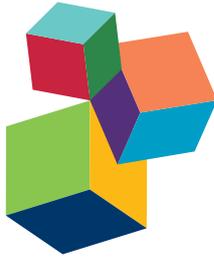


# GLOBAL CHALLENGES IN RADIATION ONCOLOGY

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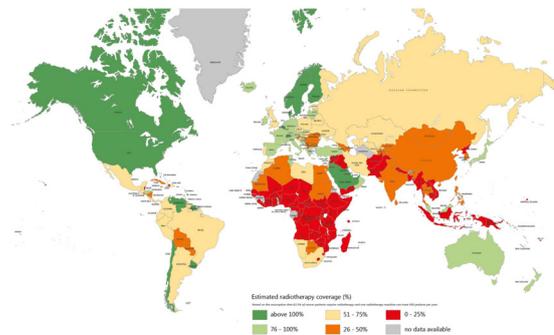
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# GLOBAL CHALLENGES IN RADIATION ONCOLOGY

Topic Editor:

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Worldwide estimation of radiotherapy needs  
(Rosenblatt E (2014) Planning national radiotherapy services. *Front. Oncol.* 4:315. doi: 10.3389/fonc.2014.00315)

is virtually non-existent to minimal, due to the complexities of their population and competing co-morbidities. As a result, there is a tremendous disparity in treatment outcomes for these populations, compared to those in developed countries. Therefore, we have asked a number of oncologists from different parts of the world to report their experience.

Topics that will be covered include locally advanced breast and cervical cancer (India, South Africa), human resources for cancer control in India, systematic review of radiation resources in low and middle income countries, planning national radiotherapy services, building sustainable partnerships through the newly formed ICEC (International Cancer Export Corps), cancer disparities among American Indians, and training radiation oncologists in these underserved parts of the world. Authors will discuss “lessons learned” from their populations, practical suggestions to address these disparities, and how we as a global oncology community can address, and mitigate these global challenges.

In the United States, much of the research is focused on developing new and very expensive technologies and drugs – often without a major therapeutic benefit. In resource limited countries, basic oncology care is frequently lacking. In addition, the benefits of various chemo-radiotherapy combinations for a number of malignancies are unknown as these populations have not been adequately investigated. For oncologists in these countries who have marginal to adequate resources, accrual to clinical trials

The editorial by Dr. Coleman and myself highlights the invaluable contributions from our global contributors. Thank you for taking the time to read this special issue on global cancer disparities. We are all energized to begin addressing the needs of our cancer patients worldwide.

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# Table of Contents

- 05 Editorial: “Global Challenges in Radiation Oncology”**  
Daniel Grant Petereit and C. Norman Coleman
- 09 A systematic review of radiotherapy capacity in low- and middle-income countries**  
Surbhi Grover, Melody J. Xu, Alyssa Yeager, Lori Rosman, Reinou S. Groen, Smita Chackungal, Danielle Rodin, Margaret Mangaali, Sommer Nurkic, Annemarie Fernandes, Lilie L. Lin, Gillian Thomas and Ana I.Tergas
- 20 Planning national radiotherapy services**  
Eduardo Rosenblatt
- 25 Human resources for cancer control in Uttar Pradesh, India: a case study for low and middle income countries**  
Maithili Daphtary, Sushma Agrawal and Bhadrasain Vikram
- 31 Training global oncologists: addressing the global cancer control problem**  
Surbhi Grover, Onyinye D. Balogun, Kosj Yamoah, Reinou Groen, Mira Shah, Danielle Rodin, Adam C. Olson, Jeremy S. Slone, Lawrence N. Shulman, C. Norman Coleman and Stephen M. Hahn
- 35 Corrigendum: “Training global oncologists: addressing the global cancer control problem”**  
Surbhi Grover, Onyinye D. Balogun, Kosj Yamoah, Reinou Groen, Mira Shah, Danielle Rodin, Yehoda Martei, Adam C. Olson, Jeremy S. Slone, Lawrence N. Shulman, C. Norman Coleman and Stephen M. Hahn
- 36 The cervix cancer research network: increasing access to cancer clinical trials in low- and middle-income countries**  
Gita Suneja, Monica Bacon, William Small Jr., Sang Y. Ryu, Henry C. Kitchener and David K. Gaffney
- 40 Locally advanced breast cancer – strategies for developing nations**  
Onyinye D. Balogun and Silvia C. Formenti
- 45 National Cancer Institute’s Cancer Disparities Research Partnership program: experience and lessons learned**  
Rosemary S. L. Wong, Bhadrasain Vikram, Frank S. Govern, Daniel G. Petereit, Patrick D. Maguire, Maggie R. Clarkson, Dwight E. Heron and C. Norman Coleman
- 53 Cultural roles of Native Patient Navigators for American Indian cancer patients**  
Linda Burhansstipanov, Lisa Harjo, Linda U. Krebs, Audrey Marshall and Denise Lindstrom
- 56 The International Cancer Expert Corps: a unique approach for sustainable cancer care in low and lower-middle income countries**  
C. Norman Coleman, Silvia C. Formenti, Tim R. Williams, Daniel G. Petereit, Khee C. Soo, John Wong, Nelson Chao, Lawrence N. Shulman, Surbhi Grover, Ian Magrath, Stephen Hahn, Fei-Fei Liu, Theodore DeWeese, Samir N. Khleif, Michael Steinberg, Lawrence Roth, David A. Pistenmaa, Richard R. Love, Majid Mohiuddin and Bhadrasain Vikram

# Editorial: “Global Challenges in Radiation Oncology”

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**Keywords:** editorial, radiation oncology, global cancer disparities, LMICs

## Introduction

In the United States, much of the research is focused on developing new and expensive technologies and drugs that are of great scientific and clinical interest, but usually providing incremental therapeutic benefit. In contrast, in resource-limited countries, basic oncology care is frequently lacking. In addition, the outcomes from various chemo–radiotherapy combinations for a number of malignancies are unknown, as these populations have not been adequately investigated. For oncologists in these countries who have marginal to barely adequate resources, accrual to clinical trials is virtually non-existent because of the complexities of social and economic issues facing their population, competing co-morbidities and lack of access. As a result, there is a tremendous disparity in outcomes for these populations, as compared to those in developed countries.

At first, it may appear odd that radiation oncologists, often associated with high-cost technology, would have leading role in global cancer disparities. However, radiation is a critical treatment modality for the majority of cancers whether the intent is curative or palliative. In fact, a single dose of palliative radiotherapy is more cost effective than a prolonged course of narcotics (1). In addition, for many solid malignancies observed in low to middle income countries (LMICs), such as breast, cervical, head and neck (H&N), upper GI, central nervous system (CNS), and lung cancers, radiation will achieve very effective palliation, and sometimes cure, even when concurrent chemotherapy cannot be given or when oncologic surgeons are unavailable. In addition, radiation oncology centers are often the hub of technologies, such as telemedicine, which can facilitate collaboration with other cancer centers worldwide.

The authors are privileged to be guest editors for this Frontiers Research Topic highlighting the issues addressing global cancer disparities. The authors have asked a number of oncologists from different parts of the world to report their experience and thank them for their time and work over the last year.

Topics covered include systematic review of radiation resources in low and middle income countries, planning national radiotherapy services, human resources for cancer control in Uttar Pradesh, India, locally advanced breast and cervical cancer (India, Africa), patient navigation, the challenges of performing clinical trials in South Africa, the cervical cancer research network (CCRN), the US Cancer Disparities Research Partnership (CDRP), training radiation oncologists in underserved parts of the world, and building sustainable partnerships through the newly formed International Cancer Export Corps (ICEC). The authors discuss “lessons learned” from their populations, practical suggestions to address these disparities, and how we as a global oncology community can address and potentially mitigate these global challenges.

According to the World Bank classification, 139 countries are considered LMICs as their gross national income (GNI) per capita is  $\leq$ USD 12,615 (2). The World Health Organization (WHO) report in 2010 and the United Nations declaration in 2012 chronicled the growing burden of non-communicable diseases (NCD) in the developing world (3, 4). In the past decade, the global

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incidence of cancer has increased by 20%, mostly because of cases in LMIC (5). By 2020, up to 70% of the 20 million new cancer cases are expected to occur in these countries (6). Furthermore, these countries are not prepared to address this cancer epidemic, and consequently, cancer survival rates are less than one-third of those for site specific cancer types in high-income countries. It is imperative that they develop and sustain the infrastructure needed to prevent, diagnose, and treat this cancer “tsunami” (7). Case burdens are also increasing in rural underserved areas in resource-rich countries with the native/aboriginal populations often having similar access and care issues as LMICs, as the Northern Plains American Indians (AIs) have the highest cancer mortality rate in the United States (8–10).

Cervical cancer is of global interest as almost 85% of the worldwide 530,000 cases in 2012 were diagnosed in developing countries. This is amenable to detection by screening and potentially preventable with vaccination (11, 12). Furthermore, even patients with advanced stages of cervical cancer are still curable if appropriate radiation doses can be given with a combination of external beam radiation and brachytherapy (13). The social and economic impact is substantial as cervical cancer disproportionately affects young women (14–16).

The International Atomic Energy Agency (IAEA) recommends a teletherapy unit, a radiation oncologist, a medical physicist, and two radiotherapists (RTTs) per 250,000 people (17, 18). The inadequacy of radiation oncology services for LMICs is reported by Grover et al. in a systematic review of five international databases. A world map of current teletherapy units from the IAEA is depicted in Figure 1 from the Rosenblatt article (18). In many parts of Africa, there is only one teletherapy unit per 10 million people! The inadequacy of radiation therapy infrastructure from the IAEA–DIRAC database was recently reported by Datta et al. (19). They estimated by 2020, 84 LMICs will need 9,169 teletherapy units, 12,149 radiation oncologists, 9,915 medical physicists, and 29,140 radiation therapy technologists. It is estimated that Africa is functioning at 25% of its potential for treating cervical cancer (20). These projected needs are simply staggering and cannot be allowed to stand.

Determining the human resources needed to treat cancer is a critical first step as it is important to guide investment and progress (21). Daphtary et al. (22) describe a unique methodology for estimating these resources needed in the state of Uttar Pradesh, India, with a population of 200 million. Using the publicly available sources of GLOBOCAN<sup>1</sup> and city population<sup>2</sup>, they explain an enormous shortage of human and other resources for cancer control (12, 23). As the data was generated from 2008, the dilemma is expected to be even more dire as the cancer cases in India is projected to increase by 30% over the next 10 years. This case study of Uttar Pradesh may serve as a road map for other interested stakeholders and policy makers in a variety of LMICs.

Rosenblatt indicates that there should be a systematic and comprehensive process of long-term planning of radiotherapy services at the national level, taking into account the regulatory

infrastructure for radiation protection, planning of centers, equipment, staff, education programs, quality assurance, and sustainability aspects. He adds that “realistic budgetary and cost considerations must also be a part of the project proposal or business plan”.

In the second article by Grover and colleagues, the need to train global oncologists from the perspective of a US resident is presented. There is an interest and potential need for US residents to have global training experience, and a concomitant urgent need for LMIC countries to develop oncology training, infrastructure, and services, possibly in collaboration with US residents. Although limited but growing, there are international options for US residents including The Paul Famer Global Surgery Fellowship, international pediatric oncology twinning programs, travel grants through the American Society of Radiation Oncology (ASTRO), and the Global Health Scholars Program through ASTRO-Association of Residents in Radiation Oncology.

Although this “tsunami” of cancer in LMICs is overwhelming and seemingly hopeless, a recent delegation of radiation oncologists, residents, and medical physicists embarked on a mission to the city of Dakar, Senegal West Africa, to implement the first high-dose-rate (HDR) remote afterloader, as this country of 13 million people only had a single Cobalt teletherapy unit with no brachytherapy services. By partnering with Radiating Hope, a non-profit organization whose mission is to update and provide radiation equipment to developing countries and founded by Dr. Brandon Fisher, the first cervical cancer patients were treated with curative intent. This “beacon” of hope may serve as a model and inspiration for other LMICs (24, 25) but is only 1/5000th or so of the need.

Conducting clinical trials for common disease sites in LMICs is of critical importance as the data generated from other countries may not be applicable for these populations. Dr. Roy Lakier, an oncologist from South Africa, kindly shared his data that chronicled the tribulations of an IAEA sponsored phase III trial investigating radiation alone versus chemo-radiation for HIV positive cervical cancer patients. Even with minimal resources to conduct research, they successfully enrolled 81 patients. No clinically relevant conclusions could be drawn because of “relatively” small numbers and incomplete follow-up. Twenty percent of patients were lost to follow-up and 6% died during the first 6 months reflecting advanced stages of disease, impaired nutritional status, and significant medical co-morbidities. Their experience detailed several problematic areas including inadequate radiation therapy equipment, delays in obtaining pathology and imaging promptly, unavailability of chemotherapy drugs, transportation, social and medical co-morbidities, and non-supportive hospital policies with the extra research expenses incurred. Lakier and his co-workers are to be commended for conducting this phase III trial in a very resource-limited environment.

As evident by Lakier, access to cancer clinical trials is scarce in LMICs with limited to unavailable research support and infrastructure. The Cervix Cancer Research Network (CCRN) was developed as a potential solution whose overall goal is to promote cervical cancer research and improve access to novel therapies. Of course, basic radiation services are a pre-requisite before novel therapies are considered. The CCRN is a subsidiary of the Gynecologic Cancer Intergroup (GCIG), and was developed under the vision of Dr. Henry Kitchener from the University of Manchester. As described

<sup>1</sup><http://globocan.iarc.fr/>

<sup>2</sup><http://www.citypopulation.de/>

by Suneja, 17 CCRN site visits have been performed with four multinational clinical trials opened that were deemed suitable. They suggest the use of cell phone technology to increase patient compliance which was problematic in Lakier's experience. We recently implemented a mobile health technology (mHealth) randomized trial using customized text messaging, counseling, and nicotine replacement to address the high smoking rates among the Northern Plains American Indians (26). In this resource-limited population, recruitment and compliance to this trial has been high. Therefore, the use of mHealth technology for LMIC populations for treatment compliance, follow-up, and clinical trials may be a potential solution.

The disparity of breast cancer in LMIC is evident as it occurs in younger women who present with a higher incidence of locally advanced breast cancer (LABC) when compared with women from developed countries as discussed by Balogun and Formenti. They make the case that "financial resources are likely better invested in public awareness campaigns and training community health workers to educate the public and perform clinical breast exams (CBE) rather than screening mammography" (27–29). Basic chemotherapeutic agents such as paclitaxel, doxorubicin, cyclophosphamide, and tamoxifen, rather than expensive targeted therapy such as herceptin, are recommended for systemic therapy. The dire need for adjuvant external beam radiation is discussed in the context of hypofractionation and concurrent with chemotherapy in order to maximize resources.

To increase access of underserved/health disparate communities to NCI clinical trials, the Radiation Research Program (RRP) piloted a unique model – the Cancer Disparities Research Partnership (CDRP) program. CDRP targeted community hospitals with a limited past NCI funding history and provided funding to establish the infrastructure for their clinical research program. Wong summarizes the results from the initial six CDRP institutions. Key findings from these community-based hospitals include enrolling ~2,300 patients to clinical trials with ~5,100 patients receiving patient navigation (PN) once the infrastructure was established. Another finding is the need for the cooperative groups to develop clinical trials for locally advanced cancers observed in these disparate populations.

American Indians experience tremendous cancer disparities with the highest 5 year mortality rates when compared with other US races (10). PN is a method to mitigate this disparity as presented by Burhansstipanov and co-workers. According to the Affordable Care Act where a navigator is an "insurance broker", the true model of patient navigation, as created by Freeman, is one who helps patients overcome barriers to accessing and using a specific health care system (30). Burhansstipanov describes a unique model of PN where navigators are AI and part of the community who navigate in a culturally appropriate fashion. In South Dakota, the authors implemented a similar model of PN for the AI community (Walking Forward) where they were able to document improved satisfaction with the health care system and improved treatment compliance for AIs undergoing radiation (8, 31).

## International Cancer Expert Corps (ICEC): Building a Sustainable Global Network

Likely because of the magnitude of the problem, when global cancer disparities are discussed, often only the problem is

presented, rather than solutions and a logical plan to address these complex economic, social, political, and healthcare inequality issues. Signaling a transformational change to respond both to the global need and to create a sustainable altruistic component to healthcare careers, Coleman and colleagues detail the newly formed ICEC whose goal is to reduce the mortality and improve the quality of life for cancer patients in LMIC. They outline key steps in this process including structured support for dedicated faculty attempting to establish a formal career path, with metrics for human service.

The goal for an ICEC Center, within the LMIC, or geographic-access limited setting within resource-rich countries, as often encountered with indigenous populations, is to develop and retain a high-quality sustainable workforce who can provide best possible cancer care for their setting, conduct research, and become a regional center of excellence from which to help other ICEC Centers develop. An international mentoring network of cancer professionals, including many of the contributors to this issue of *Frontiers*, will work with local and regional in-country groups on projects to develop and sustain expertise and local solutions for better cancer care, as detailed in Figure 1 of the Coleman article (32). The vision is a world in which everyone has access to cost-effective interventions to prevent and treat cancer and its symptoms in ways that are consistent with best possible practices for the local circumstances.

Partnering with and enhancing ongoing global health programs and "twinning" between programs in resource-rich and health disparity communities is an essential tenet of ICEC to help create a critical mass of sustainable expertise, which is difficult to obtain from the independent well-intended smaller programs (i.e., the current model). In essence, ICEC is aiming to create a "public health oncology" road map to "tap into" a global panel of experts to mentor physicians, nurses, scientists, epidemiologists, and other health care and health policy workers from LMICs (33). Global expertise will include academicians, private practitioners, and senior mentors who along with their institution are willing to commit time so that person-to-person relationships will enhance investment in and quality of cancer care where there is a need that must be met by the global community.

Although cancer at the cellular and molecular level is a complex disease that requires multiple interventions for a successful outcome, so too is cancer at the global level as multiple partners are required to address multiple barriers to mitigate these ongoing global cancer disparities. The contributors and their colleagues and partners in this issue of *Frontiers* are agents of change, addressing a problem that some might consider "too hard", or "too expensive" ... and they are demonstrating that with dedication, support, and commitment, change will occur. Two quotes come to mind from those who have changed the world. Margaret Meade noted: "Never believe that a few caring people can't change the world. For, indeed, that's all who ever have". The authors believe there are a growing number of dedicated and passionate individuals who will transform global oncology sometime in the not too distant future. The authors in the cancer community will smile when they think of the remark by Nelson Mandela, "It always looks hard until it is done!"

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# A systematic review of radiotherapy capacity in low- and middle-income countries

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**Objectives:** The cancer burden in low- and middle-income countries (LMIC) is substantial. The purpose of this study was to identify and describe country and region-specific patterns of radiotherapy (RT) facilities in LMIC.

**Methods:** A systematic review of the literature was undertaken. A search strategy was developed to include articles on radiation capacity in LMIC from the following databases: PubMed, Embase, CINAHL Plus, Global Health, and the Latin American and Caribbean System on Health Sciences Information. Searches included all literature up to April 2013.

**Results:** A total of 49 articles were included in the review. Studies reviewed were divided into one of four regions: Africa, Asia, Eastern Europe, and South America. The African continent has the least amount of resources for RT. Furthermore, a wide disparity exists, as 60% of all machines on the continent are concentrated in Egypt and South Africa while 29 countries in Africa are still lacking any RT resource. A significant heterogeneity also exists across Southeast Asia despite a threefold increase in megavoltage teletherapy machines from 1976 to 1999, which corresponds with a rise in economic status. In LMIC of the Americas, only Uruguay met the International Atomic Energy Agency recommendations of 4 MV/million population, whereas Bolivia and Venezuela had the most radiation oncologists (>1 per 1000 new cancer cases). The main concern with the review of RT resources in Eastern Europe was the lack of data.

**Conclusion:** There is a dearth of publications on RT therapy infrastructure in LMIC. However, based on limited published data, availability of RT resources reflects the countries' economic status. The challenges to delivering radiation in the discussed regions are multidimensional and include lack of physical resources, lack of human personnel, and lack of data. Furthermore, access to existing RT and affordability of care remains a large problem.

**Keywords:** radiation capacity, global health, low- and middle-income countries, radiation oncology access, systematic review, systematic review

## INTRODUCTION

As populations' age and infectious disease control extends lifespan, cancer and other non-communicable diseases are becoming increasingly significant burdens of mortality in low- and middle-income countries (LMIC) (1). Over 70% of cancer cases will be diagnosed in LMIC by 2030 (2). Yet most developing countries do not have the resources or infrastructure to prevent, diagnose, or treat this growing burden of cancer (2). Compounding the issue is the lack of cancer registries and cancer treatment capacity in most of the developing world. Existing data represents only a fraction of the true burden of cancer, with our best estimates being estimates at best.

Leading medical and public health organizations have spearheaded international initiatives to increase awareness of this issue, but great needs still exist (3). One organization, the International Atomic Energy Agency (IAEA), has organized the Directory of Radiotherapy Centres (DIRAC), which acts as a central record and quantification of international radiotherapy (RT) capacity. Apart from DIRAC, few reports exist that describe the capacity requirements necessary to deliver RT. This capacity includes country-specific infrastructure, equipment, personnel training, quality assurance, and challenges surrounding RT facilities. The objective of this study was to perform a systematic review of RT capacity in LMIC as documented in the literature. In addition, we

aimed to compare reports in the literature to that of reports from the IAEA.

**MATERIALS AND METHODS**

We searched PubMed (1946 to April 2013), Embase (1974 to April 2013), CINAHL Plus (1937 to April 2013), Global Health (1910 to April 2013), and the Latin American and Caribbean System on Health Sciences Information (LILACS) (1982 to April 2013). A core strategy was developed in PubMed and then translated for each database. All search strategies were developed using a combination of controlled vocabulary and keyword terms to define the concepts of radiation therapy, health services, and LMIC. Searches were run on April 19, 2013. (See Supplementary Material for more details on search strategies.)

All citations were imported into a reference management system and duplicates were removed. All citations were reviewed by two authors at the title and abstract level for pre-defined inclusion and exclusion criteria as defined below. A third author resolved disagreements between the initial two reviewing authors.

Articles on radiation capacity and facilities in LMIC were included. Articles not including low- or middle-income countries (as determined by the World Bank, see Supplementary Material for complete list) and radiation facilities or capacity were excluded.

Based on the initial database search, abstracts were selected for final review (Figure 1). If they met the above inclusion criteria, they were selected to be included in the review.

**RESULTS**

All the studies included in the review were divided into one of the four regions: Africa, Asia, Eastern Europe, and South America. Each of the four regions will be described separately.

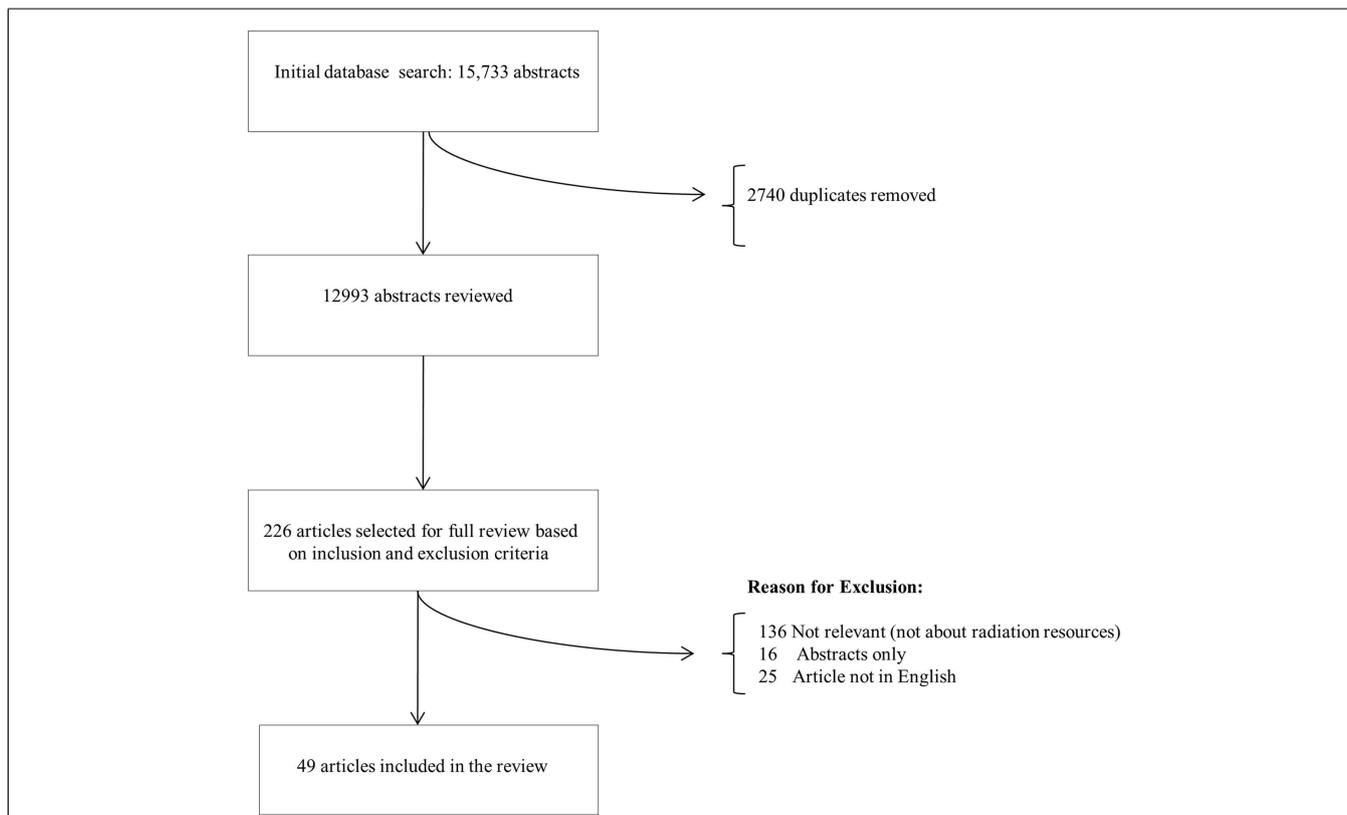
**AFRICA**

**Countries covered**

A total of 16 articles covering the Africa region were included in this review in Ref. (4–19). The countries covered were: Ghana, Liberia, Nigeria, Sierra Leone, South Africa, and Uganda (4, 7–10, 13, 14, 16, 19). Publication dates ranged from 1972 to 2013 (7, 11, 19). Six articles provided reviews and surveys on the continent as a whole and one article reported on developing countries in general (5, 6, 11, 12, 15, 17, 18). Radiation capacity is not discussed for a majority of countries on the African continent. The two most recent articles present updated data for the African continent: Denny and Anorlu reviewed cervical cancer in Africa and the IAEA reported on the status of RT resources in Africa (5, 11).

**Cancers treated**

The most common cancer addressed was cervical cancer, though seven articles included data on non-gynecological cancers (8, 11, 12, 14, 15, 17, 18). Advanced cervical cancer is treated with radiation, a combination of external beam radiation and brachytherapy. It is estimated that 80,000 African women are diagnosed with cervical cancer each year and approximately 60,000 die of the disease annually, though validation of these estimations is difficult due



**FIGURE 1 | Article selection.**

to limited availability of cancer registries (6). RT is frequently the first line of treatment for cervical cancer, and, in a single institution survey, up to 97.3% of newly diagnosed patients were referred for RT (13). However, the article did not describe where these centers are located and how many women were actually treated or able to access these centers. Unfortunately, many women do not present for follow-up at these tertiary care centers, which makes it challenging to evaluate outcomes. Radiation is also used for palliative treatment with notable improvement in survival (12). However, the 5-year cervical cancer survival rate continues to be low, ranging from 15 to 30% in Africa compared to 60% in North America (12).

### **Available equipment**

According to the latest update from the DIRAC database, there are currently 160 RT centers on the African continent (11). A total of 88 cobalt-60 machines, half of which are over 20 years old, and 189 linear accelerators are operating in those 160 centers. Sixty percent of machines are concentrated in Egypt and South Africa, while 29 of 54 countries in Africa are still lacking any RT resource. Given the ideal ratio of 4–8.1 RT centers per 1 million people or 1 MV per 250,000 people, as defined by the IAEA, every country in Africa needs more centers and machines (17). The highest capacity is in Mauritius with 2.36 centers/1 million people followed by South Africa with 1.89, Tunisia with 1.55, and Egypt with 0.93 (17). Not surprisingly, there appears to be a correlation between Gross National Income (GNI) and RT capacity (11).

There are limited reports from most of West Africa with the exception of Nigeria. Several reports on Nigeria from as early as 1972 record a gradual increase in RT delivery capacity over time. In 1972, the longest standing RT center had been in existence for 20 years, housing one linear accelerator and two sets of brachytherapy applicators (7). Between 1972 and 1990, reports from West Africa suggested that there were a total of two RT centers that served Ghana, Liberia, Nigeria, and Sierra Leone (8). During this time, cervical cancer patients were treated with brachytherapy alone. In 2000, the University College Hospital in Ibadan, Nigeria, reported a 500 case retrospective review where combined external beam RT and low dose rate brachytherapy was used to treat patients with cervical cancer, an improvement from previous reports where hospital resources allowed for only monotherapy with low dose rate brachytherapy (4, 7). In 2008, five RT centers were in operation in Nigeria, with more expected to come (10). Despite the gradual increase in RT centers, waiting lines for these machines continue to be long. Nigeria and the surrounding West African countries are clearly operating under capacity.

### **Human resources**

Data on available RT human resources were limited with specific numbers only available for South Africa. In 1994, with a population of 24 million, South Africa had 58 practicing radiation oncologists, 190 therapy radiographers, and 30 medical physicists, which represented only a fraction of total registered professionals (14). With 58 radiation oncologists, South Africa had only 1 radiation oncologist per 350 patients, falling short of the recommended IAEA ratio of 1 radiation oncologist per 200–250 patients (20). In 2011, a review of cervical cancer treatment in Africa reported that

“training facilities in cancer diagnosis and management” were few and only found in Algeria, Egypt, Libya, Morocco, Nigeria, South Africa, and Zimbabwe (6). It was unclear whether the curriculum covered RT or if the types of health care professionals trained (physicians vs. nurses vs. technicians) would be able to deliver RT after completion of the program. Multiple articles also emphasized the critical lack of pathology and laboratory services needed to make the initial diagnosis of gynecological and other cancers (12, 15). The articles from Nigeria provide limited records of their human resources. One mention is made of the RT center in 1972, where only one Cambridge-trained medical physicist was noted to be available to the entire hospital (7).

## **AMERICAS**

### **Countries covered**

A total of five full articles covering Central America, South America, and the Caribbean were included in this review in Ref. (21–25). The countries covered were: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela. Four articles provided surveys of multiple South American countries, one article reported on Mexico alone, and one abstract reported on Brazil alone. No data were found for 20 of 26 countries in this region, including Belize, Grenada, Guyana, Honduras, Jamaica, and Suriname. The earliest article was published in 1984 and detailed RT resources throughout nine Latin American countries. The next most recent survey of Latin America was published in 2004 by the IAEA, and included 19 countries that account for 96% of the cancer cases in South and Central America and the Caribbean. The most recent article included in this review was published in 2013 and reported RT patterns in Mexico. Data from this region are sparse and available for limited time periods.

### **Cancers treated**

The data on the most common cancers treated in this region were limited. In 1984, the report from nine Latin American countries found the most common cancer treated by radiation therapy to be cervical, followed by breast, head and neck, lung, and skin cancers (21). A 2013 report from Mexico suggested that the most common cancer treated by radiation therapy is breast cancer, followed by prostate, cervical, and lung (22).

### **Available equipment**

The number of radiation machines in Latin America has increased over the past 30 years, especially in countries with greater populations. From 1989 to 2004, the number of machines in Brazil rose from 165 to 270 (64% increase) and, in Venezuela, from 18 to 44 (144% increase) (21, 23). The most recent information from 2004 lists the number of RT centers, cobalt-60 machines, and linear accelerators (linacs) from 19 Latin American countries (23). The total number of centers in the region was 470, with 710 machines, slightly more than half of which were cobalt-60 units (396 cobalt-60 units, 314 linacs). However, the distribution of these centers varied widely from country to country, ranging from 0 to 151. Although there has been a steady increase in the number of machines, the capacity remains insufficient, with an estimated 100

more teletherapy machines required to meet the IAEA guidelines of 1 machine per 500 new cancer cases per year (23). The quality of the machines and downtime was not discussed in more recent papers. In 1990, the majority of linacs in these countries were older machines operating at 4–10 MV without electron capability (24). Though the numbers of teletherapy machines in these countries are on the rise, it is unclear whether these have reliable power sources (for linear accelerators) and access to adequate servicing. Similar to Africa, there continues to be an insufficient number of machines to serve the populations in these countries.

Brachytherapy was offered at the majority of centers in Latin America, but the numbers of centers varied throughout the region. In 1990, all centers in Peru and Chile had brachytherapy for treatment of gynecologic malignancies, and 90% of centers in Brazil offered manual afterloading (24). Of 12 countries that provided data on brachytherapy, there were over 260 sets of cesium and radium manual afterloading devices, 23 cesium low dose rate afterloading devices, and 6 cesium high dose rate afterloading devices. However, the break down by country was not provided. In addition, there were 103 centers with iridium high dose rate units, 61 of which were in Brazil (23).

### **Human resources**

In addition to an insufficient number of radiation therapy centers, there continues to be inadequate numbers of personnel trained to provide treatment. In 1983, of 27 radiation therapy centers studied in nine Latin American countries, 35.5% had an insufficient number of full-time radiation oncologists (<1 per 200–250 patients), 52% had an insufficient number of full-time physicists (<1 per 400 new patients), and only 15 of the centers had a dosimetrist available (21). However, they found that 25 of the 27 centers had an adequate number of radiation technicians (21). In 2004, the 19 countries studied had 933 radiation oncologists, with 642 more needed, representing a needed increase of 69% in number of radiation oncologists to meet IAEA standards (23). There were 357 medical physicists with 627 new physicists needed representing a 146% needed increase. There were 2300 radiation technologists, with 2500 more technologists needed (23). At the time of publication, only Bolivia and Venezuela had >1 radiation oncologist per 1000 cancer cases (23).

Formal training programs for radiation oncology are on the rise. In 1989, 10 out of 27 centers surveyed had radiation oncology residency programs and 14 offered formal training for radiation therapy technologists (21). By 2004, 12 of the 18 countries surveyed had postgraduate radiation oncology training at a total of 35 institutions, with the highest density of training in Argentina, Brazil, and Cuba (23). As of 2013, there are six centers in Mexico that were training radiation oncologists (22). Formal training of medical physicists is available in 7 of 18 Latin American countries at 22 centers (23). In Mexico specifically, two public universities offer a Masters in Medical Physics (22). However, the quality of these institutions and training programs was not described.

## **ASIA**

### **Countries covered**

A total of 20 full articles covering the Asia region were included in this review in Ref. (26–45). Of the countries, the United Nations

Statistics Division classified as belonging to Asia, this systematic review covers the following LMIC: Azerbaijan, Bangladesh, Cambodia, China, India, Indonesia, Malaysia, Myanmar, Philippines, Saudi Arabia, Sri Lanka, Thailand, Turkey, and Vietnam. Nepal and Papua New Guinea were not included in the UN classification, but were included in the Asia region for the purposes of this review in Ref. (46). No data were found on Armenia, Bhutan, Georgia, Islamic Republic of Iran, Jordan, Kazakhstan, Kyrgyzstan, People's Democratic Republic of Lao, Tajikistan, Uzbekistan, or Yemen. The earliest article was written about Bangladesh in 1981 and the most recent article was written about India in 2013 (26, 45).

### **Cancers treated**

Data on RT utilization were largely focused on treatment of cervical cancer (35–42). In the Philippines, 75.6% of new cervical cancer patients seen at Philippine General Hospital in 2008 were reportedly eligible for chemoradiation, yet financial constraints resulted in only 17.6% completing the recommended treatment course (39). In Indonesia, a total of 10,274 patients received RT in 2007. Eight centers were actively performing brachytherapy. In Indonesia, intracavitary insertions for cervical cancer represented the most common brachytherapy procedure (33). In Cambodia, a 2012 report noted 60 patients per day were treated with RT, but did not describe the distribution of cancer sites treated (31).

### **Available equipment**

The most recent published survey of RT machines across Asia and the Pacific region was from the IAEA in 2001 (30). They report the number of RT centers ranged from 1 to 453, cobalt-60 machines ranged from 2 to 381, and linear accelerators ranged from 0 to 286 in countries in Asia. The number of cobalt-60 units far outweighed the number of accelerators, with the exception of Thailand and Malaysia, where the ratio of accelerators to cobalt-60 units was 1.08 and 2.71, respectively.

Some of the articles included in this review published after the 2001 IAEA report provide more updated figures on machine availability. Eav et al. reported that the RT department in Phnom Penh, Cambodia, was refurbished in 2003 with a second-hand cobalt-60 unit, x-ray simulator, and 2D dosimetry system, as well as a new remote afterloading brachytherapy machine (31). Two years earlier, when IAEA report was published, Cambodia did not have any reported equipment, reflecting the relatively rapid rate of change in the state of RT in Asia over the last decade. The plan for the new national cancer center in Cambodia includes two new linear accelerators and a high dose rate brachytherapy system.

In Turkey, as of 2011, there were 40 cobalt-60 units, 146 linear accelerators (1.8 linear accelerators per 1 million population), and 35 brachytherapy units (32). Large regional gaps were reported, however, with nearly 40% of linacs concentrated in two cities. As of 2008 in Indonesia, there were 22 RT centers, 17 cobalt-60 units, and 18 linear accelerators, which represent a very large increase over the 7 years since the 2001 IAEA report (33). This rapid equipment scale-up was also seen in India, where 12 additional linear accelerators were added over a 4-year period from 2001 to 2005 (34). In 2005, there were also 113 operational brachytherapy facilities, of which 44 were high dose rate units.

### **Human resources**

Training of skilled personnel for RT was frequently cited as a major barrier to scaling up treatment delivery, despite a reported increase in human resource availability. In Cambodia, international partnerships between the University of Phnom Penh and other international centers, including Strasbourg University in France, has facilitated oncologist training (31). A 2-year program for general practitioners to obtain additional training in oncology has also been created, and, since 2011, a 5-year oncology specialization has been launched. There is currently one full professor oncologist in the country. In Indonesia, there was a 31% increase in RT personnel from 2004 to 2008 and the country has undertaken an expansion of its residency program (33).

In Turkey, the number of radiation oncologists has risen from 85 in 1985 to 446 by 2011, with an average of 30 new radiation oncologists entering practice per year (32). With this trend, Turkey will be in line with international benchmarks by 2023. There remains, however, a gap of 187–280 medical radiation physicists (representing a 10–65% personnel increase) and 600–800 RT technicians (representing 100–133% increase) in Turkey (32). To address these personnel gaps, additional university programs have been opened and working hours of existing staff have been extended.

## **EASTERN EUROPE**

### **Countries covered**

A total of two full articles covering the Eastern Europe region were included in this review. According to the United Nations Statistics Division and World Bank, the following countries are classified as LMIC in Eastern Europe: Belarus, Bulgaria, Hungary, Republic of Moldova, Romania, and Ukraine (47). The articles included covered the following four countries: Bulgaria, Hungary, Moldova, and Romania. No data were found on Belarus or the Ukraine. Both articles were international reviews; the updated results from the Patterns of Care for Brachytherapy in Europe (PCBE) was written in 2010 and the analysis of the European DIRAC database was written in 2013 (48, 49).

### **Cancers treated**

The only available data on the most commonly treated cancers were found pertaining to brachytherapy in the PCBE study (48). Eastern European LMIC included in the analysis was classified in group II (Hungary) or group III (Bulgaria, Moldova, and Romania). In both group II and III, endometrial carcinoma was the most common cancer treated using brachytherapy (38% of cases in group II and 22% of cases in group III), followed by cervical cancer (31% of cases in group II and 57% of cases in group III). Both group II and group III treated more gynecological cancers with brachytherapy than group I, which consisted of high resource countries such as the United Kingdom, Germany, and France. This was attributed to higher incidence rates of uterine and cervical cancer in group II and III countries compared to group I.

### **Available equipment**

The most updated information on the numbers of RT centers, cobalt-60 units, and linear accelerator machines were derived from the DIRAC database as follows: Bulgaria (13 centers, 10 cobalt-60

units, 5 linacs), Hungary (13 centers, 11 cobalt-60 units, 27 linacs), and Romania (19 centers, 16 cobalt, 12 linacs) (49). In Eastern Europe, cobalt-60 machines represent the majority of teletherapy machines, with linear accelerators accounting for only 31% of all teletherapy machines in countries like Bulgaria, Hungary, and Romania. The number of MV teletherapy machines per million people ranged from 1.3 in Romania to 3.8 in Hungary.

### **Human resources**

No data were available on radiation oncology healthcare provider training programs.

## **DEVELOPING WORLD**

Seven articles non-specific to a particular world region presented analyses of the cancer burden, resources, and demographic and economic trends affecting disease control in the developing world (50–56). Increased GNI and population size were found to be critical factors in the availability of radiation resources, with higher rates of equipment acquisition and an increased density of RT services in large and high-income countries (50). Experts observe that while knowledge, technology, and infrastructure to transport the technology are available, the lack of funding prevents scientific societies and international organization from transferring these resources to countries in need (51). The literature suggests that for developing countries, any plan to improve access to RT would need to be dynamic and multi-faceted, requiring buy-in at the levels of the local and state government, investment in staff training that is consistent across countries, increased physical capital and infrastructure, and improvement in patient cancer education programs (52, 53).

## **GAPS IN RADIATION FACILITIES AND GAPS IN PUBLISHED LITERATURE**

To further characterize gaps in radiation facilities, we constructed a table comparing country-specific needs in radiation oncology infrastructure and the current state of available resources per the DIRAC database (**Table 1**) (57, 58). As seen in **Table 1**, except for a few LMIC, most countries are significantly lacking in their radiation infrastructure.

Most of the recent literature in this review was derived from international databases; few articles were generated from within individual countries or regions reporting original, institution-specific, and up-to-date numbers. To highlight gaps in published literature, we compared the non-DIRAC-derived systematic review literature to the most recent DIRAC country-specific statistics (**Table 2**) (57). Only 11 countries out of the 47 included in this review had non-DIRAC-related publications. We extracted facility and equipment numbers based on non-DIRAC sources and found that most estimates were outdated and only Indonesia, Mexico, and Turkey had recent publications reflecting their current RT capacity. This demonstrates significant gap in published literature focusing on state of radiation oncology facilities in LMIC.

## **DISCUSSION**

In this report, we present the results of a comprehensive systematic review of the literature on RT capacity in LMIC. Compared to IAEA recommendations, our review found an overwhelming lack of radiation oncology capacity relative to the large cancer burden faced by these populations (20). While the situation

**Table 1 | Comparison of estimated radiotherapy machines needed taking into account cancer incidence rates vs. the reported machine counts in the DIRAC database.**

Countries	# Annual cancer incidence	# Linacs + Cobalts needed	# Linacs + Cobalts (DIRAC)	# Brachy units needed	#Brachy units (DIRAC)
<b>AFRICA</b>					
Ghana	16580	4	1	2	3
Liberia	2148	2	0	1	0
Nigeria	101797	16	8	8	6
Sierra Leone	–	–	0	–	0
South Africa	74688	48	68	25	25
Uganda	27116	2	0	1	1
<b>AMERICAS</b>					
Argentina	104859	15	80	8	34
Bolivia	8689	3	1	2	5
Brazil	320955	33	285	17	135
Chile	36047	21	41	11	19
Colombia	58534	16	43	8	23
Costa Rica	7653	3	6	2	2
Cuba	31503	9	4	5	6
Dominican Republic	13063	5	10	3	2
Ecuador	20167	7	11	4	7
El Salvador	7782	5	3	3	2
Guatemala	14155	6	7	3	5
Haiti	8414	1	0	1	0
Mexico	127604	14	74	8	60
Nicaragua	5591	3	0	2	0
Panama	4630	5	5	3	1
Paraguay	7957	6	4	3	1
Peru	–	–	26	–	4
Uruguay	14584	7	14	4	6
Venezuela	36961	4	51	2	23
<b>ASIA</b>					
Azerbaijan	13123	2	4	1	1
Bangladesh	141086	10	9	6	3
Cambodia	–	–	0	–	1
China	2817210	87	1014	44	12
India	948858	19	187	10	305
Indonesia	292629	17	21	9	11
Malaysia	31998	13	37	7	5
Myanmar	–	–	1	–	5
Nepal	27768	9	3	5	2
Papau New Guinea	–	–	0	–	1
Philippines	77184	5	29	3	13
Saudi Arabia	–	–	29	–	9
Sri Lanka	24447	8	2	4	3
Thailand	112666	54	48	32	24
Turkey	95069	30	144	15	33
Vietnam	–	–	18	–	7
<b>EUROPE</b>					
Belarus	31188	9	11	5	12
Bulgaria	30701	8	5	4	15
Hungary	–	–	32	–	11

*(Continued)*

Table 1 | Continued

Countries	# Annual cancer incidence	# Linacs + Cobalts needed	# Linacs + Cobalts (DIRAC)	# Brachy units needed	#Brachy units (DIRAC)
Republic of Moldova	9395	3	1	2	2
Romania	70262	8	19	4	6
Ukraine	142960	15	21	8	50

Only countries covered in the systematic review are included. Number of annual incidence cancers is for all cancers, based on Globocan 2008 and NCI Radiation Research Program. Estimated number of linacs, cobalt-60 units (cobalts), and brachytherapy units needed were derived from the NCI Radiation Research Program and were based on the numbers needed to treat the one to two most populous cities in each country (58). Data from DIRAC was reported according to the most updated web database (57). DIRAC, Directory of Radiotherapy Centres. “–” symbol indicates no information available.

varies across regions and countries, many major challenges were similar. The most significant challenges reported include the quality and quantity of physical resources, the scarceness of human resources, and the unequal distribution of available resources. A recently published IAEA/DIRAC report reemphasized several of these issues (59).

Across regions, the number, age, and quality of machines contribute to suboptimal RT capacity. Many countries rely on machines that are more than 20 years old, which brings their functionality and reliability to question (11, 17). Because RT is first-line treatment for the vast majority of cervical cancers, many women with cervical cancer simply do not receive any treatment at all given the paucity of available RT centers. For example, in the Philippines, less than 20% of eligible women successfully receive radiation for their cancer (40). This is reflected in abysmally low 5-year survival rates for cervical cancer (15–30% in Africa) compared to higher income countries (60% in North America) (5, 6). While the numbers of centers providing radiation therapy in Latin American countries may be on the rise, the majority of these centers do not have simulation (81%) or treatment planning systems (55%) (23). The high upfront investment required at the local, state, and national government levels makes improving the quality and quantity of physical resources particularly challenging.

The lack of adequate human resources is another factor contributing to poor RT capacity in developing countries. Most reports on radiation oncology personnel availability and training indicate that there are not enough physicians and staff to treat the numbers of patients requiring radiation treatment. High patient volumes and lack of trained personnel often lead to long waiting lines and continued disease progression long after diagnosis. In Africa, there was only one report on radiation oncology personnel, which was specific to South Africa and reported that there were not enough radiation oncologists to meet the population's needs (14). Although there are no published articles regarding human resources in other African countries, the situation is most likely similar, or more serious, than that of South Africa. In the Americas, the most recent survey of the region's capacity reported the major constraint to adequate provision of radiation therapy was an insufficient number of specialists, rather than a lack of equipment (23). The inadequate number of personnel is in part due to an insufficient number of training programs for radiation oncologists, medical physicists, and radiation technologists. However, there has been a shift from a majority of radiation oncologists

receiving training abroad to training locally; it is unclear what the impact of this will be on the numbers of providers of RT in these countries in the future (23). It is imperative that the availability of training in radiation oncology be improved to appropriately utilize existing physical resources, meet the maximum utilization potential, and account for attrition of workers over time.

The concentrated distribution of available radiation machines compounds the issue of limited capacity in many LMICs by restricting access to needed treatment. Generally, countries with higher GNI house the majority of radiation machines, with LMIC falling far short of the IAEA recommendations. Many countries do not have any radiation centers at all. For example, in Latin America, 75% of radiation oncology departments are located in the four most populous countries: Brazil, Mexico, Columbia, and Argentina (23). No published evidence suggests that Haiti has any regional access to radiation machines; however, neighboring Dominican Republic has three centers (23). It appears as if developed areas have a few large, high capacity centers, with the rest of the population having limited access to, at best, small, suboptimal centers (21). There is usually no mechanism in place for improving access for more rural populations and affordability of care remains a critical barrier (44).

Other culture, infrastructure, and systems issues contribute to poor capacity as well. In Africa, limited public knowledge and belief in traditional African healing contribute to more advanced disease at presentation, increasing requirements for palliative radiation and effective pain medication (4). While radiation can be very effective as palliative therapy, public information campaigns should go hand in hand with cancer prevention programs to urge women to seek medication attention earlier for better treatment outcomes (19). Another frequently highlighted issue was the difficulty in conducting a needs assessment for RT due to the lack of an organized cancer registry in many countries. Of the two articles about Eastern Europe, both were based on international registry and survey data. None originated internally within each country and therefore the RT capacity of this region remains limited to what is reported by DIRAC and IAEA.

Despite existing challenges, we discovered several countries working to improve their RT delivery systems. There are reports demonstrating slow and gradual increases in the number of RT centers in countries of West Africa (8). The number of Nigerian radiation centers and machines has been on the rise for over 30 years and is now also serving other countries of West Africa (7,

**Table 2 | Comparison of radiotherapy resources described in reported literature vs. the DIRAC database (57).**

Countries	# RT centers (literature)	# RT centers (DIRAC)	# Linacs + Cobalts needed	# Linacs (literature)	# Linacs (DIRAC)	# Cobalt-60s (literature)	# Cobalt-60s (DIRAC)	# Brachy units needed	# Brachy units (literature)	# Brachy units (DIRAC)
<b>AFRICA</b>										
Ghana (8)	0	3	4	–	1	–	3	2	–	3
Liberia (8)	0	0	2	0	0	0	0	1	0	0
Nigeria (5, 6)	5	9	16	–	8	–	5	8	–	6
Sierra Leone (8)	0	0	–	0	0	0	0	–	0	0
South Africa (14)	>13	39	48	20	68	19	11	25	>5	25
Uganda	–	1	2	–	0	–	1	1	–	1
<b>AMERICAS</b>										
Argentina (24)	–	82	15	12	80	80	36	8	–	34
Bolivia	–	5	3	–	1	–	5	2	–	5
Brazil (24)	–	222	33	55	285	110	63	17	–	135
Chile (24)	–	27	21	6	41	14	12	11	–	19
Colombia	–	55	16	–	43	–	35	8	–	23
Costa Rica	–	3	3	–	6	–	3	2	–	2
Cuba	–	9	9	–	4	–	10	5	–	6
Dominican Republic	–	9	5	–	10	–	3	3	–	2
Ecuador	–	10	7	–	11	–	6	4	–	7
El Salvador	–	4	5	–	3	–	3	3	–	2
Guatemala	–	8	6	–	7	–	3	3	–	5
Haiti	–	0	1	–	0	–	0	1	–	0
Mexico (22)	83	91	14	–	74	–	61	8	–	60
Nicaragua	–	1	3	–	0	–	2	2	–	0
Panama	–	2	5	–	5	–	0	3	–	1
Paraguay	–	3	6	–	4	–	1	3	–	1
Peru (24)	–	18	–	1	26	11	9	–	–	4
Uruguay	–	10	7	–	14	–	8	4	–	6
Venezuela	–	60	4	–	51	–	31	2	–	23
<b>ASIA</b>										
Azerbaijan	–	2	2	–	4	–	2	1	–	1
Bangladesh	–	14	10	–	9	1	12	6	1	3
Cambodia (31)	1	1	–	0	0	1	1	–	–	1
China (28)	–	1050	87	62	1014	186	516	44	–	12
India (27, 34)	129	314	19	47	187	184	333	10	113	305
Indonesia (33)	22	23	17	18	21	17	19	9	–	11
Malaysia	–	25	13	–	37	–	6	7	–	5
Myanmar	–	4	–	–	1	–	7	–	–	5
Nepal (35)	–	5	9	–	3	–	3	5	1	2
Papau New Guinea	–	1	–	–	0	–	2	–	–	1
Philippines	–	34	5	–	29	–	10	3	–	13
Saudi Arabia	–	12	–	–	29	–	1	–	–	9
Sri Lanka	–	7	8	–	2	–	11	4	–	3
Thailand	–	29	54	–	48	–	28	32	–	24
Turkey (32)	90	95	30	146	144	40	59	15	35	33
Vietnam (43)	9	19	–	3	18	13	19	–	12	7
<b>EUROPE</b>										
Belarus	–	12	9	–	11	–	21	5	–	12
Bulgaria	–	13	8	–	5	–	10	4	–	15
Hungary	–	13	–	–	32	–	11	–	–	11

(Continued)

Table 2 | Continued

Countries	# RT centers (literature)	# RT centers (DIRAC)	# Linacs + Cobalts needed	# Linacs (literature)	# Linacs (DIRAC)	# Cobalt-60s (literature)	# Cobalt-60s (DIRAC)	# Brachy units needed	# Brachy units (literature)	# Brachy units (DIRAC)
Republic of Moldova	–	1	3	–	1	–	3	2	–	2
Romania	–	22	8	–	19	–	15	4	–	6
Ukraine	–	56	15	–	21	–	89	8	–	50

Only countries covered in the systematic review are included. Data inferred from the literature contained only non-DIRAC or IAEA sources. Data from DIRAC were reported according to the most updated web database. DIRAC, Directory of Radiotherapy Centres. Cobalts, cobalt-60 units. “–” symbol indicates no information available.

8, 10). Recently, there have been substantial increases in teletherapy machines in Latin American countries, such as Brazil and Venezuela, and several countries now have 1–4 MV per million population. Brachytherapy is also available in the majority of Latin American countries with other RT capacity (23, 24). The data also suggest rapid changes in available technology, which reflects the economic development and modernization in the region. From 1976 to 1999, there was a threefold increase in megavolt teletherapy machines in Southeast Asian countries (30). More recently, there has been an increase of approximately 25 machines per year in India alone (44). Although there has not been a full survey of the region's RT resources since 2001, available data suggest that these trends are continuing in many countries. In 2004, Vietnam initiated a “National Program on Cancer Prevention.” Included in this program was a target of one oncology department per province, each one equipped with RT machines (43). There is some evidence that capacity is slowly improving with increased volume of machines and improved radiation oncology training programs, especially in Indonesia and Cambodia (31, 33). Cambodia's University of Phnom Penh successfully partnered with international centers and universities to provide training for oncologists (31). There also have been efforts from National Cancer Institute Center of Global Health, IAEA, Union for International Cancer Control (UICC), and academic centers in the United States to help narrow the gap in RT access and training. Many of these collaborations are still developing and require persistent effort from institutions in the US and other developing countries to make these collaborations productive and successful (60–63). African organization on Research and Training in Cancer (AORTIC) has also been leading several efforts in improving cancer care capacity in Africa (64).

Comparing the numbers of RT centers and machines enumerated by the literature in the systematic review to DIRAC, we found the literature to be out of date. Of all non-DIRAC reports included in the review, only 14 unique articles provided updated numbers for a total of 11 countries. With the exception of Indonesia, Mexico, and Turkey, most were written prior to 2008 and were no longer accurate. Many of these countries may have their own national cancer registries and databases for RT resources, but they do not appear to be publishing on this data. This may suggest that established international databases, such as DIRAC, may be sufficient and comprehensive enough to serve as the primary sources for global radiation equipment inventory. National registries may then be used for other purposes

such as directing resources toward regions that need machine maintenance and replacement or informing decisions on where to develop new RT resources.

The primary strength of this study is the robustness of the search strategy. The thoroughness of the search terms and wide scope of sources searched ensured that very few reports were missed. However, despite the robustness of the search, the review is mainly limited by data availability. While it is likely that the lack of information is directly correlated to a lack of RT services, it is also possible that institutions lack incentives to report on RT services given DIRAC's international presence and historically regular reporting. Furthermore, it is important to note that treatment of cancer requires capacity in a variety of areas in addition to RT such as radiology, surgery, medical oncology, and pathology. Therefore, this review presents a small but significant aspect of the cancer care continuum. We acknowledge that delineating the challenges of radiation capacity does not capture the entire picture of access and delivery of cancer treatment.

## CONCLUSION

Though many LMIC struggle to meet the demand for radiation therapy delivery, few reports exist in the literature about these issues. This systematic review identifies major challenges to delivering RT in these regions, including lack of physical resources, lack of human personnel, and lack of data. DIRAC reports and online resources likely reflect real-time changes in RT capacity, but non-DIRAC-originated reports tend to be out of date, even in countries with national cancer registries. Institutions should publish more data on their capacity to deliver RT and the specific challenges they face; only then can interventions aimed at mitigating these issues be developed. Where possible, neighboring countries should collaborate and share resources to improve the scope of RT delivery, particularly when there is an economic disparity between neighboring countries. Furthermore, international funding agencies should make increasing RT capacity in LMIC a priority.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at <http://www.frontiersin.org/Journal/10.3389/fonc.2014.00380/abstract>

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# Planning national radiotherapy services

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Countries, states, and island nations often need forward planning of their radiotherapy services driven by different motives. Countries without radiotherapy services sponsor patients to receive radiotherapy abroad. They often engage professionals for a feasibility study in order to establish whether it would be more cost-beneficial to establish a radiotherapy facility. Countries where radiotherapy services have developed without any central planning, find themselves in situations where many of the available centers are private and thus inaccessible for a majority of patients with limited resources. Government may decide to plan ahead when a significant exodus of cancer patients travel to another country for treatment, thus exposing the failure of the country to provide this medical service for its citizens. In developed countries, the trigger has been the existence of highly visible waiting lists for radiotherapy revealing a shortage of radiotherapy equipment. This paper suggests that there should be a systematic and comprehensive process of long-term planning of radiotherapy services at the national level, taking into account the regulatory infrastructure for radiation protection, planning of centers, equipment, staff, education programs, quality assurance, and sustainability aspects. Realistic budgetary and cost considerations must also be part of the project proposal or business plan.

**Keywords: planning, national, radiotherapy, services, cancer, treatment**

## INTRODUCTION

The contribution of radiotherapy to cancer treatment is significant. Radiotherapy represents one of the three pillars of cancer treatment (with surgery and systemic therapies) and in multiple studies has proven to be a cost-effective modality for cure and palliation. The impact of radiotherapy in cancer cure has been estimated at 40%, compared to 49% of patients being cured by surgery, and 11% of patients by systemic treatments (1).

## OBJECTIVE AND CONTEXT

The objective of radiotherapy services is the delivery of an adequate radiotherapy treatment to all patients who need it, within a culture of safety awareness. The optimal yield of radiotherapy services occurs when they are integrated into effective healthcare systems and functional national cancer control plans. The reason is simple. In countries without a coordinated national cancer control plan, cancer patients are treated when they are diagnosed, often presenting in advanced stages of disease. This in turn determines that the majority of patients are treated for palliation.

In countries or states with an effective national cancer control plan that includes preventive, early detection, and screening programs, an increased number of patients are diagnosed at an early disease stage, treated effectively, and therefore the treatment outcomes of radiotherapy improve (Figure 1).

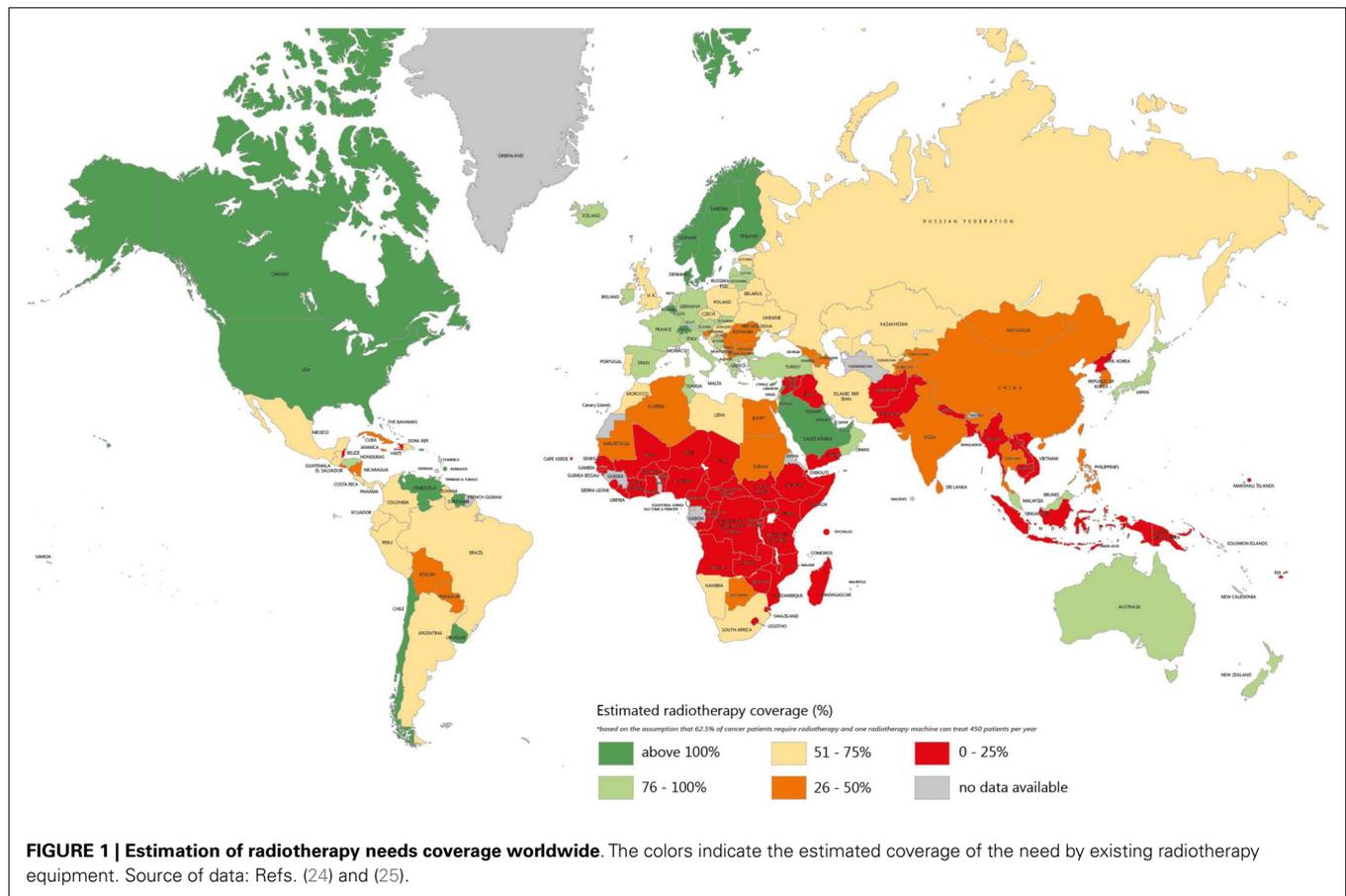
## SAFETY FIRST

Government plays a central role in the establishment of normative and regulation of the use of radiation in medicine, which needs to be satisfied before introducing radiotherapy into a country. Meeting the regulatory requirements will go toward satisfying the radiation protection and safety aspects of establishing

radiotherapy services. The range of regulatory requirements varies from country to country, but the IAEA has established, through the provision of safety standards (2), the essential components of a required regulatory infrastructure for radiation protection and safety. Regulations for the use of ionizing radiation in medicine are established in respect of the governmental, legal and regulatory framework for safety. The objective is to protect the public health and safety by preventing the availability of unsafe practices and equipment. Radiation exposure of human beings should only be considered when it is effective and potentially beneficial for diagnosis or treatment. Needless or excessive exposures are not justified and patients should be guaranteed that the treatment is reliable and that individuals administering radiotherapy are adequately trained.

Safety is the primary regulatory goal. Excessive or non-existing regulations can prohibit access to radiotherapy. A country's regulatory infrastructure needs to be in place in order to balance safety, effectiveness, the need for medical radiation practices, and access to therapy. Regulations must be in place to facilitate informed and rational decision-making and to protect against unwise, ill-informed, or negligent practices.

Dunscombe (3) made an analysis of seven sources of radiotherapy safety recommendations and distilled from them the 12 most frequently recommended initiatives. The 12 recommended initiatives were: (1) staff training, (2) adequate staffing levels, (3) adequate documentation/standard operating procedures, (4) voluntary incident learning system, (5) quality communication, (6) use of check lists, (7) quality control and preventive maintenance, (8) dosimetric audits, (9) radiation oncology specific accreditation, (10) minimizing interruptions, (11) prospective risk assessment, and (12) a safety culture.



## ESTIMATING DEMAND

How many teletherapy machines should be operational in a country in order to completely cover demand? This is a challenging question since there are large variations in radiotherapy utilization (RTU) among countries. In this discussion, we use the term teletherapy machine to refer to all including cobalt-60 units, medical accelerators, helical tomotherapy devices, and robotic radiotherapy. RTU benchmarks can be derived from evidence-based guidelines, criterion based, or based on a retrospective examination of actual practice.

Estimating demand means knowing how many *patients* will require a radiotherapy course in any given year or better yet how many *courses* of radiotherapy will be given since some patients may require more than one course. A more refined method consists in estimating the number of fractions that will be applied based on the cancer spectrum of diseases and stages. The number of new cancer cases per year in a given population (crude incidence) can be obtained from a national population based cancer registry in countries that have a reliable operational one. For countries where this variable is not measured, the International Agency for the Research on Cancer (IARC) provides a best estimate of crude incidence, which is reflected in their database Globocan-2012 (8).

Only a fraction of all cancer patients will require radiotherapy, which leads to the concept of RTU rate. Approximately, 48–62%

of all cancer patients' benefit from radiation therapy (9–11). This depends on the extent of disease at presentation and the profiles of cancer observed in a specific population. A RTU of 50% would then be a good approximation to this value for developed and middle-income countries. There is no evidence-based data for low-income countries. The total number of teletherapy machines required in a given country is given by the total number of "radiotherapy courses" in a year, divided by the teletherapy machine use. The teletherapy machine use is the number of radiotherapy courses delivered by one teletherapy machine in 1 year. The ESTRO/QUARTS Project (12) estimated a teletherapy machine use of 450 courses/year at that time. This benchmark is questioned today since the radiotherapy practice has changed significantly with the introduction of new technologies and fractionation schedules. However, an alternate benchmark that reflects current practice has not been determined so far. A more sophisticated approach to demand calculation can be attempted taking into account the full spectrum of diseases and their stages in a particular country, and the proportion of patients that will require IMRT techniques and its variations as opposed to 2D or 3D conformal techniques.

Data from Australia (13) indicates that a curative course of radiotherapy requires an average of 22 fractions and a palliative course four fractions, thus the total average would be 18 fractions per first course. The average linear accelerator treats four to five

patients per hour, so the total linac utilization will depend on the total number of hours per day that the machine is active. In Canada, the average time of machine operation per day is 10 h.

## RADIOTHERAPY CENTERS

A radiotherapy center is a medical department where patients are treated with usually megavoltage radiotherapy. The definition is not redundant. Centers that use orthovoltage only for skin lesions, radiosurgery only for intracranial disease, brachytherapy only or radiotherapy for veterinarian applications are not considered radiotherapy centers. International regulations on safety require that treatments with ionizing radiation be prescribed by a physician trained and licensed in this discipline and the dosimetry monitored by a trained medical physicist.

Radiotherapy centers location should follow the population concentration distribution in a country. A single center may suffice in small countries or even in large countries with a small population if transport services between population centers are adequate. The centralized comprehensive facility model may be adequate when the distances involved are short, but for longer distances, a fully decentralized service is warranted (14).

In large countries, a network of oncology services will be required, with a radiotherapy center within each region. For those patients, living at a distance from the radiotherapy center, funding will have to be set aside to cover for costs of transport and accommodation facilities, in particular for pediatric patients and their families. Countries where a significant proportion of the population are living at a distance or geographically isolated from the main centers, may also consider either the implementation of consultation clinics as focal points for further referral (primary care clinics can fulfill this role) or alternatively facilitate patient commuting through an organized transport service.

A study from Ontario (11) showed that the province's highly centralized radiotherapy network did not provide adequate or equitable access to care to the province's dispersed population. In this study, the actual RTU rate was 29%, which is lower than the generally accepted rate for a developed country. A similar study from the North of England showed socio-economic gradients in access to services (15) related to education levels and car use.

A radiotherapy center or department should be specifically planned and designed to fulfill its role, in terms of appropriate patient flow, location of the treatment machines, waiting rooms, physicians' offices, and patient examination rooms, planning rooms, mold room, storage, and others as required.

Once the decision to establish a radiotherapy facility has been made, careful co-ordination, and monitoring of the planning and timelines is key to the project's success. The professional team required to design, construct, and commission a radiotherapy facility needs to be multi-disciplinary because the project not only involves the construction of specialized bunkers to house the radiotherapy imaging and treatment equipment but also needs to take into account the clinical workflow as well as anticipate non-disruptive expansion in the future. Since the process of radiotherapy is closely related to key staff functions, the detail of the internal design of the facility is important to achieving sound work-place ergonomics and to facilitate workflow. An overall concept design should therefore consist of the five key

functional areas, which expedite radiotherapy workflow. These functional areas are the reception, clinical consulting areas, the imaging and treatment planning area, and the treatment suites (teletherapy and brachytherapy). The relative placement of these areas should be adapted to the proposed site and preferred local practice; however, it should expedite broader staff and patient movement, consultation, and communication. The position of the major equipment at the various duty stations within each functional area is provided for in "International Atomic Energy Agency (IAEA) Radiotherapy facilities; master planning and concept design considerations (16)". Expansion route possibilities are also indicated.

Clinically qualified medical physicists are responsible for ensuring that the shielding calculations are based on acceptable estimates of the projected local workload, use, and occupancy factors, and that the design accommodates the desired clinical workflow. In addition, the future implementation of new techniques and technologies should also be considered. The national radiation safety regulator is mandated to approve the final design prior to construction, and license the facility prior to the initiation of operations. Timeline synchronization between building a radiotherapy facility, procurement, and installation of equipment and training of staff is very important and has to be planned carefully. If the equipment is installed but the team has not completed their training, the result will be a non-operational facility, which is generating costs but not treating patients. Conversely, if staff completes their training long before the facility is ready, members may be compelled to take other job positions, change career, or emigrate in search of their livelihood. Our experience indicates that training of a radiotherapy team should start roughly 2 years before the initiation of construction. Funds for staff training must be allocated early and be part of the initial business plan or project proposal.

## EQUIPMENT

A basic radiotherapy center aiming at treating an average of 1000 patients/year should be equipped with at least a single-photon energy teletherapy unit, an orthovoltage unit, a brachytherapy afterloader (ideally for high dose-rate brachytherapy), an X-ray C-arm, full range of applicators, a simulator, preferably a CT-simulator, a computerized treatment planning system (TPS), film processing equipment, patient immobilization devices, and mold room equipment, beam measurement and quality assurance (QA) equipment. A second teletherapy unit may become necessary to expedite workflow and for back-up.

Procurement of new equipment has to be implemented through a transparent tendering process. Since technological developments in radiotherapy occur much faster than the economic lifetime of a linear accelerator, larger radiotherapy centers, which replace one or more machines every few years, enable the introduction of new technology at a faster rate.

The cost and cost-benefit of radiotherapy has been extensively studied. The cost of radiotherapy in a given facility tends to rise as the number of treated patients decreases below 1600, and extended hours of operation do not appear to generate significant, if any, savings when realistic assumptions about machine lifetime and overtime payments are made (17).

## STAFFING AND EDUCATION

A very important consideration is staffing levels. There is very little evidence-based documentation that precisely quantifies the number and type of professionals needed to support a service that is also directly related to patient workload, technology, techniques, procedures, and infrastructure. As a result, initiation of new radiotherapy services in low and middle-income countries has traditionally been planned in accordance with IAEA guidelines, which list a suite of equipment constituting a basic service that is resourced by a core number of professionals who attend to a given patient workload (18, 19). These professionals, including radiation oncologists and medical physicists, are required in the practice of radiotherapy under the IAEA International Basic Safety Standards (2).

The aforementioned basic department should have four to five radiation oncologists, three to four medical physicists, seven RTTs, three radiotherapy nurses, and one maintenance technician/engineer. Staff numbers and training should be adapted to the number of patients treated, the case-mix, the number of courses given per year, the activities performed and the level of complexity of the equipment and techniques. Staffing requirements vary greatly depending on case-mix, type, and complexity of the techniques, research, and teaching commitments. Given the complexities of today's modern radiotherapy clinics, rather than give fixed recommendations for staff numbers, the current approach is to use an algorithm that will provide the number of staffs needed for a department according to the activities implemented.

Staffing levels in the clinical environment are not only important for planning and budgetary purposes and fundamental to quality patient care and safety but they are often also specified for practice accreditation purposes and professional credentialing. The estimation of reasonable staffing levels to support radiotherapy services has often been loosely based on patient population size, infrastructure, equipment availability, and disease incidence. Retrospective subjective estimates based on existing practice are often the benchmark for predicting future staffing needs locally. Detailed measurements of how long each procedure or activity takes to perform is probably the most objective basic evidence required to estimate full-time equivalent staffing levels (20). Such measurements are logically more useful and valid if they are performed in a variety of clinics, for a range of services and applied to professionals with a wide range of experience.

## ACCESS

The concept of access (or accessibility) to radiotherapy services refers to the fact that these medical services can be utilized by all patients who need them. Access includes availability, accessibility, affordability, accommodation, and awareness of health professionals and the public. The existence of radiotherapy departments or services in a country (availability) is a necessary but not sufficient condition for access. For example, a clinic may be geographically inaccessible to patients residing in another region of the country. Or a majority of available clinics in a given country may be private clinics demanding payment for service, which makes them inaccessible to a significant sector of the population below the poverty level. It is the government's responsibility through its ministry

of health to ensure access to radiotherapy services to all cancer patients who need them.

## QUALITY AND SUSTAINABILITY

Quality in radiotherapy means providing a service that satisfies patient's expectations follows optimal professional practice by obtaining optimal results and fulfils the regulatory requirements at a minimal cost and without waste of resources. Thus, quality in radiotherapy has different meanings from the perspective of the patient, the professional, or the administrator.

The concept of total quality management (TQM) consists of organization-wide efforts to install and make permanent a climate in which an organization continuously improves its ability to deliver high-quality products or services to customers, has been borrowed from the industry, particularly from the standardized approach to quality called ISO (21). It is a set of control points that ensures that each element of a process or a series of processes conforms to a pre-established standard. The idea behind it is that if a process conforms to its standards, then the result will actually meet the expectations. In radiotherapy, the expectations are the control of a cancer with minimal and predictable negative impact on quality-of-life.

Quality can be assessed by three different approaches (22): by the infrastructure, processes, or outcomes.

Infrastructure: the rationale is that quality can only be produced within an appropriate infrastructure (buildings, staffing, competences and equipment). Process: a second approach is process control. It is based on the observation that if a process conforms to a standard, then the quality of its results is predictable. Outcomes: the ultimate goal of radiotherapy, as mentioned earlier, is disease control. Five-year survival, years of survival adjusted for quality-of-life ("quality-adjusted life years"; QALY), local control, and other clinical endpoints are all legitimate measurements of the appropriateness of radiotherapy interventions.

To assess quality in countries with established services, it is recommended to conduct an annual survey of production, equipment, and personnel of radiotherapy centers. This should include questions on the number and type of external beam and brachytherapy treatment equipment, absolute number, and number of full-time equivalent radiation oncologists, medical physicists, and radiation technologists and support personnel number of persons in training and vacancies. It is also advisable to select a set of validated quality indicators and apply this set year after year to document the dynamics of the radiotherapy system as a whole.

Budgetary provisions must be set aside for the maintenance of equipment, maintenance service and repairs, replacement of parts and sources, overheads and consumables and training and education of staff.

Radiotherapy services should be patient-centered. This means that the facilities should offer convenience for the patients and families, and patient's priorities and needs are respected. Main aspects of the service that are important to patients include: receiving the highest level of medical care, a reduction of the waiting time between diagnosis and treatment, appropriate communication with medical and other healthcare staff, obtaining information about their condition and its treatment and convenience of access.

Avoiding excessive waiting time (more than 14 days) and waiting lists is particularly important. Excessive waiting time for radiotherapy increases the risk of local tumor recurrence and eventual treatment failure (23). Waiting lists for radiotherapy are a highly visible indicator of the inability of the healthcare system to provide the service needed. Patients and families are understandably very sensitive to this problem. They may approach the media. In several countries, the direct intervention of government even through specific normative has resulted in the reduction or elimination of waiting lists.

## CONCLUSION

Obstacles to the effectiveness and efficiency of radiotherapy services at country level include: (1) the lack of a network type organizational structure that would link radiotherapy centers in such a way that it ensures access to a wide range of radiotherapy techniques available, (2) a limited quality management culture with services oriented to the professionals more than to the patients, (3) work organization oriented to the day-to-day practice rather than a medium or long-term strategic planning, and (4) lack of a system of self-evaluation based on carefully recorded clinical outcomes.

Observation and analysis of radiotherapy services planning around the world show that the optimal provision and outcomes are reached when (1) radiotherapy services are centrally planned and monitored through the continued use of validated indicators over time, (2) radiotherapy services are integrated into national cancer control plans, (3) local problems of access to radiotherapy services are systematically identified and addressed, (4) radiotherapy services are given the necessary attention through a combination of political will tapping into resources from government, international organizations and NGOs.

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# Human resources for cancer control in Uttar Pradesh, India: a case study for low and middle income countries

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For addressing the growing burden of cancer in low and middle income countries, an important first step is to estimate the human resources required for cancer control in a country, province, or city. However, few guidelines are available to decision makers in that regard. Here, we propose a methodology for estimating the human and other resources needed in the state of Uttar Pradesh (UP), India as a case study. Information about the population of UP and its cities was obtained from <http://citypopulation.de/>. The number of new cancer cases annually for the commonest cancers was estimated from GLOBOCAN 2008<sup>1</sup>. For estimating the human resources needed, the following assumptions were made: newly diagnosed cancer patients need pathology for diagnosis and for treatment surgery, chemotherapy, and/or radiotherapy. The percentage of patients requiring each of those modalities, their average lengths of stay as in-patients, and number of in-patient oncology beds were estimated. The resources already available in UP were determined by a telephone survey and by searching the websites of radiation therapy centers and medical colleges. Twenty-four radiation oncologists at 24 cancer centers in 10 cities responded to the survey. As detailed in this manuscript, an enormous shortage of human resources for cancer control exists in UP. Human resources are the key to diagnosing cancers early and treating them appropriately. Addressing the shortage will not be easy but we hope that the methodology described here can guide decision makers and form a framework for discussion among the various stakeholders. This methodology is readily adaptable to local practices and data.

**Keywords:** human resources, cancer control, low and middle income countries, Uttar Pradesh, India, cancer control planning

## INTRODUCTION

Low and middle income countries (LMIC) face an increasing burden of cancer (1, 2). To effectively address this problem, cancer control planning at the country, state, city, and community level is needed. However, the scarcity of cancer registries and lack of guidelines for cancer control planning/capacity building make this a difficult undertaking for stakeholders.

Several recent publications including the WHO report (2014) and the Global Burden of Disease reports (Lancet 2012) have discussed in detail the magnitude and the reasons for the growing burden of cancer in LMIC in general and India in particular<sup>2</sup>. The number of new cancer cases in India was 0.95 million in 2008 and projected to increase to 1.7 million in 2035. The incidence of cancer in India is lower than in Western nations, but the mortality is higher suggesting low health service effectiveness. Probably for the same reason, while the incidence of cancer among persons living in rural areas is half that of urban dwellers, their age-adjusted standardized mortality rates from cancer are similar. Contributory factors to the growing burden

of cancer include longer life spans, growing urbanization and industrialization, use of tobacco, sedentary lifestyles, etc. Strategies for preventing cancers are, therefore, a high priority for India. At the same time, for decreasing the deaths and suffering from cancers, the health systems for cancer control must be strengthened to facilitate the early diagnosis and effective treatment of those cancers that cannot be prevented for the foreseeable future. Human resources are obviously a key component of such a strategy.

Here, we propose a method for estimating the human and other resources necessary for treating the most common cancers in LMIC and compare them to those available, using the state of Uttar Pradesh (UP) in India as a case study. UP with a population of approximately 200 million is the most populous state in India and probably the most populous country subdivision on the planet. It is diverse in terms of urbanization, distribution of wealth, resources, and access to education and healthcare and has a large, well-developed transportation network. Importantly, oncologists and advocates in UP are interested in bringing this growing life-threatening cancer crisis to the attention of politicians and policy makers who can mobilize the funding for building the infrastructure – both human and physical – needed for cancer prevention and control in UP.

<sup>1</sup><http://globocan.iarc.fr> accessed on October 15, 2013

<sup>2</sup><http://www.thelancet.com/series/cancer-burden-and-health-systems-in-india>

**Table 1 | The most common cancers in Uttar Pradesh for men and women based upon GLOBOCAN 2008 data.**

	Both sexes	Rank	Men	Rank	Women	Rank
All cancers excluding non-melanoma skin cancer	160296		72659		87637	
Gynecological	28934	1			28934	1
Head and neck	26080	2	18359	1	7721	3
Breast	19470	3			19470	2
Hematological malignancies	12026	4	7301	3	4725	4
Lung	9894	5	7942	2	1952	8
Esophagus	8126	6	4867	5	3259	5
Urological	7130	7	6040	4	1090	11
Colorectal	6162	8	3406	7	2756	6
Stomach	5923	9	3561	6	2362	7
Brain, nervous system	3689	10	2211	9	1478	10
Liver	3403	11	2452	8	951	12
Gallbladder	2916	12	1001	10	1915	9
Pancreas	1513	13	858	11	655	13
Melanoma of skin	160	14	85	12	75	14

## MATERIALS AND METHODS

The population of India, UP, and its various cities was obtained from <http://citypopulation.de/>. The number of new cancer cases annually and the major types of cancers in India was obtained from GLOBOCAN 2008<sup>1</sup>. GLOBOCAN does not report data for states or cities. In the absence of UP cancer registry data, we assumed that the proportion of the various kinds of cancers in UP was the same as all of India. Thus, based on the population of UP and the number of new cancer cases in India, the number of new cancer cases for UP was estimated (Table 1). Estimates can be revised if and when more accurate data become available.

### ESTIMATING THE HUMAN AND OTHER RESOURCES NEEDED FOR TREATING NEW CANCER CASES IN UP

For estimating the human and other resources needed for treating the various kinds of cancers, several specialty societies and organizations were consulted. Except for the International Atomic Energy Agency (IAEA) of the United Nations<sup>3</sup>, most could offer no official guidelines. Therefore, numerous colleagues who are active in those fields were consulted informally and are listed in the Section "Acknowledgments." Based upon their feedback and opinions, the following assumptions were made and used for our calculations, which can be readily revised if and when more accurate data become available (or to confirm better to local practices):

<sup>3</sup>[http://www-pub.iaea.org/MTCD/publications/PDF/pub1296\\_web.pdf](http://www-pub.iaea.org/MTCD/publications/PDF/pub1296_web.pdf)

**Table 2 | The percentage of requiring patients various kinds of treatment and their average length of stay (ALOS) in hospital (in days).**

	Percent of patients requiring surgery (ALOS)	Percent of patients requiring chemotherapy (ALOS)	Percent of patients requiring radiotherapy (ALOS)
Gynecological cancers	57 (6.5)	67 (3)	40 (5)
Cervix uteri	20 (5)	80 (3)	80 (5)
Corpus uteri	80 (5)	20 (3)	20 (5)
Ovary	70 (9)	100 (3)	20 (5)
Head and neck cancers	44 (7)	66 (3.5)	71 (5)
Larynx	50 (9)	50 (3)	75 (5)
Lip and oral cavity	40 (9)	80 (3)	80 (5)
Nasopharynx	0 (0)	100 (3)	100 (5)
Other pharynx	40 (9)	80 (3)	80 (5)
Thyroid	90 (7)	20 (5)	20 (5)
Hematological malignancies	0 (0)	100 (6.5)	33 (5)
Hodgkin's lymphoma	0 (0)	100 (5)	40 (5)
Leukemia	0 (0)	100 (7)	20 (5)
Multiple myeloma	0 (0)	100 (7)	20 (5)
Non-Hodgkin's lymphoma	0 (0)	100 (7)	50 (5)
Urological cancers	74 (8)	63 (3.5)	41 (5)
Bladder	100 (9)	50 (3)	50 (5)
Kidney	75 (9)	50 (3)	20 (5)
Prostate	20 (9)	50 (3)	65 (5)
Testis	100 (5)	100 (5)	30 (5)
Brain and nervous system cancers	100 (9)	100 (3)	100 (5)
Breast cancers	100 (5)	100 (3)	100 (5)
Colorectal cancers	70 (9)	90 (3)	25 (5)
Gallbladder cancers	33 (9)	66 (3)	50 (5)
Kaposi's sarcoma	0 (0)	70 (3)	50 (5)
Liver cancers	5 (10)	20 (3)	20 (5)
Lung cancers	25 (10)	50 (3)	90 (5)
Melanoma of the skin	100 (3)	50 (3)	50 (5)
Esophagus cancers	20 (9)	90 (3)	90 (5)
Pancreas cancers	10 (10)	50 (5)	50 (5)
Stomach cancers	33 (5)	66 (3)	50 (5)

*It was assumed that for surgery or chemotherapy, all patients required hospitalization initially whereas for radiotherapy only one-quarter required hospitalization.*

- Newly diagnosed cancer patients need pathology review of their tissue for diagnosis. They also require surgery, chemotherapy, and/or radiation therapy for treatment. The percentage of patients requiring each of those therapeutic modalities and the average length of stay as in-patients were estimated for the most common cancers in UP and are shown in Table 2.

- The number of specialists needed was estimated based upon the number of patients requiring surgery, chemotherapy, and/or radiation therapy, as well as pathology annually. For LMIC, rather than implementing separate medical and radiation oncology training tracks, the IAEA recommends training radiation/clinical oncologists who can prescribe both radiation and chemotherapy for common solid cancers. The number of radiation/clinical oncologists needed is estimated at 5 per 1000 cancer patients. The number of pathologists needed is estimated at 2 per 1000 cancer patients, recognizing that most of them do not concentrate solely on cancer. The number of surgical oncologists needed is based on the number of cancer patients requiring surgery, assuming that each surgical oncologist performs two surgeries per day, 5 days per week for 48 weeks per year. The number of gynecological oncologists, urological oncologists, neurological oncologists, and hematologist-oncologists needed is 2 per 1000 patients with gynecological, urological, neurological, and hematological malignancies, respectively. Two palliative care specialists will be needed for each 1000 new cancer patients.
- Many cancer patients require hospitalization for diagnosis and/or treatment of cancer and its complications. The number of oncology beds needed per day is the sum of the number of beds needed for surgery, chemotherapy, and radiation therapy for newly diagnosed cancer patients with the most common cancers. An oncology ward is a 24-bed in-patient unit for only oncology patients that should be staffed by 15 oncology nurses, 4 oncopharmacists, and 6 pharmacy technicians.
- Many cancer patients require radiotherapy; therefore, appropriately equipped facilities are needed along with well-trained radiation oncology staff. The radiation oncology staff needed includes radiation/clinical oncologists (as discussed earlier) and for every 1000 patients requiring radiation therapy, 12 radiation therapy technicians, 4 medical physicists, 1 linear accelerator (linac) engineer, and 4 radiation therapy nurses. The minimum radiation therapy equipment requirements for every 1000 patients requiring radiation therapy are at least 1 for each of the following: megavoltage teletherapy unit (linac or cobalt), brachytherapy unit, CT Simulator, treatment planning computer system, and dosimetry/Quality Assurance package. If there is only 1 MV teletherapy unit per 1000 radiation therapy patients, it should be operated nearly non-stop, albeit with regularly scheduled downtime for preventive maintenance and quality assurance, otherwise a minimum of two such units are needed.
- Each city, in order to ensure coverage if one person leaves or goes on vacation should have at least two professionals of each kind.

#### ESTIMATING THE HUMAN AND OTHER RESOURCES ALREADY AVAILABLE IN UP

The radiation therapy resources available (radiation/clinical oncologists, radiation therapy staff, and radiation therapy equipment) were determined by telephone survey and searching websites of radiation therapy centers and medical colleges in the state of UP. A list of cancer centers with radiation therapy facilities in UP was obtained from the database of oncology centers in the Department of Radiotherapy, Sanjay Gandhi Postgraduate Institute of

Medical Sciences, Lucknow. Twenty-four radiation oncologists at 13 government and 11 private cancer centers in 10 cities were contacted for a telephone survey and all 24 responded to the survey. The telephone survey was conducted by one of the authors (SA) who was also 1 of the 24 respondents.

The number of specialists in allied departments (urology, neurosurgery, gynecology, etc.) was also estimated by telephone survey and from websites of the government and private cancer centers. The number of beds available for cancer patients was similarly estimated from those websites. No attempt was made to document the number of oncopharmacists and pharmacy technicians as those specializations did not exist in UP.

#### RESULTS

In the year 2008, there were 948,858 new cases of cancer in India and as shown in **Table 1**, there were 160,296 new cases in UP. Extrapolating those numbers to the 10 cities in UP with radiotherapy centers (population range 0.5–2.8 million) yielded the estimated number of new cancer patients in each city and the numbers requiring surgery, chemotherapy, and/or radiotherapy, as well as the required number of oncology beds in each city. It is evident that a vast proportion of the population of UP lives outside those 10 cities, therefore, the numbers needed for UP as a whole far exceed the numbers needed for the 10 cities.

**Table 3** compares the number of specialists needed in UP with those available. A comparison of the number of specialists needed and available reveals that for UP state, there is a shortage of 715 clinical/radiation oncologists, 142 pathologists, 115 surgical oncologists, 34 gynecological oncologists, and 18 hematologist-oncologists. “Gastro-surgeons” are a recognized specialty in UP; the bulk of their practice consists of gastrointestinal cancer surgery; therefore, the available 21 gastro-surgeons were added to the surgical oncologists for a total of 42 available surgical oncologists.

**Table 4** shows the number of oncology beds and professionals (nurses, oncopharmacists, and pharmacy technicians) needed and available. Comparing the numbers needed to those available reveals that, in UP state, there is a shortage of 2018 oncology beds, 1582 oncology nurses, 313 palliative care specialists, 484 oncopharmacists, and 726 pharmacy technicians.

**Tables 5** and **6** show the radiation oncology staff and equipment that is needed and available.

Comparing the number of radiation oncology staff needed to that available (**Table 5**) reveals that in UP state, there is a shortage of 715 clinical/radiation oncologists, 1055 radiotherapy technicians, 380 radiotherapy nurses, 342 medical physicists, and 95 linac engineers. Comparing the radiation oncology equipment needed to that available (**Table 6**) reveals that in UP, there is a shortage of 164 MV teletherapy units, 78 brachytherapy units, 84 CT simulators, 76 treatment planning computer systems, and 95 dosimetry/quality assurance packages.

#### DISCUSSION

We found that an enormous shortage of human and other resources for cancer control exists in the state of UP (**Tables 3–6**). In fact, the shortage may be even worse than the tables indicate, because we estimated the resources needed from year 2008 data

Table 3 | Number of oncologists needed versus those available for UP and its 10 cities with radiation therapy centers based upon GLOBOCAN 2008 data.

	Hematologist-oncologists		Number requiring surgery	Surgical oncologists		Radiation/clinical oncologists		Urologic oncologists		Gynecologic oncologists		Neurologic oncologists		Pathologists	
	Needed	Available		Needed	Available	Needed	Available	Needed	Available	Needed	Available	Needed	Available	Needed	Available
UP	25	7	74860	21	802	87	20	20	20	58	24	20	26	321	179
Agra	2 <sup>a</sup>	0	591	0	7	4	2 <sup>a</sup>	0	0	2 <sup>a</sup>	2	2 <sup>a</sup>	2	3	11
Aligarh	2 <sup>a</sup>	0	327	0	4	3	2 <sup>a</sup>	0	0	2 <sup>a</sup>	2	2 <sup>a</sup>	0	2	16
Allahabad	2 <sup>a</sup>	1	419	1	5	9	2 <sup>a</sup>	1	1	2 <sup>a</sup>	2	2 <sup>a</sup>	2	2	25
Bareilly	2 <sup>a</sup>	0	337	1	4	6	2 <sup>a</sup>	0	0	2 <sup>a</sup>	2	2 <sup>a</sup>	1	2	15
Benares	2 <sup>a</sup>	1	451	5	5	9	2 <sup>a</sup>	4	4	2 <sup>a</sup>	2	2 <sup>a</sup>	4	2	15
Gorakhpur	2 <sup>a</sup>	0	252	1	3	5	2 <sup>a</sup>	0	0	2 <sup>a</sup>	3	2 <sup>a</sup>	2	2	16
Jhansi	2 <sup>a</sup>	0	191	0	3	2	2 <sup>a</sup>	0	0	2 <sup>a</sup>	2	2 <sup>a</sup>	0	2 <sup>a</sup>	16
Kanpur	2 <sup>a</sup>	0	1038	1	12	10	2 <sup>a</sup>	1	1	2 <sup>a</sup>	2	2 <sup>a</sup>	3	5	15
Lucknow	2	3	1056	6	12	28	2 <sup>a</sup>	10	10	2 <sup>a</sup>	4	2 <sup>a</sup>	10	5	37
Noida	2 <sup>a</sup>	2	241	6	3	11	2 <sup>a</sup>	4	4	2 <sup>a</sup>	3	2 <sup>a</sup>	2	2	13

<sup>a</sup>At least two are required in each city.

whereas, according to GLOBOCAN, the number of new cancer cases in India is projected to increase from 948,858 in the year 2008 to 1,220,000 by 2016, an increase of almost 30%. Assuming that the same is true for UP, the resources needed in the year 2013 would be about 20% greater, and in the year 2016 about 30% greater, than shown in Tables 3–6 (our telephone survey for estimating the resources already available was conducted in 2013).

As a part of our survey, we learned that at present only 18 physicians enter radiation/clinical oncologist training programs in UP annually. More than 800 (probably an underestimate) are needed as shown in Table 3. Unless steps are taken to dramatically increase the training opportunities and incentives, it may take nearly a century to address the shortage.

A previous effort to address the shortages included a modest proposal in India's 11th plan (2007–2012) of the National Cancer Control Program (accessed Dec 26, 2013)<sup>4</sup> that there should be at least one radiation oncology center for every four districts. With its 75 districts, UP would accordingly require 19 centers by the year 2012, but only one was added between 2007 and 2012.

Our findings illustrate that the delivery of affordable and equitable cancer care remains one of India's greatest public health challenges. Specific figures for UP are not available but public expenditure on cancer in India remains below US\$10 per person (compared with more than US\$100 per person in high-income countries), and overall public expenditure on health care is still only slightly above 1% of gross domestic product (3). The crucial issues of infrastructure, public insurance schemes, the need to develop new political mandates and authority to set priorities, the necessity to greatly improve the quality and delivery of cost-effective cancer care are inextricably linked with the shortage of human resources necessary for the prevention and control of cancer.

Addressing this shortage will not be easy, but we hope that the data provided in this paper can form a framework for discussion among the various stakeholders. It is noteworthy that the total population of the 10 major cities with radiotherapy-containing cancer centers accounted for less than one-tenth of the population of UP. Establishing additional cancer centers will therefore be necessary in those parts of UP that are not close to any of the 10 cities. At the same time, it will be necessary to strengthen the existing cancer centers because at least some of them already appear to service quite a large number of patients from outside the cities that the cancer centers are located in. In the UP state capital Lucknow, there were just over an estimated 2000 new cancer cases in 2008, projected to increase to about 3000 by the year 2013. However, our 2013 telephone survey revealed that during the preceding 12 months, more than 8000 new cancer patients were seen at the various hospitals in Lucknow. We did not have the resources to try and determine how many of those patients originated from outside Lucknow. This discrepancy, in fact, highlights the glaring lack of the urgent need for establishing cancer registries in UP for capturing more accurate and granular data on the incidence and outcomes of cancers.

<sup>4</sup><http://mohfw.nic.in/index1.php?lang=1&level=2&sublinkid=323&lid=323>

**Table 4 | Number of oncology beds, nurses, pharmacy staff, and palliative care specialists needed versus those available for UP and its 10 cities with radiation therapy centers based upon GLOBOCAN 2008 data.**

	Number of oncology beds		Number requiring chemotherapy		Oncopharmacists		Pharmacy technicians		Palliative care specialists		Oncology nurses	
	Needed	Available	Needed	Available <sup>b</sup>	Needed	Available <sup>b</sup>	Needed	Available <sup>b</sup>	Needed	Available	Needed	Available
UP	2892	875	117172	484	0	726	0	321	8	1815	233	
Agra	22	50	925	4	0	6	0	3	0	15	10	
Aligarh	13	35	512	4	0	6	0	2	0	15	7	
Allahabad	16	90	656	4	0	6	0	2	0	15	13	
Bareilly	13	50	528	4	0	6	0	2	0	15	10	
Benares	18	100	706	4	0	6	0	2	2	15	20	
Gorakhpur	10	85	394	4	0	6	0	2	0	15	15	
Jhansi	8	40	298	4	0	6	0	2 <sup>a</sup>	0	15	8	
Kanpur	40	150	1625	8	0	12	0	5	0	30	50	
Lucknow	41	175	1653	8	0	12	0	5	5	30	75	
Noida	9	100	377	4	0	6	0	2	1	15	25	

<sup>a</sup>At least two are required in each.

<sup>b</sup>There is no oncology specialization for pharmacy technicians and pharmacists.

**Table 5 | Radiation therapy (RT) staff needed versus available for UP and its 10 cities with radiation therapy centers based upon GLOBOCAN 2008 data.**

	Number requiring radiotherapy	Radiation/clinical oncologists		RT technicians		Medical physicists		Linac engineers		RT nurses	
		Needed	Available	Needed	Available	Needed	Available	Needed	Available <sup>b</sup>	Needed	Available <sup>b</sup>
UP	94808	802	87	1138	83	380	38	95	0	380	0
Agra	748	7	4	9	5	3	2	2 <sup>a</sup>	0	3	0
Aligarh	415	4	3	5	2	2	1	2 <sup>a</sup>	0	2	0
Allahabad	531	5	9	7	11	3	5	2 <sup>a</sup>	0	3	0
Bareilly	427	4	6	6	5	2	3	2 <sup>a</sup>	0	2	0
Benares	571	5	9	7	12	3	4	2 <sup>a</sup>	0	3	0
Gorakhpur	319	3	5	4	6	2	2	2 <sup>a</sup>	0	2	0
Jhansi	241	3	2	3	2	2 <sup>a</sup>	1	2 <sup>a</sup>	0	2 <sup>a</sup>	0
Kanpur	1315	12	10	16	8	6	3	2	0	6	0
Lucknow	1338	12	28	17	20	6	11	2	0	6	0
Noida	305	3	11	4	12	2	6	2 <sup>a</sup>	0	2	0

<sup>a</sup>At least two are required in each.

<sup>b</sup>There is no specialization for RT nurses or Linac engineers in UP.

### CANCER PREVENTION AND EARLY DETECTION

Cancer prevention is, of course, preferable to cancer control. Among the cancers most common in UP, many future cancers of the uterine cervix may be preventable by vaccines (4) while many cancers of the mouth, throat, and lung may be prevented by effective tobacco control (accessed December 16, 2013)<sup>5</sup>.

For some cancers, such as the uterine cervix, early detection and treatment are also feasible. Visual inspection with acetic acid

followed by the immediate treatment of suspicious lesions has been proposed as a possibly effective strategy suitable for widespread implementation in LMIC (5). Analogous to the methodology described in this paper, we also estimated the human resources needed in different countries for implementing such a population-wide intervention. We focused on those countries where cervical cancer was among the top five cancers among women and the results are available at [http://rrp.cancer.gov/programsResources/hrn\\_cervical\\_cancer\\_screening.htm](http://rrp.cancer.gov/programsResources/hrn_cervical_cancer_screening.htm). In the case of UP, once again extrapolating from India as a whole, we found that approximately 2000 health workers would be needed to screen on three

<sup>5</sup><http://www.who.int/cancer/nccp/en/>

**Table 6 | Radiation therapy equipment needed versus available for UP and its 10 cities with radiation therapy centers based upon GLOBOCAN 2008 data.**

	Megavoltage teletherapy units		Brachytherapy units		CT simulators		Treatment planning computer systems		Dosimetry/QA packages	
	Needed	Available	Needed	Available	Needed	Available	Needed	Available	Needed	Available
UP	190	26	95	17	95	11	95	19	95	0
Agra	2	1	1	1	1	0	1	1	1	0
Aligarh	1	1	1	1	1	0	1	1	1	0
Allahabad	2	3	1	2	1	2	1	2	1	0
Bareilly	1	2	1	1	1	1	1	1	1	0
Benares	2	4	1	2	1	1	1	2	1	0
Gorakhpur	1	2	1	1	1	0	1	1	1	0
Jhansi	1	1	1	0	1	0	1	0	1	0
Kanpur	3	3	2	2	2	2	2	2	2	0
Lucknow	3	6	2	5	2	3	2	6	2	0
Noida	1	3	1	2	1	2	1	3	1	0

occasions for pre-invasive cervical cancer, and treat, when indicated, all women between the ages of 30 and 45 years. That number would include 400 supervisors (usually physicians) and 1600 other health workers (specially trained non-physicians such as nurses and midwives).

## GLOBAL IMPLICATIONS

Interventions for detecting cancers early and treating them appropriately are crucial components of cancer control planning. Human resources are the key but, unfortunately, are often neglected in LMIC. In planning new radiotherapy facilities, the major focus may be on the buildings and equipment while only a token number of staff are trained and/or hired. This results in chronically understaffed and poorly maintained facilities, leading to poor patient outcomes and low staff morale. The cost of treating each patient escalates because after making the substantial investment in buildings and equipments, fewer patients are treated than could have been in an adequately staffed facility.

One of the reasons that human resources are neglected may simply be the lack of guidance available to decision makers. We hope that the methodology described in this paper can provide a framework for discussion among the stakeholders interested in cancer control in a country, state, city, or community. As we have tried to emphasize, the methodology is readily adaptable to local practices and data.

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# Training global oncologists: addressing the global cancer control problem

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## INTRODUCTION

The global incidence of cancer has increased by approximately 20% in the past decade, an increase mostly due to cases in low- and middle-income countries (LMICs) (1). By 2020, up to 70% of the 20 million annual new cancer cases are expected to occur in LMICs (2). The incidence of cancer in LMICs is increasing rapidly; however, many countries are not prepared to address this epidemic. Cancer survival rates in LMICs are often less than one-third of those in high-income countries (3). In addition to local capacity-building efforts, the involvement of the oncology community from high-income countries will be instrumental in changing the course of this impending global cancer crisis.

There is a vital need to train global oncologists to work with colleagues in LMICs to develop sustainable capacity and infrastructure for clinical oncology care, research, and education. However, enumeration of specific goals and novel programs, and the path to implementing these programs, is not clear. Oncology programs in North America lack formal training or exposure to global oncology. Even without a formal curriculum, with the rise in global health (GH) oncology interest, several opportunities have

developed for trainees committed to GH. We describe herein current opportunities and future directions for oncology trainees in the United States (US) who are interested in pursuing careers as global oncologists.

## CURRENT OPPORTUNITIES

### MEDICAL AND PEDIATRIC ONCOLOGY

Many US training programs have responded to the growing interest in GH by offering international training opportunities. A survey of 380 US internal medicine residency programs showed that 57% of responding programs offered opportunities for international rotations (4). When selecting a residency program, 22% of pediatric residents indicated that GH training opportunities were essential/very important and 21% had a GH experience during pediatric residency (5). There has also been an increase in GH fellowships. A recent survey identified 80 GH fellowship programs, 14% of which were in internal medicine (6). For medical and pediatric oncology fellowships, there is scant information regarding trainee interest and the availability of international rotations. Few institutions have GH partnerships that offer opportunities for training, research, and career development in medical and pediatric oncology. The

available opportunities are highlighted below.

1. The American Society of Clinical Oncology (ASCO) supports the Health Volunteers Overseas (HVO) program that recruits oncologists, faculty, and senior internal medicine residents to strengthen cancer care in LMICs. The program creates a forum for oncologists to share their medical expertise and build sustainable relationships with physicians addressing cancer care in these regions (7, 8).
2. Medicine residents pursue individually tailored curriculums in the form of short-term elective rotations at cancer centers in LMICs partnered with a US based institution, such as Botswana – University of Pennsylvania (9) and Yale/Stanford Johnson & Johnson Global Health Scholars Programs (10).
3. International pediatric oncology twinning programs through institutions like St. Jude Children's Research Hospital, Children's Hospital Boston/Dana-Farber Cancer Institute, and Texas Children's Hospital/Baylor College of Medicine offer GH opportunities during pediatric hematology–oncology fellowship (11–13).

4. Graduates of internal medicine and pediatrics residencies can apply for a 1- to 2-year research and leadership role in clinical cancer care at the Butaro Cancer Center of Excellence (BCCOE) in Rwanda. They are mentored by local clinical leaders from Partners in Health, the Rwandan Ministry of Health and oncologists from the Dana-Farber Cancer Institute. More recently, funding has become available for a recent graduate of an oncology fellowship program to spend a year at the University Hospital at Mirebalais in Haiti (14).
5. The Academic Model for Providing Access to Healthcare (AMPATH) consortium, involving many North American centers led by Indiana University School of Medicine, offers oncology experience in Kenya through a partnership with Moi University School of Medicine and Moi Teaching and Referral Hospital (15).

Finally, for trainees and faculty members interested in global oncology in Africa, the African Organization for Research and Training in Cancer (AORTIC) conference brings together oncology professionals from Africa and abroad to present scientific work and participate in cancer education in Africa (16).

The existing requirements for medical and pediatric oncology fellowships in US by the Accreditation Council for Graduate Medical Education (ACGME) make active participation in global cancer activities during the core 3-year fellowship a challenge. Currently, significant barriers include the need for longitudinal patient care and on-site mentorship by board certified oncologists. For a fellow to spend significant time at a global site, it would likely need to be done after the core fellowship as an “unofficial” advanced fellowship, additional time that might thwart GH interest. Ideally, ACGME and individual programs will work together to incorporate time for optional GH activities into the core fellowship.

#### **SURGICAL ONCOLOGY**

Benefits of international rotations in LMICs for surgical residents include exposure to pathology distinct from that seen at the home institution, alternative disease

management, cultural influences on disease presentation, and relationship building (17). For surgical oncology fellows specifically, the learning benefits of rotations in LMICs are even greater as cancer patients have fewer screening options, often present at advanced stages, might have different cancer biology, fewer imaging options, as well as limited perioperative care (18–20).

There are few residencies in general surgery and gynecology with an established global rotation. One such opportunity is the Paul Farmer Global Surgery fellowship, which is typically a 1- to 2-year fellowship following surgical residency, which gives recent graduates experience in GH research and surgical oncology in resource-poor settings, such as Haiti and Rwanda (21).

Of the 243 accredited U.S. obstetrics and gynecology residency programs, 34% offer formal didactics and 28% offer a formal rotation in global women’s health (22). Residents who participate in an international rotation are often very motivated to continue their involvement. However, once they start fellowship training opportunities to spend time abroad are limited. Of the 22 surgical oncology and 46 gynecologic oncology fellowship programs, only 1 program offers an international experience on their website. The Society of Gynecologic Oncology (SGO) welcomes international research and offers membership at reduced fees to international members from LMICs; a support program is also available for international attendees of the annual conference. However, no grants are available to our knowledge for fellows who are planning overseas research or work.

#### **RADIATION ONCOLOGY**

While there is an increasing level of interest in GH oncology outreach among radiation oncology residents, available opportunities are very limited. A Global Health Interest Survey administered by the Association of Residents in Radiation Oncology (ARRO) in 2009 revealed that of 115 residents completing the survey, approximately 90% of respondents were interested in an international radiation oncology experience during their residency and 80% wished to incorporate international work in their future careers. However, <10% of the respondents had GH educational activities

within their residency. Moreover, many residents noted barriers to an international rotation (funding, elective time, program director support) as well as unavailability of faculty guidance/mentorship at their home institution to foster GH interest (23).

The American Society of Radiation Oncology (ASTRO), in conjunction with ARRO and the American College of Radiology (ACR), promote international outreach by sponsoring travel grants. Annually, the ACR Foundation Goldberg-Reeder Resident Travel Grant awards \$1500 to residents in order to spend at least 1 month assisting health care in a LMIC.

The ASTRO-ARRO Global Health Scholars Program also provides \$2500 scholarships to selected residents for self-designed research, clinical or educational projects. Similarly, the Canadian Association of Radiation Oncology (CARO) has recently launched a GH scholarship for residents and fellows, which provides 2500 CAD for a clinical or research elective in a LMIC.

A few residency programs have incorporated international outreach into their curriculum. Through the Botswana-UPenn Partnership (24), residents at the University of Pennsylvania and elsewhere can provide clinical care in a LMIC. Similarly, the University of Chicago and the University of California-San Diego allocate time and financial resources for their senior residents to pursue rotations abroad.

At present, 84 LMICs have radiation therapy facilities. By 2020, over 12,000 radiation oncologists will be needed to staff radiation therapy facilities in these nations (25, 26). We posit that radiation oncology residents *can* play a role in addressing this disparity, particularly in this era of expanding remote telecommunication tools for quality assurance and treatment planning (27). Evidence suggests that short-term rotations are beneficial for both the resident and the international site providing opportunities for clinical care, knowledge exchange, research collaboration, and sustained partnerships. Through the ACR grant, residents have engaged in projects such as training staff to use brachytherapy units in Botswana (28, 29) and examining the survival rates of Ghanaian prostate cancer patients receiving external beam radiation therapy (30). We anticipate that longitudinal follow-up of the participants in

the aforementioned programs and detailed reporting regarding their experiences will shed additional light on the specific benefits of these rotations.

### GOING BEYOND TRAINING AND A CAREER PATH IN GLOBAL HEALTH

Interested trainees in GH provide a compassionate and forward thinking potential work force to address the disparity in oncology resources in LMICs. Yet, a well-defined career path is needed. Senior mentors and leaders worldwide are coming together to pilot a novel solution to GH in oncology. Signaling a transformational change that addresses both the global need for cancer care and the desire to create a sustainable altruistic component to physicians' careers, the International Cancer Expert Corps (ICEC), recently established as an NGO, aims to reduce mortality and improve the quality of life for cancer patients in LMICs through structured support for dedicated faculty attempting to establish a formal career path, with metrics, for human service (31). This model will also cultivate faculty who will support residents pursuing their international health interests after training is completed.

### CONCLUSION

In recent years, a number of training programs have allowed oncology residents and fellows to participate in international electives and to enrich their GH perspective. These experiences have provided trainees exposure to clinical presentations of cancer and approaches to cancer treatment in diverse settings with varying availability of resources. However, a more systematic approach to mentorship in and learning about GH is needed, as well as a sustainable career path to effect change.

A proposed framework for a GH fellowship includes advanced course work such as a Masters of Public Health or degree in tropical medicine; domestic clinical medicine to maintain competencies and potential revenue creation; academic research; and international field work (32). Specifically for oncology, the curriculum should include (1) global risk factors and epidemiological trends across geographic regions and within tumor sites; (2) barriers to access to radiotherapy, chemotherapy, and surgery and innovative modalities that can be employed in different

regions; (3) international clinical experience, with pre-departure training and post-visit debriefing; and (4) research training and experience in GH, supervised by local or international designated mentors with relevant expertise. These efforts can not only be directed toward education for both U.S. trainees and in-country professionals but also must be directed at implementation and implementation research. Training is a means to an end-provision of high-quality and affordable cancer care, and implementation of this care, is much more challenging than merely training. GH could be a specific module in all oncology training and possibly be integrated longitudinally within residency and fellowship programs. Such approaches would help to ensure that the GH perspective becomes a core competency of all graduating residents.

Global health training would benefit from a GH curriculum and a mechanism to connect trainees and faculty engaged in this field. GlobalRT is one such website ([www.globalrt.org](http://www.globalrt.org)) that establishes an online global radiotherapy community (33). This site provides information about radiotherapy within the global context, ongoing projects, training experiences, and research within this area. The GlobalRT blog allows trainees and practitioners to post accounts of their experiences in any dimension of GH, allowing dialog and the exchange of information about opportunities in education, research, and clinical practice.

These initiatives are invaluable resources for oncology residents with an interest in GH. Their successes can inform the creation of a framework for training oncology residents to tackle GH issues. Furthermore, there is a need for the "clinical oncologist" skilled in multimodality cancer care who works closely with economists and experts in public health and policy to address the multi-factorial issues (34).

In conclusion, the global burden of cancer in LMICs is rising and it is imperative that the global oncology community contributes to a solution. Medicine is, by definition, a humanitarian endeavor, and bringing cancer care to those who have had no access should have an important place for all physicians including those practicing in resource-rich environments. There is increasing interest in global oncology among trainees. Although

the opportunities are currently limited, trainees are demanding more exposure and to find ways to contribute to solving this global epidemic. We hope that increased focus on GH training in the future will better prepare trainees as global oncologists. To effectively address the global need and the rising trainee interest, fundamental changes to career paths are required, which would provide global benefit and serve as a model to address other non-communicable diseases.

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# Corrigendum: “Training global oncologists: addressing the global cancer control problem”

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**Keywords:** global health, oncology training, radiation oncology, surgical oncology, medical oncology, corrigendum

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# The cervix cancer research network: increasing access to cancer clinical trials in low- and middle-income countries

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**Introduction:** The burden of cervical cancer is large and growing in developing countries, due in large part to limited access to screening services and lack of human papillomavirus (HPV) vaccination. In spite of modern advances in diagnostic and therapeutic modalities, outcomes from cervical cancer have not markedly improved in recent years. Novel clinical trials are urgently needed to improve outcomes from cervical cancer worldwide.

**Methods:** The Cervix Cancer Research Network (CCRN), a subsidiary of the Gynecologic Cancer InterGroup, is a multi-national, multi-institutional consortium of physicians and scientists focused on improving cervical cancer outcomes worldwide by making cancer clinical trials available in low-, middle-, and high-income countries. Standard operating procedures for participation in CCRN include a pre-qualifying questionnaire to evaluate clinical activities and research infrastructure, followed by a site visit. Once a site is approved, they may choose to participate in one of four currently accruing clinical trials.

**Results:** To date, 13 different CCRN site visits have been performed. Of these 13 sites visited, 10 have been approved as CCRN sites including Tata Memorial Hospital, India; Bangalore, India; Trivandrum, India; Ramathibodi, Thailand; Siriraj, Thailand; Pramongkutk-lao, Thailand; Ho Chi Minh, Vietnam; Blokhin Russian Cancer Research Center; the Hertzgen Moscow Cancer Research Institute; and the Russian Scientific Center of Roentgenoradiology. The four currently accruing clinical trials are TACO, OUTBACK, INTERLACE, and SHAPE.

**Discussion:** The CCRN has successfully enrolled eight sites in developing countries to participate in four randomized clinical trials. The primary objectives are to provide novel therapeutics to regions with the greatest need and to improve the validity and generalizability of clinical trial results by enrolling a diverse sample of patients.

**Keywords:** cervix cancer, global health, radiation oncology, clinical trials as topic, HIV cancer

## INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide with almost 530,000 cases diagnosed in 2012 (1). Of these, nearly 85% of cases occur in developing countries, due in large part to limited access to screening services and lack of human papillomavirus (HPV) vaccination (2). Lack of screening also leads to diagnosis at advanced stages of disease and with clinically debilitating symptoms. Even more concerning, nearly 90% of the estimated 270,000 deaths from cervical cancer in 2012 occurred in developing countries (1), suggesting that cancer diagnosis and treatment services are inadequate in regions of the world with the highest incidence of the disease. Furthermore, cervical cancer disproportionately affects young women, and loss of life attributable to advanced cancer has significant social and economic impact on individual families, as well as societies at large (3–5).

Treatment for cervical cancer can include surgery, chemotherapy, radiotherapy, or a combination of these treatments depending on the stage at cancer diagnosis (6). For locally advanced disease,

concurrent chemoradiation followed by brachytherapy has been the standard of care in developed nations for decades based on the results of several large, randomized clinical trials showing improvement in survival with the addition of chemotherapy to radiotherapy (7–10). However, in spite of recent advances in imaging, chemotherapy administration, and radiotherapy planning and delivery, outcomes from cervical cancer have not markedly improved, even in developed countries where the most cutting-edge therapies are readily available (11).

Novel treatment strategies are urgently needed to improve outcomes from cervical cancer. One challenge to novel therapy development is that clinical trials are often conducted in high-income countries where research resources are the greatest; however, the incidence of cervical cancer is lowest. Furthermore, outcomes from clinical trials conducted in high-income countries may not be generalizable to low- and middle-income countries, which face unique challenges in cancer treatment accessibility and administration. Partnership between clinicians and researchers in developing and

developed nations is vital to generating treatment paradigms with worldwide applicability and efficacy.

Cancer clinical trial access is scarce in many developing countries, as the research support and infrastructure needed to enroll patients is often unavailable. The Cervix Cancer Research Network (CCRN), a subsidiary of the Gynecologic Cancer InterGroup (GCIg), is a multi-national, multi-institutional consortium of physicians and scientists focused on improving cervical cancer outcomes worldwide by making cancer clinical trials available in low-, middle-, and high-income countries. In this manuscript, we describe the early activities of the CCRN, with a focus on describing a model of collaborative capacity-building, with the overall goal of promoting cervical cancer research and improving access to novel therapies.

## MATERIALS AND METHODS

### HISTORY

The CCRN is a subsidiary of the GCIg, a non-profit network of appointed representatives from international cooperative research groups for clinical trials in gynecologic cancers. The GCIg was established in 1990s with the goal of promoting and conducting high quality clinical trials to improve outcomes for women with cancers of the ovary, uterus, and cervix. The GCIg has been highly successful in completing clinical trials, publishing results, and developing consensus conferences.

The CCRN developed to address the lack of cervical cancer clinical trials, increase enrollment on existing trials, and improve

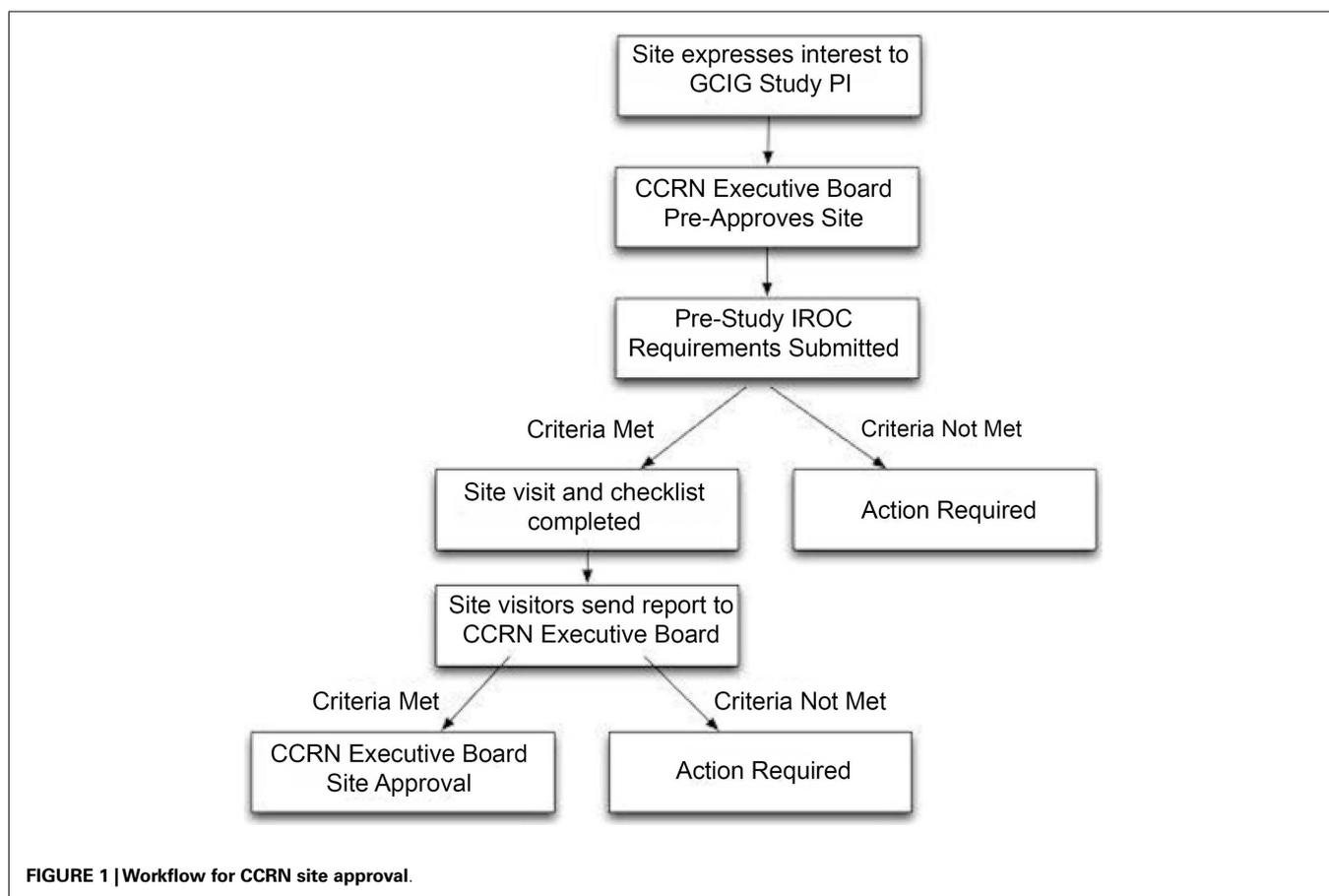
the standards of cancer care in low- and middle-income countries. In light of the limited improvement in survival in locally advanced cervical cancer in the decades since chemoradiation became the standard of care, the vision of the CCRN was to provide infrastructure and support for cancer clinical trials in developing nations that have a significant burden of cervical cancer.

### GOVERNANCE

The CCRN reports to and is guided by the Executive Board of Directors of the GCIg. This Board has regularly scheduled teleconferences and semi-annual meetings. The chair and co-chair of the CCRN are elected for 3-year terms by voting members. The chair of the CCRN serves on the Executive Board of the GCIg and a formal report of activities and progress is made to the membership at the General Assembly at each semi-annual meeting.

### EARLY DEVELOPMENT

The mission of the CCRN was formulated by the committee chair and participating members. The literature was evaluated for best practices for clinical trials within gynecologic cancers, with emphasis on methods for low- and middle-income countries in which clinical trial resources are often limited. The CCRN then developed standard operating procedures (SOP) to evaluate potential participating sites to ensure appropriate infrastructure prior to clinical trial enrollment. The principal investigators of the CCRN trials normally select potential sites. The SOP workflow is demonstrated in **Figure 1**.



The SOP includes a pre-qualifying questionnaire to evaluate clinical activity, site resources, clinical trials infrastructure, radiation therapy treatment records, radiotherapy quality assurance, and clinical management documentation (**Table 1**). Additionally, participation in a radiotherapy beam measurement program is required every 2 years to determine the stability of the output of linear accelerators from each participating center. This is typically done with thermal luminescent dosimetry or more recently, optically stimulated luminescent dosimetry. With support from the National Cancer Institute of the United States, the Imaging and Radiation Oncology Core in Houston, TX, USA, has been instrumental in partnering with the CCRN to provide quality assurance checks.

For potential study sites deemed eligible after the pre-qualifying survey, a site visit must be performed by an audit team to evaluate the appropriateness and readiness to participate in CCRN trials. Infrastructure, the physical plant, and human resources are evaluated to ensure that clinical trial participation can succeed. The audit team typically includes one clinical specialist and one clinical trials manager. Various measures of quality assurance are performed, depending on the requirements of the available clinical

trial. To date, the CCRN has received limited funding from the International Gynecologic Cancer Society (IGCS) and the GCIG, as well as support from the NCI.

## RESULTS

To date, 13 different CCRN site visits have been performed. Of these 13 sites visited, 10 have been approved as CCRN sites including Tata Memorial Hospital, India; Bangalore, India; Trivandrum, India; Ramathibodi, Thailand; Siraj, Thailand; Pramongkutklao, Thailand; Ho Chi Minh, Vietnam; Blokhin Russian Cancer Research Center; the Herten Moscow Cancer Research Institute; and the Russian Scientific Center of Roentgenradiology. Approval with contingencies has been granted to sites in Cluj, Romania, and Minsk, Belarus.

Through significant efforts within the Cervix Cancer Committee at the GCIG, four multi-national cervical cancer clinical trials suitable for both developed and developing nations have successfully been opened.

1. The Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer Trial (TACO Trial), developed by investigators from the Korean Gynecologic Oncology Group (KGOG) and the Thai Cooperative Group, is a randomized phase III study that compares weekly chemotherapy for advanced cervix cancer to every-3-week chemotherapy. Preliminary data from a phase II trial by the KGOG suggest that every-3-week chemotherapy may confer a survival benefit (12).
2. The OUTBACK Trial is led by investigators from the Australia/New Zealand Gynecologic Oncology Group (ANZGOG). This study is a randomized phase III trial evaluating the efficacy of extended adjuvant chemotherapy in women with advanced cervix cancer compared to the standard of weekly cisplatin chemotherapy and definitive radiotherapy. The OUTBACK chemotherapy consists of four cycles of carboplatin and paclitaxel chemotherapy administered after standard concurrent chemoradiotherapy. The rationale for the study is a meta-analysis of several studies that showed adjuvant chemotherapy to be a promising approach (13).
3. The INTERLACE Trial is headed by the National Cancer Research Institute (NCRI) from the United Kingdom. This is a randomized phase III study evaluating neoadjuvant chemotherapy prior to concurrent chemoradiotherapy for women with advanced cervix cancer compared to concurrent chemoradiotherapy alone. The goal of this study is to improve compliance with additional chemotherapy by giving it before standard chemoradiotherapy, as opposed to after standard chemoradiotherapy.
4. The SHAPE Trial is spearheaded by investigators from the NCIC Clinical Trials Group in Canada. This randomized phase III trial is evaluating radical hysterectomy versus simple hysterectomy in women with early-stage cervix cancer. The primary endpoint is freedom from pelvic failure.

Each approved CCRN site chooses to participate in one or more of the four available clinical trials. To date, 48 patients have been enrolled.

**Table 1 | Pre-qualifying questionnaire.**

Assessment category	Question
Clinical volume	<ul style="list-style-type: none"> <li>• Average number of new cancer patients seen per year?</li> <li>• Average number of new gynecologic cancer patients seen per year?</li> <li>• Average number of new cervix cancer patients seen per year?</li> </ul>
Pathology/hematology resources	<p>Availability of the following resources on site (yes/no)</p> <ul style="list-style-type: none"> <li>• Routine hematology</li> <li>• Routine biochemistry</li> <li>• Routine anatomic pathology</li> <li>• Long-term specimen storage</li> <li>• Designated gynecologic pathologist</li> <li>• Specialized pathology services</li> <li>• Transfusion facility</li> <li>• Critical care facility</li> </ul>
Radiology Resources	<p>Availability of the following resources on site (yes/no)</p> <ul style="list-style-type: none"> <li>• Plane X-ray</li> <li>• Ultrasound</li> <li>• Computed Tomography (CT)</li> <li>• Positron-Emission Tomography (PET)</li> <li>• Magnetic Resonance Imaging (MRI)</li> <li>• PET/CT</li> <li>• Dedicated gynecologic radiologist</li> </ul>
Technology support	<ul style="list-style-type: none"> <li>• Email available during working hours?</li> <li>• Access to computers for doctors, technologists, data managers, and nurses?</li> <li>• Is the facility capable of digital data exchange?</li> </ul>

## DISCUSSION

The greatest burden of cervical cancer is in developing countries, particularly parts of Africa, Central and South America, Eastern Europe, India, and other parts of Asia (1). The outcomes from locally advanced cancer remain suboptimal, and development and testing of novel therapies has occurred in countries with the lowest incidence of cervical cancer. The aim of the CCRN is to improve access to clinical trials, enhance clinical trial enrollment particularly in countries with high disease burden, and to produce treatment paradigms that are applicable and accessible to women worldwide.

There are many challenges in conducting multi-national clinical trials, particularly in low-resource settings (14, 15). Human resource training and research infrastructure development are necessary to ensure success; however, this may entail high costs. Rigorous quality assurance is also costly, but necessary to maintain the validity of the research question. Furthermore, open and rapid communication among study coordinators, physicians, and patients is required, but can be challenging due to language barriers and connectivity issues. Another challenge is collaboration not only with local physicians and hospitals but also with government and insurers. As an example, the CCRN sites in India have not been activated secondary to strict requirements by the Indian Government for complete trial insurance, which was too expensive to be covered by the four funded CCRN trials. Finally, extraordinary care must be taken to ensure clinical trial design and conduct is in accordance with the ethics guidelines set forth by the World Medical Association's Declaration of Helsinki and the Council for International Organization of Medical Sciences (15).

In spite of these real and complex challenges, there are tremendous opportunities to enhance clinical trials results and improve cervical cancer outcomes through collaboration, creativity, and persistence. Rapid improvements in technology, particularly internet-based approaches, have made communication and quality assurance checks more feasible, timely, and cost-effective. Investments in research training and infrastructure development have the potential to influence not only cervical cancer clinical trial involvement but also standard care and care for other types of cancers. While sophisticated translational trials involving complex imaging and biomarker measurement will be confined to core GCIG settings, pragmatic trials that are aimed at defining worldwide standard of care, as well as trials directed at practices in low- and middle-income countries, are within the capability of the CCRN.

In summary, the CCRN has developed a methodology to evaluate potential clinical trial enrollment sites in low- and middle-income countries to make cervical cancer clinical trials available in countries with the highest burden of disease. The CCRN has successfully enrolled 10 sites in developing countries to participate in four randomized clinical trials. The primary objectives are to provide novel therapeutics to regions with the greatest need and to improve the validity and generalizability of clinical trial results by enrolling a diverse sample of patients, with the ultimate goal of improving outcomes from cervical cancer worldwide.

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# Locally advanced breast cancer – strategies for developing nations

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Worldwide, cancer incidence and cancer-related deaths are steadily rising. According to the International Agency for Research on Cancer, new cancer cases rose from 12.7 million in 2008 to 14.1 million in 2012 (1). Similarly, 7.6 million cancer-related deaths occurred in 2008 compared to 8.2 million in 2012. A significant proportion of these cases are attributed to breast cancer, the predominant malignancy affecting women worldwide. Since 2008, breast cancer incidence has increased by over 20% and breast cancer deaths have risen by 14% (1). Although the incidence of breast cancer is still highest in developed countries, women in developing nations are disproportionately dying as a result of this disease. Six of the 10 countries with the highest breast cancer mortality rate are low- to middle-income countries (LMICs) (Figure 1). Moreover, breast cancer in LMICs often presents when locally advanced breast cancer (LABC) (2–4) that can be easily appreciated at physical exam but is still limited to the breast and draining lymph nodes, without clinical evidence of metastatic spread. LABC is defined as tumors: (1) more than 5 cm in diameter, (2) involve the skin or the underlying pectoral muscles, (3) involve axillary, supraclavicular, and/or infraclavicular lymph nodes, or (4) inflammatory breast cancer. Despite being confined to the breast and regional nodes, locally advanced stage often heralds the rapid onset of metastatic disease, explaining high mortality rates. Solutions are needed to address this health issue. We propose practical strategies to improve the early detection of breast cancer and the treatment of LABC within developing nations.

## DETECTION

In developed countries, national screening programs have been widely implemented. Although there are tangible benefits to mammographic screening, following the same paradigm in developing nations may not be ideal or feasible. First, women in several developing nations are diagnosed at a younger age than their counterparts in developed countries. In the United States, the median age at diagnosis is 61 years old. In comparison, the median age at diagnosis is 50 years old among women in Mexico (5) and 46 years old among Egyptian women (6). The sensitivity of mammography is affected by several factors including age and breast tissue density. In women <50 years old, the sensitivity of mammography can be as low as 68% (7). Digital mammography improves the detection of cancer in younger women but is associated with higher costs compared to film mammography. In a study of over 40,000 women, the accuracy of digital mammography was significantly higher than that of film mammography for women under 50 years old, pre- and peri-menopausal women and those with heterogeneously dense or extremely dense breasts on mammography (8). Screening mammograms are performed in women without symptoms of breast cancer. Diagnostic mammograms are used to diagnose breast cancer once suspicious findings have been noted on screening mammogram or if an individual has symptoms suggestive of breast cancer. Diagnostic mammograms involve more views of the breast and take longer to perform. In addition, a radiologist is present to immediately interpret the exam. When used for screening or diagnostic

purposes, digital mammograms cost \$11 or \$33 more per examination, respectively (9). Restricting the use of digital mammograms to women under 50 years, those most likely to benefit from a more accurate assessment of breast densities, would still prove too expensive for low- to middle-income nations. According to the World Health Organization, a cost-effective health intervention is one to three times a country's gross domestic product (GDP) per capita. Age-targeted digital mammography would cost \$26,500 per quality-adjusted life year (QALY) (10), well above the cost-effective threshold for most LMICs.

For developing nations, screening mammography programs are likely cost-prohibitive with questionable benefits. This is especially true in populations with a significant number of young breast cancer patients, for whom mammography is less likely to detect malignancies and leads to more false-positive results (11–13). It would be unwise for nations with limited resources to indiscriminately adopt the same screening strategy. Financial resources are likely better invested in public awareness campaigns and training community health workers to educate the public and perform clinical breast exams (CBE) (2, 14, 15). For example, a cost-effectiveness analysis of breast cancer interventions in Ghana revealed that mammographic screening of women 40–69 years old would cost \$12,908 per disability adjusted life year (DALY) averted. In contrast, biennial CBE and mass media awareness campaigns would cost \$1299 and \$1364 per DALY averted, respectively (16). Distrust of the medical system and myths about breast cancer persist, leading women

Country	Mortality Rate (per 100,000 women)	World Bank Classification
Fiji	28.4	Upper middle income
Bahamas	26.3	High income
Nigeria	25.9	Lower middle income
Pakistan	25.2	Lower middle income
New Caledonia	24.4	High income
Armenia	24.2	Lower middle income
Lebanon	24.0	Upper middle income
Trinidad and Tobago	23.5	High income
Ethiopia	23.0	Low income
Uruguay	22.7	High income

**FIGURE 1 |** Age-standardized mortality rates, number of deaths per 100,000 women (1).

to rely on traditional healers in lieu of health centers to their detriment (17, 18). These issues highlight a critical need to invest in education.

### MULTIMODALITY CARE

Generally, only ~15% of breast cancer patients in LMICs present with Stage I breast cancer and 20–40% present with Stage II disease (19). In sub-Saharan Africa, 40–90% of women present with Stage III–IV disease (20). The same is true for low- to middle-income Latin American countries. In Colombia, 68.2% of patients present with locally advanced disease and in Peru and Mexico, approximately 50% of patients present with advanced disease (21). Although the 3-year survival rate for Stage III patients in high-income countries ranges from 70 to 85%, the survival rate for patients with comparable stage of disease is much lower in developing nations. Optimizing treatment in this sub-population is part of a reasonable strategy to improve breast cancer mortality in developing countries.

### SURGERY

Surgery plays an important role in the management of LABC. In developing countries, modified radical mastectomy (MRM) continues to be the mainstay of surgical treatment. In Yemen, approximately 50% of women undergo MRM and an additional 10% undergo radical mastectomy

(22). Unfortunately, surgical techniques for mastectomies are sometimes suboptimal. In USA and the United Kingdom, most breast surgeons have undergone surgical oncology fellowships. In contrast, opportunities for specialty training are limited in LMICs. Moreover, quality control protocols and data regarding mastectomies in developing countries, including the rate of negative margins and the number of lymph nodes excised, are lacking (23). Studies are needed to assess the quality of mastectomies and pinpoint areas for improvement that can lead to better outcomes.

Fear of deformity is among the multiple concerns that breast cancer patients face during treatment (24). Several studies demonstrated that body image is superior in women who undergo breast conservation therapy (BCT) or mastectomy with reconstruction rather than those who have undergone mastectomy without reconstruction. Interestingly, overall quality of life is the same for patients whether they undergo mastectomy with or without reconstruction, suggesting that satisfaction with body image is only one component of global quality of life after breast cancer (25). Although providing opportunities for reconstruction would be ideal, this should be a lower priority goal in a limited resource setting, especially since this procedure can cost between \$15,000 and \$50,000.

### CHEMOTHERAPY

Neoadjuvant chemotherapy is recommended for women with LABC. In some cases, neoadjuvant chemotherapy can significantly shrink the tumor making lumpectomy possible. It is essential that developing nations implement cost-effective chemotherapeutic regimens. The WHO Model List of Essential Medicines presents a core list of the minimum medicine needs for a healthcare system. In addition, it denotes essential medicines for diseases like cancer that require specialized care. Among the 30 cytotoxic and anti-hormonal therapies, the breast cancer-related agents include carboplatin, cyclophosphamide, docetaxel, doxorubicin, fluorouracil, methotrexate, paclitaxel, and tamoxifen. Provision of these agents may be a realistic target for upper-middle-income nations. However, LMICs may be best served by focusing on access to three to four of these medications. We propose paclitaxel, doxorubicin, cyclophosphamide, and tamoxifen as the basic chemotherapeutic elements of breast cancer care. Chemotherapy recommendations according to national resources have also been published by the Breast Health Global Initiative (26).

The Academic Model Providing Access to Healthcare (AMPATH) is a successful model of chemotherapy delivery in Kenya, a low-income nation (27). AMPATH is a collaboration between Moi University

School of Medicine in Kenya and North American academic medical centers. Since 2005, cancer care services have been available and breast cancer represents over 60% of female-specific malignancies. The AMPATH Oncology Pharmacy Service (AOPS) stocks doxorubicin, cyclophosphamide, and tamoxifen in addition to 15 other chemotherapy-related agents. AC chemotherapy appears to be the most readily available for women in developing nations. Nearly 50% of patients receiving neoadjuvant chemotherapy in Ibadan, Nigeria were treated with doxorubicin and cyclophosphamide (3). The AOPS experience also provides other insights for LMICs regarding issues of cost containment, personnel training, disposal, preparation/dispensing, and storage associated with chemotherapy. For instance, by centralizing inventory and monitoring monthly use statistics, AOPS minimized the risk of drug shortages and negotiated better prices. The latter is especially important because many patients are uninsured and must bear the total out-of-pocket costs. Often, patients cannot afford chemotherapy and will forego this aspect of treatment. Ntirenganya et al. reported that 35% of women with breast masses in Sierra Leone did not seek medical care due to lack of money (18). By making chemotherapy more affordable, healthcare institutions can ensure that patients are more likely to receive optimal care thereby improving cancer outcomes. It will also be necessary to invest in supportive therapies such as antiemetics for successful implementation of chemotherapy.

Another cost-effective strategy is to combine oophorectomy and hormonal therapy. In a study of 709 premenopausal Vietnamese and Chinese women with Stage IIA–IIIA breast cancer, patients were randomized to undergo oophorectomy at the time of mastectomy and adjuvant tamoxifen versus receiving this combined hormonal treatment at recurrence (28). At 5 years, oophorectomy and tamoxifen up front led to a statistically significant disease-free and overall survival benefit. Moreover, this intervention cost \$350 per year of life saved.

Targeted agents, such as trastuzumab, are noticeably absent from the WHO Model List of Essential Medicines and

likely the pharmacies of most developing nations. Assessments in Peru, Costa Rica, and Mexico demonstrate that providing trastuzumab will cost over \$10,000 per DALY and is consequently not recommended (29, 30). Therefore, unfortunately HER2-directed therapies should not be a priority for low- to middle-income nations.

#### RADIATION THERAPY

Radiation therapy is an important component of care for women with LABC. Several randomized trials have demonstrated the local recurrence and mortality benefit associated with adjuvant radiation therapy after mastectomy (31). Unfortunately, radiation therapy services are severely lacking in LMICs. Of 139 LMICs, 55 (39.5%) have no radiation therapy facilities (32) and 29 of these are African nations (33). In most high-income countries, at least one radiotherapy machine is available for every 250,000 people. In contrast, in nearly 20 LMICs, only one machine is available for over 5 million people. Ideally, LMICs should invest in establishing radiation therapy infrastructure and training personnel. However, decision-analytic models estimate that post-mastectomy radiation therapy costs \$12,000–\$22,600 per QALY (34, 35). Although this is cost-effective for most upper-middle-income countries, it is unlikely to be sustainable for low to lower-middle-income countries. Innovative methods are needed to provide radiation therapy at lower cost in these developing nations. One strategy may be to shorten the course of radiation therapy. Hypofractionated breast radiotherapy is commonly used after lumpectomy. Although decreasing the total dose may enhance the therapeutic ratio, previous studies suggest that 3 Gy per fraction post-mastectomy is associated with unacceptable brachial plexus toxicity (36). Additional studies are needed to identify hypofractionated radiation therapy regimens that can safely treat both the chest wall and regional lymph nodes.

Concurrent chemoradiation therapy may also shorten the overall length and cost of treatment while maintaining treatment efficacy. Among 105 women treated with neoadjuvant concurrent paclitaxel and radiotherapy to the breast and

regional nodes, 34% achieved a pathological response including over 50% of triple-negative patients (37). Shortening chemotherapy and radiation therapy courses also makes treatment more convenient to patients, since patients in LMICs often have to travel long distances and temporarily live far away from their homes to undergo treatment.

Finally, simplifying the radiation therapy planning process can reduce the technical fees and overall cost of radiation therapy. Zhao et al. published their algorithm for determining the optimal placement of tangential beams (38). This method does not require manual beam placement by physicians, a time-saving feature especially in developing countries with a limited number of physicians. Similar methods for designing regional lymph node radiotherapy fields are needed.

#### CONCLUSION

Locally advanced breast cancer contributes significantly to cancer mortality among women worldwide. It is particularly important to address this disease in developing nations, where over 70% of all cancer cases will occur by 2020. There is an overwhelming need for systematic studies that pinpoint areas of need within the context of each developing nation and also within regions in a developing nation. Research in these settings and dissemination of these data (39) will guide the judicious use of available financial and human resources. In this article, we have suggested strategies for addressing LABC in LMICs. Potential solutions include (1) investing in CBE and awareness campaigns, (2) gathering data and establishing quality control protocols for mastectomies, (3) focusing on the provision of few but effective chemotherapeutic agents, and (4) investigating cost reduction methods for radiation therapy including shorter regimens.

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# National Cancer Institute's Cancer Disparities Research Partnership program: experience and lessons learned

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**Purpose:** To increase access of underserved/health disparities communities to National Cancer Institute (NCI) clinical trials, the Radiation Research Program piloted a unique model – the Cancer Disparities Research Partnership (CDRP) program. CDRP targeted community hospitals with a limited past NCI funding history and provided funding to establish the infrastructure for their clinical research program.

**Methods:** Initially, 5-year planning phase funding was awarded to six CDRP institutions through a cooperative agreement (U56). Five were subsequently eligible to compete for 5-year implementation phase (U54) funding and three received a second award. Additionally, the NCI Center to Reduce Cancer Health Disparities supported their U56 patient navigation programs.

**Results:** Community-based hospitals with little or no clinical trials experience required at least a year to develop the infrastructure and establish community outreach/education and patient navigation programs before accrual to clinical trials could begin. Once established, CDRP sites increased their yearly patient accrual mainly to NCI-sponsored cooperative group trials (~60%) and Principal Investigator/mentor-initiated trials (~30%). The total number of patients accrued on all types of trials was 2,371, while 5,147 patients received navigation services.

**Conclusion:** Despite a historical gap in participation in clinical cancer research, underserved communities are willing/eager to participate. Since a limited number of cooperative group trials address locally advanced diseases seen in health disparities populations; this shortcoming needs to be rectified. Sustainability for these programs remains a challenge. Addressing these gaps through research and public health mechanisms may have an important impact on their health, scientific progress, and efforts to increase diversity in NCI clinical trials.

**Keywords:** cancer disparities, underserved populations, patient accrual, access to clinical trials, clinical research

## INTRODUCTION

The Cancer Disparities Research Partnership (CDRP) pilot program was initiated by the radiation research program (RRP) within the National Cancer Institute (NCI)'s Division of Cancer Treatment and Diagnosis (DCTD) in 2002 as a novel strategy to address the cancer health disparities that exist in racial, ethnic,

minority, and underserved populations within the United States (1). Over half of all cancer patients are treated with radiation alone or in combination with surgery or chemotherapy. This program was focused at radiation oncologists in community-based hospitals and cancer centers that predominantly serve minority/underserved populations. Since the goal was to reach

**Abbreviations:** ACS, American Cancer Society; AI, American Indian; ASTRO, American Society for Radiation Oncology; ATM, ataxia telangiectasia mutated gene; BSA, Board of Scientific Advisors for National Cancer Institute; CCRO, Coastal Carolina Radiation Oncology; CCOP, Community Clinical Oncology Program; CDRP, Cancer Disparities Research Partnership; CRCHD, Center to Reduce Cancer Health Disparities; CRR, Community Research Representative; CTOC, Clinical Trials Operating Committee; DCTD, Division of Cancer Treatment and Diagnosis; IAEA, International Atomic Energy Agency; IRB, Institutional Review Board; MB-CCOP, Minority-Based Community Clinical Oncology Program; NACR, Native

American Cancer Research; NCI, National Cancer Institute; NCORP, National Cancer Institute Community Oncology Research Program; NHRMC, New Hanover Regional Medical Center; NIH, National Institute of Health; PACT, Program of Action for Cancer Therapy; PI, principal investigator; RCRH, Rapid City Regional Hospital; RFA, request for application; RRP, Radiation Research Program; RTOG, radiation therapy oncology group; SENC, Southeastern North Carolina; SRHS, Singing River Health System; UAB, University of Alabama Birmingham; UPMC, University of Pittsburgh Medical Center; WFP, Walking Forward Program.

populations not having access to NCI clinical trials, application criteria included limited participation in clinical trials, and NCI grant funding <\$100,000/year. Utilizing a U56 planning cooperative agreement, funding went directly to community-based institutions to establish the clinical research infrastructure required for their populations to access NCI-sponsored radiation oncology-based clinical trials. CDRP sites were required to identify academic cancer centers or mentors experienced in NCI-sponsored clinical trials as partners who received limited funding from the grantee. To facilitate the mentoring relationships, a TELESYNERGY™ (2), telemedicine system was provided to both grantee and primary mentor. Furthermore, NCI's Center to Reduce Cancer Health Disparities (CRCHD) provided supplemental funding to establish a patient navigation program addressing the specific needs of grantee's targeted populations.

The primary goal was to increase accrual of minority/underserved populations into NCI-sponsored clinical trials. Other objectives were: (1) increasing the number of staff involved in cancer health disparities research; (2) assessing the value of implementing the TELESYNERGY™ telemedicine system; (3) implementing an appropriate patient navigation program; and (4) determining whether this pilot would work in community-based institutions not historically involved in clinical research.

## MATERIALS AND METHODS

### PROCESS FOR APPROVAL OF CDRP CONCEPT INITIATIVE AND REISSUANCE

Following an NIH/NCI portfolio analysis, which determined a need for the proposed program, the CDRP concept was approved by the NCI's Board of Scientific Advisors and the request for application (RFA-CA-02-002), was issued in October 2001. An NCI Special Emphasis Panel reviewed six applications and two awards were made in September 2002. Since initial funding was approved for up to six awards, RFA-CA-03-018 was issued in August 2002 and four additional awards were made out of eight reviewed applications producing a success rate of 43% from both RFAs. **Table 1** includes information on the grantees, Principal Investigators (PIs), mentors, service areas, and target populations.

The formal process for reissuance of any currently funded NCI program changed in 2006 and required an external program evaluation. NOVA Research Company (3) was awarded the 5-year U56 CDRP Process and Outcome Evaluation contract, which helped generate the programmatic assessment data. The reissuance process used NOVA's yearly CDRP Program Evaluation Reports (2006–2008) containing qualitative and quantitative data and the evaluation report by the CDRP Program Expert Committee (see Supplementary Material). This Expert Committee and CDRP PIs met annually at the American Society for Radiation Oncology (ASTRO) meeting to help RRP evaluate yearly progress and make recommendations for program improvement. The BSA recommended not expanding the program, but to accept applications only from the five funded grantees in a limited competition RFA-CA-09-502 (October 2008). After the Special Emphasis Panel review, 5-year U54 implementation awards were made to Rapid City Regional Hospital (RCRH), New Hanover Regional Medical Center (NHRMC), and Singing River Health

System (SRHS), while UPMC McKeesport Hospital received a 2-year phase out award.

### METRICS OF SUCCESS

The metrics of success were:

- 1) Could a community-based hospital/cancer center establish a clinical research infrastructure within a reasonable period and accrue patients into radiation oncology-based clinical trials?
- 2) Was participation of underserved populations in NCI-sponsored clinical trials increased?
- 3) Were mentors helpful in providing necessary training, support, and advice to the grantees?
- 4) Was the TELESYNERGY™ telemedicine system beneficial to the CDRP programs?
- 5) Was the CDRP grantee successful in increasing the number of physicians/other staff interested in cancer disparities research?
- 6) Was the CDRP site successful in disseminating program results through publications/presentations at national meetings?

## RESULTS

### ESTABLISHMENT OF INFRASTRUCTURE

Establishing the clinical research infrastructure was challenging because institutions were unfamiliar with its value for their patients. Despite all PIs having prior clinical trials experience, it took many months to educate the hospital administration about the benefits for their patients by participating in NCI clinical trials. By offering trials near their hometowns, patients can access these clinical advances without traveling great distances.

Findings from the U56 pilot program revealed important and unique issues regarding outreach to disparities populations not encountered at academic cancer centers and their community oncology affiliates. Disparities researchers needed sufficient time to succeed in: (1) recruiting personnel due to challenges in finding qualified staff to fill positions (e.g., program/grant manager, clinical research nurse/coordinator, data manager, patient navigator, and regulatory affairs expert for writing clinical protocols); (2) identifying a back-up PI after the loss of the primary PI at Laredo Medical Center; (3) establishing an outreach program so the community gained familiarity and trust with the PI and the research team (4, 5); and (4) surveying the populations to determine their knowledge, attitudes, perceived barriers, and needs.

### PARTICIPATION IN CLINICAL TRIALS

After the infrastructure was established, there was steady patient accrual onto various NCI clinical trials (**Table 2**). The type of trials most useful to the grantees is discussed below. The fluctuation seen in patient accruals was due to the limited number of cooperative group trials available for minority/underserved populations presenting with late-stage disease and co-morbidities. The restrictive eligibility criteria for many cooperative group trials resulted in low eligibility rates, averaging only 20–24% during both U56 and U54 phases (**Table 3**) (6).

### MENTORING AND PARTNERSHIP

All grantees selected an NCI-designated Comprehensive Cancer Center as a primary or secondary (Laredo) mentor (**Table 1**)

**Table 1 | CDRP grantees, program title, PIs, mentors, service areas, and their target populations.**

Award year	Grantee/principal investigator (PI)	Service area population	Target population
FY02	Rapid City Regional Hospital, Rapid City, South Dakota Program name: Walking Forward (WF) <sup>a</sup> PI: Daniel G. Petereit, MD Primary mentor: University of Wisconsin-Madison Secondary mentor: Mayo Clinic in Rochester, MN	300,000	American Indian/Native American
FY02	Laredo Medical Center <sup>b</sup> ; Laredo, Texas Program name: Evaluating Cancer Disparities Among Hispanic Communities PI: Yadvindra S. Bains, MD Primary mentor: University of Texas Health Science Center Secondary mentor: MD Anderson Cancer Center in Houston, TX	177,000	Hispanic/Latino
FY03	Daniel Freeman Memorial Hospital <sup>c</sup> Inglewood, CA, USA Program name: Urban Latino African American Cancer (ULAAC) Disparities Project PI: Michael L. Steinberg, MD <sup>d</sup> Primary Mentor: University of Southern California Secondary Mentor: RAND Corporation, Santa Monica, CA	100,000	African American Hispanic/Latino
FY03	New Hanover Regional Medical Center Wilmington, North Carolina Program name: Improving Cancer Outcomes for African-Americans PI: Patrick D. Maguire, MD Primary mentor: University of North Carolina-Chapel Hill	616,000	African American Urban/Rural Poor
FY03	Singing River Hospital; Pascagoula, Mississippi Program name: The Mississippi/Alabama Radiation Oncology Research Partnership PI: Raymond Wynn, MD <sup>e</sup> Primary mentor: University of Alabama at Birmingham Secondary mentor: University of Mississippi Medical Center	200,000	African American
FY03	University of Pittsburgh Medical Center (UPMC) McKeesport Hospital; McKeesport, Pennsylvania Program name: Radiation Oncology Community Outreach Group (ROCOG) PI: Dwight E. Heron, MD Primary mentor: Washington University, St. Louis, MO, USA Secondary Mentor: Roswell Park Cancer Center, Buffalo, NY	935,000	African American Urban/Rural Poor

<sup>a</sup>Rapid City changed its CDRP program name early in program development from "Enhancing Native American Participation in Radiation Therapy Trials" to "Walking Forward," which was considered more culturally appropriate for their target American Indian patients.

<sup>b</sup>CDRP grant was relinquished in 2007 due to inability to find a qualified radiation oncologist to become PI when original PI resigned in 2006.

<sup>c</sup>Grant was changed to Centinela Freeman in 2004 and later was transitioned to Twenty-First Century Oncology at the Santa Monica Cancer Treatment Center in 2008.

<sup>d</sup>Dr. David Khan is the current CDRP PI and Dr. Michael Steinberg is co-PI.

<sup>e</sup>Dr. Raymond Wynn resigned in 2005 and Dr. W. Sam Dennis became the new PI.

based on clinical research expertise and/or an existing relationship; many also selected secondary partners to address specific needs. An important lesson learned was the need for the grantee to work immediately with the academic center's grants research office to obtain details on job descriptions, guidance for establishing an Institutional Review Board (IRB), and assistance in grant management. Given the complexity of a clinical trials infrastructure, grantees required a year or more before their disparity program was fully operational leading some to restructure their awards to allow an additional year.

#### DEVELOPING CANCER DISPARITIES RESEARCH INTEREST AND PATIENT NAVIGATION

Because of the limited availability of cooperative group trials as noted above, the grantees used two approaches to expand protocol participation: (1) development of PI-initiated clinical trials targeting stage of disease and/or including shorter radiation therapy schedules to address patients' transportation or accommodations barriers (7, 8) and (2) expanding access to other NCI-sponsored clinical trials beyond radiation oncology, to include surgical/medical oncology trials (Table 2). This expansion was

**Table 2 | Cumulative number of patients accrued to different types of clinical trials by fiscal year in U56 planning phase and cumulative for U54 phase.**

Type of clinical trial	FY03 <sup>a</sup>	FY04	FY05	FY06	FY07	FY08	FY09	Total U56 period <sup>b</sup> (%)	Total U54 Period <sup>c</sup> (%)
PI-initiated	0	1	44	78	78	38	62	301 (18)	139 (20)
Mentor-initiated	0	0	0	0	0	0	160	160 (10)	203 (29)
RTOG	10	7	17	26	34	24	50	168 (10)	128 (19)
Other cooperative groups <sup>d</sup>	271	349	39	75	84	98	82	998 (60)	209 (30) <sup>d</sup>
Radiation only	1	0	4	20	9	0	3	37 (4)	-
Radiation/combined treatment	65	9	14	24	19	13	14	158 (16)	-
Medical/surgical	140	25	24	27	55	79	57	407 (41)	-
Cancer control/prevention	75	316 <sup>e</sup>	6	9	10	11	14	441 (44)	71 (45 <sup>f</sup> )
Pharmaceutical/industry	0	0	5	1	8	6	31	51 (3)	14 (2)
Total	281 <sup>a</sup>	357	105	180	204	166	385	1,678 (100 <sup>g</sup> )	693 (100 <sup>g</sup> )

<sup>a</sup>Rapid City had approximately 33 active clinical protocols opened during FY03 in which they accrued 281 patients onto the STAR trial and cooperative group trials (RTOG and NCCTG) (n = 281).

<sup>b</sup>U56 data are through September 30, 2009.

<sup>c</sup>Data cumulative for FY2010 through 2013 for all U54 grantees.

<sup>d</sup>Rapid City data include patients who were enrolled onto both RTOG and other cooperative group trials. The database structure at this site did not allow segregating the different trial categories (e.g., radiation only, medical/surgical) by only cooperative group trials. For U54 grantees, segregation was also not done.

<sup>e</sup>Includes Laredo's accruals to NCI prevention trials, STAR (n = 9), and SABOR (300).

<sup>f</sup>Percent accrual to prevention trials out of total NCI cooperative group trial accruals.

<sup>g</sup>Column percents do not total 100% due to rounding.

**Table 3 | Number of patients screened and eligible for cancer clinical trials.**

Grantee sites <sup>a</sup>	Patients screened		Patients eligible		Eligibility rate <sup>b</sup> (%)	
	(U56) <sup>c</sup>	(U54) <sup>d</sup>	(U56)	(U54)	(U56)	(U54)
Rapid City	1,601	3180	457	340	29	11
Centinela Freeman	28	-	28	-	100 <sup>e</sup>	-
New Hanover	228	2578	84	839	37	33
Singing River	982	2396	166	371	17	16
UPMC McKeesport	637	376	84	29	13 <sup>f</sup>	8 <sup>f</sup>
Total	3,476	8530	819	1579	24	20

<sup>a</sup>Data were not available for Laredo.

<sup>b</sup>Eligibility rate is based on the number of patients eligible divided by the number of patients screened.

<sup>c</sup>U56 data are from FY07 through FY09 only.

<sup>d</sup>Data cumulative for FY2010 through 2013 for all U54 grantees.

<sup>e</sup>Centinela Freeman did not screen all patients.

<sup>f</sup>Only includes data on the UPMC McKeesport site out of a total of five participating hospital at this CDRP site.

facilitated starting in 2006 by Clinical Trial Operating Committee (CTOC) supplemental awards to RCRH, SRHS, and UPMC McKeesport for hiring clinical staff interacting with other oncology specialists and resulted in increased annual patient accruals (Table 2).

Having breadth in the portfolio of trials was critical to overall participation as shown in Table 2. Early on, prevention trials boosted accrual (FY03-04), but later on the increased accrual (FY06 onward) was due to availability of non-radiation trials.

A total of 2,371 patients were accrued during both phases. The PI/mentor-initiated trials (see Supplementary Material) partially addressed the shortfall of trials suitable for this population as ineligibility remained an accrual barrier (Table 3).

In addition to informing patients about the clinical trials, the patient navigators supported by CRCHD had a positive influence on reducing the number of missed appointments and addressing other barriers to patient participation (9–11). Patient navigation was found to be a critical component at all CDRP sites as 5,147 patients were navigated (Table 4). RCRH and SRHS documented the critical benefit of patient navigators for their patients. Their data helped RCRH to receive a subsequent Komen Foundation grant specifically for a patient navigator to assist all their breast cancer patients, while SRHS's patient navigator became a hospital funded position starting in 2011.

The American Indian (AI) Community Research Representatives (CRRs) were established with CDRP funding at three remote AI reservations in South Dakota. These trained community health educators and Patient Navigators helped RCRH receive a 2-year CDC grant by partnering with the South Dakota Health Department utilizing their CRRs to implement a colorectal screening program for their AI population. Additionally, RCRH partnered with the American Cancer Society to implement the "All Women Count!" Breast and Cervical Cancer Early Detection Program for their AI women at the Pine Ridge Indian Reservation whereby the goals of both ACS and RCRH's *Walking Forward Program* were implemented (Dr. Petereit, personal communication, April 2014).

#### TELESYNERGY™ – TELEMEDICINE AND EMPLOYMENT OPPORTUNITIES IN REMOTE COMMUNITIES

When the CDRP program was initiated, telemedicine was just being established and this program became a pilot test for

**Table 4 | Number of navigated patients per fiscal year by CDRP grantee.**

Grantee sites	FY04	FY05	FY06	FY07	FY08	FY09	U56 total # <sup>a</sup>	U54 total # <sup>b</sup>
Rapid City	35	77	56	66	184	211	629	786
Laredo <sup>c</sup>	183	74	90	NA	NA	NA	347	NA
Centinela Freeman	NA <sup>d</sup>	80	146	166	90	127	609	NA
New Hanover	2	17	103	117	87	48	374	276
Singing River	NC	NR	NR	208	142	325	675	526
UPMC McKeesport	NA <sup>d</sup>	96	165	252	217	116	846	79
Total	220	344	560	809	720	827	3,480	1,667

NA, not applicable; NC, data not collected by CDRP site; NR, refers to data not received.

<sup>a</sup>U56 data were consistently collected beginning in FY2007, Quarter 4 through September 30, 2009.

<sup>b</sup>Data cumulative for FY2010 through FY2013 for all U54 grantees.

<sup>c</sup>Laredo data are unconfirmed.

<sup>d</sup>Patient navigation program was not active until 2005.

**Table 5 | Use of TELESYNERGY™ for CDRP grantee activities, by fiscal year – U56 phase\*.**

CDRP grantee activity	Number of times used for activity			
	FY07, Qtr 4	FY08	FY09	Total
Administrative meetings	5	29	28	62
Research consultations	21	8	16	45
Patient consultations	612	2,037	237	2,886 <sup>a</sup>
Tumor boards	12	113	108	233
Training/education	5	10	20	35
Other <sup>b</sup>	8	4	14	26
Total	663	2,201	423	3,287

\*Data were consistently collected beginning in FY2007, quarter 4 through September 30, 2009.

<sup>a</sup>99% of the patient consultations via TELESYNERGY® were conducted by Rapid City.

<sup>b</sup>Includes TELESYNERGY® maintenance and patient rounds.

TELESYNERGY™, a system developed jointly by the NIH Center for Information Technology and NCI. **Table 5** details how it was used. Videoconferencing facilitated communication between awardees and their mentors for treatment planning (12) and follow-up consultations at remote settings (e.g., South Dakota and Pennsylvania). It was also used among CDRP sites predominantly for training clinical research staff, tumor board conferences, research consultations, and sharing of ideas. Establishing clinical consultation sites at remote centers resulted in saved patient travel time, and it also provided employment opportunities for healthcare workers on the reservations and at satellite Pennsylvania hospitals. These successes were important lessons learned from the conduct of clinical trials and medical care for remote disparities communities (12–14).

#### DISSEMINATION OF RESULTS

The CDRP institutions were very active in presentations at local meetings and nationally at the Radiation Therapy Oncology

**Table 6 | Number of CDRP-related publications by grantee site.**

Grantee	Number of publications	
	U56	U54
Laredo	1	NA
Rapid City	23 <sup>a</sup>	24
Centinela Freeman	8	NA
New Hanover	4	4
Singing River	3	0
UPMC McKeesport	14	3
Total	53	31

<sup>a</sup>Includes three book chapters.

Group (now part of NRG Oncology) and the annual ASTRO meetings. Additionally, the CDRP program helped establish an annual ASTRO/NCI Cancer Disparity Symposium to help educate members about cancer disparities issues in the U.S. (see Supplementary Material). All CDRP sites were active to various degrees in publishing results of their cancer disparities program with RCRH being the most productive with publications (**Table 6**).

#### DISCUSSION

As pointed out in a BSA discussion, CDRP took on some of the most difficult challenges to develop clinical trials because of both the disparity populations and the limited previous NIH funding history. Although a higher level of trial participation may have been possible with health disparities sites within the catchment of an NCI-designated Cancer Center and the Division of Cancer Prevention's Minority-Based Community Clinical Oncology Program site, that CDRP successfully reached into the more difficult-to-reach areas dispelled the concept that this was impossible and/or that people would reject participation in trials.

To expect health disparities sites to achieve similar rates of clinical trial accrual as major cancer centers and their catchment area is

not realistic. Implementation takes time and include: (1) developing/training personnel with the necessary research skills and staff to work with government regulations for clinical trials; (2) advising administrators and hospital leadership about the patience needed to develop infrastructure and the wisdom to see the benefit to patients and institution; and (3) establishing physical space and technological facilities needed to conduct research and manage the data.

Having an experienced team from NCI initiate the programs with a visit to the institution was also important. Although there was skepticism based on the experiences that the government would “establish a program, do research, and then leave (14),” this support helped establish trust and personal relationships demonstrating that the government was invested in the community’s problems. The initial NCI team included physicians, senior administrators, program directors, and a patient advocate provided by the National Coalition for Cancer Survivorship (15) who emphasized the central importance of community buy-in at the outset.

We suggest that the proposed metrics of success for future disparities efforts include the usual “hard” metrics such as clinical trial participation and publications, but also softer metrics such as: (1) surveys conducted, (2) the number of patients screened, (3) the extent of outreach–recruitment activity, (4) additional research efforts leveraging their infrastructure, (5) staff recruitment, (6) enhanced interest in disparities by cooperative groups (e.g., RTOG) and professional societies (ASTRO), and (7) the ability to secure additional funding. Formal program evaluation as established by NOVA was extraordinarily helpful for the awardees and RRP in assessing progress and determining both gaps and opportunities for progress. The CDRP programs shared data and trials among the awardees, which facilitated the implementation science.

Several years are needed to ramp up clinical trial participation, including the need for surveys and focus groups, time to listen to the community, understanding their needs, assessing barriers and building teams and trust (5, 16). Establishing trusting partnerships with the AI community in SD was a potential barrier for the Walking Forward (WF) program that was successfully addressed over time and became evident when there was no difficulty in consenting patients to participate in the ATM genetic study (17). For the advanced stage diseases encountered in minority/underserved populations and limited number of cooperative group studies available, designing PI- and mentor-initiated trials and the later expansion to a broader portfolio of trials beyond radiation oncology resulted in increased accrual for these patient populations (Table 2).

Telemedicine has evolved significantly as the TELESYNERGY™ system progressed from expensive ISDN phone line systems to a web-based system using off-the-shelf technology. A simplified version is now available for public purchase by outside institutions, both nationally and internationally, with the possibility for support for technical consultations, installation, and training from NIH/NCI if needed.

The establishment of CDRP led to some important changes in the radiation oncology community. The RTOG (now part of NRG Oncology) raised the issue of the need for future

“health disparities” clinical trials to fill the gaps noted above. ASTRO developed an annual health disparities scientific program (see Supplementary Material) and additional radiation oncology activities related to cancer disparities on the international level include working with the Program of Action for Cancer Therapy (PACT) of the International Atomic Energy Agency (IAEA) (18)

Perhaps, the greatest challenge now is program sustainability. There were positive outcomes that were not predicted and are strong evidence of the value of investing in NIH/NCI clinical research in health disparities regions. Examples are provided from the three 10-year awardees.

- Rapid City Regional Hospital, in addition to coordinating the state programs mentioned previously, established collaborations with the Native American Cancer Research Corporation (NACR-PI Linda Burhansstipanov, DrPH), the University of Washington-Seattle (Dedra Buchwald, MD), Marquette University (Sheikh Iqbal Ahamed, PhD), and the University of New Mexico (Emily Haozous, PhD) to increase cancer screening and palliative care programs in the remote reservations for AIs. In addition, two resident physicians from Harvard University performed their research year at RCRH: Ashleigh Guadagnolo, MD, MPH (radiation oncology) and Sunshine Dwojak, MD (head and neck surgery). RCRH was awarded a 4-year NCI Provocative Questions R01 grant in 2012 by leveraging their CRRs to implement an “*American Indian mHealth Smoking Dependency Study*” program for the AIs in South Dakota. Several publications resulted from these collaborations with the WFP that ultimately assisted with program sustainability (4–6, 19–21).
- Coastal Carolina Radiation Oncology (CCRO) used their CDRP success in patient accrual to become a full member of NRG Oncology. To sustain their disparity program, CCRO again partnered with NHRMC to form the Southeastern North Carolina (SENC) CCOP, a grant that was awarded in 2013. Because the minority population in SENC is <50% of the population, the SENC CCOP could not apply to become a new NCI’s Community Oncology Research Program (NCORP) Minority/Underserved Community Site in 2014. Instead, CCRO will revert to full membership in NRG, while NHRMC will likely be an affiliate member of the Alliance group.
- Singing River Health System is building on their mentor relationship with University of Alabama Birmingham (UAB) Cancer Center. It will expand their current patient navigation program via participation as the only Mississippi-based site participating in the CMS Health Care Innovation Challenge award – *Deep South Cancer Navigation Network* and will receive \$1 million over 3 years to support 3.5 FTEs for their patient navigation Program.

Philanthropy is another means of potential support, but community resources that major cancer centers or cooperative groups have are not accessible in these health disparities communities. For them to raise sufficient funding to sustain their infrastructure and professional staff and become competitive for the major

infrastructure, clinical trials and center grants available are not a reasonable expectation.

## CONCLUSION

Through the CDRP program, clinical trials were established in health disparities sites not previously participating in the NCI clinical trials enterprise. The initial success of this pilot program is reassuring and may lead to improved general healthcare awareness for their minority/underserved populations and an increase in the diversity in NCI clinical trials.

Health disparity is an economic issue as much as a “minority” issue. Some health disparities regions have unique populations (i.e., the AIs) and when the study of the biological basis of cancer is conducted for their benefit, trust can be established and “precision/personalized” medicine targeting their illnesses can then be investigated.

The BSA review of the program renewal raised the issue of moral obligation for sustaining programs. Federal agencies support all of the people and the CRCHD has emphasized the large potential value of applying what we already know to help improve cancer outcomes for health disparities communities. While some of what CDRP accomplished met the standard metrics of clinical research as judged by participation numbers, there are aspects that were indeed unique and fall within implementation science. Lessons learned are applicable to future programs. In regard to the moral issue, research programs must pass peer review but, perhaps, different metrics are justified for the disparities sites that suffer from a lack of infrastructure and experience when competing for grants. For all the sites, especially the three 10-year awardees, the CDRP program succeeded in bringing people to clinical trials who previously were on the periphery and without access to the potential advances from these studies. This pilot program showed that reaching health disparities communities who are new to cancer research can be done and the future challenge is not only to broaden access to appropriate cancer care for health disparities populations, but also to sustain these gains.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at <http://www.frontiersin.org/Journal/10.3389/fonc.2014.00303/abstract>

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# Cultural roles of Native Patient Navigators for American Indian cancer patients

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The purpose of this opinion article is to clarify cultural roles Native Patient Navigators (NPNs) perform in providing cancer support. NPNs, who are American Indian (AI), provide many unique services to indigenous patients who are undergoing treatment (radiation, chemotherapy, surgery, adjuvant therapy) for cancer. AIs experiences of cancer often are complex, requiring a team that not only provides comprehensive, quality cancer care, but also provides care that incorporates cultural norms and beliefs. NPNs are an essential component of AI cancer patients' recovery and healing.

American Indians in the USA have distinct and significant geographic rates of cancer incidence and mortality, whereas White rates remain homogeneous (1–5). Indigenous people living in Alaska and the Northern (e.g., ND, SD, NE, WI, MT, MI) and Southern Plains (e.g., OK, TX, KS) typically have elevated age-adjusted cancer incidence and mortality rates. The substantial progress in reducing cancer death rates experienced by Whites over the past two decades has not been experienced by AIs (6); cancer mortality rates remain the same or more commonly are increased from previous data (1–5). AIs continue to have the poorest 5-year relative survival from cancer in comparison to all other ethnic and minority groups in the US (66.7% for non-Hispanic Whites vs. 59.0% for AIs) (7, 8). Anecdotal data from Canadian First Nations or Aboriginals, New Zealand Maoris, and Australian Aboriginals report similar geographic variability in their respective countries.

According to Harold Freeman, MD, the “father” of patient navigation, navigators guide patients through and around barriers in the complex health care system, to help ensure timely diagnosis and treatment (9) of cancer and other illnesses. However, the term “navigator” has varied meanings within healthcare systems, resulting in some confusion. As an example, the federal Affordable Care Act (H.R. 3590) (10) refers to navigators as trained individuals who “establish relationships with employers and employees, consumers (including uninsured and underinsured consumers), or self-employed individuals likely to be qualified to enroll in a qualified health plan” (11). Thus, under the Act, a navigator functions mainly as an insurance broker rather than one who helps patients overcome barriers to accessing and using a specific healthcare system or treatment plan/program. Within many settings, Community Health Workers, who are culturally, well-respected members of underserved populations, help bring these community members to the doors of the clinic or healthcare facility. NPNs function similarly to Community Health Workers; however, they cross the threshold of the clinic and continue providing cultural support within clinical departments (i.e., they cross boundaries). NPNs are familiar with varying tribal beliefs about health and illness and can establish a rapport and trust with patients that allow them to share their fears and spiritual practices necessary to achieve health and healing. NPNs provide services and support that are unlikely to be addressed by other hospital staff and they need to be paid lay

professional positions. Ideally, the NPN and the hospital collaborate to provide the optimal healing environment for the AI patients.

## KEY POINTS

- NPNs should come from or be familiar with and trusted by the local community (reservations, rural or urban settings).
- NPNs in urban settings should be able to work with AIs who come from many different tribes.
- NPNs need to be respectful of the local cultures and have cross-cultural skills. All NPNs will encounter AIs from different tribes; because of trust relationships with local communities, inter-tribal cultural differences have not been an issue.
- NPNs use respect and communication skills to allow AI patients to share personal, cultural, and religious needs related to their health and possible treatment.
- NPNs are an extension of the medical community and provide services that are not duplicated within most settings. Therefore, they should be paid.

Native American Cancer Research Corporation (NACR) has paid NPNs since 1995. NACR NPNs have navigated more than 1,000 AIs. A few examples from NACR's experienced demonstrate cultural roles as well as the collaboration with clinical staff. These roles may be comparable for indigenous people living in other parts of the US as well as countries outside the US.

1. A few patients asked the NPN to remove chairs from their hospital rooms. One

patient told the NPN that in his weakened state of mind, spirits may come into the room and convince him to go with them. If the chairs were in the hallway, the spirits had no place to sit in the room. The NPN removed the chairs and placed them in the hallway; hospital staff kept moving them back. The NPN explained the patient's tribal beliefs and requested the staff to leave the chairs in the hallway. The hospital staff was appreciative that the NPN shared this information. When the NPN returned the next morning, all of the chairs were in the hallway. Everyone wanted these patients to heal in a respectful manner and the patients appreciated the attention to their cultural beliefs and healing.

2. Most AIs believe that certain traditional items such as feathers, medicine bags, or stones have healing powers. NPN explained to clinical staff the importance of such items and asked the staff to assist the patient in keeping these items in close proximity. To support this patient's belief, an oncology nurse suggested using Betadine to sterilize the outer upper thigh, placing the medicine bag inside a sterile bag, taping the bag to the sterilized area on the thigh, then applying Betadine over the entire area. Having the bag with the patient provided additional spiritual strength for healing, and the bag's placement as suggested by the nurse was in an area that would not interfere with any procedures.
3. One of the local hospitals used an owl (showing a knowledgeable bird) on hallway walls to guide patients to specific treatment rooms (radiation, chemotherapy). However, to many AI Tribal Nations, the owl signifies that death is near. The NPNs explained this belief to hospital authorities who responded that there were too few AI patients for them to change the hallway symbols. To avoid the patient being exposed to the symbol, the NPNs escorted the patients to alternative routes.
4. Many AI Tribal Nations burn natural plants (e.g., sage, cedar, sweet grass) to clean the local environment or to remove spirits that may interfere with good feelings, attitudes, and medicines.

This is called "smudging" and the plants are usually burned using a shell or rock. Several AI patients have requested to have the hospital room smudged to contribute to their healing and recovery. However, in the USA, most hospitals have smoke-free policies. NPNs worked with clinical staff and traditional healers to find compromises. The hospital staff and NPNs transported the patient to an outside area that was delineated for smokers. The patient and bed were smudged outdoors and the remaining leaves in the shell were returned to the hospital room and used as pot-pourri. In another example, the patient was too sick to take outside but the Chapel in the hospital allowed candles and incense. The NPN brought the patient to the Chapel to burn the sage.

5. NPNs understand that many Tribal Nations believe that hair should be saved throughout life. It may be used in a variety of ways including being placed in the pillow placed underneath the head when buried. Patients receiving chemotherapy frequently lose their hair. Thus, when cleaning a brush or showering, the hair should be retained and not thrown away. The NPNs explain the patients' beliefs about not disposing hair to hospital staff and caregivers to provide support to the patient.

When considered alone, each of these examples are mere illustrations of cultural issues that NPNs address on behalf of their patients. Native navigation is not limited to these examples, but is a holistic approach to meeting the patients' cultural needs.

## CONCLUSION

Native Patient Navigators play a key role in providing a supportive healing atmosphere for AI patients because they understand the culture and beliefs of the patients they serve. Healthcare staffs are dedicated to the healing and recovery of their patients and, to date, have almost always welcomed the cultural guidance provided by the NPNs. These NPNs need to receive salaries to support their invaluable expertise and skills in helping AI patients through the cancer experience. Healthcare providers can greatly assist cultural navigators to become

eligible to receive payment for their services. One possible method to provide payment might be for the state departments of public health or insurance companies to pay organizations to hire a "Native Patient Navigator." These NPNs can be on call by any and all of the identified cancer centers, dependent on the source of the funds, to assist AI patients with cancer move through the system in a respectful manner. This way, a culturally appropriate native person is available to meet the needs of AIs in varying institutions, and no one place has to foot the entire bill since there are not enough AI patients in any one cancer center at one time. Once navigators are approved through insurance as a reimbursable cost, the cost can be spread across many institutions. It could be used as a strategy for other cultural and ethnic groups as well, dependent on the location and the need. But to make this strategy work, the NPN needs to be a regular employee on a continuous basis and not month to month, or year to year.

What we have learned from AI NPNs is relevant to other populations that live with health inequities in order to improve patient care and outcomes. Other populations need to adapt their cultural components within their respective navigation programs and use cultural navigators, such as NPNs, to support health, healing, and recovery.

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# The International Cancer Expert Corps: a unique approach for sustainable cancer care in low and lower-middle income countries

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The growing burden of non-communicable diseases including cancer in low- and lower-middle income countries (LMICs) and in geographic-access limited settings within resource-rich countries requires effective and sustainable solutions. The International Cancer Expert Corps (ICEC) is pioneering a novel global mentorship-partnership model to address workforce capability and capacity within cancer disparities regions built on the requirement for local investment in personnel and infrastructure. Radiation oncology will be a key component given its efficacy for cure even for the advanced stages of disease often encountered and for palliation. The goal for an ICEC Center within these health disparities settings is to develop and retain a high-quality sustainable workforce who can provide the best possible cancer care, conduct research, and become a regional center of excellence. The ICEC Center can also serve as a focal point for economic, social, and healthcare system improvement. ICEC is establishing teams of Experts with expertise to mentor in the broad range of subjects required to establish and sustain cancer care programs. The Hubs are cancer centers or other groups and professional societies in resource-rich settings that will comprise the global infrastructure coordinated by ICEC Central. A transformational tenet of ICEC is that altruistic, human-service activity should be an integral part of a healthcare career. To achieve a critical mass of mentors ICEC is working with three groups: academia, private practice, and senior mentors/retirees. While in-kind support will be important, ICEC seeks support for the career time dedicated to this activity through grants, government support, industry, and philanthropy. Providing care for people with cancer in LMICs has been a recalcitrant problem. The alarming increase in the global burden of cancer in LMICs underscores the urgency and makes this an opportune time for novel and sustainable solutions to transform cancer care globally.

**Keywords:** health disparities, cancer, global health, underserved, non-communicable diseases

## INTRODUCTION

The growing burden of non-communicable diseases (NCDs) in the developing world has been highlighted by the World Health Organization (WHO) report in 2010 and in a United Nations

(UN) declaration in 2012 (1, 2). Love et al. (3) have proposed the concept of public health oncology, which describes the multiple levels of complexity for addressing the problems of delivery of cancer care. It emphasizes that cancer and the other NCDs are

embedded in economic, social, political, gender, healthcare, and public health issues. The discussion of NCDs does not reduce the ongoing importance of the communicable diseases but, in fact, highlights the broad spectrum of diseases now encountered globally.

Coleman and Love have addressed the need for a transformative approach to science, service, and society, emphasizing that the task of reducing the burden of disease among health disparities populations is arguably as integral a component of academic translational medicine as are laboratory and clinically based research (4). This current paper describes the organizational structure and operational approach of an international collaborative organization, the International Cancer Expert Corps (ICEC). ICEC uses a unique mentorship model to help develop and sustain a workforce within cancer health disparities setting who are capable of conducting multi-modality cancer care and research at international standards. While healthcare disparities are well known to exist in lower-middle income countries (LMICs), similar problems also occur in resource-rich countries where people have difficulty accessing cancer care as a result of poverty, cultural issues, limited economic opportunity, and geographic distance from a cancer treatment center<sup>1</sup>. Considering a frequently expressed question “Why is the focus of ICEC on international when there are domestic problems?” ICEC recognizes that there are indeed common problems and potentially similar solutions among LMICs and geographic-access limited settings within resource-rich countries. In particular, the latter involve significant numbers of “aboriginal” or native populations, so that ICEC will address the geographically access limited issue in resource-rich countries as a global problem, which will benefit from the lessons learned from international collaboration. The LMIC community will provide the local investment in personnel and necessary infrastructure with whom the ICEC will provide mentorship. It is recognized that these are significant challenges for resource-poor communities; nonetheless, local buy-in and support are deemed to be critical to a sustainable program.

Partnering with and enhancing ongoing global health programs is an essential tenet of ICEC. Given the ICEC focus on mentoring and workforce development, collaboration with existing efforts will be mutually beneficial. Potential collaborating organizations include (a) international agencies such as the Union for International Cancer Control (5) and its Global Task Force on Radiotherapy for Cancer Control (6) and the International Atomic Energy Agency’s program of action for cancer treatment (PACT) (7); (b) research focused governmental institutions such as the Center for Global Health in the National Cancer Institute (8); (c) oncology professional societies from various countries and specialties, (d) oncology projects between resource-rich and resource-limited settings, including “twinning” projects (9) between academic centers and facilities within a LMIC setting such as those of Partners-in-Health (10) and AMPATH (11), and (e) international collaborative programs for education and research including the International Network for Cancer Treatment and Research (INCTR) (12).

<sup>1</sup>These are referred to “geographic-access limited” in this paper that also includes cultural issues, poverty, and limited economic opportunity.

## METHODS

The development of the model for ICEC is the result of decades of experience of a number of the authors from working in the underserved communities in the U.S. and globally. Examples include the PACT (7) and INCTR (12) programs mentioned above, the Harvard community outreach program in Massachusetts (13), the Cancer Disparities Research Partnership Program of the National Cancer Institute (14), the Walking Forward Program in South Dakota (15), experience in breast cancer care in Bangladesh (16), and the establishment of King Hussein Cancer Center Program as a major cancer program through shared expertise between Jordan and the NCI (17). The recent emphasis on non-communicable disease burden in global health (1, 2) led to recognition of the need for innovative approaches to healthcare. This is accompanied by unprecedented opportunity across a number of economic, healthcare, social, and political sectors (4). Building on ongoing discussions among global colleagues, including experts at the National Institutes of Health Fogarty International Center (18) and Center for Global Health at NCI (8), the ICEC model continues to take shape as ICEC moves into implementation. Key underpinnings are that ICEC is a multi-national global effort at the outset and that it is taking on a very difficult challenge for which innovation and sustainability are deemed to be essential.

The ICEC has seven essential characteristics for a science-grounded strategy:

1. Decrease cancer incidence and mortality and improve quality of life globally. Use specific benchmarks and defined metrics to assess all interventions.
2. Build an international effort from the outset with collaboration across countries, sectors, and disciplines.
3. Emphasize local initiative built from community leaders or “champions.” The projects will be established from the bottom-up based on local needs and opportunities coupled with the ability of ICEC to help leverage local investment. ICEC will not build physical infrastructure.
4. Establish research efforts including implementation science (defined in Section “Research”) and programs across the cancer control spectrum from prevention to treatment to follow-up to elucidating mechanisms of cancer biology.
5. Aim for the availability of effective treatments including cure and palliation for every patient with cancer in the world within the next two decades. This is in concert with the Global Health 2035 goals (19).
6. Develop sustainable worldwide capacity and capability through public health approaches, applications of innovative economic and business models, greater knowledge sharing, and exploiting new information technologies.
7. Work to effect a cultural change that values and rewards as an integral part of a career the efforts for working on human-service efforts.

Notably, this approach to cancer is applicable to NCDs in general. The public health and systems approach is consistent with that described by Kim (20), which focuses on HIV/AIDS emphasizing a systems level analysis and interventions across the healthcare system involving broader social and economic determinants of

health. This is similar to the issues described in public health oncology by Love (3). The ICEC career approach helps meet the objectives of an international service corps described by Kerry (21) and builds on the suggestion that the more classic components of academic healthcare careers, research, education, and patient care, which have already been broadened in scope in the last few decades further expand the academic mission to include policy, social responsibility, and service to addressing overarching societal issues, including health disparities (22).

## RESULTS

### INTERNATIONAL CANCER EXPERT CORPS

#### *Description and vision*

The ICEC is an international mentoring network of cancer professionals who will work with local and regional in-country groups on projects to develop and sustain expertise and local solutions for better cancer care. The vision is a world in which everyone has access to cost-effective interventions to prevent and treat cancer and its symptoms in ways that are consistent with best possible practices for the local circumstances. Addressing and realizing this vision can benefit people everywhere because of the scientific, humanitarian, and diplomatic consequences of such projects.

#### *Intervention model*

A major issue in global health is whether national policy prescriptive approaches such as cancer plans, which are top-down efforts, should be the priority, or whether bottom-up, local community specific approaches are more likely to achieve our developmental goals over the long term (23). We believe aspects of both approaches are useful for building local capacity and capability, but the uncertainties about *how* to address the breadth of complex psychosocial–medical cancer issues indicate a need for more investigative–research driven, bottom-up efforts (3).

Therefore, the ICEC model is to establish LMIC programs from the inside out and from the bottom-up. The focus is on *people* and on sustainable mentoring and collaborative relationships among ICEC Experts and local Associates within ICEC Centers in regions/countries that will invest in solutions for the underserved. As detailed below, senior mentors and retirees will not only mentor Associates but also guide and mentor junior and mid-career faculty from resource-rich countries who aim to pursue a career path in global health. Mentoring will be accomplished by international teams of Experts whose goal is to apply guideline- and protocol-driven care at international quality standards and be capable of joining international research groups as they so choose. The product of this relationship will be cancer programs in cancer disparities settings with the capacity, capability and credibility to (a) assume a leadership role in their own region; (b) bring new knowledge and approaches to addressing cancer disparities issues globally; and (c) be equal partners among the world expert cancer educators and researchers.

#### *Organizational structure*

**Figure 1A** illustrates the ICEC functional construct and **Figure 1B** includes ICEC functional components. The focus of the ICEC is to develop expertise in ICEC centers under the guidance of local ICEC Associates. The Centers will be linked to the ICEC through a Hub in their region. Hubs are cancer centers or other groups and

professional societies in resource-rich settings that will comprise the global infrastructure coordinated by ICEC Central. While visits between Experts and Centers are critical, mentoring will largely be accomplished by scheduled teleconferences to teach and review multi-modality care through guidelines and protocols.

The focus of the ICEC is to work with *Associates* who are local change-makers or “champions” serving health disparities populations. They will work in medical facilities/locations where there is a multi-year commitment to investing in infrastructure and people toward improving the quality of care and life for their affected citizens. The facilities are designated *ICEC Centers*. Using a multi-year, jointly prepared “bottom-up” plan, the Associates progress from Associate-in-training to Junior Associate to Senior Associate based on defined metrics. The Center will progress from a Developmental Member to Provisional Member to (Full) Member, which requires passing a “cooperative group” quality site visit. Once Senior Associate and Full Member status are achieved the Center can then serve as a Hub for their region.

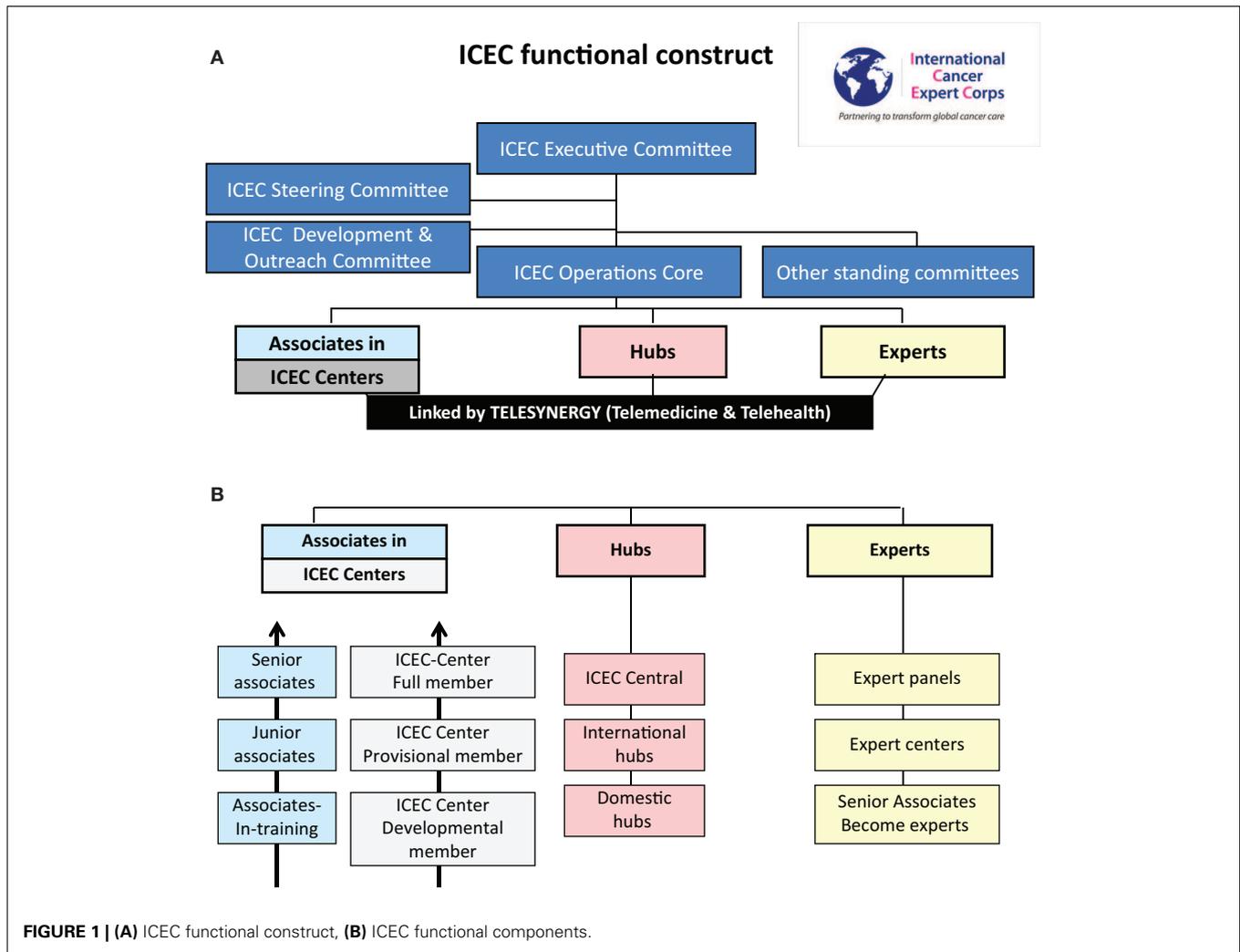
*Experts* will include the range of oncology disciplines, health-care delivery services and public health, economics, and policy specialists. The categories of the Expert Panels defined are in **Figure 2**. Multiple ICEC experts will mentor an Associate/ICEC Center in the conduct of guideline- and protocol-based care and not on individual patient management. To ensure sustainability, there will be a required commitment of time and effort for the Experts. Experts include senior expert academicians and mentors, private practitioners, faculty, and trainees in the range of academic ranks from institutions who will help design and support a formal career path for human service. Experts may join as individuals, institutions, societies, or teams.

*Hubs* provide the infrastructure and, working through ICEC Central, will coordinate the linkage between the Associate/ICEC Center with the Expert mentor so that the professional time is spent on mentoring and education. By having resource-rich Hubs worldwide share the “on call” duty there can be essentially full-time person-to-person connectivity and highly efficient coordination of time and use of resources. Hubs will be major academic cancer centers, private practices, professional societies, and others. While ICEC is worldwide and all Hubs have a global focus, some Hubs that focus primarily on LMICs will be international hubs and those that address health disparities geographic-access issues within resource-rich countries, such as the native populations in the US, Canada, and others, will be domestic Hubs recognizing that their health disparities issues have solutions in common with those of LMICs.

#### *Building partnerships*

The process for how a facility or group within a health disparities region will work with ICEC to become an ICEC Center is illustrated in **Figure 3**.

An application review will help determine the composition of the initial team from ICEC to meet on-site with the applicant. This on-site discussion includes a needs assessment and exchange of ideas that will help ICEC and Associate/Center develop a mutually acceptable multi-year plan. The new ICEC Developmental Center will be paired with a regional Hub. The initial ICEC Experts will be assigned from throughout the global network based on the initial needs of the Center. The Associate serving as the Principal



Investigator Associate (may be Associate-in-training or possibly already more senior) and the team at their ICEC Developmental Center will begin the process of establishing multi-modality cancer care. This will likely be a multi-year process, possibly up to 5 or so years. There will be occasional visits among the Associate/Center and Experts, coordinated by their regional Hub, but mentoring will be primarily accomplished through scheduled teleconferences for “case” reviews for the patients who are being treated on the specific guidelines or protocols, which are being used for the mentoring and training. The Associate and Center will progress in capability for cancer management to where an initial Quality Assurance Site Visit is passed. Further program development and mentoring will involve some of the initial Experts for continuity and also the addition of others with the growing scope of expertise in the Center.

Ongoing evaluation of progress for all components of ICEC is essential for guiding development and to learn from experience. It is anticipated that formal research will be conducted that will range from implementation science to translational research to clinical trials to social and economic research. At a point in time when there is multi-modality care, data-management systems, and the ability to adhere to guideline- or protocol-based care a “clinical

cooperative group” site visit will be passed, which indicates that the ICEC Center is ready to apply for full participation in worldwide clinical trials. ICEC is not an accreditation body so that approval of the ICEC Center’s participation in such studies would be the responsibility of the particular research program or agency. Once (a) the ICEC site visit is passed and a level of expertise achieved, (b) there is a Senior Associate as program leader and other Associates as members, and (c) the Center is a Full Member, the ICEC Center could become a regional Hub for ICEC.

#### CAREER PATH

##### *Careers that include global health*

Education and training are key activities of ICEC. It is expected that the Associates are completing or will have undergone formal training in their discipline, although it is recognized that the extent of training and specific credentials will vary. As noted above, a breadth of expertise will be required to mentor physicians, nurses, scientists, epidemiologists, and other healthcare and health policy workers from LMICs in public health oncology (3), and in global health. A key aspect of ICEC is that the Associates in LMICs can provide care and also are trained to critically analyze local cancer



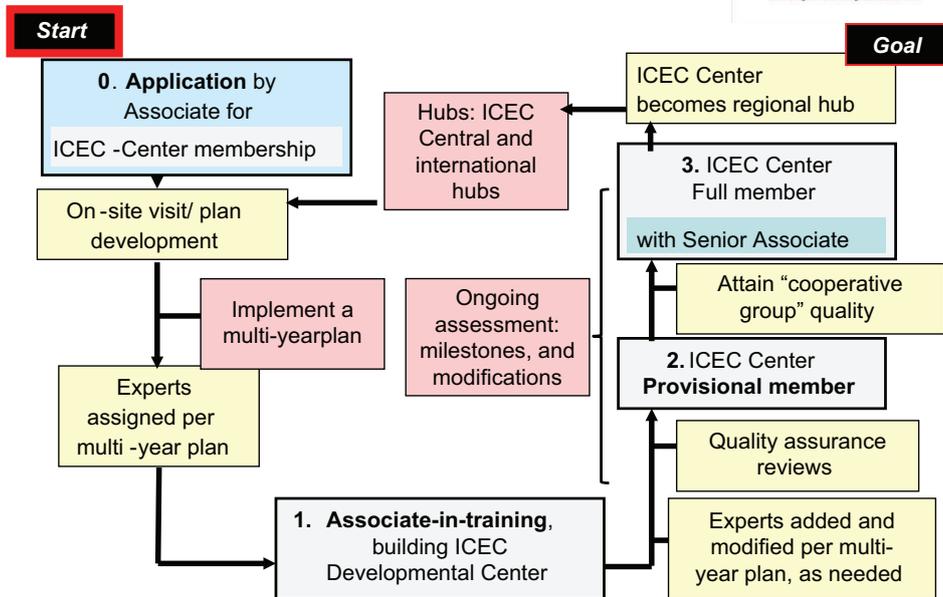
### ICEC Expert Panels: Public health oncology with broad spectrum of expertise

Medical	Science, non-MD	Support
<ul style="list-style-type: none"> <li>• Radiation oncologists</li> <li>• Medical oncologists</li> <li>• Pediatric oncologists</li> <li>• Surgical oncologists</li> <li>• Nurses</li> <li>• Pathologists</li> <li>• Radiologists</li> <li>• Surgeons - general</li> <li>• Surgical subspecialists</li> <li>• Pharmacologists</li> <li>• Psychologists</li> <li>• Public health</li> </ul>	<ul style="list-style-type: none"> <li>• Prevention and screening</li> <li>• Epidemiologists</li> <li>• Medical physicists</li> <li>• Technologists</li> <li>• Basic &amp; translational scientists</li> <li>• Treatment guidelines</li> <li>• Statisticians</li> <li>• Social scientists</li> <li>• Regulatory Affairs specialists</li> <li>• Pharmacists</li> </ul>	<ul style="list-style-type: none"> <li>• Educational tools</li> <li>• Finance</li> <li>• Clinic administration</li> <li>• International policy</li> <li>• Patient advocacy</li> <li>• Economists</li> <li>• Social workers</li> <li>• Communications</li> <li>• Cancer survivors</li> <li>• Information tech (IT)</li> <li>• Data-management</li> <li>• Legal</li> </ul>

**FIGURE 2 | ICEC expert panels.** A broad range of expertise is required, although there will initially be a focused effort. Expertise is required in the standard medical disciplines for cancer care, scientific, and medical

disciplines for research and supporting disciplines to address the economic, societal, social, and political issues the comprise public health oncology (3).

### ICEC- from application to ICEC Center that serves its region and world



**FIGURE 3 | Progression from application to Full Member and Senior Associate.**

care systems and develop approaches for improvement. The latter will be shared among ICEC and published so that others might benefit from lessons learned. Annual meetings at different locales will enhance cross-cultural education and sharing of ideas and experience.

Given its central role in treatment and cure of malignancy often encountered at advanced stage in LMIC and in its palliative potential, radiation therapy will be a requirement. If not present at the outset there must be a clear plan and timeline to obtain this capability within the first few years. Establishing radiation therapy, diagnostic imaging, and laboratory capabilities in settings that may not have stable infrastructure (power, water, communications, etc.) provides an enormous opportunity for technological research and development, creating affordable treatment paradigms, and developing novel approaches for remote-access medicine and means of utilizing and deploying information technology. While ICEC will not supply equipment, we will bring together industry partners and economists to (a) address the need for appropriate technology, including cobalt units, brachytherapy, imaging, including basic CT and linear accelerators possibly of novel modular design so that complexity of treatment will progress as skills develop; (b) investigate sustainable economic models for affordable treatment with a goal of a course of cancer treatment for approximately \$400, the approximate cost of a cataract operation in LMICs and in line with the challenge by Kerr (24); (c) examine business models that not only help fill the enormous cancer care gap and open new markets (25) but also potentially cluster facilities so that regional service centers are economically viable; and (d) develop a skilled workforce connected to international expertise who will be able to utilize the technology safely and effectively.

### **Career in global health is needed for sustainability**

The current career paths in academia involve clinical, laboratory, and translational research, education, public health/outcomes research, and patient care. While global health is being emphasized in undergraduate education and to some extent in training, it remains an area for substantial academic exploration since at present a very limited number of people are engaged in this aspect of healthcare as a routine component of their career. To that end, we believe that there is the need for a transformational approach to return this type of altruistic service to where it is an integral component of a healthcare career (4) and not a side light.

This requires pioneering institutions to create a *bona fide* career path in academia for healthcare service to the underserved by providing an organizational and academic base in resource-rich centers of excellence for public health oncology experts (26). This would involve enhancing the focus of global health programs from their current emphases on general training of medical students to emphases on service and research that can be maintained throughout faculty careers as are laboratory and translational research, teaching, and clinical care. The current value system in healthcare would be modified by providing time and academic recognition for this type of activity to further emphasize values of social responsibility and service. Allocating time and establishing a new value and reward system for altruistic service may have positive ramifications on mitigating spiraling healthcare expenditures (13, 27).

### **Global resource and expertise sharing**

Figure 4 summarizes the global interconnectivity of the ICEC model. ICEC Centers will link to the network through a Hub in their region. Coordinated through ICEC Central operations (*vide infra*) the Hub would call on Experts who are reliably available because they have time and effort predictably committed to this activity. To enhance the global nature of cultural interchange and idea sharing, a Center and Associate will have Experts that come from different countries within the global network. Senior mentors will mentor Associates and also educate early-career Experts who thereby gain access to world renowned mentors. Critically, work and family lives do not need to be disrupted for extended periods of time. Because the great majority of the time for mentoring is in scheduled educational “case” conferences (akin to radiation oncology chart rounds), the ICEC designated time can be part of a standard career in academia and practice. Educational materials developed by professional societies, the International Atomic Energy Agency and its virtual university for cancer control (VUCnet) (28), and others will be utilized to avoid duplication of efforts.

The unique aspect of ICEC is the assembling of a critical mass of global health expertise. There are already “twinning” programs among academic centers and facilities in LMICs and international programs with whom to partner and enhance breadth and depth. Sharing of expertise and resources means that the investment by any one Hub is not excessive while the system-wide aggregate is substantial.

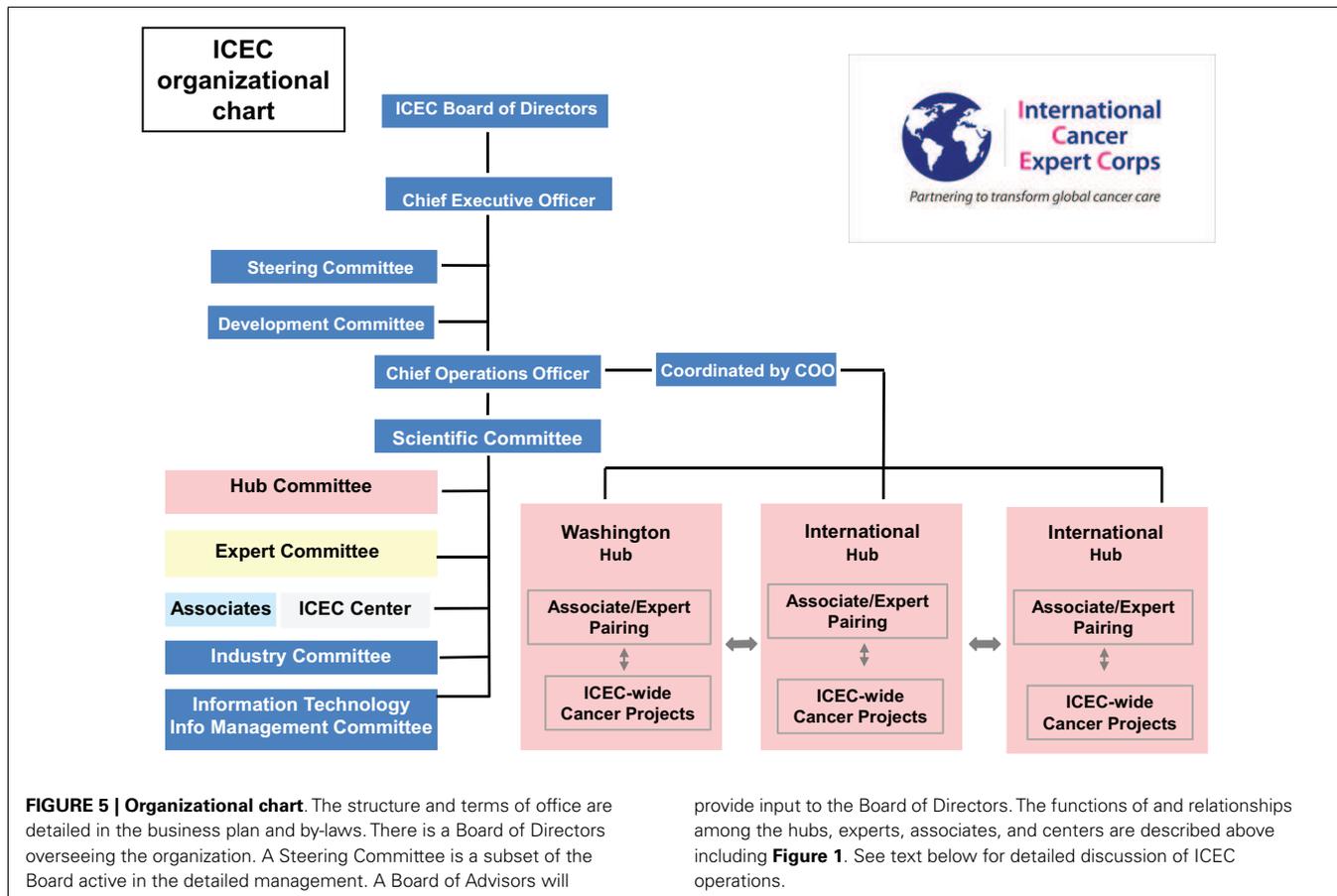
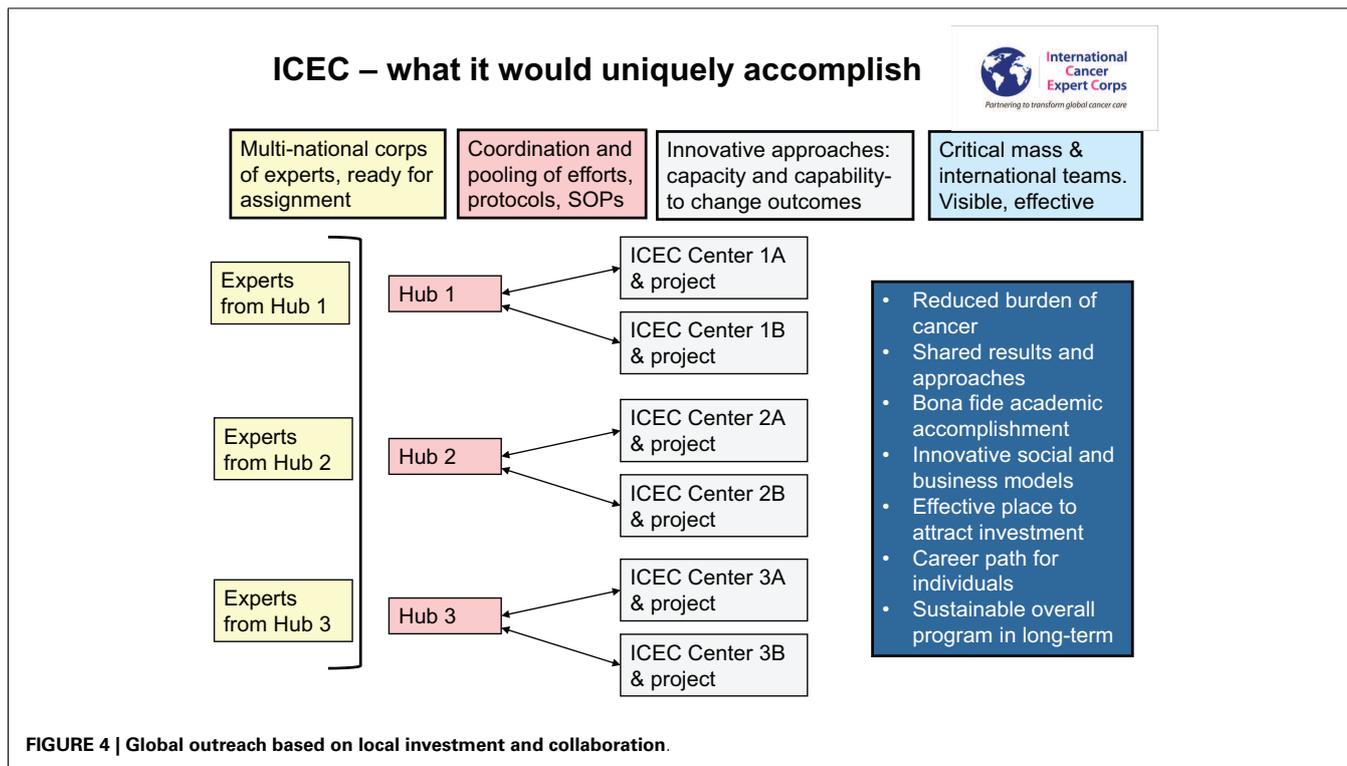
As it now stands many twinning programs between resource-rich cancer centers and LMICs depend on the efforts of a few people. By having programs work together and share ideas, models, expertise, and resources, a robust networking system can be created that can have continuity and sustainability beyond a founder. The four boxes on the top of the figure describe what will be done while the box on the right side includes the long-term goals.

### **ICEC OPERATIONS**

#### **ICEC operations**

There is an increasing interest in global health attested by the rapid growth in the consortium of universities for global health (CUGH) (29), a partner with ICEC. Many of the programs are either short or medium-term visits with no or limited follow-up. For those of us creating ICEC, it became evident that sustainability is essential with the ability to make decisions when opportunities arise. We concluded that sustainability is best achieved within a not-for-profit, non-government organization that can partner readily with government agencies and work across international boundaries. ICEC accomplishes this by having Hubs and Centers established locally that collaborate through facile central coordination, agreed-upon standard operating procedure and guidelines, and by sharing resources through mechanisms such as memoranda of understanding, contracts, grants, and other agreements. Mutual goals, addressing important problems, and trust are important components of mentoring, innovation, and growth. For the ICEC systems approach vision, organization, planning, execution, and adaptability are essential.

Figure 5 is a detailed organizational chart for ICEC. As with any complex system, attention to details, assessing progress,



and outcomes, and experience-based flexibility are critical. It is recognized that the structure and function will evolve.

Each expert panel in **Figure 2** will consist of a leader and members, the goal of which is to have at least 20% of each Expert's time committed (8 h/week, on average over the year) to ICEC efforts as a *bona fide* component of their job. The full-time equivalent (FTE) concept is used so that five people contributing 20% of their time would be one FTE. In the start-up of ICEC, there will be a limited number of ICEC Centers/Associates, Hubs, and Experts. Some of the initial groups are below, recognizing there will be rapid expansion of breadth of Expert panels:

Initial diseases (and the public health problem and oncologic opportunity included)

- Cervix (implementation of standard external beam and brachytherapy services, sexually transmitted disease, vaccine);
- Head and neck [smoking, combined modality therapy with radiation plus chemotherapy using cost-effective drugs (applicable in other cancers)];
- Lung (respiratory diseases, potential for hypo-fractionated (few-fraction) radiotherapy and novel combined modality therapy with radiation plus chemotherapy);
- Breast (women's issues, screening, genetic disease), hypofractionation, breast brachytherapy for early stage disease;
- Palliative care (reduce burden of care on families and health-care system and reduce suffering, immobility, and potential abandonment for patient);
- Lymphoma (relates to a younger population and for which collaborative programs are in place).

Initial panels (there will be other Experts as needed for diseases above)

- Radiation oncology
- Medical oncology
- Surgical oncology
- Palliative care physicians
- Medical physics, technology (including industry to develop new technology)
- Nursing (anticipated to be a key underpinning of Centers)
- Data management and Information Technology (using cell phone technology)
- Imaging (including teleradiology- basic radiology and CT)
- Pathology (including telepathology)
- Pharmacists (especially for palliative care and cost-effective chemotherapy).

### **Development and outreach**

The overarching development goal for ICEC is to provide partial salary support in the form of contracts/grants to enable altruistic service and global health to become an integral part of the spectrum of academic and professional careers. In that the goal is 20% of time, or 8 h/week on average over the year, ICEC will aim to have a matching program of ICEC support and in-kind contribution (equal match) thereby leveraging one funded ICEC FTE up to 10 Experts. The cost of any FTE supported will be based on the local pay scale with maximum limits set by the Board. (This

will be at most the NIH FTE rate for resource-rich countries). Financial support for a position will make this career path possible, especially so in the changing face of healthcare; however, as critical or even more so than compensation is the career recognition and reward, which in academia includes promotion in rank, professional recognition and career advancement.

A unique aspect of ICEC will be drawing expertise from three tracks, each of which has untapped potential:

- *Academia.* A career path will proceed from trainee to junior faculty (Assistant Professor) to mid-career (Associate Professor) to senior faculty (Full Professor). As it now stands, students and trainees are often engaged in global health but there is not a well-defined or supported career path beyond training (26). ICEC is working with visionary leaders in formulating an approach toward a formal career path that can serve as a template for other interested universities.
- *Private practice.* During the initial presentations of ICEC it became clear that private practitioners have the keen interest, clinical skills, experience, and flexibility to serve as leaders and mentors. At the time of this publication, there are two practice groups in the United States that will be pilot Hubs. ICEC will help develop an advancement scheme that provides appropriate recognition for the individual contributions in a manner similar to that of academia.
- *Retirees.* With the major oncology societies approximately 50 years old and radiation and medical oncology specialty boards approximately 40 years old, there is now a growing cohort of senior mentors and retirees whose experience, wisdom, and interest in serving will be tapped. Having new challenges and opportunities for senior people will allow those interested to extend their careers and also to open up senior opportunities to junior faculty in their home department. They will mentor Associates and also younger Experts. With their international reputations they become role models for altruistic service and global health as a sustainable career path. In that much of their costs will be in-kind, this may help develop a novel economic model for healthcare, as suggested by Christensen (27) in that some of the more expensive "solution shops" (27) can be obtained at greatly reduced cost thereby substantially enhancing the value that ICEC brings to solving the underserved problem.

### **RESEARCH**

The ICEC conducts and enables research. Mentoring will help build capacity but there is much to learn about how to solve the economic and access problems of reaching the underserved and establishing the best treatments for their resource settings. Therefore, having capability to do research and accrue credible data, there is ample opportunity for the Associates and Centers to perform different types of research in addition to the more standard clinical trials. Some examples are as follows:

- *Implementation science.* As defined by the Fogarty International Center of the National Institutes of Health (30):

Implementation science is the study of methods to promote the integration of research findings and evidence into

healthcare policy and practice. It seeks to understand the behavior of healthcare professionals and other stakeholders as a key variable in the sustainable uptake, adoption, and implementation of evidence-based interventions.

As a newly emerging field, the definition of implementation science and the type of research it encompasses may vary according setting and sponsor. However, the intent of implementation science and related research is to investigate and address major bottlenecks (e.g., social, behavioral, economic, management) that impede effective implementation, test new approaches to improve health programming, as well as determine a causal relationship between the intervention and its impact.

The ICEC is addressing a problem that is unsolved and growing – cancer care in LMICs. It is piloting a complex system solution using collaboration, mentoring, and idea-sharing among countries, cultures, and disciplines that has transformational potential. High-quality data yielded from research will inform the evolution of this challenging process.

- *Translational research.* The opportunity to study unique aspects of cancer biology including infectious and environmental causes can expand the understanding of cancer and generate new treatments. This type of research can be initiated in the early phases of ICEC Center and Associate development and can provide immediate local benefit. Having options to access research may serve as an additional motivation for the Center to establish quality data management so that they can derive further benefits from new knowledge and also bring a level of prestige and respect that can enhance investment in their Center.
- *Economics, healthcare models.* Crisp, Christensen, Love (3, 27, 31), and others emphasize that the solution to addressing cancer and NCDs requires novel economic models. The breadth of Experts in Supporting Disciplines (Figure 2) will help develop sustainable solutions through new models and a collaborative network. This includes bringing in complex technology with the needed supporting services (e.g., maintenance, supplies, and technicians) and also using novel technology to simplify care (e.g., cell phones). Given the magnitude of the shortfall of resources the ICEC approach is amenable to using a pre-competitive, collaborative approach among industry to improve outcomes and to greatly expand markets for a range of goods and services.
- *Role for radiation oncology.* A recent series of articles organized by Zeitman (32) addresses the potential role and responsibility of radiation oncology for global cancer health. Datta and colleagues (33) provide a detailed description of the infrastructure and human resources shortages using data from GLOBOCAN, International Agency for Research on Cancer. Suggested remedies include capacity building, networking, and a challenge to industry for low-cost, affordable, low-maintenance equipment. Fisher and colleagues (34) and Page and colleagues (35) discuss the shortages in Africa and the pros and cons of cobalt and linear accelerators, both of which have roles. Fisher has pioneered a program Radiation Hope (36), which aims to obtain equipment and implement treatment (37).

A key to establishing sustainable programs and to the ICEC model is support from professional societies. There is a clear interest in global education by the American Society of Radiation Oncology (38) and the Association of Residents in Radiation Oncology (39). ICEC will aim to capitalize on this interest to where it can be a sustainable career path.

## GLOBAL NETWORK COORDINATION AND PUBLIC-PRIVATE PARTNERSHIP

### ICEC central

The various components of ICEC will be coordinated by ICEC Central with policies and procedures developed by ICEC Committees (Figure 4). ICEC daily activities are conducted under the Chief Executive Officer, the Executive Secretary to the CEO, and the Chief Operating Officer with advice from the Senior Scientific Advisor. A Steering Committee of the Board of Directors is readily available as needed and will be involved in routine discussions with the Operations team. While ICEC is in start-up mode, individuals may assume more than one role. Working with the Board of Directors and Board of Advisors, the various committees are establishing the policies and procedures to be used throughout ICEC.

Initial committees are

- Experts and Application/Career Path
- ICEC Centers and Associates
- Hubs
- Operations/Information Technology-Information Management
- Scientific – which will consist of representatives from Experts, ICEC Centers and Associates and Hubs to determine research directions
- Industry – who will work with industry, including a pre-competitive model, to develop equipment and approaches for bringing technology and care to cancer health disparities populations
- Outreach and Development.

### Non-government organization and public-private partnership

The ICEC is a non-government organization incorporated in the State of Delaware, United States and recognized the Internal Revenue Service as a 501 (c) 3 tax exempt entity. Given its primary focus of patient care, the mission of the ICEC is complementary to that of the Center for Global Health of the National Cancer Institute (8). To the extent permissible by federal regulations, ICEC will partner with the federal agencies.

## DISCUSSION

A recent assessment of investment in global health pointed out diseases that cause the highest burden as measured by disability-adjusted life years (DALYs) do not get much of the international investment. The NCDs produce approximately 45% of the DALYs but receive <5% of the aid (40). Using the measure of the years of life lost (YLL), NCDs are a substantial problem starting with the 15–49-year-old age group and becoming the major cause of YLL for those age 50 and over, yet the development assistance for health (DAH) for NCDs is merely 1% of the total DAH in LMICs (41). The 2010 WHO global status report (1) and a related

2012 UN declaration (2) brought attention to the growing burden of NCDs including cancer in LMICs. Notably, case burdens are also increasing in rural underserved areas within resource-rich countries with the native/aboriginal populations often having similar access to care, poverty, economic, and social challenges as encountered in LMICs (15). Thus, for health disparities populations worldwide, cancer is a progressively urgent problem from medical, health system, business, workforce, economic, and ethical perspectives. A sustainable approach to build local capability and capacity is warranted. Cancer affects people in both resource-rich and resource-poor settings and serves as a compelling common global problem upon which to build partnerships and to develop novel highly collaborative sustainable approaches.

### BUILDING ON SUCCESS AND LESSONS OBSERVED

In addressing issues of global healthcare, Nigel Crisp suggested that critical premises for an ideal model include an understanding of the societies in which these occur focusing on public health with community and outpatient-centered services, building locally defined solutions with reliance on local skills (31). Christensen's analysis of the failure of high-income country business models in health has provided three perspectives for a different "disruptive" roadmap for innovation in cancer health: the need for technological enabling, business model innovation and value networks (27). Yunus' social business model is one upon which cancer care activities might be structured for sustainability and growth (42). These ideas all provide intellectual bases for the kinds of cancer health projects and economic and social investigation the ICEC will pursue, specifically building on the experience and assessment from those in the local setting, in addition to clinical care and research relevant to their situation. ICEC recognizes the importance of establishing metrics to assess programs and progress in order to justify ongoing investment (40). ICEC will build on the strong research culture in cancer care and on the proven outreach experience of the ICEC Hubs, the Cancer Disparities Research Partnership program from the National Cancer Institute (14), experience from the International Network of Cancer Treatment and Research (12), and collaboration with the NCI Center for Global Health (8, 43).

### ALTRUISM IN MEDICINE

Healthcare expenditures continue to grow with economic models dominating how care is delivered and how professional compensation is determined. Perhaps not sufficiently part of the discussion and solution, observers have suggested that altruism is declining in medicine (36–38, 44–46). However, human service and altruism continue to be important aspects of a physician's professional responsibilities and attitudes (26, 47), and these professionals are willing to give their time and efforts toward altruistic causes (48) a trend that appears to be growing amongst young people entering careers in medicine. However, "altruism cannot thrive due to its lack of rewards and feedback, particularly in the economic climate of today's science" (48). Programs to effectively address issues of such importance as changing the course of global health can only be reliably sustained when such activities are an integral part of daily work. We believe that while the central skills of academic medicine remain clinical care, research, teaching,

education, and mentoring, twenty-first-century responsibilities include public health, policy, and solving major societal problems and must be built on social responsibility and service (4, 22).

The establishment of ICEC itself is implementation science and ICEC will enable research to be conducted by and for the benefit of those in health disparities regions, which include those in resource-rich countries. Metrics will be established and appropriately modified based on experience to assess progress, develop novel strategies and share experience among the network of global partners. The breadth and depth of ICEC will be such that individual programs in LMICs are not dependent on single individuals so that long-term investment by the local community, industry and committed individuals has a high probability of success. We believe that the current crisis can no longer be ignored and that "it is too hard or too big a problem" are not acceptable answers. To quote Nelson Mandela: "It always seems impossible until it's done" (49). For scientific, medical diplomacy, ethical and humanitarian reasons, the time is right for a major initiative to address cancer in LMICs. ICEC welcomes participation.

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