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New Technology Needs for Noncommunicable Diseases in Developing Countries: a landscaping study

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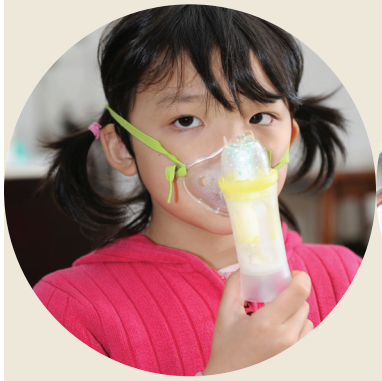
Acronyms

R&D	research and development
LMIC	low- and middle-income countries
NCD	noncommunicable diseases
WHO	World Health Organization
CVD	cardiovascular disease
UN	United Nations
NTD	neglected tropical diseases
WHA	World Health Assembly
HIC	high income countries
DALY	disability-adjusted life years
HPV	human papillomavirus
CEWG	Consultative Expert Working Group on Research and Development
POC	point-of-care
SMBG	self-monitoring blood glucose
IDA	International Diabetes Association
COPD	chronic obstructive pulmonary diseases
GINA	Global Initiative for Asthma
PEF	peak expiratory flow
SBE	self-breast examination
CBE	clinical breast examination
BHGI	Breast Health Global Intiative
ER	estrogen receptor



In recent decades, there has been growing recognition of the research and development (R&D) gap for neglected infectious diseases primarily affecting low- and middle-income countries (LMICs).

Important steps have been taken toward addressing this gap, but progress is fragile and much remains to be done.

The historic United Nations High-Level Meeting on Noncommunicable Diseases in September 2011 drew the world's attention to the burden of noncommunicable diseases (NCDs) that increasingly threaten the health and development of many LMICs; yet, analysis of the role of new product R&D in addressing this burden has been limited. This landscaping paper explores the role of new product R&D in addressing barriers to NCD prevention and control in LMICs. It offers a framework for analyzing new product needs for NCDs in low-resource settings and assesses the overall importance of R&D relative to other arms of a comprehensive prevention and control strategy.

Both rich and poor countries share the burden of NCDs, unlike neglected diseases, thereby creating powerful market incentives for the development of effective health technologies, including medicines, vaccines, diagnostics, and delivery technologies. However, technologies developed for rich countries may not always be well suited for the specific challenges faced by LMICs. The study begins by considering the economic, health system, and socio-cultural barriers to NCD prevention and control in LMICs and how each might create a need for new products specifically targeted to the circumstances of these settings. It then considers which of several kinds of new products—novel, adapted, low-cost, and acceptable technologies—might be required to fill these gaps.

The next part of the paper explores select noncommunicable diseases in greater depth, providing an overview of current prevention and control strategies, assessing barriers to implementation, and then identifying potential product gaps and opportunities for R&D. Following the World Health Organization (WHO), it focuses on four major classifications of NCDs—cardiovascular disease, diabetes, chronic respiratory disease, and cancer—which account for the greatest burden of NCDs on developing countries. Within each major disease category, one representative disease is used to conduct a detailed assessment of barriers and new product needs based on literature reviews and expert interviews.

The landscaping paper concludes that new product R&D can contribute to NCD prevention and control in LMICs, but its importance varies by disease, by technology, and by context.

- Disease: Cancer presents the greatest number of opportunities for R&D because interventions depend on specialized technology and healthcare workers, and the opportunities for innovation are made possible by advances in biotechnology. The second greatest need for new product R&D is in diabetes, followed by cardiovascular disease (CVD) and chronic respiratory disease.
- Technology: Diagnostics present the greatest opportunity for impact through new product R&D. Delivery technologies, a largely unexplored product area, may also play a significant role in addressing NCDs. The need for new vaccines and medicines specially developed for LMICs, however, is less urgent, except for the "neglected NCDs," such as Chagas cardiomyopathy and rheumatic heart disease.

- Context: In certain low-resource settings, successful efforts at health system strengthening (e.g., community health workers) may circumvent barriers to NCD control and prevention, reducing the need for new products. In settings with rudimentary health systems or fragmented care delivery, new product R&D may play a larger role in addressing NCDs.

This report offers a unique framework to examine new product needs for combating NCDs in developing countries, and it identifies examples of specific R&D gaps for selected diseases. This preliminary work is designed to stimulate discussion of strategies for accelerating the development of the needed new products.

CHAPTER 1
INTRODUCTION

1

1.1 Background

Noncommunicable diseases (NCDs) now account for the majority of global morbidity and mortality. Out of every 10 deaths globally, 6 are due to NCDs, 3 to communicable maternal health or nutritional conditions, and 1 to injuries.[1] In 2008, NCDs contributed to 36 million of the 57 million deaths worldwide, including 9 million deaths in young people and adults below age 60.[2] Due to an increase in multiple NCD risk factors, such as tobacco use and sedentary lifestyles, this trend is expected to continue. Currently, nearly 80 percent of deaths from NCDs occur in low- and middle-income countries (LMICs), and NCDs are the now the leading cause of morbidity and mortality in every region of the world except sub-Saharan Africa.[3] Unless addressed, NCD deaths will increase by 17 percent between 2005 and 2015, with the greatest increase in the African region.[4]

At the same time, LMICs continue to face the threat of infectious diseases, including HIV/AIDS, malaria, tuberculosis, and neglected tropical diseases (NTDs), and mother and child conditions. This "double burden" of disease places an inordinate strain on already under-resourced health systems.[5] Despite these challenges, major donor funding for NCDs is a fraction of that spent for communicable diseases: estimated at $3 USD per death from NCDs compared to $1,030 USD per death for HIV/AIDS.[6]

NCDs include a broad range of conditions with various risk factors and strategies for control and prevention. International attention has focused primarily on four types of NCDs—cardiovascular disease (CVD), diabetes, chronic respiratory disease, and cancer—as they present the largest contribution to mortality in the majority of LMICs yet are largely preventable and treatable.[7] Evidence suggests that up to 80 percent of heart disease, stroke, and type 2 diabetes incidents and over a third of cancers could be prevented by eliminating four shared risk factors: tobacco use, unhealthy diet, physical inactivity, and the harmful use of alcohol.[8] In addition, for each of these diseases, individual- and population-level interventions exist, many of which have been shown to be cost-effective in LMICs.[9]

In recognition of the growing threat of NCDs, the United Nations (UN) General Assembly held a high-level meeting in September 2011 on the prevention and control of the NCDs.[10] This event marked only the second time that a General Assembly held a meeting on health; the first, in 2001, was held in response to the global HIV/AIDS epidemic. The primary outcome of the 2011 meeting was a draft resolution calling for the World Health Organization (WHO) to "prepare recommendations for a set of voluntary global targets

[1] Preventing chronic disease: a vital investment. Geneva, World Health Organization, 2005.

[2] Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011.

[3] Ibid.

[4] Preventing chronic disease: a vital investment. Geneva, World Health Organization, 2005.

[5] The growing danger of non-communicable diseases: acting now to reverse the course. The World Bank, September 2011. (http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/Peer-Reviewed-Publications/WBDeepeningCrisis.pdf)

[6] Mattke S, et al. Improving access to medicines for non-communicable diseases in the developing world. RAND Corporation, 2011.

[7] 2008-2013 action plan for the global strategy for the prevention and control of noncommunicable diseases: prevent and control cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. World Health Organization, 2008.

[8] Ibid.

[9] Ibid.

[10] United Nations high-level meeting on noncommunicable disease prevention and control. (www.who.int/nmh/events/un_ncd_summit2011/en/, accessed 21 March 2012).

for the prevention and control of non-communicable diseases, before the end of 2012."[11] In the lead up to the UN General Assembly meeting, in 2008 the World Health Assembly (WHA) endorsed a five-year action plan for implementing the Global Strategy for the Prevention and Control of Noncommunicable Diseases (WHA 53.14) adopted in March 2000.[12] The action plan for 2008-2013 focuses on the growing health and economic burden of NCDs in LMICs and identifies six objectives: (1) raise the priority of NCDs, (2) strengthen national policies, (3) reduce shared risk factors, (4) promote R&D to prevent and control NCDs, (5) promote partnerships, and (6) monitor and evaluate these diseases.[13]

With increasing attention and support for addressing NCDs in LMICs, the question for global health practitioners and policymakers is how to achieve significant gains in NCD prevention and control.

1.2 Motivation

With notable exceptions,[14] much of the attention on NCDs to date has focused on funding, access to medicines, and health systems strengthening, with less emphasis on R&D on new health technologies. The implicit assumption is that the medicines, vaccines, diagnostics, and delivery technologies used to address NCDs in high-income countries (HICs) can be readily applied to LMICs, or that, where new tools are needed, demand from rich countries will drive development.

At a first glance, the assumption appears logically sound. Unlike malaria, tuberculosis, and NTDs, most NCDs that increasingly threaten LMICs are also major contributors to the burden of disease in HICs. Therefore, large markets in wealthy countries provide a powerful financial incentive for the R&D and supply of drugs, vaccines, and diagnostics for common NCDs. Indeed, although the data are limited, a recent WHO report found that approximately 66 percent of private sector R&D goes to NCDs whereas 33 percent is spent on communicable diseases and 62 percent of drugs under development are for NCDs.[15] The reasonable conclusion suggests that effective health technologies for controlling and preventing NCDs already exist or are being pursued vigorously, and the objective of policymakers should be to set disease priorities, identify cost-effective interventions, ensure access to existing medicines and other technologies, and support scale-up efforts across LMICs.

Upon closer examination, however, one finds notable examples of new products playing roles in reducing the global burden of NCD. Existing prevention and treatment technologies developed for HICs are often ill suited to the needs of LMICs. In particular, these tools may cost too much, require sophisticated infrastructure not present in low-resource settings, or rely on highly trained health workers who may be in short supply in poor countries. Moreover, differences in epidemiological context, including the greater burden of infectious diseases and maternal and child conditions in poor countries, or differences in etiology, may also mean that different tools are needed to address NCDs in LMICs. Finally, cultural and other patient-level factors may reduce the acceptability and effectiveness of existing interventions in developing countries, creating a need for new technologies.

The overall aim of this study is to determine whether the development of new drugs, vaccines, diagnostics, and delivery technologies for developing countries could have a substantial impact in reducing the burden of NCDs in LMICs. Through this report, we provide a

[11] Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases, 16 September 2011. (http://www.un.org/ga/search/view_doc.asp?symbol=A%2F66%2FL.1&Lang=E , accessed 17 September 2012)

[12] Global strategy for the prevention and control of noncommunicable diseases. Fifty-Third World Health Assembly. WHA (53.14). (http://apps.who.int/gb/archive/pdf_files/WHA53/ea14.pdf).

[13] 2008-2013 action plan for the global strategy for the prevention and control of noncommunicable diseases: prevent and control cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. World Health Organization, 2008.

[14] Discussed in the next section.

[15] Research and development coordination and financing: report of the expert working group. World Health Organization, 2010.

framework for assessing R&D needs for NCDs in low-resource settings, identify potential gaps in existing health technologies for NCDs and opportunities for new product R&D, and assess the relative importance of new product R&D compared to other priority areas. The general approach involves identifying representative diseases, reviewing current strategies for disease control and prevention, and then considering how new technologies could address barriers to implementing these strategies in LMICs.

1.3 Prior Work

In response to the 2008-2013 action plan endorsed by the WHA, the WHO published the Prioritized Research Agenda for Prevention and Control of Noncommunicable Diseases in 2011,[16] which was developed from 2008 through 2010 via a series of consultations, working papers on major NCD research domains, extensive reviews, and a survey for ranking research priorities identified by expert groups. The agenda, as stated in the report, refers to "key areas of research that seek to understand and impact polices, programs and processes for preventing and mitigating the NCD epidemic, with a special focus on low- and middle-income countries."[17] Though not the focus or primary purpose of the agenda, the need for new medicines, vaccines, diagnostics, and technologies was considered, and a number of research priorities identified by the WHO are relevant to new product development in LMICs. Our analysis builds upon, and where applicable, references these research priorities in Chapter 3 in the discussion of specific R&D gaps and opportunities.

Besides the WHO, few other groups have explored new product needs to address NCDs in LMICs. In its report "Improving Access to Medicines for Non-Communicable Diseases in the Developing World," the RAND Corporation, taking into account diverse populations, healthcare delivery systems as well as the stability of the medicines in diverse conditions, reviewed whether effective medicines for the treatment of the four major NCDs have been developed and whether they were suitable for developing countries.[18] In considering the development of new medicines for NCDs, it concluded that potent first-line treatments for non-cancer NCDs were largely available in generic form and thus "the most immediate gains in health can be achieved by improving access to existing medicines, as opposed to developing new compounds."[19] It identified potential opportunities for product innovations including technologies for supply chain management and improvement of patient adherence as well as research on fixed-dose combination products (known as "polypills"). Except in the case of neglected NCDs,[20] we largely agree with the RAND report conclusions regarding the need for new medicines. The opportunities identified for new delivery technologies and formulations are explored in Chapter 3.

In addition, recently PATH has put together a target product profile for diabetes screening technologies in low-resource settings[21] and is building a program portfolio in this area. Insights from this report have been incorporated in the diabetes discussion in Chapter 3.

[16] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[17] Ibid., p 8.

[18] Mattke S, et al. Improving access to medicines for non-communicable diseases in the developing world. RAND Corporation, 2011. (http://www.rand.org/pubs/occasional_papers/OP349.html, accessed 17 September 2012)

[19] Ibid, p. 20.

[20] Neglected non-communicable diseases are NCDs that are prevalent in LMICs but not in high-income countries, so there is little market incentive for the development of new technologies for these diseases.

[21] The report entitled "Developing an Adaptable Set of Point-of-Care Diabetes Screening Technologies for Low-Resource Settings" will be published in the peer-reviewed journal Point of Care in late 2012. A preliminary copy of the report was obtained from the corresponding author Bernhard H. Weigl.

1.4 Scope and Definitions

Selection of Noncommunicable Diseases

We focus our analysis on four major categories of NCDs: CVD, diabetes, chronic respiratory disease, and cancer. Our reasoning is two-fold. First, these conditions are among the largest contributors to morbidity and mortality from NCDs in developing countries; combined, they account for 46 percent of total deaths and 24 percent of disability-adjusted life years (DALYs) in LMICs and 85 percent of deaths and 48 percent of DALYs from NCDs.[22] Second, these NCDs have been targeted by the UN General Assembly and the WHO and thereby hold greater policy relevance.[23] Within each major NCD, we have selected a representative disease to explore in detail: atherosclerotic CVD, type 2 diabetes, asthma, and breast cancer. The rationale behind the selection of the target diseases is discussed in Chapter 3, but to summarize, it reflects three factors: disease burden, evidence of cost-effective interventions, and availability of consensus clinical guidelines in low-resource settings.

We recognize that a limitation of this approach is the exclusion of other high-burden NCDs, including mental health conditions, which alone account for nearly 10 percent of DALYs in LMICs.[24] However, our aim is to assess the overall importance for new product R&D to address NCDs in developing countries, not to develop an exhaustive list of product gaps and opportunities. Although some NCDs are not specifically addressed in this report, the frameworks we develop are directly relevant to these conditions and should be explored in future work.

Diseases versus Risk Factors

In this paper, we consider new product opportunities from the perspective of diseases rather than risk factors. Inasmuch as risk factors are relevant, they are discussed within the context of individual diseases. This framing was chosen largely because the majority of health technologies, particularly diagnostics, are disease-based. Clearly, there are important exceptions including vaccines against human papillomavirus (HPV), tobacco-cessation medications, and most recently, mobile health technologies to support behavior change.[25] More broadly, we recognize that addressing modifiable risk factors such as tobacco use, unhealthy diets, lack of physical activity, and harmful use of alcohol, may have a larger impact on the burden of NCDs in LMICs than disease control. However, our overall purpose here is to broadly assess the need for new product R&D, and this report should not be construed as exhaustive.

Defining Health Products and Technologies

Definitions of health products and health technologies vary considerably. The WHA defines health technologies as "the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives."[26] It defines a health product as drugs, medical devices, and other goods used to diagnose and treat illnesses or injuries or to maintain health.[27] Here we use the terms "health products" and "health technologies" interchangeably to include medicines, vaccines, diagnostics, and "delivery technologies." Delivery technologies are loosely defined as technologies that facilitate healthcare delivery but are neither diagnostic tools nor treatments. Examples

[22] Disease Control Priorities in Developing Countries, Second Edition. Geneva, World Bank Publications, 2 April 2006.

[23] 2008-2013 action plan for the global strategy for the prevention and control of noncommunicable diseases: prevent and control cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. World Health Organization, 2008.

[24] Ibid.

[25] Patrick K, Raab F, Adams MA, Dillon L, Zabinski M, Rock CL, Griswold WG, Norman GJ. A text message-based intervention for weight loss: randomized controlled trial. J Med Internet Res. 2009; Jan 13;11(1):e1.

[26] Health technologies. World Health Assembly. WHA60.29. (www.who.int/healthsystems/WHA60_29.pdf, accessed 21 March 2012), p. 106.

[27] Global strategy and plan of action on public health, innovation and intellectual property. Sixty-First World Health Assembly. WHA61.21. 24. May 2008. (http://www.who.int/healthsystems/WHA60_29.pdf)

of delivery technologies include health information systems, cold chain solutions, and mobile health technologies.

Defining R&D

We limit our analysis to R&D of health products and technologies. Technology by definition is an applied science. Thus, we exclude from consideration basic science or preclinical research as well as research on disease epidemiology, behavior health, and implementation science that is formative rather than translational. This decision does not suggest that this kind of research is not needed for NCDs or that such research would not create opportunities for new product innovation, but was made to limit the scope of the present study.

Specifying Target Population

The target population includes individuals in LMICs with limited access to adequate health systems. This includes the poor in most middle-income countries, but excludes, in general, the middle class. The environments for the target population should be considered consistent with the term "low resource setting."

1.5 Methods

Our research was based on a literature review of the global burden of disease and the guidelines and provisions of care for NCDs in LMICs. We also completed Internet-based research on relevant organizations doing work within the four major NCDs, across NCDs, and broadly within global health R&D. Additionally, we conducted expert interviews with key opinion leaders in academia, public health, and advocacy (Appendix 1). Experts were chosen within each category of NCDs—CVD, diabetes, chronic respiratory disease, and cancer—and within different cross-cutting areas of expertise such as medicines and diagnostics.

1.6 Overview of This Paper

Chapter 2 introduces our framework for analyzing new product R&D gaps for NCDs in developing countries. In Chapter 3, we discuss each of the four major NCD types and identify opportunities for new product R&D within the context of an overall strategy for disease control and prevention as well as barriers to implementation. In Chapter 4, we summarize our findings and discuss policy implications before concluding with suggestions for next steps.

CHAPTER 2
FRAMEWORK

2

In Chapter 2, we present a framework for assessing barriers to addressing noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs) and defining new product opportunities.

As discussed in Chapter 1 the R&D gap for NCDs in developing countries is different from that for neglected tropical diseases (NTDs) because in many cases effective interventions to address NCDs already exist. Rather, the challenge is to understand the barriers to implementing these interventions in LMICs and to identify new product opportunities that may exist as a result. We begin by providing historical context and motivation for this analysis. We then identify a partial list of the barriers to NCD prevention and control in LMICs that drive the need for new technologies. Finally, we consider the types of technologies that may be needed to address these barriers.

2.1 Historical Context and Motivation

In the context of R&D, the World Health Organization (WHO) Commission on Macroeconomics and Health categorizes diseases into three types.[28] Type I diseases are incident in both rich and poor countries, with large numbers of people affected in each; type II diseases are incident in both rich and poor countries but disproportionately affect poor countries (sometimes called "neglected diseases"); type III diseases are overwhelmingly or exclusively incident in developing countries (sometimes called "very neglected diseases"). Using this classification, most NCDs would be considered type I diseases.

Until recently, R&D gaps for type I diseases in developing countries were not considered relevant to global health funders and policymakers. In 2001, the Commission's report on Macroeconomics and Health summarized this viewpoint with the statement that because "incentives for R&D exist in rich country markets—both through public financing of basic science and patent protection for product development—products get developed, and the main policy issue, vis-à-vis the poor countries, is access to those technologies."[29]

However, in 2008, the World Health Assembly's (WHA) Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (WHA61.21) called for prioritizing R&D needs not only for type I and type II diseases, but also "specific R&D needs of developing countries in relation to type I diseases."[30] In response, in 2010, the WHO Expert Working Group on Research Development and Financing (EWG) called for the creation of a global health research and innovation coordination and funding mechanism that would provide funding for "targeted research and development for new drugs, vaccines, diagnostics and intervention strategies for health conditions of the poor, both communicable and noncommunicable diseases that are prevalent in low- and

[28] Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva, World Health Organization, 2001. (http://whqlibdoc.who.int/publications/2001/924154550x.pdf)

[29] Ibid., p. 78.

[30] Global strategy and plan of action on public health, innovation and intellectual property. Sixty-First World Health Assembly. WHA61.21. 24. (http://apps.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf, Accessed 21 March 2012).

middle-income countries, and for which adequate interventions are not presently available."[31]

Following the EWG, the Consultative Expert Working Group on Research and Development (CEWG) put forth a report in April 2012 proposing a convention to "provide effective financing and coordination mechanisms to promote R&D" that focuses on "the development of health technologies for type II and type III diseases as well as the specific needs of developing countries related to type I diseases." The report specifically recognizes that "R&D needs related to addressing noncommunicable diseases in the circumstances of developing countries are potentially large but as yet unexplored."[32]

Despite these high-level acknowledgements of the need for an R&D analysis for NCDs, most work on incentivizing health R&D for poor countries has focused on neglected infectious diseases. In the next section we build on the WHA resolution and WHO EWG and CEWG recommendations by presenting a framework for categorizing R&D needs of LMICs in relation to type I NCDs.

2.2 Barriers to Noncommunicable Disease Prevention and Control and the Role of New Technologies

Tackling the growing burden of NCDs requires a multifold and multisectoral approach, with new technology R&D comprising just a small piece of a larger strategy. A comprehensive NCD strategy would include building political will and donor support, increasing access to medicines and interventions already developed for rich-world markets, and strengthening health systems to address chronic diseases. In concert with these approaches, new technologies may play a role in overcoming specific barriers to addressing NCDs in developing countries.

Several barriers to NCD prevention and control in LMICs may be partially addressed by new product R&D. These barriers provide a framework with which to evaluate whether existing interventions are suitable for LMICs and to identify new product needs: high cost, lack of monitoring and healthcare professionals, insufficient healthcare training, problems with infrastructure, inconsistent healthcare-seeking behavior, and concerns over acceptability of tests or treatments.

Cost: One of the greatest barriers to NCD control and prevention in LMICs is cost. Not only do health systems in developing countries have constrained budgets, but patients, who often pay a large share of healthcare costs out-of-pocket, may be deterred from seeking treatment or prevention services. Technologies with lower direct costs or that lower the overall costs of care—for example, by reducing the need for services—are needed.

Lack of monitoring: Many medicines used to treat NCDs require frequent clinical monitoring and diagnostic testing, especially during initiation and dose escalation. Access barriers to care in developing countries create a need for treatments that have minimal requirements for testing and the lowest risk of harm.

Lack of health care professionals: Developing countries commonly have a shortage of healthcare professionals. New products can facilitate the shift of tasks to less skilled health workers or to automated processes, and can also enable non-physician healthcare workers to expand their roles. For example, in the Millennium Villages Project, a mobile health tool called ChildCount+ facilitates and coordinates the activities of community health workers in improving child health.[33]

Insufficient healthcare training: Health care professionals in LMICs are largely trained to address communicable diseases as well as maternal and child conditions, so they may lack sufficient knowledge and skills in the diagnosis and management of NCDs. New

[31] Research and development coordination and financing: report of the expert working group. Geneva, World Health Organization, 2010. (http://www.who.int/phi/documents/RDFinancingEN.pdf), p. 43.

[32] Research and Development to Meet Health Needs in Developing Countries: Strengthening global financing and coordination. Consultative Expert Working Group on Research and Development: Financing and Coordination, WHO, 2012. (www.who.int/phi/CEWG_Report_5_April_2012.pdf, accessed 29 May 2012).

[33] ChildCount.org (www.childcount.org/, accessed 20 March 2012).

products can automate tasks, thereby eliminating need for some skilled care (e.g., automatic blood-pressure cuffs) or reducing the level of training required (e.g., single-purpose ultrasound devices). New technologies may also be able to facilitate training; for example, e-learning tools have been designed to rapidly train individuals in breast cancer screening and facilitate ongoing quality assurance.[34]

Poor infrastructure: LMICs sometime lack basic infrastructure needed to provide healthcare (e.g., roads, power grids). Evidence suggests that only 24 percent and 35 percent of health facilities in Uganda and Tanzania have regular electricity, and only 31 percent and 34 percent have a regular water supply.[35] This situation creates a need for new products that are adapted to local field conditions (e.g., solar-powered blood-pressure cuffs), as many standard NCD interventions currently require substantial infrastructure.

Inconsistent healthcare-seeking behavior: For various reasons, such as cost of care, geographic distance, and low health literacy, individuals in developing countries may infrequently seek care except when experiencing acute conditions. Their reluctance creates a greater need for opportunistic screening technologies that do not require advanced preparation (e.g., not requiring fasting for blood samples used to diagnose diabetes) or that provide opportunities for "see and treat" interventions (e.g., not requiring women to return for their Pap smear results).

Unacceptable practices: Aspects of care considered routine in Western populations may not always be acceptable in low-income communities. These include not only specific medical procedures such as Pap smears for cervical cancer screening but also the use of medication for asymptomatic disease and frequent disease monitoring and laboratory testing. Thus, new technologies that are locally acceptable may be needed. For example, the careHPV test marketed by Qiagen, which is designed for self-collection of cervical cell samples, may be more culturally accepted in certain communities.[36]

2.3 Types of New Product Needs

Different types of new products will be required to overcome barriers to NCD management in LMICs. In general, new products for the control and prevention of NCDs can be classified into one or more of the following categories: novel, adapted, low-cost, and acceptable technology.

Novel technology

Novel technologies are products that address epidemiologic and etiologic differences between NCDs in LMICs and in high-income countries (HICs). Because not every NCD that presents in developing countries is shared with developed countries, a number of "neglected NCDs" engender little or no market incentive for development of new technologies. Neglected NCDs include diseases that are post-infectious sequelae or complications of infections that are rare or effectively treated in developed countries (e.g., rheumatic heart disease) and diseases that result from noninfectious exposures that predominantly affect people in developing countries (e.g., aflatoxin and liver cancer).

Novel products may also be needed to address differences in local epidemiology caused in part by the double burden of NCDs and infectious diseases, along with maternal and child conditions. For example, evidence suggests that glycosylated hemoglobin (HbA1c), which is the gold standard for assessing glucose control in diabetes, has reduced sensitivity in individuals with chronic anemia.[37] Thus, in malaria-endemic countries or settings with high burdens of iron deficiency, new tools for assessing glycemic control may be needed,

[34] Garra G. Imaging Communications and Education Technology for Global Health. Abstract. National Cancer Institute—Cancer Detection and Diagnostics Technologies for Global Health, August 22-23, 2011: 29. NIH Campus, Rockville, Maryland.

[35] Shelton JD. Twenty criteria to make the best of scarce health resources in developing countries. BMJ. 2011; 25;343:d7023. (http://pdf.usaid.gov/pdf_docs/PNADY987.pdf, accessed 21 March 2012).

[36] The careHPV Test. (www.qiagen.com/about/whoweare/qiagencares/the-carehpv-test.pdf, accessed 21 March 2012).

such as glycated albumin tests being developed at PATH. Because these comorbidities are less common in developed countries, the market opportunities for new product R&D are limited.

Adapted technology

Adapted technologies are versions of existing products modified to address health systems barriers or other local constraints. The underlying technology is the same as products used in HICs, but other important features of the product are adapted to overcome barriers for use in particular settings. These barriers may include poor infrastructure, lack of trained healthcare professionals, and low access to specialty care centers. Because these barriers predominantly affect low-resource settings, the market for these particular adaptations in high-income countries is limited, resulting in a gap in new product R&D. The many examples of adapted technologies include (1) heat-stable insulin that addresses weak cold chains and lack of access to home refrigeration in developing countries, (2) oral formulations of injectable vaccines that are adapted to the limited training of healthcare workers and lack of safe needle disposal in resource-poor settings, and (3) point-of-care assays that circumvent the lack of diagnostic laboratories and skilled lab technicians.

Low-cost technology

Cost is one of the greatest barriers to addressing NCDs in developing countries. While cost is also a health systems barrier, and thus may be considered a cause for under-adapted technologies, we feel the importance of cost in LMICs warrants individual consideration. Low-cost technologies are products that address the lack of affordability of existing technologies. Here the focus is on the manufacturing cost of a product, or cost of goods sold, rather than price, which is a product of market forces and regulation. That is, price is an access-to-medicine issue, while cost is a technological issue.

With some technologies, the price of a medical good is driven by patents, tariffs, and distribution costs rather than manufacturing costs. In these cases, a modest improvement in the cost of manufacturing may have little effect on the final price of the technology to ministries of health or to patients. For example, the manufacturing cost for glucose test strips in diabetes care is $0.06 USD, while the price in many settings is as much as $0.60 USD.[38] In the extreme case, by reducing the manufacturing cost to $0.06 to $0.00 USD, the price of the glucose test strips would only drop by $0.06 to $0.54 USD, a price still too high for many. However, for other technologies, the cost of manufacturing is a major driver of price, and new product R&D may significantly improve access.

In addition to reducing the cost of the health technology itself, low-cost technologies may reduce other costs of care, including the need for healthcare services, human resources, patient travel time, and waste processing. For example, for infectious diseases, needle-free injection devices have been found to increase the efficiency of mass vaccination programs and decrease the costs of safely disposing sharps.[39]

Acceptable technology

Even if a technology is effective, adapted to local health systems barriers, and affordable, it may not be acceptable to the local population. Acceptable technologies are important for diagnosing or treating any disease, but for chronic diseases, which include many NCDs, patient-level barriers are critical to address. With chronic diseases, patients are responsible for the daily care of their condition and often monitor their own symptoms and administer their own medications. Even in developed countries, evidence suggests that adherence to medications is only 50 percent.[40] This situation underscores the importance of developing technologies that are acceptable to the target population. For example, cultural norms may make a self-administered cervical-cancer screening technology preferable to

[37] Sinha N, Mishra TK, Singh T, Gupta N. Effect of iron deficiency anemia on hemoglobin A1c levels. Ann Lab Med. 2012;32(1):17-22. Epub 2011 Dec 20.

[38] Interview with Bernhard Weigl, Director of the Center for Point-of-Care Diagnostics for Global Health at PATH. February 23, 2012.

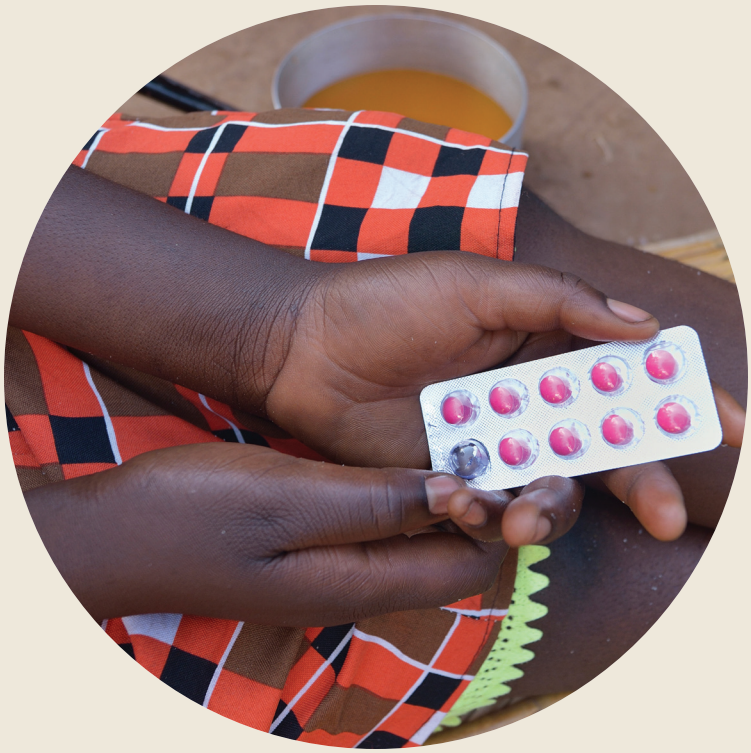
[39] PATH: jet injector. (www.path.org/projects/jet_injector.php, accessed 22 March 2012).

one that requires a healthworker to perform during a gynecologic exam. Low adherence may make a once-daily fixed-dose combination pill (polypill) more effective than multiple individual medications.[41] As a final example, innumeracy may make insulin vials that use color-coding rather than dosage volumes safer.

[40] Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002; 2; CD000011.

[41] Calmy A, Klement E, Teck R, Berman D, Pecoul B, Ferradini L, et al. Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling up. AIDS. 2004;18:2353-2360.

CHAPTER 3
NEW PRODUCT R&D FOR NONCOMMUNICABLE DISEASES



3

3.1 Cardiovascular Disease

Burden of Cardiovascular Disease

Cardiovascular diseases (CVDs) are the leading cause of death globally, contributing to nearly one-third of global mortality and one-half of all deaths from noncommunicable diseases (NCDs).[42,43] About 80 percent of the global burden of CVD death occurs in low- and middle-income countries (LMICs), and while its prevalence is declining in many high-income countries (HICs), CVD is projected to increase in LMICs over the next 10 years.[44,45]

CVD places a significant economic burden on developing economies largely because working-age adults account for a high proportion of the CVD cases.[46] Over three-quarters of the global disease burden from CVD is in people under 70 years of age, and CVD occurs at younger ages in LMICs than it does in wealthier countries.[47] In Brazil, China, India, Mexico, and South Africa, each year, at least 21 million years of future productive life are lost because of CVD, translating to a substantial direct cost. In South Africa, for example, treatment of CVD accounts for 2–3 percent of gross domestic product, or 25 percent of all health care expenditures.[48]

CVDs comprise a spectrum of conditions including atherosclerotic CVD, heart failure, rheumatic heart disease, Chagas cardiomyopathy, and congenital heart disease. Atherosclerotic CVD refers to CVDs that result from the thickening and hardening of arterial walls and includes coronary artery disease, stroke, and peripheral artery disease.

Atherosclerotic CVD was selected as the representative CVD because it accounts for at least 80 percent of the burden of CVD in all income regions[49] and is largely preventable through behavior modification and pharmacologic control of risk factors. Major CVD risk factors are high blood pressure, high blood cholesterol, elevated blood glucose, tobacco use, and obesity. Evidence suggests that over 90 percent of all CVD events (e.g., stroke, heart attack) occur in individuals with one or more of these modifiable risk factors.[50,51,52]

[42] The global burden of disease: 2004 update. Geneva, World Health Organization, 2008.

[43] Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington, DC: The National Academies Press, 2010.

[44] 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. Geneva, World Health Organization, 2008.

[45] The world health report 2002: reducing risks, promoting healthy life. Geneva, World Health Organization, 2002.

[46] Disease Control Priorities in Developing Countries, Second Edition. World Bank Publications, 2 April 2006.

[47] The World Health Report 2002: reducing risks, promoting healthy life. Geneva, World Health Organization, 2002.

[48] Disease Control Priorities in Developing Countries, Second Edition. World Bank Publications, 2 April 2006.

[49] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[50] Greenland P, Knoll, MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003;290:891-897.

[51] Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290:898-904.

[52] Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, and INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-952.

Atherosclerotic Cardiovascular Disease Prevention and Control Strategy

An atherosclerotic CVD prevention and control strategy includes population-wide and individual-level interventions. Population-wide strategies would likely involve overarching policies to address risk factor exposures and may include food pricing and availability, nutrition labeling, tobacco control measures, mass education, and sidewalk and recreation accessibility. Individual-level interventions target (1) individuals with established cardiovascular disease and at very high risk of recurrent attacks and (2) individuals who have not experienced a cardiovascular event but are at high risk of having one. Although interventions for the management of acute cardiovascular events (heart attacks, strokes) are not discussed here, they are relevant to a comprehensive atherosclerotic CVD strategy.

Individual-level interventions for CVD are largely targeted at risk-factor control. Although acute manifestations of atherosclerotic CVD are usually seen in middle-aged or elderly men and women, atherosclerosis develops over many years and may be slowed or halted by lifestyle interventions, pharmacologic interventions, or both. Lifestyle interventions include tobacco cessation and diet and exercise counseling. Pharmacological treatments for risk factor control, a distinguishing feature of CVD, include smoking cessation therapies, cholesterol-lowering medication, blood pressure-lowering medication, diabetes treatment, and antiplatelet therapy (e.g., aspirin).

Numerous barriers block the implementation of a comprehensive CVD strategy in LMICs. Individuals at risk for CVD must first be identified, but such efforts may be restricted by limited access to primary care, lack of provider training, and the relatively high cost of population-wide screening. Those at significantly elevated risk of CVD are typically prescribed a combination of lifestyle interventions, which may be limited by insufficient health literacy, and pharmacologic treatment, which is affected by limited access to medicines and cost. Finally, individuals must be monitored for response to treatment, which requires a chronic disease model of care and access to specialty care if acute complications develop.

Recommendations and Barriers to CVD Management

The WHO has developed guidelines for the assessment and management of cardiovascular risk.[53] Separate guidelines address individuals at high risk who have not yet experienced a cardiovascular event and those with established cardiovascular disease.[54] Because the former category is larger, we focus our discussion on identifying barriers and opportunities in the prevention of CVD in high-risk individuals.

The WHO guidelines are based on an individual's total, or absolute, CVD risk, which is the probability of experiencing a CVD event over a given period of time.[55] According to WHO guidelines, individuals with higher total CVD risk should receive more intensive treatment than those with lower total CVD risk. Treatment should not be based on individual risk factors such as elevated blood pressure, which is the more traditional approach commonly used in Western countries. The total CVD approach is based on a threshold level of risk above which intensive lifestyle intervention and pharmacologic treatment are initiated.[56] While the guidelines are meant to apply across developed and developing countries, different countries may set different thresholds depending on the availability of resources.

Table 3.1 summarizes the major recommendations of the WHO guidelines, which have been adapted for the present study.[57] Guidelines for each component of atherosclerotic CVD prevention are presented for standard- and low-resource settings along with barriers to implementation and opportunities for new product research and development. For example, in standard

[53] Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. World Health Organization 2007.
[54] Prevention of cardiovascular disease: pocket guidelines for assessment and management of cardiovascular risk. World Health Organization 2007.
[55] Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. World Health Organization 2007.
[56] ibid
[57] Ibid.

Table 3.1: CVD Synthesis

	Guidelines		Barriers	New Product R&D
Resource Setting	Limited	Standard		
Assessment of Total CVD Risk	Clinical history, blood pressure measurement, and urine analysis	Clinical assessment including serum glucose, body mass index (BMI; weight/height^2), blood pressure, serum cholesterol Those with 10-year risk >20% should have risk profile monitored every 3-6 months; those with risk 10-20% monitor every 6-12 months	Access to primary care Access to cholesterol and glucose assays Provider training Low healthcare-seeking behavior	Lower cost, point-of-care assays Appropriate automatic blood pressure cuffs
Behavioral Counseling	When resources are limited, individual counseling and provision of care may have to be prioritized according to cardiovascular risk	All smokers should be advised to quit; those with >20% who fail to quit with counseling should receive non-nicotine replacement therapy (NRT) and/or non-NRT (e.g., nortriptyline, bupropion) Individuals of all risk profiles should receive counseling on dietary changes, physical activity, weight control, and alcohol intake	Access to primary care, community health Provider training, lack of time Access to NRT and non-NRTS	Mobile health technologies
Anti-Hypertensive Drugs	The appropriate threshold of an individual's total risk at which intensive lifestyle interventions and drug treatment are initiated depends on the availability of resources and the impact of specific interventions	Individuals with risk >30% and persistent hypertension should be treated with medications to goal of <130/80 Those with risk 20-30% and persistent hypertension should be treated to goal of <140/90 Those with risk 10-20% should receive lifestyle interventions and be reassessed annually Those with risk 10% should receive lifestyle interventions and be reassessed every 2-5 years	Access to medications, adherence Reliable blood pressure measurement Access to primary care Provider training	Appropriate automatic blood pressure cuffs Polypill
Lipid-Lowering Drugs	The appropriate threshold of an individual's total risk at which intensive lifestyle interventions and drug treatment are initiated depends on the availability of resources and the impact of specific interventions	All individuals with total cholesterol >=320 mg/dl should be advised to follow a lipid-lowering diet and given a statin Additionally, though with risk >30% should receive statin Those with risk 20-30% and >40 years of age with persistently high cholesterol should be given a statin Those with risk 10-20% should be advised to follow lipid-lowering diet	Access to medications, adherence Access to primary care Provider training Access to cholesterol assays	Lower cost, point-of-care assays Polypill

Table 3.1: CVD Synthesis (continued)

	Guidelines		Barriers	New Product R&D
Resource Setting	Limited	Standard		
Anti-platelet Drug *	The appropriate threshold of an individual's total risk at which intensive lifestyle interventions and drug treatment are initiated depends on the availability of resources and the impact of specific interventions	Individuals with risk >30% should be given low-dose aspirin All other individuals should generally not be given aspirin	Access to medications / adherence Access to primary health centers Provider training	Polypill

* In addition, the guidelines recommend metformin to treat individuals with persistently elevated fasting blood glucose. This recommendation is not included because persistently elevated fasting blood glucose provides the diagnosis of diabetes. Diabetes management is discussed elsewhere in this report.

resource settings, the guidelines recommend that clinicians assess total CVD risk based on clinical evaluation, blood pressure, weight, blood glucose, and cholesterol measurements. In low-resource settings, urine glucose analysis can be substituted for glucose measurement and cholesterol screening is optional. Barriers to meeting these guidelines include lack of access to primary care, laboratory services, and provider training, as well as inadequate healthcare-seeking behavior. Because of the lack of access to reliable assessment tools, opportunities in R&D may be possible for low-cost, point-of-care (POC) assays and appropriate blood-pressure measuring devices that improve the sensitivity and specificity of total CVD assessment.

Product Gaps for Atherosclerotic Cardiovascular Disease

Barriers to atherosclerotic CVD management drive potential product gaps. Next we explore technology gaps and opportunities for atherosclerotic CVD.

1. Point-of-care tests for cholesterol and diabetes screening

Assessment of total CVD risk is the critical first step in CVD care. Thus, lack of access to laboratory services is a significant barrier to cardiovascular prevention and control. The WHO/ISH[58] risk prediction chart is based on age, sex, blood pressure, smoking status, presence or absence of diabetes, and, where available, total cholesterol. Although risk stratification can be performed without laboratory testing for cholesterol and diabetes, testing increases the reliability of risk prediction and therefore optimizes the use of scarce healthcare resources. In settings where cholesterol tests are not available, risk stratification is done using regional averages, which may result in over- and under-assessments of CVD risk. Similarly, the presence of sugar in the urine may serve as a substitute for diabetes screening with fasting serum glucose levels but may under-diagnose diabetes and therefore under-assess CVD risk. POC assays for cholesterol and diabetes screening would not only circumvent the lack of access

[58] International Society of Hypertension.

to central laboratories but would also reduce the need for venipuncture and blood processing, which require trained personnel, and also allow for same-day treatment. While POC tests are currently available in HICs, they are too costly for LMICs and may not always be suitable due to differences in local epidemiology and healthcare delivery systems.

2. Appropriate automated blood-pressure cuffs
Elevated blood pressure is a major controllable risk factor for CVD. In developed countries, only 20 to 30 percent of hypertensive patients have their blood pressure under control and even lower rates have been documented in low-resource settings.[59] The WHO has recognized that one of the major causes for poor blood-pressure control is the lack of reliable, easily obtainable, and affordable devices for blood pressure measurement. Current tools require trained medical personnel to assess blood pressure manually, which may be subject to measurement error in less skilled health workers. Although automatic blood-pressure devices are available, they may not be suitable for low-resource settings. In 2005, the WHO detailed technical specifications for automated blood-pressure measuring devices for office/clinic use in low-resource settings.[60,61] Recently, with the encouragement and help of the WHO, a new blood pressure device (Omron HEM-SOLAEe) has been developed that has met these specifications and was successfully pilot tested in two low-resource settings;[62] however, more research is needed. The WHO NCD Research Priorities CVD working group has also identified the need for blood-pressure measurement devices that can be used by non-physician health workers.[63]

3. Fixed-dose combination pill
Individuals at high risk of atherosclerotic CVD are often required to take three to four different medications daily to reduce their cardiac risk factors. The need for multiple medications has implications for provider training (e.g., knowing which medications to prescribe and at what dosage), procurement (e.g., supply chains, pricing), cost, and patient adherence. The development of a combination pill, or "polypill," that contains these commonly prescribed CVD medications in fixed doses may address these barriers, and evidence suggests its widespread usage would cut the occurrence of CVD by over one-half.[64,65,66] Recent clinical trials of two different polypills—one from Dr. Reddy's Laboratories in Hyderbad, India[67] and an other from Cadila Pharmaceuticals in Ahmedabad, India[68]—demonstrated early evidence of success, but more R&D is needed to determine long-term outcomes, different screening strategies, and thresholds for treatment. The WHO NCD Research Priorities CVD working group also identified a need to "evaluate screening programs based on absolute risk in a total cardiovascular risk intervention trial using fixed-dose combinations at

[59] Gaziano TA, Bitton A, Shuchi A, Weinstein MC for the International Society of Hypertension. The global cost of nonoptimal blood pressure. J Hypertens. 2009; 27:1472.

[60] Affordable technology: blood pressure measuring devices for low-resource settings. Geneva, World Health Organization, 2005.

[61] Parati G, Mendis S, Abegunde D, Asmar R, Mieke S, Murray A, Shengelia B, Steenvoorden G, Van Montfrans G, O'Brien E. Recommendations for blood pressure measuring devices for office/clinic use in low resource setting. Blood Press Monit. 2005;10:3-10.

[62] Parati G, Kilama MO, Faini A, Facelli E, Ochen K, Opira C, Mendis S, Wang J, Atkins N, O'Brien E. A new solar-powered blood pressure measuring device for low-resource settings. Hypertension. 2010;56(6):1047-53. Epub 2010 Nov 8.

[63] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[64] World Health Organization (2002) Secondary prevention of non-communicable disease in low and middle income countries through community-based and health service interventions. World Health Organization–Wellcome Trust meeting report, 1–3 August 2001, Geneva.

[65] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80 percent. BMJ. 2003; 326:1419.

[66] The World Health Report 2002: reducing risks, promoting healthy life. Geneva, World Health Organization. (http://www.who.int/whr/2002/en/whr02_en.pdf)

[67] PILL Collaborative Group. An International Randomised Placebo-Controlled Trial of a Four-Component Combination Pill ("Polypill") in People with Raised Cardiovascular Risk. PLoS ONE. 6(5):e19857. DOI: 10.1371/journal.pone.0019857.

[68] Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, Sigamani A, Mohan V, Gupta R, Thomas N. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet. 2009;18;373(9672):1341-1351. Epub 2009 Mar 30.

different thresholds of coronary risk" as a research priority.[69]

Gaps and Opportunities beyond Atherosclerotic Cardiovascular Disease

Develop technologies for rheumatic heart disease and Chagas cardiomyopathy.

Rheumatic heart disease and Chagas cardiomyopathy, while less prevalent globally than atherosclerotic CVD, contribute to a significant burden in LMICs and are largely neglected. Rheumatic heart disease is an inflammatory cause of heart disease that results from untreated infection with group A streptococcus (strep throat) and can lead to heart failure.[70] Rheumatic heart disease affects 12 million people in developing countries, mostly children,[71] and accounts for 3 percent of disability-adjusted life years (DALYs) lost to CVD.[72] Though early treatment with antibiotics can treat and cure the initial strep throat infection, an effective vaccine to prevent initial infection could significantly reduce the burden of rheumatic heart disease in communities with limited access to medical care.

Chagas heart disease is an inflammatory complication of chronic infection with the parasite Trypanosoma cruzi that can lead to heart failure and the need for heart transplantation. Chagas disease is largely regional, affecting 9 million people in South America.[73] Treatment for Chagas has limited effectiveness, particularly in the chronic phase of the disease when treatment is largely supportive and targeted therapies that specifically treat the underlying condition are needed.

Currently, there are a limited number of products in the market for Chagas disease, and few promises are in the pipeline. Old treatments for Chagas disease have long regimens and toxic side effects, no vaccine is currently available, and current diagnostic tests are insufficient for detecting or clearing chronic infection. Currently, 10 new treatments are in the development pipeline.[74] Benznidazole, developed by Pharmaceutical Laboratory of Pernambuco State and already on the market for treatment of acute disease, is currently in Stage III trials for chronic infection. Unfortunately, this drug requires a 60-day course of treatment, cannot be used by pregnant women or people with renal or hepatic insufficiency, and has toxic side effects. Furthermore, drug resistance already exists to this compound. A preventative vaccine is considered unlikely to emerge, but efforts have been directed towards developing a therapeutic vaccine. The Sabin Vaccine Institute and the Texas Children's Hospital Center for Vaccine Development currently have a therapeutic vaccine at the preclinical stage. Finally, four diagnostics are in the pipeline, three in the preclinical phase of development and one in the clinical phase, including a rapid diagnostic test by PATH. The need to "develop vaccines and safer and affordable medicines for addressing neglected CVDs such as rheumatic heart diseases and Chagas disease" was also recognized by the WHO NCD Research Priorities CVD working group.[75]

Conclusion

Atherosclerotic CVD is largely addressed through intensive risk-factor modification in individuals at high risk for cardiovascular events. The most significant barrier to addressing CVD in LMICs is access to primary

[69] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011. (http://whqlibdoc.who.int/publications/2011/9789241564205_eng.pdf)

[70] www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0001499

[71] Rheumatic fever and rheumatic heart disease. Report of a WHO Expert Consultation. Geneva, World Health Organization, 2001.

[72] Disease Control Priorities in Developing Countries, Second Edition. World Bank Publications, 2 April 2006.

[73] Control of Chagas Disease. Report of the WHO Expert Committee. Geneva, World Health Organization, 1991.

[74] Global Health Primer, Chagas Disease, Pipeline & Analysis. BIO Ventures for Global Health. (http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer/Diseases/cid/ViewDetails/ItemID/1.aspx, accessed 17 September 2012).

[75] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

care and to existing medicines. However, appropriate diagnostic tools are needed to improve the reliability of total CVD risk assessment in LMICs, including POC assays for blood cholesterol and blood glucose as well as automated blood-pressure cuffs. Additionally, opportunities may emerge to develop fixed-dose combination pills based on total CVD risk. Outside of atherosclerotic CVD, new product R&D is needed for neglected CVDs, including rheumatic heart disease and Chagas.

3.2 Diabetes

Burden of Diabetes

An estimated 285 million people had diabetes in 2010, with about 70 percent of them living in developing countries.[76] The major forms of diabetes are type 1, type 2, and gestational diabetes. Type 1 diabetes, previously called insulin dependent diabetes mellitus, is an autoimmune condition that leads to deficient insulin production. Type 2 diabetes, previously called non-insulin dependent diabetes mellitus, is a disease of insulin resistance associated with weight gain and Western lifestyles. Gestational diabetes is a condition of elevated blood sugars in women during childbearing and increases the risk of type 2 diabetes after delivery. Type 2 diabetes accounts for 85 to 95 percent of all diabetes cases worldwide and higher proportions of diabetes in LMICs.[77] Because type 2 diabetes is the predominant form of diabetes and shares risk factors with the other major NCDs, this section will focus on type 2 diabetes.

Type 2 diabetes is one of the fastest-growing public health problems in both developed and developing countries.[78] According to current projections, the global burden of diabetes will increase by 50 percent to 438 million cases in the next 20 years, largely due to a rise in developing countries, where the condition increasingly affects younger age groups.[79] The increase in type 2 diabetes is associated with a decline in physical activity and increased consumption of energy-dense foods. Therefore, type 2 diabetes is considered largely preventable through a combination of policy, public health, and individual-level interventions.

Diabetes is particularly costly because treatment often requires daily medications and frequent monitoring of glucose levels. Although it only affects 3 percent of the world's population, diabetes accounts for 10 to 15 percent of the entire global healthcare budget. In Tanzania, individuals with insulin-treated diabetes are 0.2 percent of the total population, yet account for 8 percent of the government healthcare budget.[80] Partners in Health estimates that in Rwanda the cost of glucose testing constitutes 42 percent of the annual cost of care for patients on oral treatment and between 13 to 15 percent for patients on injected insulin.[81] In India, which has the world's largest burden of diabetes, up to one-quarter of household income may be used toward the treatment of an individual with diabetes, heavily impacting the economic well-being of these families.[82]

Diabetes-related complications include microvascular diseases (e.g., blindness, kidney disease) and macrovascular diseases (e.g., cardiovascular disease, complications that result in lower extremity amputation). In 2001, diabetes accounted for 1.6 percent of all deaths in LMICs and 3.0 percent of deaths from NCDs.[83]

[76] IDF Diabetes Atlas, 4th ed. Brussels, International Diabetes Federation, 2009.

[77] Diabetes Atlas, Fifth Edition Committee. International Diabetes Federation. (www.idf.org/diabetesatlas, accessed 4 March 2012).

[78] Colagiuri S, et al. There really is an epidemic of type 2 diabetes. Diabetologia. 2005;48:1459-1463.

[79] Mendis S, Alwan A, eds. Prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[80] Insulin dilemma in resource-limited countries. Diabetologia. 2011;54:19-24.

[81] Gene Bukhman and Alice Kidder, eds. The PIH Guide to Chronic Care Integration for Endemic Non-Communicable Diseases, Rwanda Edition. Partners in Health, 2011. (http://www.pih.org/publications/entry/the-pih-guide-to-chronic-care-integration-for-endemic-ncd).

[82] Atkins R C. The epidemiology of chronic kidney disease. Kidney Int Suppl. 2005 Apr;(94):S14-8.

Type 2 Diabetes Prevention and Control Strategy

An overall type 2 diabetes prevention and control strategy includes elements of primary, secondary, and tertiary prevention. Primary prevention is the elimination of risk factors, such as obesity and physical inactivity, and prevention of diabetes. On a population level, primary prevention strategies include increasing access to healthy foods, taxation or elimination of trans fats, and mass education. At an individual level, clinical trials have demonstrated the effectiveness of intensive lifestyle interventions such as diet, exercise, and behavior modification in reducing the risk of developing diabetes by 58 percent in at-risk individuals.[84] Secondary prevention is the early detection and treatment of individuals with diabetes. Type 2 diabetes is often asymptomatic in the early stages of the disease, thereby delaying diagnosis and treatment. As a result, even in developed countries, approximately one-half of all individuals with type 2 diabetes remain undiagnosed.[85]

Tertiary prevention is the treatment of diabetes and the prevention of complications and premature morbidity and mortality.Treatment for Type 2 diabetes typically requires a combination of lifestyle changes and lifelong medication, although some individuals can be effectively managed with diet and exercise alone. For those on medication, therapies include oral medications, insulin injections, or both.

Diabetes is unique in that it requires individuals to self-manage their condition, including by self-monitoring blood glucose (SMBG). Furthermore, diabetes requires regular monitoring for long-term glycemic control (e.g., HbA1c or similar marker) to assess treatment response and micro- and macro-vascular complications of disease (e.g., annual eye screening, urine microalbumin assay), as well as more intensive treatment of common comorbid conditions (e.g., hypertension, coronary heart disease).

Numerous barriers impede the implementation of a comprehensive diabetes control and prevention strategy in LMICs. These include inadequate access to primary healthcare, limited access to medicines and diagnostic services, lack of trained health professionals, and low health literacy. There are also recognized knowledge gaps including locally validated tools for the identification of at-risk individuals, culturally tailored programs for intensive lifestyle modification, and evidence-based protocols for diabetes care in resource-poor settings.[86]

Recommendations and Barriers for Type 2 Diabetes Management

The International Diabetes Federation has developed consensus clinical guidelines for type 2 diabetes that take into account the scarcity of resources in some health care settings.[87] The guidelines establish recommendations for three different levels of care depending on resource constraints:

- Minimal level: Care that seeks to achieve the major objectives of diabetes management, but is provided in healthcare settings with very limited resources.
- Standard Care: Evidence-based care, cost-effective in most nations with a well developed service base and with healthcare funding systems consuming a significant part of their national
- Comprehensive Care: Care with some evidence-base that is provided in healthcare settings with considerable resources.

[83] Disease Control Priorities in Developing Countries, Second Edition. World Bank Publications, 2 April 2006.

[84] National Diabetes Education Program (NDEP). Diabetes Prevention Program Fact Sheet (http://ndep.nih.gov/media/dpp-fact-sheet-508.pdf, accessed 11 March 2012).

[85] Harris MI, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care. 1998; 21:518-524.

[86] Mendis S, Alwan A, eds. Prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[87] IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2005.

Table 3.2 (attached) summarizes the International Diabetes Federation guidelines, which have been adapted for the present study. For each level of care, we identify barriers to implementation and consider opportunities for new product R&D that could help address the barrier in LMICs. For example, at the minimal care level, the guidelines recommend that opportunistic screening for diabetes ideally be done using a fasting, laboratory-measured glucose level. If laboratory testing is not available, then a capillary or fingerstick fasting glucose level—though less accurate, but does not require a lab—is suggested. If neither of these serum tests is available, a urine assay can be used to detect glucose in the urine (glucosuria), which together with the presence of clinical symptoms, may guide the diagnosis of diabetes.

Barriers to implementing this guideline include lack of locally reliable tools to identify at-risk individuals. Without appropriate tools, diagnostic testing may be over-performed, thereby wasting limited diagnostic resources, or under-performed, leading to undetected cases of diabetes. The absence of appropriate diagnostic tools creates another obstacle. Laboratory services are commonly unavailable in low-resource settings, and currently available POC tests are costly and/or have limited specificity and sensitivity. Therefore, an opportunity is available for the development of an adapted, effective, low-cost POC tool for diagnosing for diabetes in LMICs.

Product Gaps for Type 2 Diabetes

Based on the review of the literature, the analysis above, and interviews with experts, we explore potential product gaps and opportunities for diagnosing and treating type 2 diabetes.

1. Point-of-care tests for screening and diagnosis

A major barrier to diabetes prevention and control is lack of access to laboratory services. Unlike many other diseases, the diagnosis of diabetes requires laboratory testing, which provides a challenge in low-resource settings. Furthermore, because screening in LMICs is often opportunistic, blood samples are rarely taken while a person is fasting. In response to this issue, the International Diabetes Association (IDA) has recently proposed elevated HbA1c as an additional or alternative diagnostic method.[88] Unlike blood glucose measurement, HbA1c measurement does not require a fasting blood sample. However, two blood samples are still required and the assay is considerably more expensive. Additionally, because of the nature of the assay, the applicability to populations with high rates of anemia, including malaria endemic settings, is questionable.

Thus, suitable POC tests are needed for the screening and diagnosis of diabetes in LMICs. If such tests are to be used widely in resource-poor settings, they would ideally be simple to use, rely on finger-prick blood sampling, be independent of instrumentation or electronics, be robust and able to withstand elevated ambient temperatures without cold-chain shipment or storage, have a long shelf-life, and be inexpensive.[89] PATH has identified the need for POC technologies for diabetes screenings, and with the help of its partners, is evaluating the efficacy of existing technologies and exploring several possibilities for effective, low-cost technologies for diabetes screening and control in India.[90,91] Development of suitable POC tests would improve access to diabetes diagnostics and care, notably in peripheral clinics and remote health centers in Africa and Asia.

[88] International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care. 2009;32:1327-1334.

[89] Harries AD, et al. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. Trop Med Int Health. 2010;15:659-663.

Table 3.2: Diabetes Guidelines, Barriers, and Gaps

	Needs		Barriers		R&D Gaps	
Level of Resources*	Minimal	Standard	Minimal	Standard	Minimal	Standard
Screening and Diagnosis	Detection should be opportunistic or only screen high-risk individuals Test fasting laboratory glucose (preferred) or capillary If lab testing unavailable, use glycosuria plus symptoms	Screen high-risk individuals Test fasting plasma glucose with diagnostic test such as repeat FPG or OGTT if asymptomatic Plasma glucose test if symptomatic	Lack of validated screening tools Lack of access to diagnostics	Lack of validated screening tools Lack of access to diagnostics	Reliable, low-cost point-of-care diagnostics	Reliable, low-cost point of care diagnostics Novel diagnostic tools for gestational diabetes
Treatment	Metformin and generic sulfonylurea, thiazolidinedione where cheaper than insulin Renal function tests where likelihood of renal impairment high	Metformin unless evidence of renal impairment Sulfonylureas as second-line unless person is not overweight Thiazolidinedione, alpha-glucosidase inhibitors as alternative options	Lack of access to medicines Lack of refrigeration	Lack of access to medicines Lack of access to laboratory services	Heat stable insulin	Low-cost blood chemistries
Monitoring	Clinical • plasma glucose measurement, target <110 before meals and <145 1-2 hours after meals • may use quality-controlled capillary glucose • visually read glucose test strips have a role in remote settings	Clinical • HbA1c <6.5% depending on risks of hypoglycemia and comorbid conditions • every 2-6 months depending on the control	Lack of access to diagnostics Limited health information systems	Lack of access to diagnostics Limited health information systems	Heat stable supplies Electronic health records	Heat stable supplies Health information systems Culturally tailored glucometers
	Self • SMBG using meters with strips or visually read blood glucose strips for those on insulin	Self • SMBG on an ongoing basis for those on insulin treatment • SMBG should be considered for people using oral agents intermittently (e.g. medication changes)				

Table 3.2: Diabetes Guidelines, Barriers, and Gaps (continued)

	Needs		Barriers		R&D Gaps	
Level of Resources*	Minimal	Standard	Minimal	Standard	Minimal	Standard
Secondary Prevention	Heart: lipid profile where available; statins where available even without lipid profile; screening and treatment for elevated blood pressure Eye: Direct fundoscopy by trained health-care team member, visual acuity, referral Kidney: annual proteinuria using dipstick or sulfosalicyclic acid, kidney function, ACE inhibitors Foot: clinical exam, antibiotics, referral Nerve: screen by history and monofilament tuning fork, pin-prick, treat with tricyclics	Heart: lipid profile where available; statins where available even without lipid profile; screening and treatment for elevated blood pressure Eye: Direct fundoscopy by trained health-care team member, visual acuity, referral Kidney: annual proteinuria using dipstick or sulfosalicyclic acid, kidney function, ACE inhibitors Foot:clinical exam, antibiotics, referral Nerve: screen by history and monofilament tuning fork, pin-prick; Use serum B12, thyroid function, biochemistry to exclude other causes; treat with tricyclics, gabapetins	Provider training Access to referral centers Access to diagnostics	Lack of access to medicines Lack of access to laboratory services	Low-cost diagnostics	Low-cost blood chemistries
Patient Educating	Education is provided by a skilled individual rather than a team Use of available technologies to best deliver education	Structured education integral part of management Trained multidisciplinary team including specialist trained in diabetes and delivery of education Culturally tailored education Use of modern communication technologies	Lack of trained health care professionals Low health literacy	Lack of trained healthcare professionals Lack of chronic disease care models	Mobile health applications	Health information systems Mobile health applications

International Diabetes Federation, 2005- Clinical Guidelines Task Force (http://www.idf.org/guidelines/type-2-diabetes) Global Guidelines for Type 2 Diabetes

** annual surveillance includes education, lifestyle management (e.g., nutrition, physical activity, smoking), psychological care, self-monitoring, glucose monitoring, blood pressure monitoring, foot care, eye screening, nerve screening, kidney screening, pregnancy counseling

** OGTT– oral glucose tolerance test; FBG– fasting blood glucose; SMBG– self-monitoring of blood glucose;

2. Point-of-care tests for monitoring of diabetes
Diabetes not only requires technologies for diagnosis but also for monitoring. Diabetes monitoring not only includes a clinical assessment by a healthcare professional, but also laboratory testing to measure glucose control using HbA1c. While protocols vary, patients with diabetes typically receive a HbA1c test every three to six months. In Rwanda, Partners in Health measures HbA1c for all patients with diabetes every six months at the cost of $30 USD per annum.[92] Unfortunately, POC tests for HbA1c are costly and not necessarily the ideal means of glucose control and monitoring.

In addition, diabetes is distinct from other chronic illnesses in that patients often monitor their own blood-glucose levels at home. While the current guidelines do not set a strict standard for SMBG for patients on oral treatment alone, SMBG is mandatory for patients on insulin therapy. Patients typically check their blood glucose multiple times per week, if not multiple times per day— at a cost of $0.35 USD per test in Rwanda, for example— which quickly poses a substantial economic burden. Currently, patients use lancets, glucose test strips, and glucometers for SMBG. In some areas, users experience difficulty in safely disposing lancets. Also, glucose test strips require refrigeration and electronic glucometers work via electricity or batteries, presenting additional challenges in low-resource settings.

Finally, patients with diabetes require other diagnostic services to monitor for disease complications. These services include regular laboratory measurements of kidney function (serum creatinine), urine protein (microalbuminemia), and cholesterol levels as well as annual eye examinations, to screen for diabetic retinopathy, which require ophthalmoscopes and specialized training.

Thus, development of telemedicine technologies could make a large impact on diabetes control and monitoring in low-resource settings. For example, new technologies could allow a community worker to take a photo of the retina and transmit it to an e-reader or to a remote ophthalmologist for a quicker diagnosis, or patients could use technologies that make blood glucose measurement easier and cheaper.

3. Heat-stable diabetes products
Another barrier to diabetes control in LMICs is lack of refrigeration. Currently, both insulin and glucose monitoring strips require refrigeration for optimal performance. At 25 degrees centigrade (C), insulin commercially available in India is stable for three months.[93] At higher temperature and longer durations, insulin titers may decrease and the preparation may not have the desired effect, though this outcome has been called into question by some. For example, Sanofi-Aventis found that its insulin product gained impurities but did not lose activity when stored at 35-39 degrees C for one month.[94] Furthermore, some environments allowed for circumventing the need for refrigeration. In Rwanda, Partners in Health reported that by placing insulin vials in small containers of water or in clay pots filled with sand and water, patients have been able to use insulin to good effect.[95] However, Rwanda has a temperate climate, which is not the case in most other LMICs. Thus, although the evidence is limited, heat-stable insulin and glucose monitoring equipment as well as heat indicator technology for assessing insulin titers or measuring heat exposure may still be needed.[96] The WHO NCD Research Priorities diabetes working group also identified "cost-effective technologies for glucose monitoring and insulin, including stable insulin preparations" as a research priority.[97]

[90] DiagnOptics and PATH partner on project on diabetes screening in India. February 6, 2012. (www.diagnoptics.com/en/news/diagnoptics-and-path-partner-on-project-on-diabetes-screening-in-india-18-18/).

[91] PATH Toward New Point-of-Care Diagnostics for Low-Resource Settings: September 30, 2010. (www.nibib.nih.gov/NewsEvents/ResearchHighlights/Archive/2010/30Sep10).

[92] The PIH Guide to Chronic Care Integration for Endemic Non-Communicable Diseases, Rwanda Edition. Partners in Health, 2011.

[93] Interview with Bernhard Weigl, Director of the Center for Point-of-Care Diagnostics for Global Health at PATH. Feb 23, 2012.

[94] Grajower M. M., et al. How long should insulin be used once a vial is started? Diabetes Care. 2003;26: 2665-2666.

[95] The PIH Guide to Chronic Care Integration for Endemic Non-Communicable Diseases, Rwanda Edition. Partners in Health, 2011.

4. Fixed-dose combination pill

The tertiary prevention of diabetes includes reducing the risk of diabetes-related complications, such as kidney disease and coronary artery disease. Evidence suggests that at-risk individuals with diabetes can reduce their risk of kidney disease by taking ACE (angiotensin-converting-enzyme) inhibitor medications. Additionally, individuals with Type 2 diabetes frequently have comorbid conditions such as hypertension and dyslipidemia, which have similar risk factors. As a result, patients with diabetes commonly take multiple medications intended to control these various shared risk factors.

In low-resource settings, the need for individuals to take multiple medications presents a challenge in terms of procurement, provider training, and patient adherence. Similar to the polypill for the primary or secondary prevention of cardiovascular disease, there is interest in developing and evaluating a fixed-dose combination pill for diabetes ("diabetes polypill"). The WHO NCD Research Priorities diabetes working group also identified the need for such a combination pill."[98]

5. Integrated diagnostic tools for infectious diseases and diabetes

LMICs face a double burden of infectious disease and diabetes, which in certain cases, may interact to produce an even greater public health burden. Studies estimate a three-fold greater risk of tuberculosis among individuals with diabetes, and some speculate that tuberculosis infection may increase the risk of developing diabetes.[99–103] Similarly, HIV/AIDS has been linked to an increased risk of diabetes, at least partially resulting from anti-retroviral therapy.[104] HIV/AIDS and tuberculosis are frequently treated in vertical disease programs, which may not have the resources to screen patients for diabetes. In LMICs that face a double burden of infectious disease, such as tuberculosis and HIV, and of diabetes, new technologies such as diagnostic platforms for tuberculosis and diabetes may help integrate the diagnosis and management of infectious diseases and diabetes. In certain cases, there may also be opportunities for new treatments that mitigate the risk of developing diabetes. The WHO NCD Research Priorities diabetes working group also identified a need to "develop and evaluate diabetes-related interventions to manage major chronic communicable diseases shown to be associated with diabetes (HIV, tuberculosis)" as a research priority.[105]

6. Mobile health technologies for chronic disease management

For chronic diseases such as diabetes, patients often require frequent monitoring and titration of their treatment regimens. Given the large geographic distances between patients and providers and the shortages trained health professionals, LMICs face significant barriers to providing the intensity of care required for chronic disease management. Due to their widespread availability, even in low-resource settings, mobile phone technologies are increasingly being recognized as a viable platform for improving chronic disease management.[106] For diabetes and other diseases, mobile health technologies need to be developed

[96] Interview with Bernhard Weigl, Director of the Center for Point-of-Care Diagnostics for Global Health at PATH. Feb 23, 2012.

[97] Mendis S, Alwan A, eds. Prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[98] Ibid.

[99] Young F, et al. A review of co-morbidity between infectious and chronic disease in sub-Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. Global Health. 2009;5:9.

[100] Stevenson CR, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health? Chronic Illn. 2007;3:228-245.

[101] Stevenson CR, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007;7:234.

[102] Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5:e152.

[103] Harries AD, et al. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. Trop Med and Int Health. 2010;15:659-663.

[104] Carr A, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS. 1998;12:F51–F58.

[105] Mendis S, Alwan A, eds. Prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

for LMICs that address health workforce and access barriers by facilitating remote monitoring and disease management.[107]

Gaps and Opportunities beyond Type 2 Diabetes

1. Diagnosis of gestational diabetes

Gestational diabetes is defined as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy."[108] Gestational diabetes has a number of health effects not only on the mother, but also on the fetus, and it can lead to increased risk of newborn death and stillbirth, delivery complications, and low blood glucose in the newborn. Gestational diabetes is diagnosed during pregnancy through an oral glucose-tolerance test. For the test, women who have fasted for at least 8 hours have their blood glucose levels measured immediately before consuming a liquid formulation of glucose and then are retested 30 and 50 minutes after ingestion. The challenges of performing an oral glucose tolerance test in LMICs are well-recognized and create new product opportunities. This test presents a number of challenges in LMICs, and this lack of a good diagnostic for gestational diabetes in LMICs is well recognized.

2. Classification of diabetes at diagnosis

The diagnosis of type 1 versus type 2 diabetes is typically made based on clinical presentation, including age of diagnosis. Historically, type 1 diabetes was diagnosed during childhood and type 2 was rarely seen before adulthood. With the increasing incidence of childhood obesity, the instances of type 2 diabetes in children has increased, which means the need for antibody assays to differentiate between type 1 and type 2 diabetes has also increased. These antibody tests are costly and require sophisticated equipment, and therefore we share the WHO NCD Research Priorities diabetes working group's recognition of a need to "develop practical, affordable and culturally specific tools for appropriate diabetes classification (into type 1 and type 2 diabetes) at diagnosis to guide management."[109]

3. Rare forms of diabetes

Type 1, type 2, and gestational diabetes are the predominant forms of diabetes in both HICs and LMICs. This suggests that the same therapies used to treat diabetes in the developed world can also be used in developing countries. However, several other forms of diabetes are seen and evidence suggests that a disproportionate number of these forms are being observed in LMICs.[110] An example are forms of diabetes thought to be related to malnutrition, which if present, would be epidemiologically distinct from the typical presentation of type 2 diabetes in an overweight or obese individual. Although little is known about the relative prevalence of malnutrition-related diabetes in LMICs and its etiologic cause, additional research may identify a need for new diagnostic technologies and therapies.

Conclusion

Diagnosis and monitoring is a major barrier to diabetes prevention and control in LMICs that may be amenable to new technologies. We identified opportunities for POC tools for diabetes that facilitate opportunistic screening and clinical monitoring, including in settings with high rates of anemia and the double burden of infectious diseases. In addition, mobile health technologies may be an important delivery technology for reducing the burden of self-management support and monitoring on limited number of healthcare workers. Finally, though the evidence is mixed, there may be

[106] Donner J. Research approaches to mobile use in the developing world: a review of the literature. Inf Soc. 2008;24(3):140-159.

[107] Krishna S, Boren SA, Balas EA. Healthcare via cell phones: a systematic review. Telemed J E Health. 2009; 15(3):231-40. Schectman JM, Nadkarni MM, Voss JD.

[108] Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. WHO/NCD/NCS/99.2 ed. Geneva, World Health Organization, 1999.

[109] Mendis S, Alwan A, eds. Prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011. p. 88.

[110] Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. WHO/NCD/NCS/99.2 ed. Geneva, World Health Organization, 1999.

opportunities for heat-stable insulin and glucose monitoring products in settings of extreme heat without cold chains.

3.3 Chronic Respiratory Disease

Burden of Chronic Respiratory Disease

Several hundred million people suffer from chronic respiratory diseases, including 235 million individuals with asthma[111] and 64 million with chronic obstructive pulmonary disease,[112] with the majority living in LMICs.[113] In 2004, chronic respiratory diseases accounted for 4 million, or 7 percent, of all deaths globally and nearly 4 percent of DALYs,[114] and it is projected that the burden from those diseases will considerably increase in the future due to rising rates of tobacco use and urbanization.

The major forms of chronic respiratory disease are asthma and chronic obstructive pulmonary disease (COPD). Other chronic respiratory diseases include occupational lung diseases, obstructive sleep apnea, pulmonary hypertension, bronchiectasis, and interstitial lung diseases.[115]

Although they have similarities, COPD and asthma differ significantly in terms of disease burden. COPD is primarily a disease of older adults and is typically diagnosed after the age of 40 years, although it often results from exposures beginning in childhood. Tobacco smoke is the primary cause of COPD and accounts for 90 percent of deaths from COPD.[116] Other risk factors include indoor air pollution (particularly biomass fuels), outdoor air pollution, and occupational exposures. Over 90 percent of deaths from COPD occur in LMICs, and total deaths are projected to increase by more than 30 percent over the next 10 years.[117]

In contrast, people of all ages suffer from asthma, which is the most common chronic disease in children.[118] Asthma is caused by a combination of genetic predisposition and environmental exposures including tobacco smoke, indoor and outdoor allergens (dust mites, pollens), and air pollution. Asthma is largely not preventable but can be controlled with appropriate management.

Because asthma is a major contributor to the burden of disease in all age groups and is less preventable than COPD, it is the focus of the remaining sections. We briefly discuss COPD and other chronic respiratory diseases at the end of the section.

Asthma Prevention and Control Strategy

Asthma prevention and control largely focuses on individual-level interventions for diagnosis and management that include a combination of lifestyle and pharmacologic interventions. Unlike for other chronic diseases, primary prevention strategies for asthma, such as reduction in environmental exposures, have had limited success.[119] Furthermore, while in theory population-wide interventions, such as reducing indoor biomass fuel use and secondhand smoke, could reduce asthma rates, evidence of their effectiveness is limited.[120]

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[111] WHO Global Alliance for Chronic Respiratory Disease, Asthma Fact Sheet May 2011. (www.who.int/mediacentre/factsheets/fs307/en/index.html, accessed 18 March 2012).

[112] WHO Global Alliance for Chronic Respiratory Disease, Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet,November 2011. (www.who.int/mediacentre/factsheets/fs315/en/index.html, accessed 18 March 2012)

[113] Aït-Khaled N, Enarson DA, Ottmani S, El Sony A, Eltigani M, Sepulveda R. Chronic airflow limitation in developing countries: burden and priorities. Int J Chron Obstruct Pulmon Dis. 2007; 2(2):141-150.

[114] Global burden of disease: 2004 update. Geneva, World Health Organization, 2008. (http://who.int/topics/global_burden_of_disease/en, accessed 18 March 2012).

[115] Bousquet J, Khaltaev N. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. Global Alliance against Chronic Respiratory Diseases. Geneva, World Health Organization, 2007.

[116] WHO Global Alliance for Chronic Respiratory Disease, Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet (November 2011). (www.who.int/mediacentre/factsheets/fs315/en/index.html, accessed 18 March 2012).

[117] Ibid.

[118] WHO Global Alliance for Chronic Respiratory Disease, Asthma Fact Sheet (May 2011). (www.who.int/mediacentre/factsheets/fs307/en/index.html, accessed 18 March 2012).

The mainstays of pharmacologic treatment are inhaled bronchodilators (e.g., salbutamol) and inhaled corticosteroids (e.g., beclometasone). In addition, individuals are trained to avoid common triggers such as tobacco smoke, airborne allergens, and indoor pollution. The criteria for successful asthma management include no (or very mild) symptoms, attacks, emergency visits, limitation of activities, or airflow limitation (peak expiratory flow >80 percent of predicted) with minimal bronchodilator use (< 2 times/week), and the fewest side effects possible.[121] With currently available tools the vast majority of asthma patients can reach this level of control.

However, numerous barriers impede successful asthma control, such as diagnosing the condition in symptomatic individuals, prescribing the most effective medications, teaching patients self-management and avoidance of triggers, and lack of adherence. Even in a high-resource country such as the United States, a national survey showed that only 26 percent of individuals with persistent asthma symptoms in the prior month reported using inhaled corticosteroids.[122] In low-resource settings like Nigeria, a number of barriers to asthma management have been identified, including lack of diagnostic and monitoring facilities, inadequate knowledge of current management of asthma by healthcare workers, poor compliance by patients, use of traditional medicines of unproven efficacy, fake and substandard drugs, and lack of guidelines specifically designed for local resources.[123]

Asthma and COPD are distinguished from other NCDs by the fact that the primary medications used to manage them are delivered by inhalation. Delivering medicines via inhalers is preferred because the medication can reach the lung tissue directly, allowing for more rapid onset of action as well as decreased systemic absorption and subsequent side effects. However, inhalers create additional barriers to asthma care. In addition to the problem of improper and therefore ineffective use of inhalers, though the active compounds used in inhalers are no longer under patent (salbutamol, beclometasone), the actual inhaler devices are still protected.[124] Patents contribute to the limited access to low-cost inhalers in the developing world. In one study in India, the price of inhalers available in the public sector equaled 2 days wages.[125]

Recommendations and Barriers in Asthma Management

The International Union against Tuberculosis and Lung Disease ("The Union") and the Global Initiative for Asthma (GINA) have developed consensus clinical guidelines for the management of asthma. The recommendations do not differ by resource availability, but instead have been developed and piloted to be inclusive of low-income countries. Table 3.3 summarizes these guidelines, which have been adapted for the present study. We use the Union guidelines[126] as a primary reference and the GINA guidelines[127] as a secondary reference.

The recommendations are organized into components of asthma management including diagnosis and classification, identification/control of risk factors, long-term treatment, treatment of acute attacks, and self-management. For each component we identify barriers to implementation and opportunities for new products that may help overcome one or more of these barriers.

[119] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[120] Ibid.

[121] Aït-Khaled N, Enarson DA, Ottmani S, El Sony A, Eltigani M, Sepulveda R. Chronic airflow limitation in developing countries: burden and priorities. Int J Chron Obstruct Pulmon Dis. 2007; 2(2): 141-150.

[122] Ait-Khaled N, Enarson DA, Chiang C-Y, Marks G, Bissell K. Management of Asthma: A Guide to the Essentials of Good Clinical Practice. Paris, France: International Union Against Tuberculosis and Lung Disease, 2008.

[123] Fawibe AE. Management of asthma in sub-Saharan Africa: the Nigerian perspective. AJRM; 3(3) 17-21. 2008.

[124] Mattke S, Haims MC, Ayivi-Guedehoussou N, Gillen EM, Hunter L, Klautzer L, Mengistu T. Improving Access to Medicines for Non-Communicable Diseases in the Developing World. RAND. (www.rand.org/content/dam/rand/pubs/occasional_papers/2011/RAND_OP349.pdf, accessed 18 March 2012).

[125] Kotwani A. Availability, price and affordability of asthma medicines in five Indian states. Int J Tuberc Lung Dis. 13(5): 574-579. 2009.

Table 3.3: Asthma Synthesis

	Recommendations	Barriers	New Product R&D Gaps
Diagnosis and Classification	Diagnosis based on history and PEF + bronchodilator response or variability * May require TB sputum smear examination	Access to peak flow meters and inhaled bronchodilators Access to asthma diagnostic and referral centers Provider training Low healthcare-seeking behavior	None
Identification/ Control Risk Factors **	Clinical assessment +/- home-based assessment Influenza vaccination +/- pneumonia vaccine	Provider training Lack of local knowledge of triggers Low community awareness	Alternative home fuels or cooking/ventilator designs
Long-term Treatment	Clinical assessment of symptom frequency and severity PEF testing with comparison to prior results Inhaled corticosteroid is medication of choice for cases of persistent asthma Beta2-agonists preferred for immediate relief or for cases of intermittent asthma Assessment of inhaler technique and adherence Initially visits every week, gradually every 3 months	Access to inhaled medications Oversupply of oral therapies (prednisone, theophylline) Access to metered dose inhalers (HFA preferred to CFC) Access to peak flow meters Provider training	Low-cost inhaler devices
Acute Attacks	Clinical assessment with PEF Oxygen by nasal annula or mask Admission to hospital or intensive care	Provider training Access to referral centers Access to oral and IV corticosteroids Access to short-acting beta2 beta2-agnoist	None
Self-Management	Education materials Training on inhaler technique Access to medications Treatment plans	Low health awareness/literacy Poor inhaler technique Cost Oversupply of traditional healers Access to primary health centers	Appropriate inhalers

-Primary reference: International Union Against Tuberculosis and Lung Disease ("The Union") – Management of Asthma, A Guide to the Essentials of Good Clinical Practice, Third Edition 2008 (http://www.theunion.org).

-Secondary reference: Pocket Guide for Asthma Management and Prevention (for Adults and Children Over 5 Years), Global Initiative for Asthma (GINA), updated 2011

* GINA recommends spirometry as preferred method of diagnosing asthma but recognizes PEF as an important aid for diagnosis and monitoring; GINA also recommends methacholine and histamine challenge in certain cases (e.g., normal lung function) and skin tests for allergens

** GINA identifies 4 components of asthma care: 1. Develop patient/doctor relationship, 2. Identify and reduce exposure to risk factors, 3. Assess, treat, and monitor asthma, 4. Manage asthma exacerbations

*** PEF– peak expiratory flow; HFA– hydrofluoroalkanes (type of inhaler); CFC– chlorofluorocarbons (type of inhaler)

For example, the guidelines recommend that clinicians evaluate an individual for asthma when they present with characteristic symptoms including wheeze, chest tightness, breathlessness, and cough. The evaluation should include a clinical history followed by peak expiratory flow (PEF) measurements for those in whom asthma is suspected and other diseases have been excluded, which may include sputum smear examination to rule out tuberculosis. Barriers to diagnosis include provider training or access to asthma diagnostic and referral centers, access to peak flow meters for measuring PEF, and low healthcare seeking behavior. Opportunities for new products to address these barriers are limited. Unlike other NCDs, new diagnostic technologies have limited potential for improving asthma control. Although the diagnosis of asthma requires PEF measurements, the peak flow meter is a simple, quantitative, and reproducible measure of airflow obstruction that is affordable, low-tech, and does not require specialized training or electrical power.

Gaps and Opportunities for Asthma Products

We have identified few opportunities for new product R&D for asthma diagnosis and treatment. Our conclusions reflect those of the WHO chronic respiratory disease working group, which did not include any new health technologies among the identified research priorities.[128] That said, there is some speculation that the chronic respiratory diseases present in LMICs may differ from those in HICs due to a different mixture of exposures and genetic risk factors. Defining or characterizing these different "phenotypes" of asthma may lead to different control and treatment strategies. However, this observation is nascent, and more basic research is needed before new product needs can be clearly identified.

Gaps and Opportunities beyond Asthma–Alternative Fuels and Ventilators

Studies have demonstrated that improvement in household stoves, including better ventilation, may reduce the incidence and severity of COPD.[129,130] A landscaping study by the United States Agency for International Development (USAID) has assessed knowledge gaps in improving indoor air pollution mitigation technologies and is currently supporting a number of initiatives to support research in this area.[131]

Conclusion

Access to medicines and provider training are the primary barriers to chronic respiratory disease control and prevention. The opportunity for new products to significantly address the burden on chronic respiratory diseases in LMICs is limited. However, there may be a need for locally manufactured, appropriate inhaler devices for the delivery of first line therapies for asthma and COPD and for indoor air pollution mitigation technologies.

3.4 Cancer

Burden of Cancer

The global burden of cancer now accounts for 27 percent of deaths from NCD in people under the age of 70 years—the second largest proportion after deaths

[126] Ait-Khaled N, Enarson DA, Chiang C-Y, Marks G, Bissell K. Management of Asthma: A Guide to the Essentials of Good Clinical Practice. Paris, France: International Union Against Tuberculosis and Lung Disease, 2008.

[127] Pocket Guide for Asthma Management and Prevention (for Adults and Children Over 5 Years), Global Initiative for Asthma (GINA), updated 2011

[128] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011.

[129] Chapman RS, He X, Blair AE, Lan Q. Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study. BMJ. 2005;331(7524):1050. Epub 2005 Oct 18.

[130] Romieu I, Riojas-Rodríguez H, Marrón-Mares AT, Schilmann A, Perez-Padilla R, Masera O. Improved biomass stove intervention in rural Mexico: impact on the respiratory health of women. Am J Respir Crit Care Med. 2009;180(7):649-656.

[131] Mitchell A. Indoor Air Pollution—Technologies to Reduce Emissions Harmful to Health: report of a landscape analysis of evidence and experience. USAID-TRAction Project, 12 November 2010. (http://www.tractionproject.org/sites/default/files/upload/Reports/IAP%20Landscape%20Analysis%20Report.pdf)

caused by CVDs. An estimated 12.7 million new cases of cancer and 7.6 million deaths from cancer occurred worldwide in 2008.[132] The burden of cancer is expected to increase to 21.4 million cases by 2030, largely due to the aging of the population. Cancer is far from a developed-world disease as currently one-half of newly reported cancers and two-thirds of all cancer deaths occur in LMICs, which are expected to bear two-thirds of all cancer cases by 2030. Although LMICs account for 80 percent of years of life lost to cancer, only 5 percent of global spending on cancer is in LMICs, resulting in a "5/80 disequilibrium" in global spending in cancer.[133]

Cancer constitutes not one disease but many, and the prevalence of specific cancers varies. Lung, breast, colorectal, stomach, and liver cancers cause the majority of cancer deaths worldwide.[134] In HICs, the most commonly diagnosed cancers are prostate cancer in men and breast cancer in women, while the leading cause of cancer deaths is lung cancer.[135] In low-income countries, lung and breast cancer are also among the most common diagnoses and causes of cancer deaths, but cancers of the cervix, stomach, and liver are also common.[136] In sub-Saharan Africa, for example, cervical cancer is the leading cause of cancer death among women.[137]

Risk factors also vary widely by specific cancer. Some cancers share the same four major risk factors as the other major NCDs: tobacco use (lung cancer, head and neck cancer), unhealthy diet (stomach, breast, and colorectal cancer), insufficient physical activity (breast and colorectal cancer), and the harmful use of alcohol (liver cancer). Other cancers are infectious in origin, including cervical (human papillomavirus), liver (hepatitis B and C), and gastric (H. pylori) cancers. Overall, infectious agents are responsible for almost 25 percent of cancer deaths in the developing world, compared to only 6 percent in industrialized countries.[138] Other risk factors include environmental exposures such as aflatoxin (liver cancer) and occupational exposures such as asbestos (lung cancer).

Cancer Prevention and Control Strategy

Cost-effective interventions are available across the five major components of the cancer control and prevention continuum: prevention and risk reduction, screening and early detection, diagnosis and staging, treatment and long-term follow-up, and palliation.

- Prevention and risk reduction strategies (or primary prevention) can be divided into three major categories: lifestyle modification, infection control, and exposure control. Tobacco cessation is arguably the most effective lifestyle modification for preventing cancer. Exercise, healthy eating, and moderate alcohol consumption are also associated with lowered risks of cancer. For cancers of infectious origins, vaccines are key tools for population-wide intervention. The HPV vaccine prevents cervical and anal cancer caused by infection with human papillomavirus, and the vaccine against hepatitis B prevents liver cancer. Lastly, protection against environmental or occupational risk factors for cancer, such as aflatoxin and asbestos, are in effective prevention strategies.
- Screening in asymptomatic individuals and the early detection of cancer in individuals with signs or symptoms of the disease are also important for cancer control and prevention. Because early stage cancers are more treatable than late stage cancers, and often with less intensive therapies, screening and early detection can increase the chances of

[132] Ferlay J, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-2917.

[133] Knaul F M, Frenk J, Shulman L. The Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries report: Closing the cancer divide: a blueprint to expand access in low and middle income countries. Harvard Global Equity Initiative, Boston, MA, October 2011.

[134] Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011. (http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf).

[135] Ibid.

[136] Ibid.

[137] Ibid.

[138] Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006;118:3030-3044.

successful treatment and decrease the morbidity and cost of treatment. In the case of pre-cancers, removal of suspicious lesions identified through screening can even prevent the onset of cancer.

- Once cancer is identified, definitive diagnosis from pathologic examination and further testing to assess the stage, size, and spread of disease is necessary. Diagnosis and staging often include imaging, laboratory and pathology analysis, and physical examination.
- Cancer treatment includes one or more the following elements: surgery, radiation therapy, systemic therapy (e.g., chemotherapy, hormonal therapy, and biologic therapy), and supportive care. Following treatment, individuals require long-term follow-up including surveillance for recurrence and monitoring for short- and long-term complications of their disease and treatment.
- Palliation includes the provision of relief from physical pain and suffering associated with cancer and major illness.

The relative importance and cost-effectiveness of each component of a cancer prevention and control strategy varies by disease. On one hand, prevention and risk reduction is critical for lung cancer through tobacco cessation but more limited for breast cancer. On the other hand, screening and early detection is the mainstay of preventive care for breast cancer (e.g., mammography, ultrasound), while no evidence-based screening strategies are currently available for lung cancer. Table 3.4, adapted from the Global Task Force on Expanded Access to Cancer Care and Control report, "Closing the Cancer Divide," illustrates the cancer care continuum, characterizing specific cancers.[139]

Significant barriers impede implementation of each component of cancer care and prevention in LMICs. Low levels of awareness in the community and among healthcare practitioners about cancer and risk factors limit preventive strategies. Screening and early detection are limited by lack of access to primary care and to appropriate technologies. Unlike other NCDs, diagnosis and staging in cancer requires sophisticated technologies including imaging and pathology services. In addition, both diagnosis and treatment require healthcare practitioners with specialized training in oncology, and they are in short supply in LMICs. In Honduras, which has a population of 8 million people, fewer than 20 oncologists are available; in Ethiopia, four oncologists provide care for a population of over 80 million people.[140]

Lack of access to medicines and specialty care centers create additional barriers to treatment. Surgery and radiation treatment are critical to the treatment of many cancers and yet are unavailable in many settings. According to the International Atomic Energy Association, 30 countries, one-half of which are in Africa, do not have any facilities at all for radiation therapy.[141] For those that can access properly equipped facilities, cancer medicines are often expensive and, in the case of systemic therapies, are often given intravenously and require close clinical monitoring.

The subject of cancer is vast and a complete review is beyond the scope of this work. Because of breast cancer's increasing prevalence in LMICs, non-infectious origins, and availability of effective interventions across the cancer control continuum, we have chosen to focus our discussion on breast cancer. Although we do not specifically address other cancers in this section, many of the approaches and opportunities for tackling breast cancer are also directly relevant to these conditions. We briefly discuss gaps in new product R&D beyond breast cancer at the end of the section.

[139] Knaul FM, Frenk, J, Shulman L. The Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries report: Closing the cancer divide: a blueprint to expand access in low and middle income Countries. Harvard Global Equity Initiative, Boston, MA, October 2011.

[140] Ibid.

[141] International Atomic Energy Agency, 2011.

Table 3.4

Prevention	Lifestyle related	- Tobacco (including increased risk from secondhand exposure): lung, head and neck, bladder, and throat cancers; - Alcohol: hepatocellular carcinoma
	Infection related	- HPV: cervical cancer - Hepatitis B: hepatocellular carcinoma - H. pylori: stomach cancer
Early detection and treatment		- Cervical cancer - Breast cancer - Retinoblastoma in children
Treatment based primarily on systemic therapy		- Burkitt's lymphoma (particularly childhood) - Hodgkin's lymphoma - Childhood acute lymphocytic leukemia - Non-Hodgkin's lymphomas
Life extension and palliation with systemic therapy		- Kaposi's sarcoma - Chronic myelogenous leukemia - Survivorship - All cancers and population groups
Pain palliation		- All cancers

Burden of Breast Cancer

Among women, breast cancer is the most common cancer worldwide and the most common cause of cancer-related death, including in LMICs where breast cancer mortality has surpassed that of cervical cancer.[142] In 2010, an estimated 1.5 million new cases of breast cancer and 411,000 deaths were reported globally.[143] Between 1980 and 2010, breast cancer incidences and mortality rates increased globally, though with a greater increase in poorer countries. In LMICs, incidences increased by 60 percent and mortality by 53 percent, while in HICs the incidence and mortality rates increased by 47 percent and 20 percent, respectively.[144]

The burden of breast cancer in LMICs is expected to increase further. By some estimates, breast cancer incidence and mortality will increase by 50 percent between 2002 and 2020 due to demographic shifts alone, with greater increases in LMICs.[145] These projections may underestimate the actual increase of disease because they do not account for the increasing adoption of Western lifestyles, including decreased parity, delayed childbirth, physical inactivity, and dietary changes—all of which are risk factors for breast cancer.

Breast Cancer Prevention and Control Strategy

A comprehensive breast cancer prevention and control strategy contains all of the components described in the general cancer prevention and control discussion above. While clinical trial evidence is lacking, data suggest that prolonged lactation, regular physical activity, weight control, avoiding excess alcohol intake, and avoiding

prolonged use of exogenous hormone therapy may reduce the risk of breast cancer.[147] Early detection and screening is vital in breast cancer control as outcomes in breast cancer are closely associated with stage of detection. Currently, 60-70 percent of breast cancer cases in LMICs are detected in late stages with regional disease and metastasis, compared to less than 20 percent in most HICs.[148,149] Early detection programs include public education and training of healthcare professionals to appropriately triage women presenting with breast symptoms. Common screening modalities in breast cancer include self-breast examination (SBE), clinical breast examination (CBE), ultrasound, and mammography. Diagnosis and staging consists of clinical evaluation, imaging and laboratory studies, and surgical pathology, ideally from needle sampling. Treatment depends largely on stage and may consist of surgery (lumpectomy or mastectomy), radiation therapy, and systemic therapy (including chemotherapy, hormonal therapy, and biologic therapy). Major barriers to breast cancer prevention and control identified in LMICs include low levels of community awareness of the availability and benefits of breast cancer care, lack of pathology services for diagnosis and staging, and fragmented treatment options, especially for radiation therapy and the full range of systemic treatments.[150]

Recommendations and Barriers for Breast Cancer Management

The Breast Health Global Initiative (BHGI) has developed a guideline model for stratifying resource-appropriate breast cancer services within each of the core elements for LMICs.[151] The guidelines establish recommendations for four levels of care depending on healthcare resources: basic, limited, enhanced, and maximal.

Table 3.5 summarizes these guidelines, which have been simplified and adapted for the present study. At each level of care, we identify barriers to implementation and consider opportunities for new product R&D that could help address barriers in LMICs. For example, at the basic care level, the guidelines recommend that early detection be performed by clinical history and CBE. Barriers to implementing this guideline include lack of clinical competence in performing CBE among healthcare professionals. Thus there may an opportunity for the development of learning tools to provide rapid and high-quality CBE training for non-physician healthcare workers.

Gaps and Opportunities for Breast Cancer

1. Genetic and biomarker assays for diagnosis and treatment

Using immunohistochemistry for prognosis and treatment is a recent advancement in treating breast cancer. In developed countries, all women with

142 Parkin DM, Bray F, Ferlay J, Pisano P. Global cancer statistics, 2002. CA Cancer J Clan. 2005;55:74-108.

143 Ferlay J, Bray F, Pisano P, Parkin DM. GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. I ARC Cancer Base No. 5. version 2.0. Lyon, France, IARC Press, 2004.

144 Knaul FM, Frenk J, Shulman, L. The Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries. Closing the Cancer Divide: a blueprint to expand access in low and middle income countries. Harvard Global Equity Initiative, Boston, MA, October 2011.

145 Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E, Harford J. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer 2008 Oct 15;113(8 Suppl):2221-2243.

146 Ibid.

147 Ibid.

148 American Cancer Society. Breast Cancer Facts & Figures 2009-2010. American Cancer Society, 2010. (http://www.cancer.org/Research/CancerFactsFigures/BreastCancerFactsFigures/breast-cancer-facts--figures-2009-2010).

149 Shulman LN, Willett W, Sievers A, Knaul FM. Breast Cancer in Developing Countries: Opportunities for Improved Survival. J Oncol. 2010; 2010:1-6.

150 Anderson, et al. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. The Lancet Oncology, 2011;4:387-98.

151 Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E, Harford J. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer 2008 Oct 15;113(8 Suppl):2221-43.

invasive breast cancer are tested for estrogen receptor (ER) status, progesterone receptor status, and the HER-2/neu oncogene, which are then used to guide treatment.[152] Immunohistochemical testing requires specialized laboratory equipment and technicians and thus is commonly not available in LMICs. Even when it is performed, errors in reporting ER and HER-2/neu have been observed to be as high as 18 percent.[153] The remarkable advances in genomics and molecular medicine have created opportunities for new technologies that may greatly reduce the cost and expertise needed to assess these important biomarkers. Polymerase chain reaction and other amplification techniques have the potential to largely automate the genetic analysis of ER and other biomarkers relevant to breast cancer.[154] The WHO NCD research priorities working group for cancer identified the importance of "the discovery and application of biomarkers within the specific etiological and pathological context of cancers common in LMICs."[155]

2. Appropriate ultrasound technologies for screening and diagnosis

Although mammography is the gold-standard imaging test for screening in developed countries, it may not be suitable for screening in LMICs. To be effective, mammography programs require considerable investment in equipment and health infrastructure as well as trained operators and radiologists. Ultrasound is more promising because the equipment is less expensive, portable, and easier to operate, and the images are easier to interpret than mammograms. However, currently available ultrasound devices may not always be appropriate for low-resource settings. Ultrasound devices are often designed for experienced operators in the developed world for multiple applications and thus have unnecessary functionality that complicate their use and add to their cost (currently $25,000 to $40,000 USD).[156] Additionally, traditional imaging training takes 6 to 24 months and requires trainers to travel great distances to centers where only a few can be trained at a time.[157] An opportunity is evident for the development of appropriate ultrasound technologies for the early detection and diagnosis of breast cancer in LMICs. Such technologies should be simple to operate, employ simplified scanning methods (e.g., external landmarks), low cost ($500-$1,000 USD), and field-ready; ideally, they will combine electronic learning and image sharing to facilitate rapid training and quality assurance.[158]

3. Breast prostheses for training

A central issue in CBE is the ability to palpate breast lumps and appropriately refer women with suspicious findings. Inexperienced clinicians may miss malignant breast lumps, thereby delaying diagnosis (low sensitivity), or may over-refer women who have benign breast changes (low specificity) leading to unnecessary biopsies and costs. Because of the inherent challenges to health workforce training in LMICs, there may be opportunities for the development of affordable breast prostheses to help facilitate CBE training for healthcare workers and clinicians.[159] Ideally, these prostheses would simulate actual breast tissue and allow healthcare professionals to practice differentiating normal breast tissue from suspicious breast lesions requiring referral.

While such products exist in the developed world, the widespread availability of mammography has made CBE a less important tool for the early detection and

[152] Adjuvant Systemic Therapy – Early and Locally Advanced Breast Cancer: Diagnosis and Treatment. NCBI Bookshelf. (www.ncbi.nlm.nih.gov/books/NBK11632/, accessed 22 March 2012).

[153] Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E, Harford J. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer 2008 Oct 15;113(8 Suppl):2221-2243.

[154] Interview with Benjamin O. Anderson, Chair of the Breast Health Global Initiative. March 19, 2012.

[155] Mendis S, Alwan A, eds. A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, World Health Organization, 2011. p. 47.

[156] Interview with Rengaswamy Sankaranarayanan, WHO International Agency for Research on Cancer. February 21, 2012.

[157] Garra G. Imaging Communications and Education Technology for Global Health. Abstract. National Cancer Institute – Cancer Detection and Diagnostics Technologies for Global Health. August 22-23, 2011, 29.

[158] Ibid.

Table 3.5: Breast Cancer Synthesis

	Needs			Barriers			R&D Gaps		
Level of Resources*	Basic	Limited	Enhanced	Basic	Limited	Enhanced	Basic	Limited	Enhanced
Early Detection	Clinical history and CBE	Breast US +/- mammography in women with positive CBE	Screening mammography	Healthcare professionals trained in CBE, community awareness and organization	Access to imaging, experienced operators, experienced interpreters	Access to imaging, experienced operators, experienced interpreters	Mobile technology to increase community awareness, devices to facilitate CBE training	Appropriate, low-cost US	Appropriate mammography
Diagnosis	Tissue sampling for dancer diagnosis +/- hormone receptor status	Tissue sampling for cancer diagnosis +/- hormone receptor status	Image-guided breast sampling, bone scan, CT scan, cardiac function monitoring, HER-2/neu status, PR status by IHC	Healthcare professionals trained in tissue sampling, pathology services	Trained healthcare professionals, access to imaging, pathology services	Advanced imaging and pathology, specialty centers	Telepathology, telemedicine, low-cost IHC, automated tissue processing	Telepathology, low-cost lab testing, biomarker assays	Low-cost IHC, biomarker assays
Treatment	Stage 1 Modified radical mastectomy, oopherectomy, tamoxifen	Stage 1 Breast conserving surgery, systemic chemotherapy	Stage 1 Same as "Basic" plus: aromatase inhibitors and trastuzamab	Healthcare professionals trained in treatments, access to tamoxifen, chemotherapy, and opioids	Trained healthcare professionals, access to radiation therapy, access to chemotherapy	Access to medicines, access to specialty centers, access to specialists	Telemedicine	Telemedicine	Telemedicine
	Stage 2 Systemic chemotherapy	Stage 2 Radiation therapy	Stage 2 Same as "Basic"						
	Locally advanced Systemic chemotherapy	Locally advanced Radiation therapy	Locally advanced Same as "Basic"						
	Stage 4 Systemic chemotherapy + opioids	Stage 4 Radiation therapy	Stage 4 Same as "Basic" plus: bisphosphonates						

** CBE– clinical breast exam; breast U/S— breast ultrasound; FNAB—fine-needle aspiration biopsy; IHC—immunohistochemistry; CAD—computer-assisted detection;

Examples cited in BHGI papers:—

- telepathology at Tata Memorial Hospital (summary, page 19/23)—
- simplifying tools commonly used in high-income countries to reduce cost and burden on training, example: modular diagnostics clinics that integrate across clinical evaluation, basic imaging, tissue sampling, and histopathologic assessment

diagnosis of breast cancer. The latest guidelines from the U. S. Preventive Services Task Force has concluded that the current evidence is insufficient to assess the benefits and harms of CBE in addition to mammography and, in fact, recommend against teaching SBE.[160] In turn, the potential market size for effective breast prostheses for teaching CBE, much less low-cost ones, is small, creating a product gap for LMICs. The importance of effective CBE is underscored in low-resource settings in which population screening is not feasible and early detection and triage of breast lumps is the principal means of downstaging.

Gaps and Opportunities beyond Breast Cancer

Through our interviews we identified a wide range of gaps for new products for cancer. Some of these products addressed cancers that disproportionately affect LMICs (oral, gastric, and liver cancer from aflatoxin); others are adapted or low-cost technologies; and still others are wholly novel. A complete discussion of these opportunities is beyond the scope of the chapter. Representative examples follow:

1. Alternative technologies for screening, early detection, and diagnosis

Standard imaging modalities such as MRI, PET, and CT require significant financial resources and infrastructure, limiting access to these modalities to those patients in high-resource settings. Additionally, traditional pathology services, which involve sample preparation, processing, and staining, are resource intensive and require sophisticated laboratory equipment and trained technologists. Opportunities exist for new technologies that can broadly serve these needs yet be appropriate for low-resource settings. For example, optical imaging is used to detect signals arising from cancer biomarkers.[161] These tools are relatively inexpensive because they use mass fabricated components and are readily portable and battery powered. Potential applications of this technology in global cancer management include screening, early detection at the POC, biopsy guidance, and real-time histology.[162]

2. Vaccines for cancer prevention

The HPV vaccine protects against two cancer-causing subtypes of the human papillomavirus, HPV 16 and HPV 18, which account for approximately 70 percent of cervical cancer worldwide. However, the vaccine does not provide protection against other cancer-causing subtypes. As a result, cervical cancer screening is still recommended for women who have been vaccinated. In developed countries where Pap smears are widely available the need for a polyvalent HPV vaccine is less relevant than in low-resource settings. An opportunity is evident for the development of a polyvalent vaccine against HPV (L1 antigen) or alternatively a novel vaccine that targets the L2 antigen, which is shared across HPV subtypes.[163] There are also opportunities for HPV vaccines with alternative routes of administration including oral and nasal, which decrease barriers to administration and supply chain management.[164]

3. Telemedicine and telepathology technologies for improved access to care and training

Lack of access to cancer specialists and to advanced imaging and pathology services presents a significant barrier to cancer control. Both telemedicine—the use of telecommunications technology to allow healthcare professionals to evaluate, diagnose, and treat patients in a remote location—and telepathology, the use of similar technology to allow for the remote interpretation of pathology specimens to aid in cancer diagnosis, have been used successfully in LMICs to improve access to care for cancer. For example, in El Salvador, a telemedicine program in conjunction with St. Jude's Hospital increased survival rates for acute

[159] Interview with Rengaswamy Sankaranarayanan, WHO International Agency for Research on Cancer. February 21, 2012.

[160] Screening for Breast Cancer. U.S. Preventive Services Task Force (USPSTF). December 2009. (www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm, accessed 20 March 2012).

[161] Richards-Kortum R. Multi-Modal Optical Imaging to Improve Early Detection of Cancer in Low Resource Settings: Experience from China, India, Guatemala, and Botswana. Abstract. National Cancer Institute – Cancer Detection and Diagnostics Technologies for Global Health. August 22-23, 2011, 42.

[162] Ibid.

lymphoblastic leukemia from 10 to 60 percent over a five-year period.[165] By allowing radiologists to review images, dermatologists to examine skin lesions, pathologists to review pathology, and oncologists to monitor reactions, primary care physicians could administer treatment locally without the physical presence of these specialists. Ideally, these technologies could be used not only to provide care, but also for capacity building and training. As an example, Project ECHO at the University of New Mexico has used telemedicine to train primary care physicians in remote areas in the treatment of complex conditions such as hepatitis B and refractory hypertension, which are typically managed by specialists.[166]

Conclusion

Most currently available technologies for cancer detection and diagnostics are not suitable for low-resource settings. This reality presents a number of opportunities for the development of appropriate diagnostic technologies for global cancer control, particularly those related to recent advances in genomics and biomarkers. For breast cancer, we identified genetic biomarkers, appropriate ultrasound technologies, and breast prostheses as potential areas for new product R&D.

[163] Interview with Rengaswamy Sankaranarayanan, WHO International Agency for Research on Cancer. February 21, 2012.

[164] Ibid.

[165] Knaul FM, Frenk J Shulman L. The Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries. Closing the Cancer Divide: A Blueprint to Expand Access in Low and Middle Income Countries. Harvard Global Equity Initiative, Boston, MA, October 2011.

[166] University of New Mexico, Project Echo, Robert Wood Johnson. (http://echo.unm.edu/).

CHAPTER 4
DISCUSSION AND CONCLUSION

4

4.1 Discussion

In this paper, we identify an unmet need for new technologies to address the burden of noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs), but we recognize that this need is fundamentally different from that of neglected tropical diseases (NTDs). While NTDs largely affect LMICs and thus provide few market incentives for new product development, the burden of NCDs is shared by both high-income countries (HICs) and LMICs, thereby creating a large market for relevant technologies. As a consequence, unlike for NTDs, many effective technologies for NCD control and prevention have been developed through market forces and are in widespread use in many settings. The problem, rather, is that these technologies are not always suitable for the unique challenges faced by LMICs.

For selected NCDs, we have identified barriers to the use of existing technologies in LMICs and opportunities for several kinds of new products—particularly adapted, low-cost, and acceptable technologies—that may be required to address these barriers. Because these barriers are predominantly faced by LMICs, the market incentives for developing these products are limited, driving an important gap in new product R&D for NCDs.

Because of this fundamental difference between HICs and LMICs, new product R&D for NCDs must, in general, be context-driven—developed technologies for LMICs must address local constraints determined by health systems, resources, and socio-cultural characteristics rather than disease burden alone. For example, we learned from Dr. Samad Shera that in his center in Karachi, Pakistan, the need for new health technologies to address diabetes care is limited. He and his team have developed a community-based approach to diabetes diagnosis and management that is well suited to the urban South Asian community it serves and the resources it has available. Using adapted protocols for glucose measurement, for example, families in nearby dwellings share diabetes testing materials, which reduces the need for lower-cost testing materials. However, in more remote environments, in which access to care is limited and health systems are more fragmented, new diabetes products may have a substantial impact on the burden of NCDs. Context-dependence suggests that the relative importance of any new technology varies across settings as barriers to NCD prevention and control vary even within the same region or country. This further fragments the market opportunity for new technologies that address these barriers, weakening incentives for their development and widening the R&D gap.

In addition to context-driven solutions, opportunities exist for "disruptive technologies" that may reduce the burden of NCDs in LMICs across a wide range of settings.[167] These technologies fundamentally change the way care is delivered and can bring complex and expensive healthcare products and services to greater levels of affordability and accessibility. For example, the development of biomarker assays for the diagnosis and treatment of breast cancer would dramatically reduce the need for advanced pathology services. In some cases, although the initial need for the technology is defined by LMICs, the technology may replace existing products in HICs. The potential for "global to local" adoption increases the market opportunity for disruptive technologies, increasing incentives for R&D for NCDs.

We find that the need for new product R&D varies by disease, technology, and context. Although our review

[167] Term coined by Clayton M. Christensen. Reference: Christensen, C M. The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail. Boston, MA, Harvard Business School Press, 1997.

was not exhaustive, we found the greatest opportunity for new products in relation to cancer, which is unsurprising since cancer has the largest barriers to access in LMICs due to the dependence on resource-intensive equipment and highly trained specialists. The second greatest need for new product R&D was for diabetes, followed by cardiovascular disease, and then chronic respiratory disease. Among types of technology, the largest opportunity for new product innovation is for diagnostics followed by delivery technologies. We found little need for new product R&D for vaccines or medicines, except in the cases of neglected NCDs, such as rheumatic heart disease and Chagas disease, and for heat-stable preparations such as insulin. By and large, NCDs in LMICs are not qualitatively different than diseases in developed countries, and many existing medicines and vaccines made for HIC markets remain effective in LMICs.

Similarly, the relative importance of new product R&D for NCDs varies by context. Even in low-resource settings, a well-functioning health system may be able to effectively utilize existing health technologies used in HICs and thus have little need for adapted or low-cost products. However, in environments with multiple barriers to implementation, new product R&D may complement other prevention and control strategies. For example, adapted technologies that simplify training and allow for task-shifting of complex tasks to less skilled healthcare workers may complement capacity building and health workforce development.

Finally, a number of experts we interviewed emphasized the importance of integrating new technologies within and across existing health systems to avoid increasing the burden of addressing NCDs on fragile health systems. For example, the use of platform technologies for diagnosis that can be used for a variety of diseases, both infectious and noncommunicable, may simplify supply chain management, training, and uptake by frontline providers. This strategy underscores the importance of coordinating product development and funding initiatives.

4.2 Conclusion

We conclude that new products can serve an important role in overcoming barriers to the prevention and control of NCDs in LMICs. A crucial next step will be to analyze how to accelerate the development of these needed new products. In some cases, markets may be sufficient to drive their development by industry, but in other cases, concerted action will be necessary to support global R&D efforts. Future work in this area should explore mechanisms to address the new product R&D gap for NCDs and prioritize needed technologies based on disease burden, shared barriers, and lack of market incentives.

ANNEXES

Annex I: Interviews

Expert	Title	Expertise
Bernhard H. Weigl, PhD, MSc	Director, NIBIB Center for POC Diagnostics for Global Health, PATH	Diabetes, Diagnostics
Rengaswamy Sankaranarayanan, MD	Head of the Early Detection & Prevention Section and Screening Group, International Agency for Research on Cancer (WHO-IARC)	Cancer Diagnostics
Marcus M. Reidenberg, MD, FACP	Professor of Pharmacology, Medicine, and Public Health, Weill Cornell Medical College	Medicines
Rebecca Richards-Kortum, PhD	Interim Chair, Department of Bioengineering, Rice Founder, Beyond Traditional Borders Director, Rice 360°: Institute for Global Health Technology	Cancer Diagnostics
Samad Shera, MBBS	President, International Federation of Diabetes	Diabetes, Clinician
Michael J. Free, OBE, PhD	Vice President and Senior Advisor for Technologies, PATH	Diagnostics, R&D

Expert	Title	Expertise
Benjamin O. Anderson, MD	Professor of Surgery, University of Washington School of Medicine Chair, Breast Global Health Initiative	Breast Cancer, Clinician
Shanthi Mendis, MBBS, MD, FRCP, FACC	Coordinator, Global Program for Prevention and Management of Noncommunicable Diseases, WHO	Cardio-vascular Disease, Public Health
Lynette L A. Denny, MD, PhD	Principal Specialist and Professor of Obstetrics & Gynaecology University of Cape Town	Cancer Diagnostics, Treatment

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