhood cancer survivors is described with a modified HUI Mark 2</td>
</tr>
<tr>
<td></td>
<td>Speechley et al., 1999 (36)</td>
<td>1999</td>
<td>Multicenter, Canada</td>
<td>244 children aged 7–6 y, mean age 12 y; 55% male</td>
<td>34% had leukemia</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>≥5 y after cancer diagnosis</td>
<td>Not stated</td>
<td>No original findings reported</td>
<td>Construct: convergent</td>
<td>CHQ and HUI Mark 2/3 appeared to capture similar constructs in childhood cancer survivors</td>
<td></td>
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Table 2 (continued), Applications of health-related quality-of-life (HRQL) measures to acute lymphoblastic leukemia (ALL)*

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<tr>
<td>Torrance et al., 1998 (74); Furlong et al., 2001 (59)</td>
<td>Not stated</td>
<td>Hamilton, Canada</td>
<td>18 patients aged 1–14 y</td>
<td>9 standard- and 9 high-risk ALL</td>
<td>Patient or parent, doctor, nurse (primary assessor)</td>
<td>Prospective</td>
<td>Continuing chemotherapy following successful remission induction</td>
<td>First 5 days oral corticosteroid during maintenance phase</td>
<td>Interrater: no significant effect due to type of rater</td>
<td>Construct: convergent, discriminant, responsiveness: effect size 2.80 (ANOVA, P&lt;.05), paired t tests of weeks 1 and 2 scores significantly different (P&lt;.001)</td>
<td>No, no</td>
<td>All responsiveness results for global HUI Mark 3 score the same or better than HUI Mark 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trudel et al., 1998 (21)</td>
<td>1995</td>
<td>Single center, Montreal, Canada</td>
<td>61 children aged 4–18, mean age 9 y</td>
<td>25 children with some form of leukemia</td>
<td>Parent (mothers only)</td>
<td>Cross-sectional</td>
<td>20 on active treatment and 41 off treatment (2 wk to 7 y)</td>
<td>Test–retest for domains: all weighted kappas &gt;0.40</td>
<td>Content, construct: convergent with CBCL, PPOQLS, POMS</td>
<td>No, no</td>
<td>Overall, the results indicate the HUI Mark 2 is a reliable and valid measure of HRQL for pediatric cancer patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Well-Being Scale (QWB)</td>
<td>Bradlyn et al., 1993 (22)</td>
<td>Not stated</td>
<td>West Virginia, United States</td>
<td>30 patients aged 4–18 y, mean age 10 y</td>
<td>16 patients</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>Within 2 y of treatment completion</td>
<td>Internal consistency alpha &gt;0.92</td>
<td>Construct: convergent with PPSC</td>
<td>No, no</td>
<td>QWB scores were significantly correlated with performance status ratings provided by the parent and physician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Gamble Utilities</td>
<td>Feeny et al., 1991 (75)</td>
<td>1987–1988</td>
<td>Ontario, Canada</td>
<td>293 parents</td>
<td>40 parents</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>Hypothetical health states</td>
<td>Various stages of treatment</td>
<td>Scores by parents of patients and healthy children were similar for some states, significantly different for a few states</td>
<td>Construct: convergent discriminant</td>
<td>No, no</td>
<td>Utility approach can be used to assess the quality-of-life effects of therapy</td>
<td></td>
</tr>
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<tr>
<td>Behavioral, Affective and Somatic Experiences Scale (BASES)</td>
<td>Phipps et al., 1999 (33)</td>
<td>1995–1997</td>
<td>Memphis, TN, United States</td>
<td>105 children up to 20 y old, mean age 8.3 y</td>
<td>19</td>
<td>Patient, parent, nurse</td>
<td>Prospective longitudinal</td>
<td>BMT</td>
<td>Not stated</td>
<td>Internal consistency and interrater reliability for various version of BASES provided. Construct: convergent, discriminant, clear patterns of change over time found on measures of all respondents.</td>
<td>BASES scales are most appropriate for patient undergoing aggressive therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIE</td>
<td>Eiser et al., 1995 (23)</td>
<td>Not stated</td>
<td>Newcastle, United Kingdom</td>
<td>41 patients aged 8–24 y, mean age 14.6 y</td>
<td>28</td>
<td>Patient (child)</td>
<td>Cross-sectional</td>
<td>Maintenance and follow-up</td>
<td>Not stated</td>
<td>Internal consistency alpha = 0.61–0.88; test-retest for total score r = .92</td>
<td>Content, construct</td>
<td>First evidence to emerge on this instrument</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Play Performance Scale for Children (PPSC)</td>
<td>Eiser et al., 1997 (76)</td>
<td>Not stated</td>
<td>Newcastle, United Kingdom</td>
<td>47 children aged 4–19 y (mean age 14.5 y); 26 boys, 21 girls</td>
<td>Entire sample</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>12 remission, 35 maintenance therapy</td>
<td>Not stated</td>
<td>None</td>
<td>Construct: convergent</td>
<td>No, no</td>
<td>PPSC was used for cross-validation</td>
<td></td>
</tr>
<tr>
<td>Lansky et al., 1987 (20)</td>
<td>Not stated</td>
<td>Chicago, IL, United States</td>
<td>98 patients (mean age 8 y, range 1–16 y)</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>20 off treatment, 78 on active treatment</td>
<td>Not stated</td>
<td>Internal consistency (parent pairs) r = .71</td>
<td>Content, construct</td>
<td>First evidence to emerge on this instrument</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradlyn et al., 1995 (22)</td>
<td>Not stated</td>
<td>West Virginia, United States</td>
<td>30 patients aged 4–18 y, mean age 10 y</td>
<td>Parent</td>
<td>Cross-sectional</td>
<td>Within 2 y of treatment completion</td>
<td>Not stated</td>
<td>Interrater reliability between physician and parent scores r = .64, P&lt;.01</td>
<td>Construct: convergent with QWB</td>
<td>QWB scores were significantly correlated with performance status ratings provided by the parent and physician for patients.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Cancer Quality of Life Inventory-32 (PCQL-32)</td>
<td>Varni et al., 1998 (34)</td>
<td>1994–1996</td>
<td>Multicenter, southern California, United States</td>
<td>291 patients aged 8–18 y</td>
<td>128</td>
<td>Patient, parent</td>
<td>Cross-sectional</td>
<td>On and off treatment</td>
<td>Not stated</td>
<td>Internal consistency of each scale assessed; patient/parent correlations r = .36–.59</td>
<td>Content and construct: convergent and discriminative (clinical)</td>
<td>The PCQL-32 has acceptable internal consistency reliability and construct validity for both patient and parent report</td>
<td></td>
<td></td>
</tr>
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<tr>
<td>Varni et al., 1998 (35)</td>
<td>1994–1996</td>
<td>Multicenter, southern California, United States</td>
<td>291 patients aged 8–18 y</td>
<td>128</td>
<td>Patient, parent</td>
<td>Cross-sectional</td>
<td>On and off treatment</td>
<td>Not stated</td>
<td>Patient/parent concordance measured for each item</td>
<td>None reported</td>
<td>—</td>
<td>Need to be aware of the differing perspective of multiple informants when assessing HRQL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varni et al., 1999 (65)</td>
<td>1994–1996</td>
<td>Multicenter, southern California, United States</td>
<td>291 patients aged 8–18 y</td>
<td>128</td>
<td>Patient, parent</td>
<td>Cross-sectional</td>
<td>On and off treatment</td>
<td>Not stated</td>
<td>None</td>
<td>Ceiling and floor effects examined</td>
<td>—</td>
<td>Results demonstrate the feasibility and range of measurement of the PCQL-32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEDQOL®: quality of life in children and adolescents with cancer</td>
<td>Calaminus et al., 2000 (66)</td>
<td>Not stated</td>
<td>Germany</td>
<td>49 patients aged 8–17 y</td>
<td>16</td>
<td>Patient (leukemia, type not specified)</td>
<td>Cross-sectional</td>
<td>Off treatment</td>
<td>Not stated</td>
<td>Patient group responses compared with responses by 62 healthy schoolchildren</td>
<td>Reliability coefficients (Cronbach’s alpha)</td>
<td>—</td>
<td>QoL was scored as good by both healthy and off-treatment children. Children who survived leukemia rated their QoL (in most domains) lower than that among children who survived solid cancers</td>
<td></td>
</tr>
<tr>
<td>PedsQL: Measurement Model for the Pediatric Quality of Life Inventory</td>
<td>Varni et al., 1999 (67)</td>
<td>1994–1996</td>
<td>Multicenter, California, United States</td>
<td>291 patients aged 8–19 y, mean age 12 y</td>
<td>128</td>
<td>Patient, parent</td>
<td>Cross-sectional</td>
<td>50% induction remission; 50% off therapy</td>
<td>Not stated</td>
<td>Internal consistencyalpha = 0.69–0.83 (patient) and 0.59–0.89 (parent) for scales, 0.93 total score (patient and parent); correlations between parent–patient ratings</td>
<td>Construct: convergent and discriminant</td>
<td>—</td>
<td>Results support the PedsQL as a reliable and valid measure</td>
<td></td>
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<tbody>
<tr>
<td>Pediatric Oncology Quality of Life Scale (POQOLS)</td>
<td>Goodwin et al., 1994 (24)</td>
<td>Not stated</td>
<td>2 centers in Florida, United States</td>
<td>1st generation: 210 parents of children with cancer; 2nd generation: 107 parents</td>
<td>Not stated</td>
<td>Parent (mothers only)</td>
<td>Cross-sectional</td>
<td>For 2nd generation measure testing: group 1 (n = 27) off therapy; group 2 (n = 30) on active treatment</td>
<td>Internal consistency alphas for factors 1, 2, 3: 0.87, 0.79, 0.68; interrater r between mother/father: r = .87 (total score), .91, .87, .75 (factors 1, 2, 3)</td>
<td>Content, construct: convergent and discriminant</td>
<td>—</td>
<td>Results are promising; further evaluation necessary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trudel et al., 1998 (21)</td>
<td>1995</td>
<td>Single center, Montreal, Canada</td>
<td>61 children aged 4–18, mean age 9 y</td>
<td>25 children with some form of leukemia</td>
<td>Parent (mothers only)</td>
<td>Cross-sectional</td>
<td>20 on active treatment and 41 off treatment (2 wk to 7 y)</td>
<td>None</td>
<td>Construct: convergent with HUI Mark 2</td>
<td>No, no</td>
<td>Evidence of good construct validity based on correlations with HUI Mark 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kazak et al., 1995 (77)</td>
<td>1991</td>
<td>Philadelphia, PA, United States</td>
<td>70 patients &lt;19 y old</td>
<td>56</td>
<td>Parent (1 or 2 caregivers per patient)</td>
<td>Cross-sectional</td>
<td>First remission</td>
<td>Chemotherapy not stated</td>
<td>None</td>
<td>Construct: convergent</td>
<td>No, no</td>
<td>New measure Perceptions of Procedures Questionnaire (PPQ) discussed Distress ratings on PPQ are correlated with distress scale on POQOLS</td>
</tr>
<tr>
<td></td>
<td>Kazak et al., 1996 (78)</td>
<td>Not stated</td>
<td>Philadelphia, PA, United States</td>
<td>144 (77 male, 67 female) aged 1 mo to 17.5 y; 87% Caucasian, 9% Afro-American, 2% Asian, 1% Hispanic, 1% Asian Indian</td>
<td>121</td>
<td>Parents, nurses</td>
<td>Cross-sectional</td>
<td>First remission</td>
<td>Multimodal chemotherapy</td>
<td>None</td>
<td>Construct: convergent</td>
<td>No, no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kazak et al., 1996 (40)</td>
<td>1991</td>
<td>Philadelphia, PA, United States</td>
<td>45 (drug only group); 47 (combined drugs and psychologic); 70 (control); table on gender, age, ethnicity of each group included</td>
<td>78% drug only (PO) group; 87% combined drugs and psychologic (CI); 80% control (CC)</td>
<td>Parent, doctors, nurses</td>
<td>Prospective RCT</td>
<td>Patients in first remission</td>
<td>None</td>
<td>Construct: discriminant; longitudinal detected significant changes in POQOLS scores over time</td>
<td>No, no</td>
<td>Found increases in both mothers' and fathers' perceptions of their child's quality of life</td>
<td></td>
</tr>
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*(Table continues)*
Table 2 (continued). Applications of health-related quality-of-life (HRQL) measures to acute lymphoblastic leukemia (ALL)*

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<tr>
<td>Royal Marsden Hospital Paediatric Quality of Life Questionnaire (RMH-PQLQ)</td>
<td>Kazak et al., 1997 (79)</td>
<td>1991, 1993–1995</td>
<td>Philadelphia, PA, United States</td>
<td>29 children and adolescents mean age 7.64 y at time of in-treatment study; 55% female, 45% male, 97% Caucasian, 3% Asian</td>
<td>90% were ALL survivors</td>
<td>Patient, both parents</td>
<td>Cross-sectional</td>
<td>POQOLS given during active treatment</td>
<td>Not stated</td>
<td>None</td>
<td>Construct: convergent</td>
<td>No, no</td>
<td>Children-rated anxiety discussed in relation to parent ratings</td>
</tr>
<tr>
<td></td>
<td>Watson et al., 1999 (69)</td>
<td>Not stated</td>
<td>Sutton, United Kingdom; Uppsala, Sweden</td>
<td>90 families; patients aged 3–19 y, mean age 9 y</td>
<td>13 from the United Kingdom, 17 from Sweden</td>
<td>Parent—primary caregiver</td>
<td>Pre- and post-design</td>
<td>72 on and 17 off treatment, 1 unknown; 1–2 wk after diagnosis (time 1); 6–8 wk later during active therapy (time 2)</td>
<td>ALL patients received radiation therapy and chemotherapy</td>
<td>Internal consistency alpha = 0.65–0.85</td>
<td>Content, construct: discriminant; longitudinal: significant differences between times 1 and 2 on several domains</td>
<td>—</td>
<td>Suggest further development of the new measure</td>
</tr>
<tr>
<td>12-item instrument concerning physical and psychosocial functioning (unnamed)</td>
<td>Matthes-Martin et al., 1999 (80)</td>
<td>1980–1996</td>
<td>Vienna, Austria</td>
<td>73 children after BMT</td>
<td>27 patients</td>
<td>Patient (if &gt;12 y old); parent (if patient &lt;12 y old)</td>
<td>Retrospective cross-sectional</td>
<td>After BMT</td>
<td>Varied</td>
<td>None stated</td>
<td>Construct: discriminant (?)</td>
<td>No, no</td>
<td>Quality-of-life instrument unable to discriminate between groups with an interval of more and &lt;3 y after BMT</td>
</tr>
<tr>
<td>DII-BMT</td>
<td>Parsons et al., 1999 (31)</td>
<td>Not stated</td>
<td>Boston, MA, United States</td>
<td>61 children aged 5–12 y</td>
<td>Not stated</td>
<td>Patient, parent, doctor</td>
<td>2-part cross-sectional</td>
<td>After BMT</td>
<td>Not stated</td>
<td>Internal consistency alpha ≥0.60 excepting energy (0.47); fragmentary interrater reliability</td>
<td>Longitudinal construct: effect size on DII-BMT 1.21; CHRI effect size 0.50</td>
<td>—</td>
<td>Responses of all raters were reliable; parental reports lower than children’s scores</td>
</tr>
</tbody>
</table>

*ANOVA = analysis of variance; BMT = bone marrow transplantation; HUI = Health Utilities Index; ICC = intra-class correlation; MANOVA = multivariate ANOVA; PIE = Perceived Illness Experience Scale; POMS = Profile of Moods Scale; DII-BMT = disease impairment inventories–bone marrow transplantation; POQOLS = Pediatric Oncology Quality of Life Scale; PPSC = Play Performance Scale for Children; QoL = Quality of Life; RCT = randomized controlled clinical trial. — Indicates that information was not abstracted.
†Information excerpted from Connolly and Johnson, 1998 (1).
<table>
<thead>
<tr>
<th>Study description</th>
<th>Author, y (reference No.)</th>
<th>Study design</th>
<th>Type of evaluation</th>
<th>Patient population/indication</th>
<th>Sample size</th>
<th>No. of ALL patients</th>
<th>Intervention/ treatment comparators</th>
<th>Perspective of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost comparison of laboratory charges in treating childhood leukemia</td>
<td>Baranko, 1994 (81)</td>
<td>Retrospective: 2 protocols compared</td>
<td>Cost identification</td>
<td>Pediatric ALL</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Protocol treatments “X and Y”</td>
<td>Hospital (laboratory department)</td>
</tr>
<tr>
<td>Family costs of childhood cancer</td>
<td>Barr et al., 1996 (43)</td>
<td>Prospective cohort</td>
<td>Cost identification</td>
<td>Families of children with high/very high risk ALL, Wilms tumor, metastatic neuroblastoma</td>
<td>64 families completed 103 diaries</td>
<td>52 families completed 85 diaries</td>
<td>N/A</td>
<td>Patient</td>
</tr>
<tr>
<td>Early hospital discharge of lower risk children with cancer admitted for fever and neutropenia</td>
<td>Bash et al., 1994 (82)</td>
<td>Prospective cohort</td>
<td>Cost minimization</td>
<td>Children with cancer admitted with fever during neutropenia</td>
<td>74</td>
<td>37</td>
<td>Early discharge vs. no early discharge of neutropenic patient</td>
<td>Hospital (laboratory department)</td>
</tr>
<tr>
<td>Financial burden of childhood cancer</td>
<td>Bodkin et al., 1982 (83)</td>
<td>Prospective</td>
<td>Cost identification</td>
<td>Families of children with cancer</td>
<td>59 families (of 73) agreed to participate and complied</td>
<td>ALL—N/A leukemia = 27</td>
<td>N/A</td>
<td>Individual/family</td>
</tr>
<tr>
<td>Consequences of exposure and varicella infection in children receiving maintenance therapy for ALL</td>
<td>Buda et al., 1996 (84)</td>
<td>Retrospective, decision analysis models</td>
<td>Cost identification</td>
<td>Children receiving maintenance chemotherapy for ALL</td>
<td>472 children aged 1–21 y</td>
<td>Entire sample</td>
<td>Prophylaxis with varicella vaccination vs. no vaccine</td>
<td>Hospital</td>
</tr>
<tr>
<td>Once-daily ceftriaxone plus amikacin for children with cancer</td>
<td>Castagnola et al., 1999 (85)</td>
<td>Retrospective cohort</td>
<td>Cost minimization</td>
<td>Febrile granulocytopenic children with cancer</td>
<td>101 episodes in 89 patients</td>
<td>9 episodes in 9 ALL patients</td>
<td>Ceftriaxone + amikacin (CXA); ceftazidime + amikacin (CZA)</td>
<td>Hospital</td>
</tr>
<tr>
<td>Antibiotics in febrile neutropenia</td>
<td>Charnas et al., 1997 (47)</td>
<td>Prospective randomized</td>
<td>Cost identification</td>
<td>Febrile neutropenic children with cancer aged 1–17 y</td>
<td>364 patient episodes</td>
<td>165 patient episodes</td>
<td>Ceftriaxone + amikacin (CXA); ceftazidime + amikacin (CZA)</td>
<td>Hospital</td>
</tr>
<tr>
<td>Cost effectiveness of therapy with antibiotics in cancer patients</td>
<td>Cimino et al., 1994 (86)</td>
<td>Before–after observational</td>
<td>Cost identification</td>
<td>Cancer patients requiring antibiotic therapy</td>
<td>149</td>
<td>Not stated</td>
<td>Service 1 (pharmacist promoting guidelines); service 2 (guidelines provided without pharmacist); service 3 (guidelines adopted prior to baseline evaluation)</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

(Table continues)
<table>
<thead>
<tr>
<th>Analytic horizon (and discount rate, if applicable)</th>
<th>Care setting</th>
<th>Outcome measures</th>
<th>Resources included: formal health care</th>
<th>Resources included: patient-related</th>
<th>Sources of resource information</th>
<th>Results</th>
<th>Sensitivity analysis (no/yes: univariate/multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unclear</td>
<td>Single institution, Phoenix, AZ, United States</td>
<td>Cost (charges)</td>
<td>Mandatory laboratory and radiographic charges for inpatients and outpatients</td>
<td>None</td>
<td>Hospital</td>
<td>Group Y protocol had consistently higher charges</td>
<td>No</td>
</tr>
<tr>
<td>107 wk</td>
<td>2 tertiary care institutions in Canada (Toronto, Hamilton)</td>
<td>Cost</td>
<td>None</td>
<td>Daily costs borne by families related to child’s therapy for sample weeks; cost of work loss</td>
<td>Daily costs born by family (diary); productivity losses (1986 Statistics Canada)</td>
<td>Mean costs per disease case of ALL $26 070 (Canadian) median cost $19 938 (Canadian)</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Dallas, TX, United States</td>
<td>Cost (charges)</td>
<td>Total hospital charges for 24-h period prior to discharge multiplied by days after discharge that patient was neutropenic (outpatient charges not included)</td>
<td>None</td>
<td>Hospital (?)</td>
<td>Average total savings for each patient discharged early was $5058 (SD $4890)</td>
<td>No</td>
</tr>
<tr>
<td>1 wk of inpatient expenses and 1 wk of outpatient expenses</td>
<td>Hospital (in and outpatient), Birmingham, United Kingdom</td>
<td>Cost of illness (to parents for child’s cancer care)</td>
<td>None</td>
<td>Lost income, travel costs, accommodation, funeral costs, etc.</td>
<td>Form completed by investigator from interview with parents</td>
<td>Inpatient care was twice as expensive as outpatient care for families. Families of children with cancer need more financial assistance</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Multi-institutional (United States): 12 sites</td>
<td>Cost</td>
<td>Outpatient management, inpatient room cost, isolation fee, physician visit charges, blood work, laboratory tests, radiographs, medications</td>
<td>Costs to parents projected from literature</td>
<td>Hospital charges in Denver (specific source not stated)</td>
<td>$394 000–$402 000 medical charges in exposed group vs. $81 034 in vaccinated group</td>
<td>Some</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Genoa, Italy</td>
<td>Cost</td>
<td>Antibiotics, injection materials</td>
<td>None</td>
<td>Official hospital drug prices in Italy, (L’informatore Farmaceutico, Nov. 1997)</td>
<td>CXA resulted in a daily cost saving of U.S. $11 (1-day treatment) and U.S. $66 (6-day treatment) over CZA</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Multicenter, 8 countries</td>
<td>Cost; complete response, improvement, failure</td>
<td>Drug acquisition, drug delivery, toxicity testing and monitoring, daily hospital costs</td>
<td>None</td>
<td>Referenced published U.S. sources of cost data</td>
<td>Similar response, improvement and failure rates; CXA more cost-effective than CZA (daily cost $162 vs. $244)</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Buffalo, NY, United States</td>
<td>Cost</td>
<td>Antibiotics (acquisition, preparation, dispensing, administration)</td>
<td>None</td>
<td>Hospital (?)</td>
<td>Service group 1 experienced a 13% improvement in clinical response (P&lt;.05) and $597 reduction in mean cost of therapy per patient</td>
<td>No</td>
</tr>
<tr>
<td>Study description</td>
<td>Author, y (reference No.)</td>
<td>Study design</td>
<td>Type of evaluation</td>
<td>Patient population/indication</td>
<td>Sample size</td>
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<td>Intervention/treatment comparators</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------</td>
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<td>--------------------</td>
<td>-------------------------------</td>
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<td>------------------------------------</td>
</tr>
<tr>
<td>Outpatient irradiation for pediatric patients undergoing stem cell transplantation</td>
<td>Dagher et al., 1997 (87)</td>
<td>Retrospective</td>
<td>Cost identification</td>
<td>Children undergoing stem cell transplantation receiving TBI</td>
<td>10</td>
<td>3</td>
<td>Outpatient TBI vs. inpatient TBI</td>
</tr>
<tr>
<td>Economic evaluation of G-CSF after BMT in children</td>
<td>Duncan et al., 1997 (88)</td>
<td>Retrospective case–control (before and after observational)</td>
<td>Cost identification</td>
<td>Children receiving autologous or allogenic BMTs</td>
<td>18 received G-CSF; 22 control subjects</td>
<td>3 received G-CSF; 3 control subjects</td>
<td>G-CSF vs. no G-CSF</td>
</tr>
<tr>
<td>Safety and cost effectiveness of outpatient irradiation in pediatric patients undergoing stem cell transplantation</td>
<td>Farah et al., 1998 (89)</td>
<td>Retrospective case–control</td>
<td>Cost identification</td>
<td>Children with hematopoietic malignancies</td>
<td>16 inpatient TBI; 17 outpatient TBI</td>
<td>Inpatient TBI (n = 5); outpatient TBI (n = 8)</td>
<td>Outpatient TBI vs. inpatient TBI</td>
</tr>
<tr>
<td>Home chemotherapy for children with cancer</td>
<td>Jayabose et al., 1992 (90)</td>
<td>Before and after observational</td>
<td>Cost identification</td>
<td>Consolation phase of high-risk ALL</td>
<td>20 children</td>
<td>Entire sample</td>
<td>Chemotherapy at home vs. at hospital</td>
</tr>
<tr>
<td>Childhood cancer: nonmedical costs of the illness</td>
<td>Lansky et al., 1979 (91)</td>
<td>Prospective</td>
<td>Cost identification</td>
<td>Burden of illness of childhood cancer</td>
<td>70 patients’ families</td>
<td>Not stated</td>
<td>N/A</td>
</tr>
<tr>
<td>Cost of chickenpox in Canada</td>
<td>Law et al., 1999 (92)</td>
<td>Retrospective and prospective convenience sample</td>
<td>Cost identification (cost of illness)</td>
<td>Children with chickenpox</td>
<td>160 otherwise healthy children and 40 children with leukemia</td>
<td>Not stated</td>
<td>N/A</td>
</tr>
<tr>
<td>Recombinant human GM-CSF after BMT for lymphoid cancer</td>
<td>Luce et al., 1994 (42)</td>
<td>Retrospective, based on double-blinded prospective RCT</td>
<td>Cost-effectiveness analysis</td>
<td>Patients of all ages with lymphoid cancer following autologous BMT</td>
<td>22 rhGM-CSF; 18 placebo</td>
<td>7 rhGM-CSF; 10 placebo</td>
<td>rhGM-CSF, placebo</td>
</tr>
<tr>
<td>Use of concurrent G-CSF + GM-CSF vs. G-CSF alone for mobilization of peripheral blood stem cells in children with malignant disease</td>
<td>Madero et al., 2000 (93)</td>
<td>Prospective</td>
<td>Cost-effectiveness analysis</td>
<td>Children aged &lt;16 y undergoing peripheral blood progenitor cell transplantation between 1997 and 1999</td>
<td>42 (21 in each group)</td>
<td>1 in each group</td>
<td>Group 1: peripheral blood stem cell transplantation with G-CSF + GM-CSF vs. group 2: G-CSF alone</td>
</tr>
</tbody>
</table>

(Table continues)
Table 3 (continued), Costing studies and economic evaluations in pediatric acute lymphoblastic leukemia (ALL)*

<table>
<thead>
<tr>
<th>Analytic horizon (and discount rate, if applicable)</th>
<th>Care setting</th>
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<th>Resources included: patient-related</th>
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<th>Sensitivity analysis (no/yes: univariate/multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 y (100 days following BMT)</td>
<td>Multicenter United States (Boston, Omaha, Seattle)</td>
<td>Cost (charges)</td>
<td>Hospitalization per diem (includes allied health care, laboratory tests, surgical and medical procedures, medication), additional physician fees</td>
<td>Productivity losses (daily activities, time lost from work) based on caregiver interviews</td>
<td>Ontario and Quebec Ministries of Health (MOH) (1997/1998)</td>
<td>Societal cost of chickenpox: $112.4 million; 19.6% are direct costs to MOH ($24 million); 53.3% of direct costs attributable to cost of treating complicated cases</td>
<td>Yes; e.g., varied major cost drivers by 20%</td>
</tr>
<tr>
<td>+100 days</td>
<td>Single-institution, Italy</td>
<td>Collected CD3/4+ cells; hematopoietic recovery; cost in U.S. dollars</td>
<td>Direct medical costs (e.g., laboratory, hospital, drugs, blood)</td>
<td>None</td>
<td>Material costs from institution and regional laboratory; hospitalization cost from Spanish health department</td>
<td>PBPC with G-CSF + GM-CSF in children does not offer an improvement over G-CSF alone, nor do overall transplant costs increase substantially</td>
<td>No</td>
</tr>
<tr>
<td>3 mo</td>
<td>Single institution</td>
<td>Cost of illness</td>
<td>N/A</td>
<td>Nonmedical costs</td>
<td>Transportation, family care for siblings, extra clothing, loss of pay, etc.</td>
<td>Mean loss of pay and out-of-pocket expenses 43.7% of income; the economic burden adds to family’s overall distress</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Dallas, TX, United States</td>
<td>Cost</td>
<td>Per-diem hospital bed charges, ambulance transportation to and from hospital, clinic visits, fluid administration when needed</td>
<td>None</td>
<td></td>
<td>TBI in outpatient setting saved approximately $3250 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Sutton, United Kingdom</td>
<td>Cost</td>
<td>Hospitalization, TPN, drugs, growth factors, blood products, laboratory costs</td>
<td>None</td>
<td>Hospital pharmacy department (drug costs); finance department (all other costs)</td>
<td>Mean cost per patient in G-CSF was UK £15 001, control group UK £15 482 (1995); G-CSF did not result in faster discharge</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution</td>
<td>Cost (charges)</td>
<td>Hospitalization, clinical visits, chemotherapy-related items (drugs, IV materials, nursing services)</td>
<td>None</td>
<td>Insurance reimbursement for each individual; hospital billing charges; HCO itemized charges for various services</td>
<td>Total cost savings $117 327; mean cost savings $5866 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Indianapolis, IN, United States</td>
<td>Cost</td>
<td>Routine daily bed charges, transportation to and from radiation facility for inpatients, outpatients charges for clinic visits, fluid administration, home care nursing</td>
<td>None</td>
<td>Not stated</td>
<td>TBI in outpatient setting saved approximately $2400 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Sutton, United Kingdom</td>
<td>Cost</td>
<td>Hospitalization, TPN, drugs, growth factors, blood products, laboratory costs</td>
<td>None</td>
<td>Hospital pharmacy department (drug costs); finance department (all other costs)</td>
<td>Mean cost per patient in G-CSF was UK £15 001, control group UK £15 482 (1995); G-CSF did not result in faster discharge</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Dallas, TX, United States</td>
<td>Cost</td>
<td>Per-diem hospital bed charges, ambulance transportation to and from hospital, clinic visits, fluid administration when needed</td>
<td>None</td>
<td>Hospital (?)</td>
<td>TBI in outpatient setting saved approximately $3250 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Indianapolis, IN, United States</td>
<td>Cost</td>
<td>Routine daily bed charges, transportation to and from radiation facility for inpatients, outpatients charges for clinic visits, fluid administration, home care nursing</td>
<td>None</td>
<td>Not stated</td>
<td>TBI in outpatient setting saved approximately $2400 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Sutton, United Kingdom</td>
<td>Cost</td>
<td>Hospitalization, TPN, drugs, growth factors, blood products, laboratory costs</td>
<td>None</td>
<td>Hospital pharmacy department (drug costs); finance department (all other costs)</td>
<td>Mean cost per patient in G-CSF was UK £15 001, control group UK £15 482 (1995); G-CSF did not result in faster discharge</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution, Dallas, TX, United States</td>
<td>Cost</td>
<td>Per-diem hospital bed charges, ambulance transportation to and from hospital, clinic visits, fluid administration when needed</td>
<td>None</td>
<td>Hospital (?)</td>
<td>TBI in outpatient setting saved approximately $3250 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution</td>
<td>Cost (charges)</td>
<td>Hospitalization, clinical visits, chemotherapy-related items (drugs, IV materials, nursing services)</td>
<td>None</td>
<td>Insurance reimbursement for each individual; hospital billing charges; HCO itemized charges for various services</td>
<td>Total cost savings $117 327; mean cost savings $5866 per patient</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>Single institution</td>
<td>Cost of illness</td>
<td>N/A</td>
<td>Nonmedical costs</td>
<td>Transportation, family care for siblings, extra clothing, loss of pay, etc.</td>
<td>Mean loss of pay and out-of-pocket expenses 43.7% of income; the economic burden adds to family’s overall distress</td>
<td>No</td>
</tr>
<tr>
<td>3 mo</td>
<td>Single institution</td>
<td>Cost of illness</td>
<td>N/A</td>
<td>Nonmedical costs</td>
<td>Transportation, family care for siblings, extra clothing, loss of pay, etc.</td>
<td>Mean loss of pay and out-of-pocket expenses 43.7% of income; the economic burden adds to family’s overall distress</td>
<td>No</td>
</tr>
</tbody>
</table>
### Table 3 (continued), Costing studies and economic evaluations in pediatric acute lymphoblastic leukemia (ALL)*

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<tr>
<th>Study description</th>
<th>Author, y (reference No.)</th>
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<th>No. of ALL patients</th>
<th>Intervention/ treatment comparators</th>
<th>Perspective of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of allogeneic peripheral blood progenitor cell and bone marrow transplantation for ALL in children</td>
<td>Madero et al., 2000 (94)</td>
<td>Prospective</td>
<td>Cost-effectiveness analysis</td>
<td>Children &lt;16 y old with ALL in remission who underwent PBPC or BMT</td>
<td>25 (13 PBPC and 12 BMT)</td>
<td>25</td>
<td>Peripheral blood progenitor cell vs. bone marrow transplantation</td>
<td>Hospital</td>
</tr>
<tr>
<td>Treatment of childhood ALL in Thailand: outcome and cost analysis</td>
<td>Nuchprayoon et al., 2000 (95)</td>
<td>Retrospective</td>
<td>Cost-effectiveness analysis</td>
<td>Children with ALL</td>
<td>27 patients (14 low risk and 13 high risk) selected for cost analysis</td>
<td>27</td>
<td>Different treatment protocols (A, B, and C)</td>
<td>Health care provider (i.e., 3rd party insurer)</td>
</tr>
<tr>
<td>Use of G-CSF in pediatric cancer</td>
<td>Pajeau et al., 1997 (96)</td>
<td>Retrospective</td>
<td>Costing</td>
<td>Children aged 1–22 y receiving both induction and maintenance therapies</td>
<td>45 G-CSF and 43 placebo</td>
<td>Entire sample</td>
<td>G-CSF vs. placebo</td>
<td>Hospital</td>
</tr>
<tr>
<td>Cost-effectiveness of ceftriaxone and amikacin in children with cancer</td>
<td>Pession et al., 1997 (97)</td>
<td>Prospective cohort</td>
<td>Costing (cost-minimization analysis)</td>
<td>Feverish granulocytopenic children with cancer</td>
<td>183 patient episodes</td>
<td>45 episodes in 25 ALL patients</td>
<td>Ceftriaxone + amikacin (CXA); ceftriaxone + amikacin (CZA)</td>
<td>Hospital</td>
</tr>
<tr>
<td>G-CSF after induction chemotherapy</td>
<td>Pui et al., 1997 (98)</td>
<td>Double blinded prospective RCT</td>
<td>Costing</td>
<td>Newly diagnosed ALL patients aged 2 mo to 17 y</td>
<td>Final sample: 73 G-CSF; 75 placebo</td>
<td>Entire sample</td>
<td>Recombinant human G-CSF; placebo</td>
<td>Hospital</td>
</tr>
<tr>
<td>Cost analysis of the treatment of childhood ALL according to Nordic protocols</td>
<td>Rahiala et al., 2000 (99)</td>
<td>Prospective</td>
<td>Costing</td>
<td>Children diagnosed with ALL between 1991 and 1994 (not including patients who relapsed or who had BMT)</td>
<td>11</td>
<td>11</td>
<td></td>
<td>Hospital</td>
</tr>
<tr>
<td>Cost of BMT compared with conventional treatment</td>
<td>Rollinson, 1982 (100)</td>
<td>Case–control</td>
<td>Costing</td>
<td>Patients with life-threatening blood disorders</td>
<td>6 BMT; 21 conventional therapy</td>
<td>1 BMT; 5 conventional</td>
<td>BMT, conventional therapy</td>
<td>Hospital</td>
</tr>
<tr>
<td>Prophylaxis, cost and effectiveness of therapy in neutropenic children</td>
<td>Schaison et al., 1991 (101)</td>
<td>RCT</td>
<td>Costing</td>
<td>Febrile episodes in neutropenic children with acute leukemias</td>
<td>71 patients</td>
<td>58</td>
<td>Vancomycin + cefazidime (VC); ticarcillin + ceftriaxone (TC) once daily</td>
<td>Hospital</td>
</tr>
<tr>
<td>Laboratory costs in the context of disease</td>
<td>Young et al., 2000 (102)</td>
<td>Retrospective</td>
<td>Costing</td>
<td>Laboratory costs for major DRGs in a consortium of 60 hospitals</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Hospital</td>
</tr>
<tr>
<td>Toxicity, supportive care, and costs of chemotherapy protocols for childhood ALL in Russia</td>
<td>von Stackelberg et al., 1999 (103)</td>
<td>Randomized, prospective</td>
<td>Costing</td>
<td>Non-B-ALL pediatric patients</td>
<td>25 in ALL protocol BFM 90 (modified); 32 in ALL the new Russian protocol Moscow-Berlin 91 (MB)</td>
<td>Entire sample</td>
<td>Protocol BFM 90 vs. MB</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*Table continues*
Table 3 (continued). Costing studies and economic evaluations in pediatric acute lymphoblastic leukemia (ALL)*

<table>
<thead>
<tr>
<th>Analytic horizon (and discount rate, if applicable)</th>
<th>Care setting</th>
<th>Outcome measures</th>
<th>Resources included: formal health care</th>
<th>Resources included: patient-related</th>
<th>Sources of resource information</th>
<th>Sensitivity analysis (mo/yes: univariate multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100+ days Single institution, Italy</td>
<td>Cost in U.S. dollars; number of life-years saved</td>
<td>Hospital costs (e.g., length of stay, diagnostic tests, blood)</td>
<td>None</td>
<td>Hospital and blood center costs</td>
<td>PBPC is a safe and effective procedure in children with ALL and achieves faster hematologic recovery than does BMT; overall cost is lower for PBPC</td>
<td>No</td>
</tr>
<tr>
<td>5 y Not stated</td>
<td>Cost per life saved; average provider costs</td>
<td>Material and labor cost, excluding capital and administrative cost</td>
<td>None</td>
<td>Not stated</td>
<td>Average cost of ALL treatment U.S. $9563; treatment without consolidation is inadequate and not cost-effective</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y Not stated</td>
<td>Cost</td>
<td>Hospitalization, antibiotics, blood products</td>
<td>None</td>
<td>Hospitalization costs (U.S. children’s hospital: NEJM); billing records from a representative study institution</td>
<td>G-CSF unlikely to be associated with substantial cost savings for pediatric ALL</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y Single institution, Bologna, Italy</td>
<td>Cost</td>
<td>Antibiotics, non-reusable materials, injection materials</td>
<td>None</td>
<td>Official hospital drug prices in Italy, injection material from hospital</td>
<td>CXA resulted in a daily cost saving of U.S. $11 (1-day treatment) and U.S. $65.6 (6-day treatment) over CZA</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y Single institution; Memphis, TN, United States</td>
<td>Median costs, cost of supportive care, rate of hospitalization, survival time</td>
<td>Hospitalization, IV antibiotics, transfusions, G-CSF</td>
<td>None</td>
<td>1996–1997 almanac of hospital financial and operating indicators; costs reported but sources unclear</td>
<td>Similar median costs: G-CSF $8768, placebo $8616; G-CSF did not reduce rate of hospitalization, supportive care costs or prolong survival</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y Single institution, Finland</td>
<td>Cost</td>
<td>All direct treatment-related costs</td>
<td>None</td>
<td>Hospital</td>
<td>Treatment of childhood ALL required about 150 hospital days; total costs approximately $100 000 per patient (varying among risk groups)</td>
<td>No</td>
</tr>
<tr>
<td>Varied; up to 7 y</td>
<td>Single institution; Christ-church, New Zealand</td>
<td>Cost</td>
<td>Hospital bed, outpatient visits, drugs, preparation of blood products</td>
<td>Transport and accommodation for patient and family</td>
<td>Hospital board, person communications, arbitrary</td>
<td>Average cost per patient for BMT NZ $14 609 conventional therapy NZ $7276 (1981$)</td>
</tr>
<tr>
<td>&lt;1 y Not stated</td>
<td>Cost, nursing time</td>
<td>Antibiotic and material costs, nursing time</td>
<td>None</td>
<td>Not stated; U.S. dollars converted from French francs</td>
<td>For 16-day treatment, TC once daily saved U.S. $80 and 10 h of nursing time</td>
<td>No</td>
</tr>
<tr>
<td>Unclear United States</td>
<td>Cost</td>
<td>Laboratory tests (point-of-care, blood and other laboratory tests)</td>
<td>None</td>
<td>UHC database (60 university hospitals)</td>
<td>Acute leukemia in children absorbed 18.3% of total laboratory costs</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1 y Moscow, Russia</td>
<td>Cost/person per m²</td>
<td>Medications, supportive care (IV antibiotics, antymycotics, transfusion of erythrocytes and platelets)</td>
<td>None</td>
<td>German “Rote Liste” 1995; German high-standard blood bank prices</td>
<td>Total costs (mean cost/person per m² of body surface) were 1.73-fold higher for the BFM90 protocol</td>
<td>No</td>
</tr>
</tbody>
</table>

*8BMT = bone marrow transplantation; DRGs = diagnosis-related groups; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte–macrophage colony-stimulating factor; HCO = Home Care Organization; N/A = not available; NEJM = New England Journal of Medicine; PBPC = peripheral blood progenitor cell; PBPTC = peripheral blood progenitor cell transplantation; RCT = randomized controlled clinical trial; rhGM-CSF = recombinant human GM-CSF; SD = standard deviation; TBI = total-body irradiation; TC = teizoplanin plus ceftiraxone; TPN = total parental nutrition; UHC = University Hospital Consortium.
HUI3 in detecting changes in HRQL during 3-week cycles of high-dose corticosteroids during “maintenance” therapy for ALL (Table 2). As predicted a priori, patients experienced difficulties with mobility/ambulation, pain, and emotion during the week that they were on high-dose corticosteroids and demonstrated few problems during the week off all therapy. Nonetheless, given the coarseness of the generic measures, there is reason to suspect that these measures may not capture all of the important HRQL trends experienced during therapy. The complementary use of specific, targeted measures is therefore desirable.

Kazak et al. (40) provided evidence on the responsiveness of the POQOLS. Statistically significant changes in POQOLS scores were detected over time in the context of a randomized controlled clinical trial. Within the context of a prospective study, Parsons et al. (31) provided evidence of responsiveness for the Child Health Rating Inventories.

Studies involving the costing of health care services in pediatric ALL have started to emerge only recently (Table 3). There are a number of narrowly focused studies reporting on estimates of the cost of particular components of treatment, such as the cost of treating febrile neutropenia or using granulocyte colony-stimulating factor. For instance, Charnas et al. (41) examined alternatives for the treatment of febrile neutropenia in children with cancer. Luce et al. (42) retrospectively analyzed data from a randomized controlled clinical trial of patients undergoing bone marrow transplantation. The mean charges were lower for patients receiving recombinant human granulocyte–macrophage colony-stimulating factor than for those receiving placebo. The availability of these studies may well reflect sponsorship by pharmaceutical firms. There are relatively few cost-effectiveness studies in which the costs and consequences of two (or more) relevant treatment options (e.g., inpatient versus home care) are compared. Only one study focuses on costs borne by families (43). There are no published, comprehensive economic analyses of pediatric ALL.

With respect to the areas of application, approximately 73.1% of the economic studies listed in Table 3 focus on establishing cost-effectiveness, whereas 26.9% provide descriptive evidence on the cost of illness.

During the 1990s, there was a trend toward an increase in the annual number of publications (Fig. 1). Few HRQL or costing studies in ALL were published prior to 1990. Although numerous generic and pediatric cancer-specific measures were identified that could potentially be used to study pediatric ALL, most have only been applied in a handful of studies (Table 4). Among the generic measures, the HUI2 and HUI3 were the most widely applied. Overall, the POQOLS (24) pediatric cancer-specific HRQL measure was the most widely used instrument in studies including children with ALL.

**DISCUSSION**

Historically, HRQL measures have not often been used to supplement traditional end points of treatment effectiveness in pediatric oncology (8). HRQL measurement in pediatric oncology is particularly challenging. The development of measures requires access to a sufficient number of patients (and families). Adequate instrument development requires the accumulation of evidence on the measurement properties of instruments. Relevant properties include test–retest reliability, interrater reliability, sensitivity to change (or responsiveness), and validity. Given the absence of a “gold standard” for assessing HRQL, the investigation of validity is largely accomplished through construct validation. Although commentators tend to declare that instruments have been shown to be reliable and valid, in reality such evidence tends to be context specific (27). In particular, construct validity involves the accumulation of evidence over time.

Given that the incidence of pediatric ALL, the most common of all cancers in childhood, is (fortunately) low and that even large tertiary care centers typically have at most only a modest number of patients, the extent of evidence on HRQL in pediatric ALL gathered during the 1990s is impressive. It is also remarkable that investigators have been able to develop a number of promising measures. In general, the pediatric oncology-specific and pediatric oncology disease-specific instruments focus on health status and HRQL during therapy. Thus, it may be wise to use these measures along with generic measures that are also relevant for the assessment of long-term outcomes. Despite the limited patient numbers and resources available, there has been
substantial progress on HRQL assessment in childhood cancer.

To date, investigators from a wide variety of disciplines have contributed to the development of HRQL measures for use in pediatric oncology. The disciplines included pediatric oncology, epidemiology, economics, decision science, psychology, health services research, nursing, and statistics. Experience in instrument development in pediatric oncology is consistent with experience in adult HRQL in which three major measurement traditions are represented: psychometrics, clinimetrics, and economics. Although the involvement of a number of disciplines may raise the cost of studies, it has enriched the variety and quality of the measures developed. In general, it is important to involve a range of disciplines in work on HRQL in pediatric oncology.

Toward the objective of enriching the evidence on HRQL measurement in pediatric oncology, several themes emerge from this review. [These themes build upon earlier publications by Feeny et al. (16,44).]  

### Theme 1: HRQL Tools Address Important Questions

Survival rates for most cancers in childhood have risen dramatically over the last five decades. Pediatric ALL was almost universally fatal in the early 1940s; today the survival rate is greater than 85%. An important reaction among clinical researchers has been a shift in focus to finding therapies that lessen the toxicity burden during treatment and reduce sequelae, without sacrificing survival. HRQL measures provide crucial information on whether or not the new therapies really are toxicity and sequelae sparing. HRQL tools provide a solid evidential basis for assessing quality-adjusted survival and can serve as inputs into economic evaluations. Greater use needs to be made of the measures that have been developed, especially in longitudinal studies. Surrogate clinical measures are often incomplete and can be misleading. The formal assessment of HRQL during treatment and the assessment of the HRQL associated with long-term outcomes are essential in answering many of the key clinical questions.

### Theme 2: Measures Are Available

As this review demonstrates, there are a number of generic and specific measures that have been used productively in pediatric ALL. There is substantial evidence on the reliability, responsiveness, and validity of some measures; in other cases, the evidence is still emerging. Twenty years ago an investigator interested in assessing HRQL in pediatric ALL would have had little choice of measures. Today there are a number of measures from which to choose; the availability of useful measures is no longer a barrier. Efforts focused on accelerating the accumulation of evidence are needed (see theme 5 below); nonetheless, suitable measures already exist. The lack of availability of a credible instrument is seldom a valid reason for not measuring HRQL in pediatric ALL studies.

### Theme 3: Children Can Respond on Their Own Behalf

Early studies on HRQL in pediatric ALL tended to rely on reports by parents and health care professionals. More recently in pediatric studies in general and pediatric ALL in particular, a number of studies have also asked children to complete questionnaires. In general, results indicate that by the age of 7 or 8 years, children generally provide reliable responses. Furthermore, a number of studies [e.g., Parsons et al. (31)] indicate that children can often provide information that is unavailable from parental reports. Thus, children should be engaged as respondents whenever possible.

### Theme 4: There Are Multiple Valid Viewpoints

Information provided by patients, parents, and healthcare professionals is often complementary. Each type of respondent has a valid and important perspective. Children can provide insights on their HRQL, particularly the intrinsically subjective elements such as pain and emotion. Parents observe their children in a variety of contexts and social settings, and their responses can incorporate that information. Healthcare professionals are often more aware of the full range of experiences and are well informed about norms both for children with pediatric ALL and for the general pediatric population. Information from each of these three types of respondents is potentially valuable. Thus, rather than rely on only one source of information, it is important to develop strategies to share information. Furthermore, evidence on interrater reliability (or agreement) indicates that, in general, the responses of children, parents, and health care professionals are not interchangeable. This is especially germane for subjective dimensions (domains) of health status.

### Theme 5: Implications—Harness the Cooperative Groups

The overwhelming majority of children with ALL in the United States and Canada are treated on established protocols for which there is rigorous evidence of clinical effectiveness based on results from randomized controlled clinical trials (4). Many children being treated for ALL are enrolled in clinical trials and related studies. This pediatric experience (which, in general, contrasts with the situation in adult oncology) is a reflection of the considerable accomplishments of the two major cooperative groups: the Pediatric Oncology Group and the
Childhood Cancer Study Group. Recently, these two groups have merged into the Children’s Oncology Group (COG). The use of the cooperative group will help to overcome the limited sample sizes available at even the largest treatment centers. It is now time to add HRQL to the scope of activities of the cooperative group. First, modest funds should be made available for methodological assessments of HRQL measures. Second, expertise on HRQL measurement (including specific, generic, and preference-based measures) should be added to at least some of the teams that design future trials. Third, the cooperative group needs to start to include existing measures in their studies. In particular, there are no examples in the published literature of studies using HRQL throughout the process of treatment from diagnosis and induction of remission, to discharge and to long-term follow-up. More information on the natural history of HRQL during all phases of treatment and survival is needed. Currently, we have a number of useful snapshots of portions of that experience, but we lack comprehensive longitudinal evidence. Given the recent inclusion of HRQL measures in a few trials, preliminary evidence on the patterns of HRQL over time will be emerging soon. Fourth, when the assessment of existing tools or experience in studies identifies a major gap, the cooperative group could be used to expedite the development of new instruments to ameliorate those gaps. Of course, the inclusion of HRQL measures in any study must be linked explicitly to specific study objectives or hypotheses to be tested.

If the methodological work on HRQL in pediatric oncology and the application of existing HRQL measures in the COG trials become reasonably common, if not routine, the rate of progress on HRQL in pediatric oncology will be increased substantially. The spectrum of morbidities in many other illnesses of children is encompassed by the morbidities among children with cancer (16). Therefore, a focus on HRQL in pediatric oncology affords a context within which to build a prototype strategy for the assessment of HRQL among all children. In fact, several approaches originally developed in the context of childhood cancer have been applied already in other areas in pediatrics, such as the use of the HUI in follow-up studies among survivors of extremely low birth weight and population health surveys of children. HRQL studies in pediatric oncology can serve as a foundation for HRQL studies in other areas of pediatrics. Tools developed in pediatric HRQL may be directly transferable to other areas or may serve as a useful starting point for the development of other specific pediatric HRQL instruments.

Theme 6: Implications—Identification of Topics for the Research Agenda

The accumulation of additional evidence on the existing measures is a key item for the research agenda. The generation of such evidence will help investigators to learn which measures are suitable for which purposes and how to interpret HRQL scores. Evidence on the lack of adequate measures in particular situations will help to identify priorities for the development of new measures. Only by subjecting existing instruments to appropriate assessments will we know if new measures need to be developed. In particular, additional evidence on responsiveness is needed. In addition, evidence on the entire path of HRQL experience from diagnosis through adulthood is needed.

The measures that have been used to date have primarily been used for discriminative (distinguish among persons or groups at a point in time; cross-sectional study) or evaluative (assessment of within-person change or time; prospective studies such as clinical trials) purposes. Another set of issues for the research agenda concerns the use of these measures in managing individual patients and their families. Can HRQL scores be used to identify patients with elevated treatment morbidity for whom additional interventions may be indicated? Can simple HRQL measures be used as screening tools to identify subjects for more extensive evaluation?

A related issue that has received little attention is the prognostic value of baseline observations of health status and HRQL. In a number of (but not all) areas in adult oncology, baseline HRQL measures have been shown to have independent prognostic value for survival, controlling for standard clinical prognostic indicators [see for instance Clinch (17), Coates et al. (45), Dancey et al. (46), and Ganz et al. (47)]. It will be interesting to see if the HRQL measures have predictive value in pediatric oncology settings.

Most work to date involving self-report by children has been in school-aged children, yet many of the children with ALL are preschoolers. A number of investigators are exploring innovative approaches to obtaining HRQL information from younger children; such approaches include cartoon and touch-screen computer formats. Clearly, additional work on developing and assessing these and other approaches is needed. In general, HRQL measures for children need to make allowances for the development stages of childhood; this will be particularly important for measures that are used for preschool children.

Finally, the accumulation of evidence on interpretability and usefulness of HRQL in pediatric oncology are important research priorities (16,48–50). Interpretability refers to the extent to which one can assign meaning, both qualitatively and quantitatively, to HRQL scores (51). Usefulness refers to the impact that assessing HRQL has on decisions that are made, including the management of specific patients and families, the development of clinical policy and guidelines, the conduct of clinical trials, resource allocation, and the identification of research priorities. There is relatively little evidence on interpretability in the context of pediatric oncology and even less on usefulness. These gaps should be filled.

In summary, HRQL measures have the potential to assist in the identification of the morbidity burdens of treatment, assessment of the quality of survival, evaluation of new treatments and interventions in pediatric oncology, and the management of patients and families. There is a small but impressive collection of measures with proven track records. A variety of disciplines have contributed to the existing body of knowledge. The instruments and expertise to support vigorous application of HRQL tools to clinically important questions in cancer care in pediatric settings exist. Investments in the application of these tools will likely pay handsome returns.

APPENDIX 1. DATA ABSTRACTION FORMS

Data Abstraction Form I: Description of HRQL Instruments in Pediatric ALL

1) Type of instrument (profile, preference-based, cancer-specific, cancer subtype specific)
2) Instrument name (relevant references) ([ref.]—author, journal, volume, number, month, pages)
3) Source of items (health professionals, general public, parents—specific type, family members, literature review)
4) Criteria for selection of items (factor analysis, ratings of importance/clinical impact)
5) Response options (dichotomous, 5-point Likert, 7-point Likert, categorical)
6) Recall period
7) Domains
8) Scoring
9) Intended respondent
10) Target age group
11) Number of items
12) Format (interviewer, self-report)
13) Country (language)
14) Translations
15) Validity (content, construct, discriminant, concurrent, face)
16) Reliability (internal consistency, test–retest, interrater agreement)

Data Abstraction Form II: Applications of HRQL Instruments in ALL

1) Instrument
2) Reference (paper reporting application of instrument: author, year)
3) Data collection period (year[s])
4) Site of data collection
5) Demographics (sex, age range)
6) Sample size (total and by demographic group)
7) Description of ALL sample
8) Respondents (patient, parent, patient/parent, doctor, nurse, other...)
9) Study design (phase I, II, or III randomized trial; nonrandomized intervention trial; prospective or retrospective cohort study; case–control study; cross-sectional study)
10) Phase of care (remission, induction, relapse, maintenance, bone marrow transplantation [BMT], intensification)
11) Medication regimen
12) Evidence on reliability (internal consistency, test–retest, interrater agreement)
13) Validity (content, construct, convergent, discriminant, concurrent, face)
14) Responsiveness (longitudinal construct validity)
15) Results
16) Statistical power of design mentioned? (yes/no)
17) Confidence intervals provided for point estimates? (yes/no)
18) Clinical importance of outcomes discussed? (yes/no)

Data Abstraction Form III: Studies of Economic Resource Use in Pediatric ALL

1) Brief description
2) Reference (author, year)
3) Study design (prospective, retrospective, decision modeling, meta-analysis, case–control)
4) Analytic design (cost-identification, cost minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis)
5) Description of patient population
6) Sample size (n of each group; ALL sample n = _______)
7) Intervention/treatment comparators (if applicable)
8) Perspective of study (e.g., hospital, health maintenance organization [HMO], societal)
9) Analytic horizon (and discount rate, if applicable)
10) Care setting (single-institution, multi-institutional, HMO, city-wide, nation-wide)
11) Outcome measures (e.g., quality-adjusted life years [QALY], natural units)
12) Source of preferences (if applicable, e.g., HUI, direct utilities)
13) Resources included— formal health care
14) Resources included—patient resources
15) Sources of resource information (standard cost list, hospital, etc.)
16) Results
17) Sensitivity analyses (no/yes [univariate or multivariate])

References


NOTES

Editor’s note: D. H. Feeny is an owner of Health Utilities, Inc., which owns the copyright to the Health Utilities Index and related materials discussed in this review.

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