Global Pediatric Oncology: Lessons From Partnerships Between High-Income Countries and Low- to Mid-Income Countries

Raul C. Ribeiro, Federico Antillon, Francisco Pedrosa, and Ching-Hon Pui

A B S T R A C T

Partnerships between medical institutions in high-income countries (HICs) and low- to mid-income countries (LMICs) have succeeded in initiating and expanding pediatric cancer control efforts. The long-term goal is consistently a sustainable national pediatric cancer program. Here, we review the elements required for successful implementation, development, and long-term sustainability of pediatric cancer programs in LMICs that first arise as partnerships with institutions in HICs. Although plans must be adapted to each country's resources, certain components are unfailingly necessary. First, an essential step is provision of treatment regardless of ability to pay. Second, financial support for program development and long-term sustainability must be sought from sources both international and local, public and private. A local leader, typically a well-trained pediatric oncologist who devotes full-time effort to the project, should direct medical care and collaborate with hospital, governmental, and community leadership and international agencies. Third, nurses must be trained in pediatric cancer care and allowed to practice this specialty full-time. It is also essential to develop a grassroots organization, such as a foundation, dedicated solely to pediatric oncology. Its members must be trained and educated to provide pediatric cancer advocacy, fundraising, and (in concert with government) program sustainability. Finally, a project mentor in the HIC is crucial and should explore the possibility of collaborative research in the LMIC, which may offer significant opportunities. Relationships between the partnership's leaders and influential individuals in the community, hospital, grassroots foundation, and government will lay the foundation for productive collaboration and a sustainable pediatric oncology program.

J Clin Oncol 34:53-61. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Survival rates for pediatric malignancies, now approaching 80% overall and 100% for some subtypes, with appropriate treatment, are considered a triumph of modern medicine. In contrast, progress is dismal when the worldwide burden of pediatric cancer is considered.¹ In the countries with 80% of these occurrences, survival rates are negligible in some and only 40% at best.² Narrowing this survival gap between poor and rich countries is among the most difficult challenges of our time. Although the medicines and procedures needed to treat most pediatric malignancies are relatively simple and inexpensive, it is a complex task to integrate them across the continuum of care in resource-constrained settings (Fig 1A). This continuum is made up of the sociocultural, psychological, economic, political, and medical factors that shape the cure rates for childhood cancer.³ For example, in countries with deficient primary care programs, cancer is often not suspected and children may die of infection or hemorrhage before they reach a tertiary

pediatric treatment center. In countries without government health coverage, private financial support is required to launch the program, but government financial support is ultimately required for program expansion and long-term sustainability (Fig 1B). The incidence of pediatric malignancy varies worldwide, from 70 to 140 occurrences per million.⁴ Moreover, solid tumors are documented more frequently than leukemia in low-income countries,⁵ where leukemia is often mistaken for tropical infectious diseases, such as dengue or malaria (Fig 2). These misdiagnoses condemn a young patient to death. Finally, the incidence of disfiguring malignancies, such as retinoblastoma, is considered more frequent in many low-income countries, partly because they are more likely to be diagnosed and referred to tertiary cancer centers.

Because countries classified by World Bank criteria as low- to mid-income countries (LMICs)⁶ have a lower incidence of pediatric cancer, some have suggested that pediatric cancer is a disease of affluence related to industrial and urban settings. This misconception and others, including the opinion that cancer is

Raul C. Ribeiro and Ching-Hon Pui, St Jude Children's Research Hospital, Memphis, TN; Federico Antillon, Unidad Nacional de Oncología Pediátrica and Universidad Francisco Marroquín, Guatemala City, Guatemala; and Francisco Pedrosa, Instituto de Medicina Integral Fernando Figueira, Recife, Brazil.

Published online ahead of print at www.jco.org on November 17, 2015.

Supported by Grants No. CA-21765 and CA-71907 from the National Institutes of Health (US Department of Health and Human Services), by a Center of Excellence grant from the State of Tennessee, and by the American Lebanese Syrian Associated Charities.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Raul C. Ribeiro, MD, Department of Oncology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105; e-mail: raul.ribeiro@stjude.org.

© 2015 by American Society of Clinical Oncology

0732-183X/16/3401w-53w/\$20.00

DOI: 10.1200/JCO.2015.61.9148

Fig 1. (A) The continuum of care: essential components that must be integrated to implement and expand pediatric cancer care in low- to mid-income countries (LMICs). (B) Sources of financial support and their relative roles in starting and sustaining a pediatric oncology unit in a hospital in LMICs.

incurable or too expensive to manage, have kept pediatric cancer from becoming a priority in LMIC health agendas. It is true that implementing effective cancer care in LMICs is a daunting proposition. Health care professionals must be equipped with more than medical pediatric oncology knowledge. They must be prepared to understand and act in complex social (religion, beliefs, and established practices), economic (frequent extreme poverty), and political (centralized governments and weak institutions) contexts.

During the past 20 years, partnerships between pediatric oncologists in high-income countries (HICs) and LMICs have created opportunities for treatment of childhood cancer.^{3,7-10} However, collaborative pediatric oncology programs with curative intent require the desire and commitment of local medical teams and the financial support of local governments and grassroots foundations. Although such programs can begin modestly and are attainable even in low-income countries, they require, at a minimum, adequate hospital infrastructure to provide safe chemotherapy and supportive care, a core of trained individuals dedicated to the program, visits from international mentors, and public security that allows safe travel of patients between home and hospital. The diseases of poverty must be adequately addressed in low-income countries before pediatric cancer can become a priority, but some countries, particularly those

known as failed states, cannot guarantee even minimal security. Therefore, different models and greater support are needed to establish partnerships in some low-income countries. Despite the many challenges, we review here examples of programs that have achieved substantial progress in a relatively short period and identify factors associated with their success.

NATIONAL PEDIATRIC CANCER UNIT IN GUATEMALA CITY

Guatemala is the most populous country in Central America; it has a per capita income of US\$3,340,¹¹ and many residents live below the international poverty line.¹² In Guatemala's two tertiary pediatric hospitals, the outcome of pediatric cancer was poor until 1996. At the time of a retrospective analysis of any childhood malignancy treated in these two hospitals between 1990 and 1995,¹³ only approximately 100 of the expected 600 new occurrences per year were managed at the two hospitals. Of these patients, 42% abandoned treatment, and 2-year event-free survival (EFS) was only 28%.

To address the problem, a public-private partnership was formed by the International Outreach Program of St Jude Children's Research Hospital (St Jude), Guatemalan medical and nonmedical leaders, and

Fig 2. Distribution of the most common cancers in children age younger than 15 years in selected populations.

the Guatemalan government Ministry of Health and Social Welfare to establish a national pediatric oncology unit. A local grassroots organization, Fundación Ayúdame a Vivir (AYUVI; Help Me to Live¹⁴), was created in 1997, and its advocacy made possible several crucial steps: (1) In 1998, the Guatemalan president signed a bill to create the Unidad Nacional de Oncología Pediátrica (UNOP; National Pediatric Cancer Unit), a dedicated freestanding center to provide standard pediatric cancer treatment; (2) UNOP and St Jude signed a technical collaboration agreement; and (3) UNOP opened in 2000. AYUVI developed as a professional advocacy and fundraising organization dedicated exclusively to pediatric oncology. UNOP provides cancer care to all Guatemalan children, regardless of ability to pay. Other key components that were addressed included specialized training of personnel, continued improvement of infrastructure, and access to pediatric intensive care. UNOP's family-centered care is based on four pillars: (1) correct diagnosis and staging to allow appropriate curative or palliative care, (2) clinician training and public education about childhood cancer, (3) treatment adapted to local resources, and (4) community involvement. Table 1 describes changes in selected outcome measures since the unit opened.

The range of pediatric hematology/oncology services provided at UNOP supported the establishment of a fellowship training program adapted to the needs of LMICs. In 2003, in collaboration with St Jude and with partial support from the US

National Cancer Institute Center for Global Health, UNOP established a 3-year postdoctoral pediatric hematology/oncology fellowship program accredited by the Guatemala Universidad Francisco Marroquín School of Medicine.¹⁵ By December 2014, there were 15 graduates from Panama, Nicaragua, Honduras, Guatemala, Dominican Republic, Haiti, and Ecuador. Building on the success of this program, in 2013, a 2-year fellowship was established for pediatric critical care, with a focus on pediatric cancer (F. Antillón, personal communication, December 2014).

One attribute that notably differentiates UNOP from many other pediatric cancer centers in LMICs is the nurses' high-quality training (including continuing education) and expertise in pediatric hematology/oncology. The incorporation of Joint Commission international nursing standards at UNOP improved the nurses' competency in multiple skill sets, as verified by assessments and test scores. Reduced staff turnover and nurse-to-patient ratios that are based on the acuity of care also demonstrated the achievement of highly professional nursing, a fundamental and imperative element of quality pediatric oncology care.^{16,17} Other specialty services, including pathology, radiation therapy, flow cytometry, blood products, and imaging, are provided via partnerships and service agreements in Guatemala City. In 2014, 498 patients were seen for the first time at UNOP. Of these patients, 405 had a confirmed diagnosis of cancer and were eligible for curative therapy. Almost 2,000 patients were seen for outpatient

Table 1. Outcome Indicators Before and After the Opening of UNOP in 2000

Event	Year and Phase							
	1990-1995 (pre-UNOP)	UNOP						
		2000	2007	2008	2009	2012	2013	2014
Abandonment of therapy, %	42.0	17.0	8.2	3.5	2.3	2.2	1.2	0.3
Overall survival, all patients, %	28.0							65.0
No. of new patients per year	100	129	280	287	302	407	406	405
No. of hospital beds	0	28						60*
No. of pediatric hematologist/oncologists	0	3						7

Abbreviation: UNOP, Unidad Nacional de Oncología Pediátrica (National Pediatric Oncology Unit, Guatemala).

*Includes seven intensive care unit beds.

Table 2. UNOP Clinical Personnel as of December 2014

Specialty	No. of FTEs
Pediatric hematologist/oncologists	7
Pediatricians	15
Pediatric hematology/oncology fellows	8
Physician subspecialists (eg, infectious disease or ICU)	15
Nursing	215
Medical laboratory	14
Clinical pharmacy	19
Clinical nutritionists	4
Psychologists	2.5
Social workers	3
Child life psychologist	1
Respiratory therapists	17

Abbreviations: FTE, full-time employee; ICU, intensive care unit; UNOP, Unidad Nacional de Oncología Pediátrica (National Pediatric Oncology Unit, Guatemala).

follow-up care, and 123 were receiving palliative care. The nurse-to-inpatient ratio varied: one nurse to one patient in the intensive care unit (ICU), one nurse to two patients in the step-down ICU, and one nurse to five patients in the regular inpatient rooms. The ratio of pediatric hematologist/oncologists to new patients with cancer was one to 58 in 2014. There is no waiting list. The current staffing of UNOP is detailed in Table 2. Another distinguishing feature of UNOP is its unique approach to nonmedical needs of the patients and families, which often determines whether curative therapy will be completed or held. A program that incorporates psychosocial, economic, spiritual, and palliative care needs has been developed and adapted to the Guatemalan population. Ongoing assessment of needs begins at diagnosis, and UNOP provides housing, food, travel assistance, and psychosocial support as needed. Palliative care, which may begin immediately after diagnosis, provides symptom management and emotional and spiritual support. A nurses' training program has begun for pediatric cancer palliative care, with partial support from the public-private partnership My Child Matters.¹⁸ The holistic approach to addressing patient and family nonmedical needs has dramatically reduced abandonment of treatment.

A comprehensive review of patients treated at UNOP since its opening (April 2000) to December 2014 reveals a diagnosis of 4,593 childhood cancers in 4,581 patients. The most common diagnoses, comprising 96% of occurrences, were acute leukemias (45%), lymphomas (14%), retinoblastoma (9%), CNS tumors (6%), bone tumors (6%), sarcomas (5%), renal tumors (4%), germ cell tumors (4%), and hepatic tumors (3%).

Dedicated (and therefore uninterrupted) daily medical laboratory service provides CBCs, serum chemistries, microbiology, and serology. Diagnosis of leukemia is established by customary methods. A diagnostic flow cytometry laboratory, established in 1998, serves UNOP and regional pediatric cancer units in El Salvador and Honduras^{19,20} by using a basic panel of cell surface markers. Personnel were trained and quality control was implemented through a combination of face-to-face and computer-based distance consulting. As local technicians gained expertise, the need for consultation decreased to less than 1% of diagnoses. This approach allows the correct risk stratification of acute leukemia at a relatively low cost. However, accurate diagnosis of solid tumors remains a problem. Although

most diagnoses are resolved by an anatomic pathologist trained at St Jude, a substantial number of samples must be referred to St Jude for diagnosis. Despite occasional shortages, high-quality chemotherapy agents and antibiotics are generally available at UNOP.

UNOP's operational expenses are covered by a public-private partnership between the Guatemalan Ministry of Health and the Foundation AYUVI. The UNOP budget for 2015 is US\$12 million. AYUVI provides approximately 60% and the Ministry of Health, approximately 40%. For the past several years, AYUVI has raised US\$5 million per year from corporate donors. Other nongovernmental organizations, including the Guatemala City Rotary Club, raise approximately US\$150,000 per year. St Jude, the National Cancer Institute, and My Child Matters contribute an additional US\$400,000 per year.

UNOP and AYUVI still face major challenges. The most important is limited access to UNOP; each year, only approximately 50% of Guatemala's 800 pediatric patients with new cancer occurrences arrive at UNOP. Moreover, the occupancy rate of UNOP is consistently near 95%. To resolve these problems, it will be necessary to expand the UNOP infrastructure and build a second pediatric oncology unit in another large urban area. These projects would require substantial startup capital and operational funds. Another important challenge is to reduce the proportion of children who arrive with advanced-stage disease.

PEDIATRIC ONCOLOGY UNIT IN RECIFE, BRAZIL

Recife is one of the largest metropolitan areas in Brazil (3,309,000 inhabitants) and is the capital of the state of Pernambuco,²¹ with an estimated population of 9.2 million people.²² Approximately 30% of the population is younger than 14 years; therefore, approximately 400 cases of pediatric cancer per year are expected. Approximately 20% of the population is rural. Currently, the average per capita income is approximately US\$3,120; 25% of the population earns approximately US\$2 per day.

Before 1980, pediatric cancer specialists were not available in Pernambuco; children with cancer were treated at local or regional general pediatric hospitals. The Instituto de Medicina Integral Professor Fernando Figueira (IMIP), the largest pediatric hospital in Recife, was dedicated to maternal-child diseases and did not manage pediatric cancer.

In 1980, the Recife Hospital Barao de Lucena, a part of the Brazilian Social Welfare System, hired two physicians for pediatric hematology/oncology care. The unit comprised a one-room ward with 10 beds. No dedicated nursing staff, support staff, or ICU beds were available. Diagnoses were made on the basis of morphologic criteria alone. Abandonment of therapy exceeded 20%, and mortality from the disease or treatment toxicity was approximately 50%. Only approximately 25% of children with cancer were long-term survivors.

In 1985, a grassroots organization (Nucleo de Apoio a Criança com Câncer; NACC) was created in Recife to support the families of children with cancer and help cover the cost of treatment. However, because of lack of support from the hospital and difficulty establishing a public-private partnership with the hospital, the pediatric oncology unit was discontinued. In the late 1980s, the Brazilian government implemented universal medical coverage, including the cost of medicines and hospitalization for children with cancer. Although the level

of reimbursement did not cover all expenses, creating a particular hardship for poor families, supplementary assistance from NACC made free, high-quality treatment feasible for all patients. However, most of the pediatric hospitals in Recife lacked the infrastructure and trained personnel to provide adequate pediatric cancer care.

Between 1990 and 1994, two authors (F.P. and R.C.R.) made several visits to the IMIP leadership to encourage the creation of a pediatric oncology unit, because the quality of medical services at IMIP would support such a unit. The IMIP leadership declined because of the concern of the complexity and cost of cancer treatment. The main doubts they expressed were their lack of experience in public-private partnerships, uncertainty about the new Brazilian universal coverage system, and the scarcity of clinicians trained in the management of pediatric cancer. In response, NACC fundraising activities were expanded and several local pediatricians, nurses, and laboratory technicians were trained in the management of pediatric cancer. Finally, in 1994, IMIP leadership agreed to implement a pediatric oncology unit at IMIP. An essential points in the agreement was that NACC would cover the cost of all medications, including anti-cancer, antibacterial, and antifungal agents and other supportive care drugs (antiemetics and growth factors); St Jude would supplement the salaries of key personnel and be responsible for the training and education of physicians, nurses, surgeons, pathologists, and others who provided care for children with cancer. The initial goal was to improve the survival rate of children with acute lymphoblastic leukemia (ALL). ALL is highly curable and was the most common cancer diagnosis at IMIP; furthermore, guidelines for its treatment were available. The infrastructure required to adequately diagnose and treat ALL was expected also to support the management of other pediatric malignancies curable by chemotherapy, such as non-Hodgkin²³ and Hodgkin lymphomas²⁴ and Wilms tumor. It was envisioned that a successful ALL program would demonstrate that pediatric cancer could be cured locally with the help of community resources. Between 1994 and 1997, 78 children with leukemia were treated according to published guidelines, which were adapted to the local resources.²⁵ The 5-year EFS of the 78 children with ALL was 47% (95% CI, 36% to 58%). Death as a result of toxicity, whether associated or not associated with infection, was the most common cause of mortality. During this period, efforts focused on improving the training of nurses, physicians, and laboratory staff and on improving supportive care. NACC expanded its support of families and began a broad public education campaign to advocate pediatric cancer care and awareness. Families of children with cancer who had been treated abroad were invited to participate in these initiatives. A small house that accommodated 20 families was replaced with a nine-story building with the capacity for 120 families (each comprising one patient and one parent). Funds for construction of this facility were provided by a private-public grant. In addition, NACC developed a partnership with the state's community health worker program to improve the early detection of pediatric cancer and referral of patients.

With the implementation of measures to improve supportive care, the 5-year EFS of newly diagnosed ALL increased to 63% (95% CI, 55% to 71%). These results are inferior to those of institutions in HICs. Thus, optimal adaptation of pediatric cancer therapy in LMIC remains an area of active investigation. In the early 1990s, we introduced an unmodified St Jude ALL protocol in El Salvador and experienced prohibitively high early mortality because of toxicity. Therefore, in LMIC, our main concern has been toxicity. As the

hospital infrastructure improves and personnel are better trained to prevent and manage complications, treatment intensity can be increased. Clearly, the best survival rates are achieved by effectively balancing the risks of toxicity with those of relapse that result from reduced therapy intensity and lack of effective salvage therapy, including hematopoietic stem-cell transplantation. With these constraints, overall ALL survival has improved greatly but has still remained 20% to 30% lower in LMIC than in HICs. In acute myeloid leukemia, reduced treatment intensity is associated with a high relapse rate, and the difference in survival is much greater.

Currently, the IMIP pediatric oncology unit manages all types of pediatric cancer, excluding bone tumors that are managed on the orthopedic service of the adult Cancer Hospital in Recife. The overall survival of children with cancer at IMIP is approximately 65%. In 2002, a new pediatric oncology unit was built on the IMIP campus. It has a capacity for 38 beds (two beds per room), six dedicated intensive care beds, and continuous medical supervision by trained pediatricians. The annual operational budget of the unit is approximately US\$5 million. Approximately half of the budget is supplied by public donors (NACC and the Alice Figueira Foundation), and the remainder, by the Brazilian government. St Jude provides an additional US\$90,000 per year. Approximately half of the expected 400 new occurrences of cancer per year in Pernambuco are managed at IMIP. Other centers in the region manage most of the remaining occurrences. A pediatric cancer unit was recently created in Petrolina (400 miles from Recife). The pediatric oncologist at this new unit was trained at IMIP and continues to receive technical support from IMIP. Currently, the annual operating budget of NACC is approximately US\$2 million and provides support for the families of patients at pediatric facilities other than IMIP, including the new site in Petrolina.

PEDIATRIC HEMATOLOGY/ONCOLOGY UNITS IN SHANGHAI AND BEIJING

China is the most populous country in the world, with a population of 1.3 billion, including an estimated 300 million younger than 15 years. Assuming a rate of 135 to 145 occurrences of cancer per million children younger than 15 years, approximately 40,000 to 43,000 new occurrences of pediatric cancer are expected per year. Approximately 50% of the Chinese population is rural. The gross domestic product per capita is US\$6,807,²⁶ and less than 5% of the population lives below the international poverty line. Shanghai is the most populous city; its population in 2013 was an estimated 23.9 million, whereas the current population of Beijing is an estimated 19.6 million.

Until recently, there was no public medical insurance; therefore, treatment for pediatric cancer depended on the family's financial resources. Not surprisingly, only approximately 10% of children with cancer completed treatment. Since 1990, St Jude has collaborated with colleagues at Beijing Children's Hospital (BCH) and Shanghai Children's Medical Center (SCMC) to improve cancer care. The initial agreement was to provide professional training and continuing education. In 1994, St Jude was invited by Project Hope to provide technical assistance for development of the pediatric hematology/oncology unit at SCMC, an 80-bed unit within a 500-bed general pediatric hospital. Although the medical care of children with cancer was adequate in these two units, it was impossible to ignore the many

children with chemotherapy-curable malignancies, particularly low-risk ALL, who did not start or did not finish treatment because of inability to pay. In 2004, two authors (C.-H.P. and R.C.R.) collaborated with colleagues at BCH and SCMC to develop a treatment protocol for children with ALL. We envisioned that a relatively simple and inexpensive treatment aimed at a cure rate of at least 80% for low- or intermediate-risk ALL (70% to 80% of total ALL occurrences) would expand access to treatment and save thousands of lives. This was a single-arm protocol stratified by risk of relapse, which used evidence-based therapies. In January 2005, funds became available from a private foundation in Hong Kong to reimburse the hospitals for medical expenses in the treatment of children with low-risk ALL who did not have other financial support. This program was extended to children with intermediate-risk ALL in March 2006. We were aware that this initiative would not substantially reduce overall leukemia mortality in China; however, demonstration that a relatively inexpensive protocol could cure many children with low- or intermediate-risk ALL could attract the attention of other funding sources.

In 2009, the results of treating the first 45 children was reported by Liu et al.²⁷ The 30-month EFS estimate was 94.1% for low-risk patients and was 82.8% for intermediate-risk patients. The average treatment cost was approximately US\$11,000. This report caught the attention of Chinese government officials.²⁸ In 2011, the Health Minister of China added the treatment of low- or intermediate-risk ALL to the national health insurance coverage,

reimbursing hospitals for 75% of expenses. This action immediately increased the number of children with access to care and reduced the rate of abandonment.²⁹ One of the most successful accomplishments of the St Jude International Outreach Program was to demonstrate the feasibility, efficacy, and cost effectiveness of such a protocol in the two major hospitals in China, leading the Chinese government to cover the cost of treatment for patients with low- and intermediate-risk ALL. Furthermore, SCMC has built a new seven-floor, 11,000-m², 194-room pediatric hematology/oncology unit on its campus. It includes dedicated beds for intensive care and hematopoietic stem-cell transplantation and space for clinical and research laboratories. BCH plans to expand its hospital and add a new pediatric hematology/oncology unit. A collaborative group protocol was initiated in January 2015 with 20 participating institutions and an expected enrollment of 1,500 to 2,000 children with ALL per year.

LESSONS LEARNED

During the past few years, a considerable body of literature has described the epidemiologic characteristics of pediatric oncology in LMICs and the barriers to effective pediatric cancer control.³⁰⁻³⁵ Table 3 describes some of the opportunities available to surmount

Table 3. Health Care System Constraints and Potential Responses in Pediatric Oncology

Level	Constraint	Potential Response
Community and household	Lack of demand for effective interventions	Provide incentives to encourage use of services and mobilize communities (eg, create organizations dedicated to supporting children with cancer and their families).
	Late diagnosis	Integrate these organizations into the governance of pediatric oncology programs.
	Abandonment of therapy	Provide transportation, food, and shelter for patients and their families.
	Unavailability of effective interventions	Expand referrals via close-to-client services (eg, those provided by village health workers, general practitioners, or nurses).
Service delivery	Shortage and poor distribution of appropriately qualified staff, especially at the primary care level	Increase number of health workers. Enhance close-to-client workers' awareness (eg, by training community health workers to recognize first signs of cancer).
	Low staff pay and motivation	Increase pay and improve communication and nonmonetary incentives.
	Weak technical guidance, problem management, and supervision	Strengthen training and supervision.
	Inadequate drugs and medical supplies	Strengthen public supply systems and use private retail system.
	Lack of equipment and infrastructure, including poor accessibility of health services	Renovate, upgrade, and expand public facilities and establish partnerships with nongovernmental organizations to provide services.
Health sector policy and strategic management	Weak and overly centralized systems for planning and management	Decentralize planning and management.
	Lack of cooperative action and health service partnerships between government and civic organizations	Promote engagement of civic organizations and their oversight of planning and services.
Government policy	Bureaucracy (eg, civil service rules and remuneration and centralized management)	Create a national plan for pediatric cancer care with shared management by government and pediatric oncology representatives.
Global	Fragmented governance and management structures for global health	Improve global coordination.
	Migration of physicians and nurses from public to private sector and to high-income countries	Provide financial support and nonmonetary incentives for pediatric oncology physicians and nurses.

NOTE. Adapted from Mills.³⁶

these barriers.³⁶ The accumulated experience of implementing pediatric oncology programs in countries with limited resources suggests several broad concepts.

First, each country has different strengths, weaknesses, and barriers. A thorough assessment of the current status of pediatric oncology and its context, including the country's geopolitical, economic, and cultural characteristics, national health care coverage, involvement of civil society in health economics, participation of charitable organizations, government expenditures on health, and willingness to explore new partnership modalities (public-private), is necessary. These data form the basis of a needs and resources assessment and allow the elaboration of an action plan. When a partnership between institutions in HICs and LMICs is contemplated, multiple visits to the LMIC by individuals from

the HIC and from different backgrounds (medical, nursing, public health, epidemiology, and hospital administration) are necessary to obtain data.²

Second, the presence of a local advocate, typically a pediatric oncologist who is fully dedicated to the project, is essential. This individual must be well trained in pediatric oncology, well respected by local peers, and willing to accept the role of a leader. The pediatric oncologist should be mature enough to understand the complexities of pediatric cancer care in settings with resource constraints and able to clearly articulate these concepts to government, private organizations, and the general public. Funds to support the salary of the pediatric oncologist(s) and other key individuals in the pediatric oncology unit are required to retain high-quality, trained personnel and

Table 4. Features of the St Jude Children's Research Hospital Collaborative Childhood Cancer Care Programs in Low- to Mid-Income Countries

Feature	Component	Content	Constraint
Commitment of both partners: in the HICs and the LMICs	A leader in the HIC and a leader in the LMIC who are willing to devote time and effort to the program Institutional commitment	Committed leaders are necessary to define, develop, initiate, implement, and maintain the collaborative program The leaders facilitate intrainstitutional and interinstitutional communication and encourage the hospital to mobilize resources (human, technical, and financial).	Lack of leadership in either the HIC or the LMIC reduces the likelihood of the collaboration's success.
Community advocacy and fundraising in LMICs	A nonprofit, nongovernmental foundation dedicated to support childhood cancer care One cancer foundation per geographic area	Members of the foundation should include influential members of society, professionals, and parents/relatives of patients. The foundation works with both government and the medical team to effect change. Credibility of the foundation is established annually by independent audit.	If multiple foundations develop in a single region, their message is diluted and their ability to raise money and advocate is diminished.
Collaborative spirit	Respect Trust Humility Collegiality	The collaboration must be a culturally sensitive relationship of equals who are willing to learn from each other. In the best programs, the association is beneficial and rewarding to both sides.	A focus on individual accomplishments is less helpful than a focus on the shared mission to cure patients with cancer.
Communication	Effective Comprehensive Multimodal	Rapid, honest, in a shared language Addresses programmatic aspects (contracts, financial matters, documentation), patient care (individual cases, supportive care, protocols), continuing education, hospital infrastructure E-mail, online meetings, telephone conversations, exchange visits of key personnel	Without honest communication, a collaborative program is not possible.
Core activities	On the basis of the needs identified in the LMIC and the HIC's capacity to address the needs Data collection and analysis must always be included.	Goals and specific activities must be well defined in writing. Goals may change over time by mutual agreement. Documentation of causes of treatment failure and death is essential to target interventions and measure progress.	Improvements in cancer diagnosis, infection control, protocol design, education, nursing, and outcome evaluation are all important; these needs must be prioritized by the partners.
Capital and operational budget	The HICs provide initial funding to implement and maintain the program. Increasing local fundraising capacity should be part of most collaborative programs. Ultimately, alliance with government is necessary to scale up the program and ensure long-term sustainability.	Funding is needed to support key salaries in the LMIC (medical director, nurse educator, data manager), provide some equipment and supplies, and support exchange visits. Expenditures should be specifically tied to desired outcomes, with a focus on developing leaders and implementing simple and effective methods to improve cure rates. Approximately US\$100,000 per year plus the time of the HIC participants are sufficient to develop a strong demonstration project in a public hospital that manages approximately 200 annual new occurrences of childhood cancer.	Large expenditures on advanced technology or bench research should be deferred until basic cancer care is excellent.
Continuity	A long-term relationship is essential to attain the goal of a self-sustaining program.	At least a 5-year plan should be developed at the beginning so that both partners can agree on the goals of the collaboration and the timing of planned activities.	Short-term projects have some value, but a long-term relationship is necessary to reap the full benefits of the collaboration.

NOTE. St Jude Children's Research Hospital is located in Memphis, TN.
Abbreviations: HIC, high-income country; LMIC, low- to mid-income country.

protect their time for practice and to establish and cultivate relationships within the country. Although the pediatric oncology unit has a separate setting, it should be functionally integrated into the hospital. Hospital leaders and other pediatric discipline leaders participate in integrating the pediatric oncology unit into the hospital mainstream. Many of the improvements required for the pediatric oncology unit can be shared with other subspecialties, particularly the training, education, and core laboratory facilities.

Third, a grassroots organization dedicated solely to pediatric oncology must be created. These organizations have three main purposes. The first purpose is to provide assistance to children with cancer and their families. In this context, pediatric cancer is not a disease of the child but of the entire family. Most families served by pediatric oncology units in LMICs are vulnerable, even before the child's diagnosis, to socioeconomic and cultural hardships.³⁷ Their needs include housing during the child's treatment, transportation from home to the hospital and vice versa, food, and ongoing care for other family members. As shown by experience in Recife, the medical cost of treating a child with low-risk leukemia who lives 200 miles from the pediatric cancer unit is approximately \$US15,000, and family support (housing, food, and transportation) during the 2.5 to 3 years of treatment is approximately US\$6,000. Without this support, poor families often must abandon treatment.³⁸ The second purpose is to maintain ongoing public education about pediatric cancer. These activities include all types of media (radio, television, and newspaper), community meetings, sports events, and school events and are directed to medical (medical students, community primary care physicians, and community health workers) and nonmedical individuals. The main messages are the curability of pediatric cancer, the signs and symptoms suggestive of cancer, and the importance of early detection and referral to the pediatric oncology units. These foundations do not affiliate themselves with political parties or religions. The third purpose is to develop fundraising programs to meet capital and operating expenses and complement medical costs that are not covered by the government. In the pediatric oncology units in Guatemala City and Recife, approximately 50% of medical costs are covered by grassroots foundations. The pediatric cancer foundations establish partnerships with local and international charitable organizations or group services to additionally expand their hospital or community support programs.

Fourth, implementation of clinical or laboratory research in LMICs is possible. Many pediatric oncologists working in LMICs would like to engage in research. Participation in research is extremely gratifying and rewarding to these physicians, who are positioned to explore the unique aspects of pediatric oncology in their countries. Moreover, there are ample opportunities for medical or biologic research in pediatric oncology in LMICs. From the perspective of research in a single disease (Burkitt's lymphoma, retinoblastoma, Hodgkin lymphoma, ALL, and acute

promyelocytic leukemia), the question is whether increased incidence is caused by environmental or constitutional factors or both. Because these patients present with advanced-stage disease, tumor samples can easily be obtained for analysis by using sophisticated technologies. Studies of these samples may identify genes and pathways associated with tumorigenesis and chemotherapy resistance and suggest new drugs and treatment strategies. Hopefully, these new drugs and procedures will be inexpensive enough to reach patients in these countries and, thus, reduce the burden of that specific tumor. From the global health perspective, the questions and interventions might be different. Is the apparent high incidence of the malignancy accurate? Why are children arriving at the treatment center with such advanced disease? Does the apparent high incidence of a given tumor reflect the frequency of incorrect diagnosis of common pediatric malignancies, such as acute leukemias? If the latter is true, what factors contribute to incorrect diagnosis and late referral? Although all of the single-disease and public health research questions have merit and studies to address them are not mutually exclusive, interventions in local health systems to eliminate systemic deficiencies may reduce the burden of pediatric malignancy more rapidly. However, intervention in local health systems will require a broad coalition of various community leaders from the public and private sectors. The approach is focused on increasing the number of local individuals trained to address local problems and the creation of local mechanisms that can ensure long-term sustainability.

Finally, the role of the project's mentor in the HIC is crucial. Ideally, mentors are able to communicate with LMIC partners in their language and know the cultural nuances of the partner countries. Frequent (every 2 or 3 weeks) contact with the local medical teams is necessary when medical and administrative topics are being discussed. Regular visits to partner sites demonstrate support for the local team and provide an opportunity to connect with individuals in government and in grassroots foundations. Cultivating relationships with community, hospital, foundation, and government leaders is a long-term process and may not bear immediate fruit, but it will lay the foundation for genuine, productive collaboration. Table 4 summarizes the key elements necessary for successful pediatric oncology partnerships between HICs and LMICs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

- Magrath I, Steliarova-Foucher E, Epelman S, et al: Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 14:e104-e116, 2013
- Ribeiro RC, Steliarova-Foucher E, Magrath I, et al: Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: A descriptive study. *Lancet Oncol* 9:721-729, 2008
- Gupta S, Rivera-Luna R, Ribeiro RC, et al: Pediatric oncology as the next global child health priority: The need for national childhood cancer strategies in low- and middle-income countries. *PLoS Med* 11:e1001656, 2014
- Murphy MF, Bithell JF, Stiller CA, et al: Childhood and adult cancers: Contrasts and commonalities. *Maturitas* 76:95-98, 2013
- Howard SC, Metzger ML, Wilimas JA, et al: Childhood cancer epidemiology in low-income countries. *Cancer* 112:461-472, 2008
- World Bank: Criteria of low- and mid-income countries (LMIC). <http://data.worldbank.org/about/country-and-lending-groups>
- Rivera GK, Ribeiro RC: Improving treatment of children with acute lymphoblastic leukemia in developing countries through technology sharing, collaboration and partnerships. *Expert Rev Hematol* 7:649-657, 2014
- Rodriguez-Galindo C, Friedrich P, Morrissey L, et al: Global challenges in pediatric oncology. *Curr Opin Pediatr* 25:3-15, 2013

9. Hopkins J, Burns E, Eden T: International twinning partnerships: An effective method of improving diagnosis, treatment and care for children with cancer in low-middle income countries. *J Cancer Policy* 1:e8-e19, 2013
10. Kellie SJ, Howard SC: Global child health priorities: What role for paediatric oncologists? *Eur J Cancer* 44:2388-2396, 2008
11. World Bank: Guatemala per capita income. <http://data.worldbank.org/indicator/NY.GNP.PCAP.CD>
12. UNICEF: Population living with income below the international poverty line. http://www.unicef.org/infobycountry/guatemala_statistics.html
13. Luna-Fineman S, Slowing K, Valverde P, et al: Pediatric cancer in Guatemala: A retrospective study. *Med Pediatr Oncol* 29:353, 1997 (abstr O131)
14. Fundación Ayúdame a Vivir (AYUVI): Help Me to Live. <http://www.ayuvi.org.gt>
15. Antillón-Klussmann F, Valverde P, Castellanos M, et al: Training pediatric oncologist for developing countries: The experience of the Association of Pediatric Hematologist-Oncologist in Central America and Dominican Republic (AHOPCA). *Pediatr Blood Cancer* 55:975, 2010 (abstr PT 015)
16. Day SW, Garcia J, Antillon F, et al: A sustainable model for pediatric oncology nursing education in low-income countries. *Pediatr Blood Cancer* 58:163-166, 2012
17. Day SW, McKeon LM, Garcia J, et al: Use of Joint Commission International standards to evaluate and improve pediatric oncology nursing care in Guatemala. *Pediatr Blood Cancer* 60:810-815, 2013
18. Fondation Sanofi Espoir. My Child Matters. http://fondation-sanofi-espoir.com/en/ngo_child-matters.php
19. Lorenzana R, Coustan-Smith E, Antillon F, et al: Simple methods for the rapid exchange of flow cytometric data between remote centers. *Leukemia* 14:336-337, 2000
20. Howard SC, Campana D, Coustan-Smith E, et al: Development of a regional flow cytometry center for diagnosis of childhood leukemia in Central America. *Leukemia* 19:323-325, 2005
21. The Brazilian Institute of Geography and Statistics (IBGE): <http://www.ibge.gov.br/home/presidencia/noticias/imprensa/ppts/00000007614302102012433717554689.pdf>
22. The Brazilian Institute of Geography and Statistics (IBGE): Pernambuco estimated population. <http://www.ibge.gov.br/estadosat/perfil.php?sigla=pe>
23. Pedrosa MF, Pedrosa F, Lins MM, et al: Non-Hodgkin's lymphoma in childhood: Clinical and epidemiological characteristics and survival analysis at a single center in Northeast Brazil. *J Pediatr (Rio J)* 83:547-554, 2007
24. Hsu SC, Metzger ML, Hudson MM, et al: Comparison of treatment outcomes of childhood Hodgkin lymphoma in two US centers and a center in Recife, Brazil. *Pediatr Blood Cancer* 49:139-144, 2007
25. Howard SC, Pedrosa M, Lins M, et al: Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA* 291:2471-2475, 2004
26. World Bank. The GDP per capita in China. <http://data.worldbank.org/indicator/NY.GDP.PCAP.CD>
27. Liu Y, Chen J, Tang J, et al: Cost of childhood acute lymphoblastic leukemia care in Shanghai, China. *Pediatr Blood Cancer* 53:557-562, 2009
28. Zhang Z-R, Mi J-Q, Gu L-J, et al: Using sound clinical paths and diagnosis-related groups (DRGs)-based payment reform to bring benefits to patient care: A case study of leukemia therapy. *Front Med China* 4:8-15, 2010
29. Zhou Q, Hong D, Lu J, et al: Pediatric medical care system in China has significantly reduced abandonment of acute lymphoblastic leukemia treatment. *J Pediatr Hematol Oncol* 37:181-184, 2015
30. Howard SC, Ortiz R, Baez LF, et al: Protocol-based treatment for children with cancer in low income countries in Latin America: A report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)—Part II. *Pediatr Blood Cancer* 48:486-490, 2007
31. De Angelis C, Pacheco C, Lucchini G, et al: The experience in Nicaragua: Childhood leukemia in low income countries—the main cause of late diagnosis may be “medical delay.” *Int J Pediatr* 2012:129707, 2012
32. Barr RD, Antillon Klussmann F, Baez F, et al: Asociacion de Hemato-Oncologia Pediatrica de Centro America (AHOPCA): A model for sustainable development in pediatric oncology. *Pediatr Blood Cancer* 61:345-354, 2014
33. Ramirez-Ortiz MA, Ponce-Castaneda MV, Cabrera-Munoz ML, et al: Diagnostic delay and sociodemographic predictors of stage at diagnosis and mortality in unilateral and bilateral retinoblastoma. *Cancer Epidemiol Biomarkers Prev* 23:784-792, 2014
34. Pacheco C, Lucchini G, Valsecchi MG, et al: Childhood acute lymphoblastic leukemia in Nicaragua: Long-term results in the context of an international cooperative program. *Pediatr Blood Cancer* 61:827-832, 2014
35. Mostert S, Gunawan S, Wolters E, et al: Socio-economic status plays important roles in childhood cancer treatment outcome in Indonesia. *Asian Pac J Cancer Prev* 13:6491-6496, 2012
36. Mills A: Health care systems in low- and middle-income countries. *N Engl J Med* 370:552-557, 2014
37. De Pernillo M, Rivas S, Fuentes L, et al: Measurement of socio-economic status in families of children with cancer in Guatemala. *Pediatr Blood Cancer* 61:2071-2073, 2014
38. Gupta S, Yeh S, Martiniuk A, et al: The magnitude and predictors of abandonment of therapy in paediatric acute leukaemia in middle-income countries: A systematic review and meta-analysis. *Eur J Cancer* 49:2555-2564, 2013

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Global Pediatric Oncology: Lessons From Partnerships Between High-Income Countries and Low- to Mid-Income Countries

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Raul C. Ribeiro

No relationship to disclose

Federico Antillon

No relationship to disclose

Francisco Pedrosa

No relationship to disclose

Ching-Hon Pui

No relationship to disclose