Improving health-care delivery in low-resource settings with nanotechnology: Challenges in multiple dimensions

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Abstract
In the two decades after 1990, the rates of child and maternal mortality dropped by over 40% and 47%, respectively. Despite these improvements, which are in part due to increased access to medical technologies, profound health disparities exist. In 2015, a child born in a developing region is nearly eight times as likely to die before the age of 5 than one born in a developed region and developing regions accounted for nearly 99% of the maternal deaths. Recent developments in nanotechnology, however, have great potential to ameliorate these and other health disparities by providing new cost-effective solutions for diagnosis or treatment of a variety of medical conditions. Affordability is only one of the several challenges that will need to be met to translate new ideas into a medical product that addresses a global health need. This article aims to describe some of the other challenges that will be faced by nanotechnologists who seek to make an impact in low-resource settings across the globe.

Keywords
Nanotechnology, global health, low-resource settings, technology transfer, commercialization, partnerships, medical device design, task shifting

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Introduction
Recent analysis of data derived from the Global Burden of Disease Report¹–¹³ indicated that globally, life expectancy increased by more than 11 years during the period from 1970 to 2010.¹⁴ This improvement was largely driven by profound reductions in child mortality (>60%) and adult female mortality (>40%), with lower reductions in adult male mortality that varied widely by age group (15%–35%).¹⁴,¹⁵ Throughout this 40-year period, however, the life expectancy of a person born in one of the world’s poorer countries was consistently more than 30 years shorter than that of a person born in one of the wealthiest.¹⁴ In much of the world, the burden of preventable and treatable diseases is still staggering and poses formidable challenges for health-care systems. In 2015, nearly six million children under the age of 5 died¹⁶ due to preventable and treatable diseases such as diarrhea (nearly 600,000 in 2013) or malaria (over 450,000 in 2013).¹⁶ In 2015, more than 800 women died each day due to complications in childbirth.⁵ Notably, the contribution of noncommunicable diseases, such as heart disease and diabetes, to the global burden of disease rose from 43% to 54% between 1990 and

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Collectively, these data indicate that there remains a great need for improvements in healthcare. There exists an urgent and persistent need to improve maternal and child health, along with an evolving landscape with a growing concern that over the next few decades climate change will strongly affect population health, with the greatest impact being that of infectious diseases on people with few resources to prevent, diagnose, or treat such diseases.25,26

Hence, in this era, there are four defining features of the global health landscape: (i) a lingering need to treat and eradicate infectious diseases, (ii) a growing need to address health issues related to noncommunicable diseases,19,27,28 (iii) the persistence of profound health disparities,20,22–24 and (iv) the ongoing effects of climate change.25,26 The success of the ongoing and emerging efforts to improve global health will depend strongly on the ability of medical technology developers to innovate new and affordable products and deliver them to the marketplace.

A number of emerging technologies hold great potential to address these global health needs. In particular, the convergence of developments in nanotechnology, mobile technology, and information technology is enabling development of (i) affordable laboratory or point-of-care diagnostics,9,10,12,29–41 (ii) remote clinic, home-based therapeutics, or technology for prevention,31,42–46 (iii) improved communication with patients and across healthcare facilities,47–49 and (iv) technology for broad-based health surveillance.50,51 These approaches, some of which are highlighted in this special issue,52,53 may be able to effectively leverage cost reductions driven by consumer technologies. While these emerging technologies hold great promise, efforts to commercialize and successfully deploy new medical technology are certain to face a number of challenges, especially in the areas of greatest need.

This article describes the types of challenges that might be faced in the development and deployment of nanotechnology to improve health care in low-resource settings. These include a set of challenges that would be faced in any health-care technology venture and others that may be unique to deployment in low-resource settings. In addition, we provide a sampling of innovative strategies and approaches that could support nanotechnology ventures. In medical nanotechnology, as in other fields, the greatest opportunities lie in the areas of greatest need. The broad array of emerging nanotechnologies and their potential for addressing clinical issues in global health have been described in other recent reviews.37,44–46,54–62 This review aims to motivate nanotechnologists to seek out opportunities in the areas of greatest need and to enable them to identify and directly address the challenges faced in translating lab-based success into clinical impact in low-resource settings.

**Challenges**

Emerging technologies offer an array of opportunities to address critical issues in global health, but a variety of challenges may be faced in the pursuit of successful deployment of a new medical product. Technical challenges must be overcome to generate new knowledge and/or produce new technology; market-related challenges must be addressed to appropriately target the product for the market conditions; human resource–related challenges must be overcome to match human resource demands with capacity; and finally, a range of logistical challenges must be met to manufacture and deliver the product. Each of these four categories of challenges is described in the following sections. Embedded within each of these four categories are specific infrastructure-related challenges that arise due to the lack of high-quality infrastructure for business and medical care delivery in low-resource settings.

**Technical challenges**

Recent advancements in technology have enabled improved device versatility and functionality in a wide variety of scenarios. This is mainly the result of advanced material properties, miniaturization, and overall robustness of the end products. However promising, many devices fail to meet the challenges imposed by extreme environmental conditions or shortcomings in the healthcare infrastructure.

In many low-resource settings, the physical environment can present extreme demands on the ability of technology to function properly. Most notably, the technology must be able to function in the presence of humidity, temperature, and/or dust. The climatic conditions in some low-resource settings may reach temperature and/or humidity levels outside the range of typical technical specifications. For example, the temperatures in Mali or Pakistan can reach as high as 45°C; in Mongolia or northern Alaska as low as −30°C; and the humidity in the rain forest of Brazil, the Democratic Republic of the Congo, or Papua New Guinea can be consistently above 80%. During the summer of 2015, the combination of high temperature and humidity put the heat index at 74°C in parts of Iraq, where air conditioning is not widely used and electricity and refrigeration are unreliable. One study that monitored conditions along the supply chain in four different countries found that samples of rapid diagnostic tests were regularly exposed to temperatures and humidity levels that far exceeded general guidelines for pharmaceuticals. However, due to fact that the specific tests were designed to withstand high heat and humidity, they were only rarely exposed to conditions that exceeded the manufacturers’ guidelines. Such studies underscore the importance of designing technology with...
the ability to withstand conditions that might be experienced in such settings. In the desert and in the tropics, the high levels of moisture, dust, and/or other contaminants can push the limits of the core principles that underlie the operation of a certain class of technologies or may place additional demands on the engineering design of a specific device.

In addition to the extremes of climatic conditions, the medical product may also have to survive and function properly in conditions that are not well controlled. On-site and in-transit refrigeration or humidity control may be nonexistent or at best, unreliable.\textsuperscript{9,32} The levels of dust or contaminants in the clinic, clinical laboratory facility, or at home may be similar to those experienced in the external environment. In a recent visit to a newly constructed hospital in a capital city in sub-Saharan Africa, it was disturbing to note that the only ventilation in the clinical laboratory facilities was provided through open windows, which invited the dust and grime of a rapidly developing metropolis. The designers of the imported benchtop technology to analyze blood or urine samples may not have envisioned their device operating under such conditions, but the validity of the measurements and ultimately patient safety depend on the ability of the technology to function properly in the presence of a substantial amount of airborne pollutants.

A number of recent technological advancements have been implemented to address or sidestep known challenges such as refrigeration. These point-of-care tests avoid the need for refrigeration through the use of dry reagents\textsuperscript{9,65} and vaccine technologies, such as vaccines with improved temperature stability and vaccine vial monitors—that use temperature-sensitive dyes to indicate if a vaccine has been exposed to temperatures that would render it ineffective.\textsuperscript{66}

**Market-related challenges**

With any medical technology, the question of “who are you marketing to?” can be important to consider at an early stage of technology development. The decision to purchase a medical product may be made by national authorities, insurance providers, hospitals or clinics, health-care providers, or by individual users.\textsuperscript{10,11,67} Although the critical factors in the decision-making process may primarily be that of documented performance in randomized clinical trials, other factors may also play a role, such as cost, brand recognition, brand loyalty, personal contacts, or individual preferences.

In low-resource settings, the question of who are you marketing to? may also be influenced by a number of other factors. For large-scale efforts to reduce mortality due to infectious disease, the dominant purchaser of medical products may be United Nations (UN) agencies (e.g. United Nations International Children’s Emergency Fund (UNICEF), United Nations Development Programme (UNDP), United Nations Population Fund (UNFPA)); major international not-for-profit aid agencies (e.g. Bill and Melinda Gates Foundation, Cooperative for Assistance and Relief Everywhere (CARE), Doctors Without Borders, Oxfam); or governmental international aid organizations (e.g. United States Agency for International Development (USAID), Department for International Development (DFID)). For many developers of medical products, a single contract with one of these organizations can not only provide an initial boost in sales and capital but it can often lead to a stable influx of major contracts from other institutions or governments due to the visibility and high degree of respect afforded to these organizations.

Acquisition of a major contract with a nationalized health-care system will necessitate successful integration into their procurement system.\textsuperscript{68} This may require registration, documentation, price negotiation, and several levels of approval through processes that can be opaque and byzantine.\textsuperscript{59} As with many of these challenges, a well-informed local contact who has experience with the processes can be a very valuable asset to the business development team.

Some medical nanotechnologies may be directly marketed to the consumer, which would place a different set of demands on pricing and distribution strategies. Most importantly, however, selling directly to the consumer in low-resource settings presents a multifaceted challenge to marketing. The lack of telecommunications infrastructure, poor literacy rates, brand loyalty, and aversion to innovation can all limit the ability to reach and penetrate new markets.

Many technology developers are required to put forth great efforts to protect intellectual property even when manufacturing, production, and sales all take place within one country. International considerations drastically increase the cost, effort, and expertise required for patent protection.\textsuperscript{12,33,43,67} These concerns may be heightened in many low-income countries that may not have well-established patent regulations or enforcement capabilities. In some instances, countries have formed regional organizations (e.g. Africa Regional Intellectual Property Organization) to pool resources and simplify procedures for inventors to obtain patent protection across a region. A related concern for many producers is the growing prevalence of counterfeit medical products.\textsuperscript{11,67,70} This has huge implications for the pharmaceutical industry—both in terms of patient safety and commercial competitiveness. Multiagency, multinational efforts are underway to reduce the impact of such products, and the affected industries are essential partners in preventing such crimes.\textsuperscript{11,67,70} Some efforts are focused on the development of affordable and simple-to-use technologies that can be used at the point of administration, to detect counterfeit medicines.\textsuperscript{5,7,11,67,70} For medical devices, a design that incorporates security and traceability features to increase the difficulty for counterfeit production may greatly facilitate anti-counterfeiting enforcement.

A final market-related challenge is that of interdependence. Many technologies address only one step in a complex multistep process required for clinical success. The
simplest and most widespread example may be the interdependence of diagnosis and treatment. The least expensive and simplest technology for diagnosis would be useless without an ability to treat and vice versa. Furthermore, the value of any diagnostic may be lost in an environment where treatment is available, inexpensive, and has historically been widely utilized. For example, one extensive clinical trial demonstrated that an inexpensive rapid diagnostic test for malaria could accurately produce a positive or negative test result, but the treatment was still highly prescribed after a negative test result due to the expectations of the patient and caution on the part of the clinician. Other studies have also documented a reluctance to accept negative test results by both patients and health-care workers. While there have been successful demonstrations of the positive impact of rapid diagnostic tests on treatment decisions, this interdependence is complex and may require a comprehensive integration of new technologies into the clinic environment.

**Human resource challenges**

In areas that have limited access to medical products, there is often a scarcity of trained and credentialed medical personnel. The shortage of health-care workers is most severe in many countries in sub-Saharan Africa, the Indian subcontinent, and Southeast Asia. For example, it has been reported that sub-Saharan Africa has 10% of the world’s population and 25% of the world’s burden of disease, yet only has 1% of the world’s health-care workers. This paucity of suitably trained personnel may be the most significant of all of the infrastructure-related challenges.

The notion of **task shifting** is the redistribution of tasks from a highly trained individual (such as a physician) to someone with less training, such as a nurse or a health-care worker who has received specific training for limited number of tasks. Task shifting may help to reduce health-care costs in any setting but may have its greatest impact in low-resource settings that have a shortage of trained health-care workers. Although there are only a handful of randomized clinical trials that have investigated the effects of task shifting, there is some evidence indicating that the practice can be effective in improving health outcomes. For technology developers, explicitly designing a technology that enables task shifting may greatly increase the likelihood that it could be widely adopted and used effectively in a variety of settings. Fortunately, the nature of many nanotechnologies and their application in rapid diagnostics are extremely well suited to enable task shifting and their eventual success may be primarily or entirely due to the fact that they can be readily and reliably administered by health-care workers with limited training. Developers should keep in mind, however, that specific aspects of procedures could have a profound impact on adoption and eventual efficacy when used in the field. For example, one study that investigated three different rapid diagnostic test kits for cholera demonstrated that two of the systems performed equivalently when used by a laboratory technician or when task shifted to a community health worker, but the third system did not perform as well in the hands of community health workers.

**Design for ease-of-use** is a core principle of engineering design practices that is recommended for any technology in any setting. However, ease-of-use often involves trade-offs with versatility and the balance of the scale may be different in low-resource settings than in a state-of-the-art health facility. For example, in a well-staffed, well-funded state-of-the-art facility, it might be preferable to purchase a device that has the versatility to be used on infants as well as adults but requires careful adjustments or to purchase a multifunctional device that can perform a battery of diagnostics but requires more reagents and more careful and sophisticated interpretation of results. In low-resource settings, the need for ease-of-use might tip the scales in the other direction where simple procedures for administration and interpretation may be preferred.

An important aspect of design for ease-of-use is to avoid or minimize the need for technology-specific training. Integration of new technology is more likely to be successful when its functionality is similar to those routinely used by health-care workers. In some cases, however, it may be necessary to develop and deliver programs to train users in the appropriate use of a device. Minimizing the need for technology-specific training can greatly improve the likelihood of success and widespread use of a new medical technology.

**Design for ease-of-maintenance-and-repair** is an important adjunct to design for ease-of-use. Many medical technologies require the services of clinical engineers and/or biomedical engineering technicians (BMETs) to ensure proper use. The clinical engineering team is responsible for all aspects of health technology management: (i) checking technical specifications, (ii) recommending specific products for procurement, (iii) configuring the device, (iv) training clinical staff in its use, (v) communicating with the manufacturer, (vi) establishing test and maintenance protocols, (vii) scheduling its use to optimize availability, (viii) maintaining a suitable supply of consumables, (ix) device replacement, and (x) eventual decommissioning. The BMET is responsible for performing routine maintenance and repairs, which is often sufficient to keep critical equipment in condition for safe and reliable operation. However, some manufacturers require that maintenance and repairs be performed by a technician employed by the manufacturer or by an independent technician who has specific certification on that device. Violation of this requirement could invalidate a warranty on a substantial capital investment. Such policies are usually imposed to ensure continued safe operation of the device but are a clear deterrent to purchase and/or use in low-resource settings. Since many clinics in low-resource settings have severe shortages in suitably trained clinical engineers and BMETs,
staff, this produces another level of human resource challenges. Given these shortages, technology developers could greatly facilitate the adoption and long-term successful deployment of their products if they designed to reduce demands on the technical staff in the clinic. This could include a clear demonstration of compliance with published technical specifications; simple procedures for setup, configuration, use, and decommissioning; and clear and straightforward procedures for safe maintenance and repair (of at least the most common problems) by a locally based BMET without device-specific training.

Of course, addressing any or all of these challenges could introduce trade-offs with cost that might prove to be devastating for sales. A simple injection system can simplify the prophylactic administration of a drug to reduce postpartum hemorrhage in a manner that enables task shifting to a community health worker. 86 However, although seemingly inexpensive (~US$1 per dose), this successful example of task shifting, design for ease-of-use, and design for ease-of-maintenance-and-repair increased the per-dose cost enough to severely limit adoption and use. 80

Successful deployment of many medical technologies requires the expertise of individuals in addition to that of the health-care worker performing the procedure and the clinical/biomedical engineering team. These may include in-country sales and distribution teams, procurement specialists, and experts to train customers in the use of the technology. Assembling the cohort of people with the requisite expertise and resources may be particularly challenging in low-resource settings.

Logistical challenges

Perhaps the most daunting and unpredictable set of challenges can be grouped together as “logistics.” Collectively, these factors can contribute greatly to the depth and width of the valley of death. 11 Many of the design decisions that are made early in the product development process can have a profound impact on the team’s ability to successfully meet these logistical challenges. For this reason, it is very advantageous—perhaps essential—for technology developers to at least consider these issues, as they traverse the stages of technical development. 33 When planning for deployment in low-resource settings, each of these challenges can be amplified by limitations in the business infrastructure—especially in the health-care sector.

The first of these challenges is that of field testing, 33,87 or testing in the target environment. These initial trials can profoundly impact the product development process and can provide powerful data to help justify the substantial investments that will be required to bring a product to the market. An effective plan for field testing might include several rounds of tests to evaluate initial prototypes, confirm product relevance in terms of environmental and cultural acceptance, evaluate the level of difficulty for product application compliance by individuals with little or no training, validate performance of the final design, and to demonstrate efficacy in the target environment. 33 Even when initial field tests have shown positive results, lack of field testing to establish operational guidelines could substantially slow the adoption of new technology, as has been the case with a diagnostic test for human papilloma virus. 80 Execution of a field trial may require approval of an institutional review board and/or approval by local governmental agencies. Planning and performance of the field trial is likely to be greatly facilitated by a strong partnership with local clinical contacts, government agencies, and possibly international organizations that are active in the area.

For most medical technologies, the process of obtaining regulatory approval for sale and marketing can pose substantial, time-consuming, and expensive challenges. 40 The need for, or the type of, approval that will be required will depend on the technology, its purpose and use, and the country in which it will be deployed. 67,88 The processes for obtaining the Food and Drug Administration approval for marketing in the United States are typically time consuming and resource intensive but vary greatly depending on the nature of the device, the perceived risk, and the existence of predicate devices. For use in low-resource settings outside of the United States, approval by the regulatory body of the country-of-use may be required. This process may be simplified if the device has already been approved for marketing in the United States or in Europe. For example, in Ethiopia, the process can be greatly streamlined if the product is already registered and marketed by members of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 89 For many developers of nanotechnology or other types of medical devices, the clinical need and target markets are not restricted to a particular country or region and therefore the process of obtaining regulatory approval in each country of use can require a substantial investment of time and resources. To streamline this multinational approval process, the World Health Organization (WHO), other international institutions, and many national regulatory agencies are actively promoting the harmonization of regulations so that medical products can more rapidly and efficiently reach the end user. 67

The logistics involved in manufacturing present a set of challenges that are strongly influenced by policies. For example, medical products must be manufactured in a manner that complies with specific standards. 67 As with regulatory approval, the specific standards may depend upon the nature of the product as well as the country-of-use. Following the established trend with consumer products, many medical products are now manufactured in China, India, Brazil, and other countries. For the nanotechnologist seeking to establish manufacturing capabilities, the most straightforward option may be to keep manufacturing operations close to the home base of the R&D laboratory, but this approach should be carefully considered in light of alternative options. The primary advantages of setting up
manufacturing facilities close to the research labs may include ease of transfer of technologies and techniques, ability to perform testing early and often during the development of manufacturing processes, familiarity with regulations and procedures, and open communication between technologists, manufacturers, and business managers. On the other hand, the primary advantages of setting up manufacturing facilities overseas may be a reduction in manufacturing costs, the ability to leverage existing manufacturing capabilities and expertise, and proximity to some of the larger target markets.

To distribute the product to the point of care in low-resource settings, there are some challenges that are shared across sectors. In the World Bank index of “Ease of Doing Business,” only two countries in sub-Saharan Africa rank in the top quartile (South Africa and Rwanda); approximately 70% of the countries in the region rank in the lowest quartile.69 Other challenges in these regions may be unique to the health sector.10 Upon arrival into the country-of-use, import regulations and tariffs may be burdensome and bureaucratic delays can be substantial and unpredictable.67 Transportation from the port-of-entry to the point-of-care may require a variety of modes of transport, each of which may present specific demands on coordination and handling. Throughout the process, security of the product from theft, destruction, or contamination must be assured. For health-care products, there may be additional concerns if the product utilizes controlled substances or if there is a potential for misuse or off-market sales. Some newly developed products may be able to tap into existing distribution channels and procedures, especially if they are being sold to or administered by the national health-care system or by a major nongovernmental organization (NGO). Other products may require the development of new distribution channels or modifications to the procedures that are in place. In either situation, successful distribution usually requires a partnership with informed local contacts that have the authority and incentive to guide the creation and maintenance of distribution channels and procedures.

As mentioned earlier, for medical products that require refrigeration, the need for storage may present very specific logistical challenges, most of which can be directly tied to the reliability of the electrical grid or backup systems. Other storage requirements may not be as obvious, such as the inherent trade-offs between access and security. For a medical product to be useful, the health-care worker must have access to the device and any consumables at the time of need. If the product is stored in a locked cabinet that is only accessible to a supervisor, the product may be useless when the supervisor is off duty or in a different part of the facility. Alternatively, storage in a location that is accessible to a large number of employees may result in depletion of stock due to theft. Systems that enable traceability can greatly expand access on the front lines without compromising security.

In considering the usability of a medical device, the most obvious considerations are those of the user at the point-of-care. The user must have the requisite skills and training, and procedures should be fool proof and efficient. To maximize efficiency, it might be advantageous to consider integration with concomitant procedures that are likely to be administered. A technological solution for diagnosis or treatment is more likely to be used effectively if it can be (i) administered in a single dose, minimizing the need for patient compliance,9,32 (ii) synchronized with an existing checkup or treatment, (iii) useful without involving substantial preparation or planning,9 (iv) a shared process (such as a blood draw) with other procedures, performed during a single visit to the clinic,10 and (v) used as a non- or minimally invasive procedure. Some of the less obvious factors that could adversely affect the usability of a medical product are the need for (i) planning (e.g. fasting prior to a blood draw), (ii) preparation (e.g. heating or mixing), (iii) teamwork (e.g. a procedure that requires one person to attend to the technology while the other attends to the patient),10 (iv) time-sensitive procedures,33 (v) customization (e.g. dosing or scaling based on age or body weight), and (vi) calibration (establishing a reference to a gold standard prior to use). Removing such obstacles in the hectic environment of an outpatient clinic or overcrowded hospital ward would ensure wider and more accurate use of the medical technology.

Among clinical engineers, it is often cited that the cost of purchasing a medical device is the “tip of the iceberg” and represents only a small portion of the cost of ownership.9,31 The up-front capital costs are often only a small portion of what will be spent on installation, consumables, maintenance, repairs, and decommissioning.83 For some medical applications of nanotechnology, such as certain rapid diagnostic systems, the design of the system might completely eliminate many of these costs and the primary cost factor would be that of consumables. For these systems, minimizing the cost of consumables minimizes the cost of ownership; systems that require costly single-use cartridges—especially those that must be provided by the equipment manufacturer—may incur operational costs that are prohibitively high. In addition, systems that use handheld or benchtop units for measurements or administration may require costly regular maintenance and repair to ensure patient safety. For use in any setting, but particularly in low-resource settings, it is advantageous to design a system in a manner that minimizes the need for maintenance, simplifies maintenance procedures, requires only standard tools and parts to perform maintenance procedures, and has built-in capability to verify proper execution of maintenance procedures. In addition, the decommissioning of medical equipment can incur substantial financial as well as environment costs.83 Finally, the cost of operation may not only include the price, difficulties, and uncertainties of stocking a suitable supply of nonexpired consumables but may also include the costs for specialized handling (such as refrigeration, mixing, or secure storage) and specialized procedures for sample disposal.32
The final logistical challenge in this list is that of postmarket surveillance and outcomes assessment. A system that produces good results in a research lab, in a teaching hospital, and then in a clinical trial may fail in everyday use. Such failures can be due to poor product performance in the field, a failure to follow usage protocols, poor storage practices, use of expired samples or components, or simply failure to use the product. Thorough postmarket surveillance is challenging in any environment and will be particularly challenging in low-resource settings. Systems designed to facilitate good record keeping or mobile phone–based data collection can greatly enhance the quality and quantity of postmarket surveillance in a manner that will ultimately improve the efficacy of the device. However, more data do not always add value and eHealth or mobile phone–based solutions are themselves subject to the same concerns about efficacy and cost-effectiveness in real-world settings. Recent reviews point to the need for more field-testing and more outcomes data.

### Addressing the multidimensional challenge

In the design of medical technology, the most obvious and immediate design objectives are to address an important clinical need in an affordable manner. When targeted usage is in low-resource settings, the design and development teams will be faced with the array of challenges outlined above. In most instances, it would be advantageous, if not imperative, to identify those challenges and to work with end users to address them head-on, early in the design and development process. Such an undertaking would constitute a multiobjective optimization problem that is riddled with the uncertainties inherent in the technology, physiology, international markets, regulations, procurement policies, human factors, and cross-cultural dynamics. Achieving the optimal design may not be possible or feasible, but the likelihood of substantial clinical impact can be greatly increased by attending to the array of challenges and designing to achieve the characteristics outlined in Figure 1 that are specifically identified by the end user or are highly relevant to the targeted application.

#### Promising trends and innovative approaches to translation

The challenges described above can be intimidating not only because they are numerous and substantial but also because they are interrelated. Some of these challenges may have implications for the technical specifications and technical design characteristics of the device; others may have implications for the selection of a suitable business model and/or for the composition of the business team. Collectively, they emphasize the need for nanotechnologists to take a thoughtful and comprehensive approach to product development and translation into low-resource settings. In addition, these challenges highlight the further need to recognize and plan early on in the venture in order to facilitate efficient progress.

Although the mountain of challenges forebodes a long and difficult climb, it is encouraging to note that there have been many recent successes. In addition, a number of new programs have been initiated that are designed to facilitate the process of developing and deploying technology in low-resource settings. These include the Stanford-India Biodesign Program, Rice 360°, Engineering World Health, and the IDEAS Program at Washington University School of Medicine. Some emerging technologies show great promise, especially in the space that is at the intersection of nanotechnology and information technology. In addition to the rapid advances in technology, there are also a number of new initiatives and trends on the international development landscape and innovative approaches to translation that could accelerate the adoption and impact of new technologies in low-resource settings. Some of these promising trends and innovative approaches to translation are briefly discussed below.
Emerging economies and expanding markets

While the array of market challenges may be daunting, there are many indications that new markets are emerging and that the sizes of potential markets are increasing. Economic development around the world has drastically increased the purchasing capacity of a number of countries and private individuals. In the year 2000, 57 countries were classified by the World Bank as “low income”; by 2015, 21 of those countries had transitioned to “lower-middle income,” 4 to “upper-middle income,” and 1 to “high income.” 100 These included several countries from Southeast Asia and sub-Saharan Africa. Such economic development can result in improved markets for medical technologies through increased public sector support for national health programs and through increased purchasing capacity in the private sector. The growth in the private sector is primarily due to the increased demand for healthcare services by the growing middle class that will be paid for by direct payment or through private insurance carriers.

International initiatives

Since the turn of the century, a number of international initiatives have been directed at improving lives by increasing the intensity, efficacy, efficiency, and impact of development activities. These initiatives have been either directed or strongly supported by the United Nations and have been the result of a coordinated effort from a number of UN agencies, member state governments, and NGOs. For technologists interested in meeting clinical needs in low-resource settings, such initiatives are important because they can help to rally the international community around specific technologies, to create or stabilize markets, and to promote best practices that are technology-based. Some of the most important of these initiatives include:

- Millennium Development Goals: At the UN Millennium Declaration in the year 2000, world leaders adopted a number of development targets to be achieved worldwide by the year 2015; these are now known as the Millennium Development Goals (MDGs). This list included several health-related goals: most notably reduce child mortality (MDG 4); improve maternal health (MDG 5); and combat HIV/AIDS, malaria, and other diseases (MDG 6). For each goal, the Declaration adopted specific metrics and targets. This Declaration provided a framework for the development community and governments that has been used to promote and coordinate efforts to reach those goals. In 2016, it is now clear that these goals have not yet been fully achieved, but it is also clear that substantial progress has been made. 101

- Sustainable Development Goals: Over the past several years, the post-2015 Development Agenda has defined a framework that will serve to continue to guide the development community beyond the MDG era. At the 2015 UN Summit, world leaders adopted a new set of goals that build upon the progress over the previous 15 years and have a strong emphasis on sustainability; these have been termed the Sustainable Development Goals (SDGs).102

- UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) 103: In 2012, the UNCoLSC was established to promote and galvanize efforts to increase access for women and children to critical medical products. The Commission identified 13 affordable lifesaving commodities and developed a set of recommendations for improving their effectiveness and accessibility.

- Interagency list of medical devices for essential interventions for reproductive, maternal, newborn, and child health (RMNCH) 104: Recently, a coordinated effort by UNICEF, UNFPA, and WHO produced this comprehensive report, 104 which aims to strengthen health-care systems by identifying the medical devices required to provide the essential RMNCH interventions defined by existing WHO guidelines and publications. Specifically, it provides guidance for equipping various types of medical facilities and information describing the needs for medical equipment at each point in the continuum of care in RMNCH. 104

- Action Agenda from the Third International Conference on Financing for Development 105: In Addis Ababa in the summer of 2015, world leaders met and committed to an agenda of investment and cooperation to promote development. The Action Agenda includes a number of articles that specifically address public health, public health infrastructure, health product research and development, human resource capacity, technology, innovation, regulations, international trade, intellectual property protection, multisector collaborations, and enhancements to the business environment. 105

For technology developers seeking to address critical global health issues, these international initiatives and commitments can help to define R&D targets, provide a framework and opportunities for collaboration, and offer a strong justification for financial support in proposals for grants or investment.

Local production of medical products in low-resource settings

In many countries, all or the majority of health-care equipment and supplies are imported and acquired with funds from one of two primary sources: (i) the national health...
programs—leading to depletion in foreign reserves and contributing to unfavorable trade deficits or (ii) NGOs—which provide donations through an unsustainable model. There is a growing interest in reducing this dependence on imported medical products by establishing and strengthening the local health industry sector. Such initiatives to support “local production” are intended to simultaneously improve health and promote economic development and therefore would address the core issues in the SDGs in an integrated manner.

Recently, WHO has completed a set of studies to investigate the feasibility of local production of medical products in Sub-Saharan Africa. These studies identify a broad array of challenges—most of which are those described in the previous section of this report. Ventures that pursue local production are likely to find an additional set of challenges associated with manufacturing in low-resource settings. These often include issues related to supply chain, workforce, regulations, taxes, and so on. The barriers to local production will vary across countries and across regions, depending predominately upon the nature of the medical product. For example, the demands on infrastructure would be different for the production of pharmaceuticals, consumables (e.g. gloves, syringes, gowns), small medical devices (e.g. blood pressure monitors, ultrasound probes), or larger medical devices (e.g. X-ray machines). In addition to the infrastructure and logistical issues, local production ventures might also confront obstacles to market penetration due to substantial bias toward imported products, not only from potential end users (such as clinicians or patients) but also from government procurement agencies.

Despite these challenges, there is considerable interest in promoting local production, particularly in sub-Saharan Africa because of the untapped potential for innovation both in terms of increased access to medical products and in terms of economic development. In addition, there are examples of success in Brazil, Russia, India, and China, as well as in other countries such as South Africa, Nigeria, and Jordan.

For foreign technology developers, successful promotion of local production could result in the creation of a local competitor for an imported product, but only if the local product could be used as a direct substitute for the imported one. The most probable and substantial impacts of efforts to develop local industry are likely to provide an improvement in the business environment, favorable to both domestic and foreign producers. Efforts to promote local production could channel resources toward improvements in physical and health-care infrastructure, increases in quantity and quality of the healthcare workforce, simplification of regulatory policies and procedures, and increased transparency in government procurement procedures. Lastly, the development of a local health technology industry will produce potential partners for foreign technology developers. Such partnerships may prove to be the most efficient way to accelerate and amplify the impact of new technologies.

**Innovative partnerships**

Recently, a number of partnerships between governmental, nongovernmental, academic and for-profit institutions have been developed to address a variety of issues related to the shortage of access to medical products and quality healthcare. Such partnerships, some of which involve institutions from more than one country, are helping to address the need for innovation that is highly focused on user needs and shortages in human resources, the failures of distribution systems and the obstacles in doing business described in the previous section. The collective impact of these partnerships may help to improve the environment for emerging medical nanotechnologies. Perhaps more importantly, some technology developers may be able to join into existing partnerships or use them as models for developing new ones.

In the specific realm of medical technology, several partnerships have been established to address the shortages in biomedical and clinical engineers, as well as BMETs. One program, which is supported by the Fogarty International Centre, is directed at “Developing Innovative Interdisciplinary Biomedical Engineering Programs in Africa.” This program provides training for biomedical engineers and other medical and business professionals through a partnership that involves Northwestern University (USA), the University of Cape Town (South Africa), the University of Ibadan and Lagos University (Nigeria), the University of Bamako (Mali), and the University of Nairobi (Kenya). To train BMETs, Engineering World Health, a US-based not-for-profit organization, has partnered with Duke University (USA) and several hospitals in Rwanda, Cambodia, Honduras, Ghana, and Nigeria. A unique aspect of this extensive program is that it includes a for-profit company, General Electric, which provides financial support for the training program.

The expanding and evolving landscape of partnerships between private foundations, international organizations, multinational corporations, government aid agencies, and host governments has helped to expand or produce new markets for medical products. Several broad-based partnerships are directed at increasing access to medical products by shaping the economic landscape, coordinating R&D and business development efforts, and supporting innovation in technology, business, and government practices. For example, to address the barriers faced in adopting a more effective treatment of severe malaria (injectable artemesunate), the Clinton Health Access Initiative partnered with UNITAID, the United Kingdom’s DFID, Medicines for Malaria Venture, and the governments of Nigeria, Uganda, Cameroon, Malawi, Kenya, and Zambia. One of the partners, UNITAID, is itself a multinational organization with 29
member countries that is supported in large part through an air ticket levies imposed in some member countries. Medical technology developers may be able to greatly accelerate testing, distribution, and adoption of their products by tapping into such broad-based networks of partners.

An important feature for most, if not all, of these efforts is that they strive to be true partnerships. This emphasis on bidirectional exchange and collaboration is part of a growing trend in development activities to shift away from direct aid and to focus on partnership and cross-sector collaboration to achieve sustainable development.\(^{33,40,110,118,121–124}\) The growing emphasis on an approach that values all partners as potential innovators has perhaps never been as prominent as in the recent 2015 International Conference on Financing for Development.\(^{105}\)

### Concluding remarks

The success of the persistent, and hopefully accelerating, efforts to improve global health will depend strongly on the ability of medical technology developers not only to innovate new and affordable products but also to deliver them to the marketplace. As a developer sets off to pursue these goals, the challenges, as outlined in this review, will be numerous and formidable.\(^{80}\) However, the confluence of a number of factors—the growing base of science and engineering knowledge to support new technological developments, the widespread availability of communication and information technologies,\(^{37,125–127}\) the expanding array of intersector and international partnerships,\(^{105,122}\) and the emerging economies in many parts of the world—may work to remove some of these obstacles and accelerate progress. Technology developers may be able to increase their likelihood of success by identifying key trends in global health and the global health community, by carefully characterizing the multidimensional array of challenges specific to their technology, and by adopting strategies for technology and business development that maximize their ability to benefit from ongoing trends as they work to address the complex set of challenges on the path to clinical impact.

Readers considering deployment of nanotechnology in global health are recommended to review specific case studies.\(^{33,80,112}\) Suggested readings are also available on specific topics, such as global burden of disease,\(^ {13} \) human resource capacity,\(^ {76} \) task shifting,\(^ {79} \) noncommunicable diseases,\(^ {19,28} \) and infectious diseases.\(^ {54–62} \)

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### References

1. United Nations Children’s Fund. United Nations Inter-agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality Report 2012. New York: United Nations Children’s Fund, 2012.

2. UN Inter-agency Group for Maternal Mortality Estimation. Trends in maternal mortality: 1990 to 2010: WHO, UNICEF, UNFPA and The World Bank estimates. Geneva: World Health Organization, 2012.

3. Jamison DT, Summers LH, Alleyne G, et al. Global health 2035: a world converging within a generation. Lancet 2013; 382: 1898–1955.

4. United Nations Children’s Fund. United Nations Inter-agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality Report 2015. New York: United Nations Children’s Fund, 2015.

5. Maternal Mortality Estimation Inter-Agency Group. Trends in maternal mortality: 1990 to 2015: estimates by WHO, UNICEF, UNFPA. World Bank Group and the United Nations Population Division. Geneva: World Health Organization, 2015.

6. Frost LJ and Reich MR. ACCESS: How do good health technologies get to poor people in poor countries? Cambridge: Harvard Center for Population and Development Studies, 2008.

7. Simiyu K, Daer AS and Singer PA. Stagnant health technologies. Science 2010; 330: 1483–1484.

8. Labarre P. Engineering global health. IEEE Pulse 2011; 2(1): 18–25.

9. Yager P, Domingo GJ and Gerdes J. Point-of-care diagnostics for global health. Annu Rev Biomed Eng 2008: 10: 107–144.

10. Pai NP, Vadnais C, Denkinger C, et al. Point-of-care testing for infectious diseases: diversity, complexity, and barriers in low- and middle-income countries. PLoS Med 2012; 9: e1001306.

11. World Health Organization. Medical devices: managing the mismatch: an outcome of the priority medical devices project. Geneva: World Health Organization, 2010.

12. Derda R, Gitaka J, Klapperich CM, et al. Enabling the development and deployment of next generation point-of-care diagnostics. PLoS Negl Trop Dis 2015; 9: e0003676.

13. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385: 117–171.

14. Wang H, Dwyer-Lindgren L, Lofgren KT, et al. Age-specific and sex-specific mortality in 187 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2071–2094.

15. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-Agency Group for Child Mortality Estimation. Lancet 2015; 386: 2275–2286.
16. World Health Organization. Global Health Observatory data repository. Geneva: World Health Organization, 2016.
17. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2197–2223.
18. Hogerzeil HV, Liberman J, Wirtz VJ, et al. Promotion of access to essential medicines for non-communicable diseases: practical implications of the UN Political Declaration. Lancet 2013; 381: 680–689.
19. Horton R. Non-communicable diseases: 2015 to 2025. Lancet 2013; 381: 509–510.
20. Webster J, Lines J, Bruce J, et al. Which delivery systems reach the poor? A review of equity of coverage of ever-treated nets, never-treated nets, and immunisation to reduce child mortality in Africa. Lancet Infec Dis 2005; 5: 709–717.
21. Engle PL, Fernald LCH, Alderman H, et al. Strategies for reducing inequalities and improving developmental outcomes for young children in low-income and middle-income countries. Lancet 2011; 378: 1339–1353.
22. Walker SP, Wachs TD, Grantham-McGregor S, et al. Inequality in early childhood: risk and protective factors for early child development. Lancet 2011; 378: 1325–1338.
23. Nachega JB, Uthman OA, Peltzer K, et al. Association between antiretroviral therapy adherence and employment status: systematic review and meta-analysis. Bull World Health Organ 2015; 93: 29–41.
24. Di Cesare M, Khang Y-H, Asaria P, et al. Inequalities in non-communicable diseases and effective responses. Lancet 2013; 381: 585–597.
25. McMichael AJ. Globalization, climate change, and human health. N Engl J Med 2013; 368: 1335–1343.
26. Haines A, Smith KR, Anderson D, et al. Policies for accelerating access to clean energy, improving health, advancing development, and mitigating climate change. Lancet 2007; 370: 1264–1281.
27. Clark H. NCDs: a challenge to sustainable human development. Lancet 2013; 381: 510–511.
28. Alleyne G, Binagwaho A, Haines A, et al. Embedding non-communicable diseases in the post-2015 development agenda. Lancet 2013; 381: 566–574.
29. Yansouni CP, Bottieau E, Lutumba P, et al. Rapid diagnostic tests for neurological infections in Central Africa. Lancet Infec Dis 2013; 13: 546–558.
30. Lawn SD, Mwaba P, Bates M, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. Lancet Infec Dis 2013; 13: 349–361.
31. das Neves J, Amiji MM, Bahia MF, et al. Nanotechnology-based systems for the treatment and prevention of HIV/AIDS. Adv Drug Deliv Rev 2010; 62: 458–477.
32. Weigl B, Boyle D, de los Santos T, et al. Simplicity of use: a critical feature for widespread adoption of diagnostic technologies in low-resource settings. Expert Rev Med Devices 2009; 6: 461–464.
33. Kumar AA, Hennek JW, Smith BS, et al. From the bench to the field in low-cost diagnostics: two case studies. Angew Chem Int Ed Engl 2015; 54: 5836–5853.
34. Martinez AW, Phillips ST, Butte MJ, et al. Patterned paper as a platform for inexpensive, low-volume, portable bioassays. Angew Chem Int Ed Engl 2007; 46: 1318–1320.
35. Ozcan A. Mobile phones democratize and cultivate next-generation imaging, diagnostics and measurement tools. Lab Chip 2014; 14: 3187–3194.
36. Nemiroski A, Christodoules DC, Hennek JW, et al. Universal mobile electrochemical detector designed for use in resource-limited applications. Proc Natl Acad Sci U S A 2014; 111: 11984–11989.
37. Tallury P, Malhotra A, Byrne LM, et al. Nanobiomimicking and sensing of infectious diseases. Adv Drug Deliv Rev 2010; 62: 424–437.
38. van Herden A, Tomlinson M and Swartz L. Point of care in your pocket: a research agenda for the field of m-health. Bull World Health Organ 2012; 90: 393–394.
39. Whitesides G. The lab finally comes to the chip! Lab Chip 2014; 14: 3125–3126.
40. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics for infectious diseases. Clin Infect Dis 2013; 57(suppl 3): SI39–SI70.
41. Laknanasopin T, Guo T, Nayak S, et al. A smartphone dongle for diagnosis of infectious diseases at the point of care. Sci Transl Med 2015; 7: 1–9.
42. Shet A and de Costa A. India calling: harnessing the promise of mobile phones for HIV healthcare. Trop Med Int Health. 2011; 16: 214–216.
43. du Toit LC, Pillay V and Choonara YE. Nano-microbicides: challenges in drug delivery, patient ethics and intellectual property in the war against HIV/AIDS. Adv Drug Deliv Rev 2010; 62: 532–546.
44. Sharma P and Garg S. Pure drug and polymer based nanotechnologies for the improved solubility, stability, bioavailability and targeting of anti-HIV drugs. Adv Drug Deliv Rev 2010; 62: 491–502.
45. Santos-Magalhaes NS and Mosqueira VC. Nanotechnology applied to the treatment of malaria. Adv Drug Deliv Rev 2010; 62: 560–575.
46. Romero EL and Morilla MJ. Nanotechnological approaches against Chagas disease. Adv Drug Deliv Rev 2010; 62: 576–588.
47. Seidenberg P, Nicholson S, Schaefer M, et al. Early infant diagnosis of HIV infection in Zambia through mobile phone texting of blood test results. Bull World Health Organ 2012; 90: 348–356.
48. Free C, Phillips G, Galli L, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. PLoS Med 2013; 10: e1001362.
49. Thirumurthy H and Lester RT. M-health for health behaviour change in resource-limited settings: applications to HIV care and beyond. Bull World Health Organ 2012; 90: 390–392.
50. Rajatonirina S, Heraud JM, Randrianasolo L, et al. Short message service sentinel surveillance of influenza-like illness in Madagascar, 2008–2012. Bull World Health Organ 2012; 90: 385–389.

51. World Health Organization. mHealth – new horizons for health through mobile technologies. Geneva: World Health Organization, 2011.

52. Miller E and Sikes HD. Addressing barriers to the development and adoption of rapid diagnostic tests in global health. Nanobiomedicine 2015; 2: 6.

53. Myers NM, Strydom EE, Sweet J, et al. saltPAD: a new analytical tool for monitoring salt iodization in low resource settings. Nanobiomedicine 2016; 1: 1–9.

54. Abou Neel EA, Bozec L, Perez RA, et al. Nanotechnology in dentistry: prevention, diagnosis, and therapy. Int J Nanomed 2015; 10: 6371–6394.

55. Antiochia R, Bollella P, Favero G, et al. Nanotechnology-based surface plasmon resonance affinity biosensors for in vitro diagnostics. Int J Anal Chem 2016; 2016: 2981931.

56. Bobo D, Robinson KJ, Islam J, et al. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res 2016; 33: 2373–2387.

57. Cheon SA, Cho HH, Kim J, et al. Recent tuberculosis diagnosis toward the end TB strategy. J Microbiol Methods 2016; 123: 51–61.

58. Lifson MA, Ozen MO, Inci F, et al. Advances in biosensing strategies for HIV-1 detection, diagnosis, and therapeutic monitoring. Adv Drug Deliv Rev 2016; 103: 90–104.

59. Liu Y and Chen C. Role of nanotechnology in HIV/AIDS vaccine development. Adv Drug Deliv Rev 2016; 103: 76–89.

60. Syedmoradi L, Daneshpour M, Alvandpour M, et al. Point of care testing: the impact of nanotechnology. Biosens Bioelectron 2017; 87: 373–387.

61. Torres-Sangiao E, Holban AM, and Gestal MC. Advanced nanobiomaterials: vaccines, diagnosis and treatment of infectious diseases. Molecules 2016; 21: E867.

62. Wen AM and Steinmetz NF. Design of virus-based nanomaterials for medicine, biotechnology, and energy. Chem Soc Rev 2016; 45: 4074–4126.

63. Andronikou S, McHugh K, Abdurahman N, et al. Paediatric radiology seen from Africa. Part I: providing diagnostic imaging to a young population. Pediatr Radiol 2011; 41: 811–825.

64. Albertini A, Lee E, Coulibaly SO, et al. Malaria rapid diagnostic test transport and storage conditions in Burkina Faso, Senegal, Ethiopia and the Philippines. Malar J 2012; 11: 406.

65. Stevens DY, Petri CR, Osborn JL, et al. Enabling a microfluidic immunoassay for the developing world by integration of on-card dry reagent storage. Lab Chip 2008; 8: 2038–2045.

66. Kartoglu U and Milsien J. Tools and approaches to ensure quality of vaccines throughout the cold chain. Expert Rev Vaccines 2014; 13: 843–854.

67. World Health Organization, World Intellectual Property Organization and World Trade Organization. Promoting access to medical technologies and innovation: Intersections between public health, intellectual property and trade. Geneva: World Health Organization, World Intellectual Property Organization, World Trade Organization, 2012.

68. Procurement Process Resource Guide. WHO medical device technical series. Geneva: World Health Organization, 2011.

69. Doing Business 2015. Going beyond efficiency. Washington, DC: The World Bank, 2014.

70. Kumar B and Baldi A. The challenge of counterfeit drugs: a comprehensive review on prevalence, detection and preventive measures. Curr Drug Saf 2016; 11(2): 112–120.

71. Weaver AA and Lieberman M. Paper test cards for presumptive testing of very low quality antimalarial medications. Am J Trop Med Hyg 2015; 92: 17–23.

72. Lubell Y, Reyburn H, Mbakilwa H, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. BMJ 2008; 336: 202–205.

73. Diggle E, Asgary R, Gore-Langton G, et al. Perceptions of malaria and acceptance of rapid diagnostic tests and related treatment practises. Malar J 2014; 13: 502.

74. Kyabayinze D, Asiimwe C, Nakanjako D, et al. Use of RDTs to improve malaria diagnosis and fever case management at primary health care facilities in Uganda. Malar J 2010; 9: 200.

75. Sidibe M and Campbell J. Reversing a global health workforce crisis. Bull World Health Organ 2015; 93: 3.

76. Crisp N. Global health capacity and workforce development: turning the world upside down. Infect Dis Clin North Am 2011; 25: 359–367.

77. World Medical Association. WMA resolution on task shifting from the medical profession. New Delhi: World Medical Association, 2009.

78. Engelman D, Kado JH, Reméniyi B, et al. Focused cardiac ultrasound screening for rheumatic heart disease by briefly trained health workers: a study of diagnostic accuracy. Lancet Glob Health 2016; 4: e386–e394.

79. Joshi R, Alim M, Kengne AP, et al. Task shifting for non-communicable disease management in low and middle income countries – a systematic review. PLoS One 2014; 9: e103754.

80. Matthias DM, Taylor CH, Sen D, et al. Local markets for global health technologies: lessons learned from advancing 6 new products. Glob Health Sci Pract 2014; 2(2): 152–164.

81. Ogdedegbe G, Gyamfi J, Plange-Rhule J, et al. Task shifting interventions for cardiovascular risk reduction in low-income and middle-income countries: a systematic review of randomised controlled trials. BMJ Open 2014; 4: e005983.

82. Kalluri P, Naheed A, Rahman S, et al. Evaluation of three rapid diagnostic tests for cholera: does the skill level of the technician matter? Trop Med Int Health 2006; 11(1): 49–55.

83. Malkin RA. Design of health care technologies for the developing world. Adv Drug Deliv Rev 2011; 63: 51–61.

84. World Health Organization. Medical equipment maintenance programme overview. Geneva: World Health Organization, 2011.

85. Wang B. Medical equipment maintenance: management and oversight. London: Morgan & Claypool, 2012.
86. Stanton CK, Newton S, Mullany LC, et al. Effect on postpartum hemorrhage of prophylactic oxytocin (10 IU) by injection by community health officers in Ghana: a community-based, cluster-randomized trial. *PLoS Med* 2013; 10: e1001524.
87. Kumar AA, Chunda-Liyoka C, Hennek JW, et al. Evaluation of a density-based rapid diagnostic test for sickle cell disease in a clinical setting in Zambia. *PLoS One* 2014; 9: e114540.
88. The Law Library of Congress Global Legal Research Center. *Approval of medical devices*. Washington: The Law Library of Congress Global Legal Research Center, 2014.
89. Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA). *Guideline for registration of medicines*. Addis Ababa: Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA), 2014.
90. World Health Organization. *Medical devices: managing the mismatch – barriers to innovation in the field of medical devices*. Geneva: World Health Organization, 2010.
91. World Bank. *An overview of medical device policy and regulation*. Washington, DC: World Bank, 2007.
92. van Gemert-Pijnen JE, Wynchank S, Covvey HD, et al. Improving the credibility of electronic health technologies. *Bull World Health Organ* 2012; 90: 323–323A.
93. Wootton R, Geissbuhler A, Jethwani K, et al. Long-running telemedicine networks delivering humanitarian services: experience, performance and scientific output. *Bull World Health Organ* 2012; 90: 341D–347D.
94. Piette JD, Lun KC, Moura LA Jr, et al. Impacts of e-health on the outcomes of care in low- and middle-income countries: where do we go from here? *Bull World Health Organ* 2012; 90: 365–372.
95. World Health Organization. *Local production and technology transfer to increase access to medical devices*. Geneva: World Health Organization, 2012.
96. World Health Organization. *Compendium of innovative health technologies for low-resource settings*. Geneva: World Health Organization, 2014.
97. Britton TJ, Kurihara CQ, Camarillo DB, et al. Outcomes from a postgraduate biomedical technology innovation training program: the first 12 years of Stanford biosign. *Ann Biomed Eng* 2013; 41: 1803–1810.
98. Rice University, Rice 360 Institute for Global Health Technologies, 2016. [Online]. Available: http://www.rice360.rice.edu/.
99. Som A, Charanya T, Linderman SW, et al. Bridging the gap between invention and commercialization in medical devices. *Nat Biotechnol* 2014; 32: 1063–1065.
100. World Bank. *World Bank open data*. Washington, DC: World Bank, 2015.
101. The United Nations. *The Millennium Development Goals report*. New York: The United Nations, 2015.
102. Victora CG, Requejo JH, Barros AJD, et al. Countdown to 2015: a decade of tracking progress for maternal, newborn, and child survival. *Lancet* 2016; 387: 2049–2059.
103. UN Commission on Life-Saving Commodities for Women and Children, UN Commission on Life-Saving Commodities for Women and Children; Commissioner’s Report. New York: United Nations, 2012.
104. World Health Organization. *Interagency list of medical devices for essential interventions for reproductive, maternal, newborn and child health*. Geneva: World Health Organization, 2015.
105. United Nations. *Outcome document of the Third International Conference on Financing for Development – Addis Ababa Action Agenda*. New York: United Nations, 2015.
106. Policy Brief. *Local production for access to medical products developing a framework to improve public health*. Geneva: World Health Organization, 2011.
107. Local production for access to medical products: developing a framework to improve public health. Geneva: World Health Organization, 2011.
108. World Health Organization. *Towards improving access to medical devices through local production phase II: report of a case study in four Sub-Saharan countries*. Geneva: World Health Organization, 2016.
109. Masum H, Chakma J, Simiyu K, et al. Venture funding for science-based African health innovation. *BMC Int Health Hum Rights* 2010; 10(suppl 1): S12.
110. Reddy P. *Global innovation in emerging economies*. New York: Routledge, Taylor & Francis Group, 2011.
111. Waning B, Diedrichsen E, and Moon S. A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries. *J Int AIDS Soc* 2010; 13: 35.
112. Jarosławski S and Saberwal G. Case studies of innovative medical device companies from India. *BMC Health Serv Res* 2013; 13: 199.
113. Caldwell A, Young A, Gomez-Marquez J, et al. Global innovation in emerging economies: South Africa’s health biotech sector. *Nature Biotechnol* 2009; 27: 427–445.
114. Fogel R and Limson J. Developing biosensors in developing countries: South Africa as a case study. *Biosensos (Basel)* 2016; 6: 5.
115. World Health Organization. *Pharmaceutical production and related technology transfer*. Geneva: World Health Organization, 2011.
116. Pallas SW, Nonvignon J, Aikins M, et al. Responses to donor proliferation in Ghana’s health sector: a qualitative case study. *Bull World Health Organ* 2015; 93: 11–18.
117. Caldwell A, Young A, Gomez-Marquez J, et al. Global health technology 2.0. *IEEE Pulse* 2011; 2: 63–67.
118. Thorsteinsdottir H, Ray M, Kapoor A, et al. Health biotechnology innovation on a global stage. *Nat Rev Microbiol* 2011; 9: 137–143.
119. Samb B, Evans T, Dybul M, et al. An assessment of interactions between global health initiatives and country health systems. *Lancet* 2009; 373: 2137–2169.
120. World Health Organization. *African partnerships for patient safety*. Geneva: World Health Organization, 2009.
121. Bhan A, Singh JA, Upshur RE, et al. Grand challenges in global health: engaging civil society organizations in biomedical research in developing countries. *PLoS Med* 2007; 4: e272.

122. Crisp N. Mutual learning and reverse innovation – where next? *Global Health* 2014; 10: 14.

123. Rottingen JA, Chamas C, Goyal LC, et al. Securing the public good of health research and development for developing countries. *Bull World Health Organ* 2012; 90: 398–400.

124. Juma C. Biotechnology in a globalizing world: the coevolution of technology and social institutions. *BioScience* 2005; 55: 265.

125. Meir A and Rubinska B. Distributed network, wireless and cloud computing enabled 3-D ultrasound; a new medical technology paradigm. *PLoS One* 2009; 4: e7974.

126. Mair FS, May C, O’Donnell C, et al. Factors that promote or inhibit the implementation of e-health systems: an explanatory systematic review. *Bull World Health Organ* 2012; 90: 357–364.

127. Lewis T, Synowiec C, Lagomarsino G, et al. E-health in low- and middle-income countries: findings from the center for health market innovations. *Bull World Health Organ* 2012; 90: 332–340.