TREATMENT, NOT TERROR: A UNIQUE CANCER TREATMENT PARADIGM FOR DEVELOPING NOVEL LINEAR ACCELERATORS FOR RESOURCE- LIMITED SETTINGS[1,2].

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Abstract

A transformational approach to two difficult global problems is being pioneered under the concept of "Treatment, not Terror". The first challenge is the potential purposeful (terrorist) or accidental misuse of cobalt-60 radioactive sources intended

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for radiotherapy; the second challenge is the dire need for effective cancer care in low-resource settings globally, including low-middle income countries (LMICs) and geographically isolated populations in high income countries. Radiation therapy is an essential component of cancer care, needed by about 60% of cancer patients. There is the need for a robust linear accelerator (LINAC) that can provide better cancer treatment and avoid the security risks posed by outmoded cobalt-60 radiotherapy machines. Such novel machines could function reliably in challenging environments with harsh climate conditions, unreliable energy sources and potentially long delays for the repair of breakdowns. Also required is a sustainable local workforce with the expertise to operate the LINAC safely and effectively. This paper outlines a novel approach that sees cancer care as part of a healthcare systems solution being developed by the International Cancer Expert Corps (Flex-competence©). This project brings together linear accelerator experts and medical physics and engineering communities, public health and medical experts committed to addressing global health disparities and the nonproliferation community that understand this solution not only improves cancer care and a local economy but also helps build global networks of trusted partners. This substantial global collaborative approach not only uses physics and engineering expertise but also builds on the essential characteristics of physics research for solving large complex problems, building on the synergy that occurs when groups with complementary expertise come together to create and implement unique solutions.

1. INTRODUCTION: THE CONFLUENCE OF PROBLEMS BEING ADDRESSED

In the last decade, experts have recognized that two major socioeconomic challenges could be addressed with the development of a novel linear accelerator (LINAC). With World Health Organization data [1] indicating the rising burden of noncommunicable diseases (NCDs) (predominantly cardiovascular, oncologic, respiratory and metabolic diseases in LMICs) in 2011 the United Nations General Assembly formally recognized NCDs as a global problem. Simultaneously, terrorism concerns and a 2008 National Academy of Sciences study led Congress and the US National Nuclear Security Administration to see the substitution of non-isotopic technology as a means of permanently reducing the threat of radiological terrorism, such as a terrorist "dirty bomb." This view won global endorsement at the 2014 and 2016 Nuclear Security Summit, particularly in a 2016 joint statement in which 22 countries pledged to substitute such technology and replace high-risk radioactive sources, where technologically and economically feasible. Such high-risk sources included cobalt-60 used in radiotherapy machines in many poorer countries [2]. However, a 2015 meeting on non-isotopic alternatives to radiological sources ("alt tech") recognized that cobalt-60 radiotherapy may be the only radiation therapy available for cancer treatment particularly in places with limited infrastructure and relatively poor-security regions, In response, Pomper and Delnoki-Veress promoted an approach termed "Treatment, not Terror" to simultaneously address cancer care and the potential terrorist threat from dangerous radiation sources.[3.4] The International Cancer Expert Corps (ICEC) [5, 6], a global NGO, recognized the need for novel technology for challenging environments [7, 8] and the essential requirement for expertise on-the-ground to manage the patients and sophisticated cancer treatment technology. ICEC has since partnered with LINAC and healthcare systems experts to develop the novel systems solution presented.

2. BUILDING COLLABORATIONS AND DEFINING THE PROBLEM TO BE SOLVED

In the necessary first step, ICEC set out to define, understand and address the challenges faced by the health professionals at the grassroots in LMICs who treat cancer patients with radiotherapy (RT). A number of workshops were held from 2016 – 2020 [6, 7] involving medical and technical experts from CERN, the ICEC and its global membership and, since 2017, the UK Science and Technology Facilities Council (STFC) [9]. ICEC especially involved representatives from LMICs and Official Development Assistance (ODA) countries to understand the challenges and develop effective, innovative solutions, for partners across Africa and in similar resource-limited settings globally.

2.1. Technology challenges

Current RT LINAC technology requires a large number of expert professional staff including radiation oncologists, medical physicists, dosimetrists, service engineers, and radiation therapy technologists to treat patients and to maintain the equipment. In most LMICs there is both a shortage of machines as well as too few engineers to keep the machines working leading to more frequent failures and extended repair timescales.

A landmark study by Atun et al "*Expanding global access to radiotherapy*"[10] spelled out substantial gaps in radiotherapy machines and personnel. It indicated that there was a global shortfall of over 5,000 LINACS in LMICs [10, 11] and many tens of thousands of personnel including radiation oncologists, medical physicists and radiation technologists [10]. Economic modeling demonstrated that in addition to the approximately one million lives saved each year there is a positive return on investment [10]. Perhaps it is the overwhelming size of the gap that leads to the pessimism toward taking on the global cancer care problem. While there are certainly sincere efforts to improve the situation there has been limited impact on the gap since the 2015 Atun report.[10]

The physicist and global health partnership had a seminal moment during a presentation of ICEC by Drs. Norman Coleman, Manjit Dosanjh, Jacques Bernier and Ugo Amaldi in the *physics section* of the International Conference on Translational Research in Radio-Oncology and Physics for Health in Europe [12]. Amaldi's remarkable offer to help solve the LINAC problem prompted ICEC and collaborators to address this problem as a Grand Challenge and consider innovative models for technology, capacity building and global mentorship.

A call to action was not new, being recognized by global health leaders Paul Farmer, Julio Frenk, Felicia Knaul and others in 2010.[13] But the lack of progress despite calls for action and the Atun models [10] demonstrating RT was good for the economy led to the realization that novel approaches and disruptive changes were necessary to move toward the exponential solution needed to fill the enormous gaps. Simultaneous efforts were undertaken to develop innovative "alternate technology" with a novel linear LINAC [7, 8], the "Flex-competence" healthcare systems approach [14] to bring a collaborative rather than the extant dichotomous approach to infectious diseases and NCDs and alter the skewed funding between the burden of disease versus investment in attacking infectious disease and NCDs [15]. At the American Society of Radiation Oncology in 2020, Coleman emphasized "The Century Challenge" with the need for innovative, global collaborative approaches in that if one well-staffed linear accelerator could be commissioned each week it would take 100 years to meet the existing gap! The "Century Challenge" proposed is how this goal could be accomplished much more rapidly.

2.2. Data

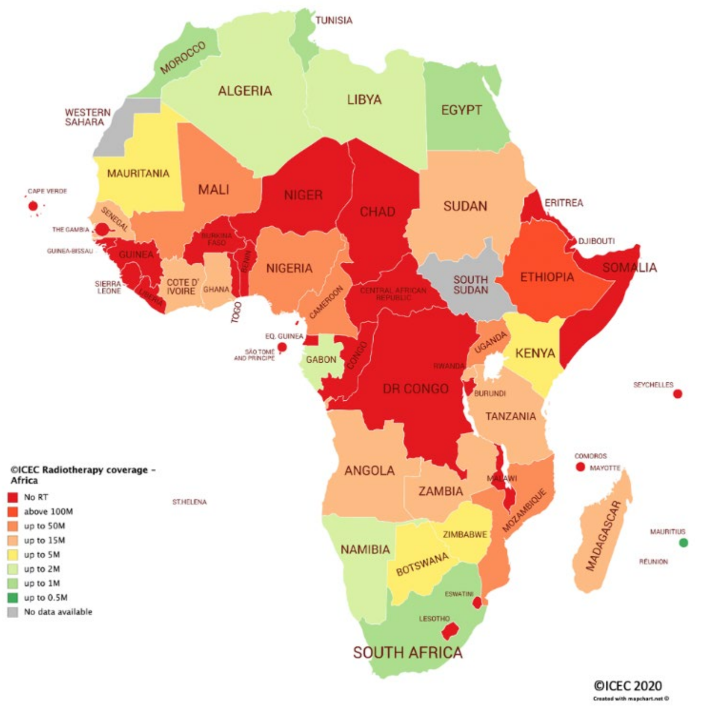

Figure 1: Size of the population per LINAC from Ige et al.[16] *At the time of this survey of all 28 African countries that had LINAC-RT, 27 contries had no LINACS and 12 had only one. Details from the survey and potential solutions are in Linacs to Narrow the Radiotherapy Gap in the CERN Courier [17]. (From [16] with permission.)*

From the series of ICEC workshops, it became clear that while the LINACS used in high- and upper-middle income countries are well suited for their stable infrastructure, technology development was needed to produce a modular, robust machine suited for the challenging environmental conditions and poorer infrastructure in resource-limited locales, while requiring fewer qualified experts to provide reliable treatments.[17] Wroe et al examined log books for dual-energy linacs in LMICS and UMICs in Africa compared to UK (Oxford) as an HIC to evaluate failure rates and duration of the failure in 12 subsystems focusing the analysis on faults that lasted > 1h. For example, air/cooling/generator subsystems systems were problematic in LMICs compared to the HIC.

Vacuum failures caused prolonged problems in LMICs and none in HICs.[18[Detailed data forthcoming from the study by Ige et al (16) demonstrate substantial downtime for linacs in Africa. While the HICs downtime is measured in hours or days, in Africa it is often weeks to months with a machine out of service. That a need for linacs suitable to the challenging environment is apparent to address the ICEC approach of building capacity, capability and credibility so that patients will have treatment outcomes similar to those in well-resourced locales. Moreover, the excellent quality and exciting challenge of building such practices as part of a global effort would encourage people to remain in-country and thereby reduce "brain drain" from LMICs.

3. HEALTHCARE SYSTEM INNOVATION: FLEX-COMPETENCE

3.1. Expertise

ICEC's overarching goal is capacity building through a person-to-person sustainable mentorship model. It builds on the concept of the Peace Corps that ICEC President L. Roth served with in Lesotho in the 1960s. Figure 2 illustrates ICEC's essential mission of mentorship, leading to sustainable on-the-ground programs with the opportunity for global exponential growth.

Fiigure 2: International Cancer Expert Corps implementation of "Treatment not terror"*.* *Capacity building includes innovative enabling technology that will incorporate rapidly changing accomplishments in artificial intelligence (AI) and machine learning (ML) throughout all processes to help enhance the clinician expertise, reduce the need for support personnel and enable the technical personnel to use their time as efficiently as possible for patient-centered cancer care. While RT is an essential component of treatment, the ICEC emphasizes that the entire spectrum of cancer care is necessary including prevention, diagnosis (imaging and pathology), treatment (multi-modality as appropriate), supportive care and long-term follow-up.*
(Figure-original by ICEC)

3.2. Healthcare system: Flex-competence [14]

Well-resourced settings can have a healthcare system responsible for the entire spectrum of disease. Such systems have central referral hospitals with networks of hospitals and clinics within the local communities. The challenges in resource-limited settings reflect not only resource limitations but also how development funders have focused their investments on infectious disease and maternal-child health. These are most worthy of investment, but it is important to balance investment in the NCDs as they have a larger disease burden on the population as reported by Enserink.[15]

Understanding that causes of cancer include both infectious diseases and NCDs makes the dichotomy of investment outdated. Of the NCDs, the spectrum of cancer care includes prevention which addresses the other major NCDs- respiratory, cardiovascular and metabolic. Upon diagnosis cancer requires immediate intervention as do infectious diseases. Furthermore, a number of the major infectious diseases such as tuberculosis and HIV require long-term management akin to that of cancer care.

The Flex-competence approach is illustrated in Figure 3 [14].

4. BUILDING THE TRUSTED GLOBAL NETWORK

4.1. Career paths

The lack of progress in global health is related in part to the lack of value attached professionally to time dedicated to this activity. According to both senior academic leaders and from early career trainees, time spent on global health activities is often perceived negatively as not contributing toward academic advancement and faces difficulty in winning grant support. It also is seen as taking time away from clinical and billable activities. Indeed, time for this is often relegated to weekends and vacations causing personal and family stress. Encouraging counterpoints come from early-career leaders who have made call-to-action,[19] emphasizing the need for global oncologists,[20] and defining a career path.[21] For the field of radiation oncology, Vapiwala and experts with a range of career paths provided an approach to "expanding the denominator" to broaden the appeal of radiation oncology and, in particular, increase the impact from the diverse set of expertise that radiation oncology includes.[22] The recent emphasis on Equity, Inclusion and Diversity by many governments, international agencies, professional organizations, businesses and funding agencies as exemplified by the National Institutes of Health [23] has the potential to enhance and greatly expand careers in global health.

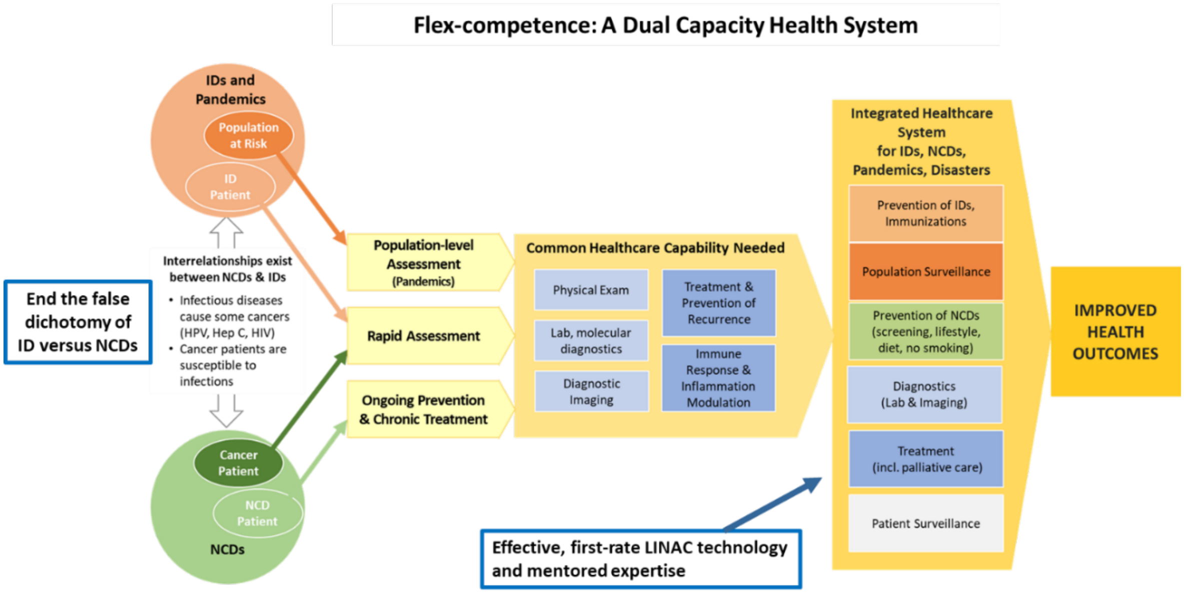

Figure 3: Flex-competence health system approach. *The current approach of dividing investment between infectious diseases and NCDs is not compatible with disease etiology, management approaches and healthcare equity. Bringing cancer care into the system at an early point, as seen in Figure 1, versus much later or almost not at all, is not logical. [Figure from the presentation at the "International Conference on Accelerators for Research and Sustainable Development: From good Practices Towards Socioeconomic Impact (Adapted from [14] with permission.)]*

4.2. Capturing career-long wisdom:

The societal challenge of the increasing proportion of senior professionals who retire with outstanding experience in career-long mentorship led the ICEC to build a model that utilizes senior mentors to mentor both more junior global health mentors and mentees in LMICs. The approach "*Capturing Acquired Wisdom, Enabling Healthful Aging, and Building Multinational Partnerships Through Senior Global Health Mentorship*" is a key part of enabling the exponential growth.[24] Indeed, the practical hands-on approach required by senior mentors who started their careers before the advent of the current enabing technologies can provide highly useful skills to those in LMICs who will likely need them in their more challenging resource-limited environments

5. GLOBAL HEALTH AT AN IAEA LINAC MEETING?!

5.3. Socioeconomic impact

Treating RT as an essential component of effective cancer care will have a broad impact globally. Enabling LINAC technology encompassing a less expensive and more robust machine, the AI/ML assistance in enhancing machine and enabling medical expertise can help fill the current shortfall of >5,000 LINACs worldwide and the gap of many thousands of skilled personnel needed. The vision of Ugo Amaldi, his colleagues from CERN and partnership with STFC has brought the potential solution to global cancer care to a place where the enormity of the problem looks a lot more solvable. While this remains to be accomplished, the components of the complex systems solutions are falling into place. The recognition of this shortfall is decades old but new paradigms such as "*Treatment, not Terror*" and Flex-competence demonstrate innovative thinking that comes from collaborative ventures.

5.4. African proverb: If you want to go fast, go alone; if you want to go far, go together.

That the key component of ICECs model (Figure 2) began with a discussion with linear accelerator physicists and engineers emphasizes how the team approach of physicists and engineers to address some of the most difficult problems in knowledge and society enable answers unlikely or impossible from individual projects. Both individual and large projects are essential for disruptive thinking and creating paradigm-changing solutions to problems often considered "too hard". Solving the RT gap will also form a foundation for addressing NCDs more generally and infectious diseases including infrastructure for pandemics.[14] Such an innovative healthcare system model has the potential for the necessary exponential growth in cancer care capacity by addressing it as an essential component and not an expensive add-on years later.

Blanchard and colleagues understand the need for big solutions in "*Multisector Collaborations and Global Oncology: The Only Way Forward*."[25] Learning from those who live with the results of healthcare inequality comes the African proverb "If you want to go fast, go alone; if you want to go far, go together." That the cancer care systems needed in LMICs already exists resource-rich settings, perhaps not as efficiently and cost-effective as it might be, indicates that the problem is solvable given the investment. Nelson Mandela perfectly summarized that this global cancer care problem now often considered "too hard" might be viewed: "It always seems impossible, until it is done".

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