Technological Solutions for Global Hematology and Oncology

Ami S. Bhatt, MD, PhD

Assistant Professor of Medicine (Hematology) and Genetics, Stanford University

Director of Global Oncology, Stanford Center for Innovation in Global Health

Co-founder, Global Oncology, Inc.

asbhatt@stanford.edu

269 Campus Drive, Stanford, CA 94305

A.S.B. carried out the background research and wrote the manuscript.

No relevant financial disclosures to declare.

Acknowledgements: ASB is supported by funding from the Damon Runyon Cancer Research Foundation, NCI K08 CA184420, a Stanford Center for Innovation in Global Health Seed Grant and the Rosenkranz Award. The author would like to gratefully acknowledge Donna Barry, Franklin W. Huang and Billy Andre of Global Oncology, Inc. for helpful feedback on this manuscript.

Script:

Increasingly, non-communicable diseases are being recognized as significant and sizeable health threats across the globe[1]. According to estimates provided by the Global Burden of Disease project, noncommunicable diseases were responsible for more deaths in the 20th century than communicable diseases[2,3]; despite this fact, there is a misconception that these diseases are significant causes of patient morbidity and mortality only in countries designated as "high-income" by the World Bank[4]. There is a lack of high quality epidemiological data regarding the incidence, prevalence and mortality attributable to diseases such as cancer in low- and middle-income countries[5]. Despite this, estimates based on hospital and limited population-based registries suggest that the mortality-to-incidence ratio of these diseases is much higher in low and middle income countries than in high income countries[6,7]. Furthermore, the lack of screening programs for diseases such as cancer and the lack of availability of diagnostic tests for diseases such as anemia, myelodysplastic syndromes, and malignancy suggests that these diseases likely remain undiagnosed and underreported in LMICs. As we look toward the coming decades, improved management of infectious diseases, public sanitation, nutrition and maternal child health is expected to result in continued increased life span. Thus, the vast majority of noncommunicable disease cases and NCD-related deaths will occur outside of high income countries in the next decade[6].

Among noncommunicable diseases, hematologic and oncologic disorders affect individuals from childhood to late adulthood and have epidemiological patterns that vary broadly based on exposures, geography and host genetics. This was, perhaps, most dramatically noted in our own field, when Dennis Burkitt, an Irish surgeon stationed in Kenya, Somaliland and later in Uganda, first noted an unusually high prevalence of an aggressive hematological neoplasm in children living in equatorial Africa[8]. Interestingly this disease, now eponymously termed Burkitt's

lymphoma, remains notoriously challenging to treat in the resource-limited settings where it occurs at the highest rate despite the existence of proven treatment regimens.

Unfortunately, unlike treating many infectious diseases, treating hematological and oncologic disorders such as Burkitt's lymphoma often requires sophisticated and complex health care systems. As these diseases become more treatable and more prevalent worldwide, only a minority of countries are adequately prepared to address the complex healthcare needs associated with these diseases. This is sadly reflected in the vastly varying outcomes not only of hyper-aggressive, endemic diseases such as Burkitt's lymphoma, but also of more evenly widespread diagnoses such as pediatric acute lymphoblastic leukemia (ALL)[9]. While in high-income countries, we strive to improve already impressive 10-year ALL survival rates from the mid- to the high 90th percentile range, in most middle and low income countries survival rates, even after presenting to clinical care and receiving a diagnosis, remain in the 10-35% range. Indeed, it is likely that the most important predictor of 10-year survival for most pediatric cancer patients is the country in which they were born.

Paul Farmer, co-founder of the international NGO Partners In Health, famously stated that challenges in global health typically fall into four main categories of "the stuff, staff, systems and space"[10]. By adding "sense" as another category, one can identify some of the key but surmountable roadblocks in global hematology and oncology care. Drugs, diagnostic tests, surgical tools, and physical resources critical for care provision constitute the "stuff" category. Staffing and training needs include nursing, pharmacy, surgery, medical oncology, radiology, hematology, surgery, palliative care, pathology and possibly new roles to help fill gaps of traditional roles. While some geographic settings such as Cuba and India have a large mobilizable workforce, others, such as many countries in sub-Saharan Africa have limited training programs for healthcare staff, and thus a dearth of trained providers. Many of the

existing staff in LMICs are very well trained, but without access to diagnostic and treatment tools required for complex hematology/oncology care, they have limited experience or “sense” in providing these types of care. Thus, the provision of new agents and devices as well as education aimed at updating skills and knowledge-base to use the new tools are critical in developing comprehensive care programs in these areas. Lastly, all of this care is reliant upon having well-organized and maintained spaces and systems in which these services can be provided and coordinated.

Examining the case example of pediatric ALL a bit more closely, we can identify existing challenges and opportunities for advancing disease diagnosis and management. In the case of treating pediatric ALL, the drugs used for routine clinical care are off-patent and are also included on the WHO Essential Medicines list, which was updated in 2015 to include several chemotherapeutic and supportive care agents[11]. The challenges to providing care vary based on location, but range from issues related to the lack of trained staff to render a timely diagnosis, administer chemotherapy and supportive treatments such as antibiotics and antiemetics, challenges in obtaining a reliable and safe supply of blood products for transfusion, to limited infrastructure within which to provide coordinated care for these complicated patients. In the case of other hematological disorders such as iron deficiency anemia, nutritional deficiencies and broad-scale food insecurity lie at the source of the challenge. In other diseases, such as diffuse large B-cell lymphomas, access to critical medical and radiation therapies can be a limiting factor. In fact, anti-CD20 targeting antibodies, which constitute a major advance in the management of these lymphomas, are considered unaffordable in most of the world. Thus, drugs such as rituximab, which have revolutionized management of many B-cell lymphomas, and growth factors, such as G-CSF, solidly fall into a “luxury item” market. There is a growing industry of biosimilars being developed to fill this gap, but the need still dramatically outstrips the available supply of these agents. As is evident, there are many stakeholders in this healthcare

space – coordination of efforts from industry, government, local and international NGOs, academia, public and private insurers, philanthropists and policy makers will be critical if we are to achieve the rapid and meaningful progress that is both possible and needed.

The United Nations Millennium Development Goals, which were announced in 2000 with six major targets for 2015, did not specifically focus on noncommunicable disease. Likely in response to considerable global pressure, as well as the growing awareness of the population health importance of noncommunicable diseases, noncommunicable diseases are included as specific targets in the subsequently developed Sustainable Development Goals. Specifically, goal 3 of the 17 SDGs strives to “ensure healthy lives and promote well-being for all at all ages”. Relevant to improved hematology and oncology care, goal 3.4 makes a quantitative target of “By 2030, reduc[ing] by one third premature mortality from non-communicable diseases through prevention and treatment”, goal 3.8 strives for universal health coverage, goal 3.10 aims for strengthened tobacco control, 3.11 focuses on vaccine development for both communicable and non-communicable diseases, and 3.12 commits to substantially increasing health financing and improved health workforce recruitment and retention. The codification of these targets is an important first step – subsequent steps include the development of creative interventions that will allow for sustainable, scalable and efficient achievement as well as identifying and distributing funding to potentiate these advances. Unlike many other global health challenges, such as infectious diseases, maternal child health, safe water/sanitation access – major philanthropists, such as The Bill and Melinda Gates Foundation, have not yet stepped in to fill the funding gap that exists. Similarly, unlike for HIV, malaria and tuberculosis, there is no global fund for noncommunicable diseases, in general, or cancer and hematological disorders, specifically. As such, if we are to achieve the SDGs by 2030, as has been targeted, creative and coordinated efforts will need to be developed. Many have argued that in order to make the most progress in a setting of severely limited resources, the various stakeholders involved in this

mission must work together. The increased efficiency by better coordination and collaboration, along with application of innovative solutions to address as many of the challenges noted above is likely to catalyze improved access to staff, stuff, systems, space and sense.

There are several examples of how technology has accelerated innovation in the space of global hematology and oncology. Here, I will highlight six examples:

As was noted previously, improved data regarding disease incidence, prevalence and mortality is the cornerstone of raising awareness and making these diseases public health and business priorities. Classically, disease registration is a time-consuming, manual process that involves coverage of entire populations. In areas where personal identifiers, such as social security numbers, do not exist, unambiguously following individuals to track disease incidence and outcomes is nearly impossible. In order to overcome this challenge of population-based registries, creative efforts are being undertaken as collaborations between data scientists in academia and large country-wide insurance systems, such as the IMSS system in Mexico, which insures approximately 1/3 of the Mexican population. While likely not as accurate as traditional disease registration, the collaboration will seek to develop insurance-based registries through utilization of over 10 years of electronic medical records. Complementing existing efforts to develop population-based registries in a handful of provinces in Mexico, through International Agency for Research on Cancer (IARC) standards, this effort is expected to vastly improve our “sense” and understanding of cancer epidemiology in Mexico.

In a second example, a novel collaboration between the American Cancer Society, the Clinton Health Access Initiative and IBM has resulted in the development of “ChemoQuant”, a “smart” tool to assist with quantifying and forecasting chemotherapy requirements, thus improving the ability of governments and hospitals in estimating the needs for “stuff” such as cancer

chemotherapies and supportive care agents, and aiding in collective bargaining and purchasing strategies.

The third example, aimed at “disrupting diagnostics”, is led by the company Cepheid. Already a leader in providing rapid, modular, molecular diagnostic tools for infectious diseases such as tuberculosis, Cepheid has developed tools for rapid BCR/Abl testing for CML diagnosis and monitoring and is also innovating in the space of other solid and liquid malignancies. Through the application of PCR- and methylome-based technologies, the company hopes to develop rapid, reliable and robust diagnostics that may leapfrog the need for expensive and complicated tissue processing through traditional histopathological methods.

A fourth example, which seeks to more directly engage the engineering, technology and design sector, is the execution of events that raise awareness about health challenges among individuals from multiple disciplines. Such activities and events provide a structure in which multidisciplinary team formation is facilitated, and those who are knowledgeable about existing “problems” are paired with experts in the realm of solution creation. At least in the short term, this has been efficiently accomplished by borrowing an intensive “team challenge” conference structure from the world of computer science by organizing short and medium term “hackathons”. These events, typically lasting 24-48 hours, allow self- or guided-assembly of diverse teams to tackle problems that share a common theme. The solutions are generally technical in nature, and teams are encouraged to develop and test prototypes during the event. Several recent events, such as the MIT Hacks and health++ event at Stanford, have focused on global and affordable health topics.

An example of an idea developed and prototyped at such a Hackathon serves as the fifth of a technological solution to a global health problem. The GO Map, an online tool to facilitate

figuring out “who is doing what and where”, is a freely accessible resource that collects, houses and displays information regarding ongoing hematology, oncology and palliative care related projects being carried out globally. Many global health professionals note the challenges of working in relative isolation from other like-minded individuals and groups; this tool holds great promise in connecting these professionals to one another, convening diverse stakeholders to collaboratively solve problems in the global health space. This is especially important given the continued lack of global awareness of the urgent challenges in the hematology oncology space, and the relative paucity of and delay in published information on these topics in the academic literature.

The final example, spearheaded by the American Society of Clinical Pathology, demonstrates the role of distance-based diagnostics. Through cloud-based distribution of automatically scanned immunohistochemistry-stained pathology slides, local limitations in pathology staff can be surmounted. In this system, automatic slide processing platforms are placed in remote or underserved locations, allowing communities to overcome severe backlogs in specimen processing and evaluation – ultimately allowing for the delivery of more timely diagnoses. Many other examples of technological solutions to geographic and resource barriers have been and will continue to be creatively developed and in some cases applied – these range from using internet tools to facilitate global “tumor boards”, to arranging for online “consulting and advising” regarding challenging cases, to affordable technologies to continuously monitor temperature in the outpatient setting to trigger administration of empiric therapy for fever and neutropenia.

As has been outlined, the global hematology and oncology problem is large and growing. Disparities in clinical outcomes of patients with diseases that range from anemia to leukemia and lymphoma are startling and disheartening. As hematology researchers and practitioners, we are cognizant that the impact of advances made in high income countries have not “trickled

down” to low and middle income countries. We must move beyond a world in which cancer and hematology care are “luxury items”, reserved for the world’s wealthiest individuals and countries. While challenges in obtaining the right “staff, stuff, space, systems and sense” abound, the sustainable development goals have set a bold and important target for improved cancer and hematological disease care by 2030. Through improved advocacy and awareness-raising, the clever application of technological solutions, and a commitment to developing knowledge in this space through research and investigation, much progress can be made.

References

1. Daniels MED, T.E.; Bollyky, T.J. The emerging global health crisis: noncommunicable diseases in low-and middle-income countries. Council on Foreign Relations Independent Task Force Report. Vol. 72; 2014.

2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-1504.

3. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349(9061):1269-1276.

4. World Bank Country and Lending Groups – World Bank Data Help Desk. .

5. Curado MP, Voti L, Sortino-Rachou AM. Cancer registration data and quality indicators in low and middle income countries: their interpretation and potential use for the improvement of cancer care. *Cancer Causes Control*. 2009;20(5):751-756.

6. Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet*. 2010;376(9747):1186-1193.

7. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):16-27.

8. Burkitt DPW, D.H. Burkitt's Lymphoma. Edinburgh: Livingstone; 1970.

9. Israels T, Challinor J, Howard S, Arora RH. Treating Children With Cancer Worldwide--Challenges and Interventions. *Pediatrics*. 2015;136(4):607-610.

10. Boozary AS, Farmer PE, Jha AK. The Ebola outbreak, fragile health systems, and quality as a cure. *JAMA*. 2014;312(18):1859-1860.

11. Shulman LN, Wagner CM, Barr R, et al. Proposing Essential Medicines to Treat Cancer: Methodologies, Processes, and Outcomes. *J Clin Oncol*. 2016;34(1):69-75.