

Perspectives from NHLBI Global Health Think Tank Meeting for Late Stage (T4) Translation Research



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Almost three-quarters (74%) of all the noncommunicable disease burden is found within low- and middle-income countries. In September 2014, the National Heart, Lung, and Blood Institute held a Global Health Think Tank meeting to obtain expert advice and recommendations for addressing compelling scientific questions for late stage (T4) research—research that studies implementation strategies for proven effective interventions—to inform and guide the National Heart, Lung, and Blood Institute’s global health research and training efforts. Major themes emerged in two broad categories: 1) developing research capacity; and 2) efficiently defining compelling scientific questions within the local context. Compelling scientific questions included how to deliver inexpensive, scalable, and sustainable interventions using alternative health delivery models that leverage existing human capital, technologies and therapeutics, and entrepreneurial strategies. These broad themes provide perspectives that inform an overarching strategy needed to reduce the heart, lung, blood, and sleep disorders disease burden and global health disparities.

TABLE OF CONTENTS

NHLBI Global Health Think Tank	342
Perspectives for advancing global T4 translation research: developing research capacity and addressing compelling scientific questions	342
Developing research capacity	343
Theme 1: Awareness and scope of T4 research’s value and need for building capacity	343
Theme 2: Partnerships for successful T4 research	344
Theme 3: Platforms and consortia to foster T4 research	344
Theme 4: Building a cadre of T4 researchers ..	345
Theme 5: Creative and sustainable support strategies for T4 research	345
Addressing compelling scientific questions	345
Theme 6: Developing high-quality methods and metrics	345
Theme 7: Addressing health inequities	346
Discussion	346
Conclusions	347

Acknowledgments	347
References	347

During the past 2 decades, the proportion of the global disease burden due to noncommunicable diseases (NCD) increased from 43% to 54% [1]. Almost three-quarters (74%) of all the NCD burden is found within low- and middle-income countries [2]. In addition to persistent unfavorable levels of NCD risk factors, population growth and population aging have also contributed substantially to the expanding NCD burden trends—both the latter are rapidly occurring within low- and middle-income country populations [3,4]. During this same time frame, major NCD had substantial reductions in their age-specific mortality rates, although these reductions have been uneven across high-, middle-, and low-income countries [5]. For example, recent country comparative studies have found higher mortality and health disadvantages in the U.S. population than in other high-income countries [6,7].

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Within low- and middle-income countries, the age-specific mortality reductions for NCD seen in high-income countries have not been fully realized, leaving their national average rates often 2- to 3-fold higher than the rates for high-income country populations [5].

These findings have led to efforts addressing the global NCD burden and specifically to tackling health inequities. In 2011, the U.N. High-Level Meeting on Non-Communicable Diseases called for global action [8] that led to global prevention and control targets [5], and currently, the United Nations is formulating global Sustainable Development Goals that plan to include a health subtarget calling for a one-third reduction in premature deaths from NCD from 2016 to 2030 [9]. In 2014, the U.S. Council on Foreign Relations recommended more robust U.S. engagement in global health, especially for NCD [10]. Finally, in response to the lagging U.S. health indicators, calls have been made for a research portfolio to better understand the key factors responsible for the U.S. health disadvantage [6,7].

At the National Institutes of Health (NIH), global health research has been a high priority endeavor for the NIH director [11]. In support of this NIH priority, the National Heart, Lung, and Blood Institute (NHLBI) has developed a full spectrum of global health research from fundamental discovery science to population health research and research training. These efforts align with the 3 goals of NHLBI's Global Health Strategic Plan (2012 to 2017), which includes basic and fundamental discovery; better clinical mechanisms for prevention, diagnosis and treatment; and innovative translation into public health gains for heart, lung, and blood diseases and sleep disorders [12]. To date, the majority of NHLBI-funded global research activities focus on basic, clinical, and population science research that emphasizes fundamental discoveries and early stages (T1 to T3) of the translational science research spectrum. The Center for Translation Research and Implementation Science (CTRIS), recently established by NHLBI, serves as the focal point and catalyst for domestic and global late-stage (T4) translation research and tackling health inequities for heart, lung, blood, and sleep (HLBS) disorders. CTRIS studies strategies for broad implementation of proven-effective interventions across populations while moving knowledge into practice and also learning from intervention and policy application [13,14].

The importance of T4 research and its scholarship that results in discovering implementation strategies for delivering proven effective interventions is insufficiently appreciated. However, this situation is changing. Global institutions such as the World Bank acknowledge that policies fail most often because implementation is ineffective, and thus, their new frontier will be to advance the "science of delivery" [15]. Others are also recognizing the need for T4 research for global health gains. Whereas T4 research is occurring, albeit suboptimally, within high-income countries, this is rarely the case in low- and middle-income countries [16].

NHLBI GLOBAL HEALTH THINK TANK

Crafting a strategic course to move forward and build on both NHLBI's Global Health Strategic Plan [12], and its current Strategic Vision [17], NHLBI held a Global Health Think Tank in September 2014. During the one-and-a-half day meeting, the Think Tank Panel was asked to provide expert advice on compelling scientific questions for T4 research that will inform and guide NHLBI's global health research in areas including:

- Catalyzing T4 translation research for HLBS disorders with targeted strategic approaches for low-, middle-, and high-income countries.
- Developing the T4 translation research infrastructure for global health research that leverages previous NHLBI global investments.
- Training and mentoring the next generation of global health researchers to conduct rigorous T4 translation research.

The panel included members of NHLBI's National Advisory Council and its Board of External Experts, along with academic global health research experts within HLBS areas; NIH experts from other institutes with global health portfolios including the National Cancer Institute, National Institute for Neurological Diseases and Stroke, National Institute of Mental Health, and the Fogarty International Center, U.S. federal agency experts from the Department of Health and Human Services Office of Global Affairs, U.S. Agency for International Development, the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, along with World Health Organization (WHO) and World Bank experts.

The Think Tank reviewed the global burden of HLBS diseases; the health status in the United States compared with that of peer high-income countries [1,6,7,18–24]; a synopsis of NHLBI investments in global health research; and CTRIS's role as the focal point for advancing T4 translation research in global health. To inform the Think Tank Panel member deliberations, T4 translation research was characterized as the science of intervention delivery that creates generalizable knowledge used to scale up and disseminate proven effective interventions—across highly diverse countries—and results in favorable population impact [25].

PERSPECTIVES FOR ADVANCING GLOBAL T4 TRANSLATION RESEARCH: DEVELOPING RESEARCH CAPACITY AND ADDRESSING COMPELLING SCIENTIFIC QUESTIONS

Major themes developed during the Think Tank's deliberations were synthesized into 2 broad categories: 1) developing research capacity; and 2) developing compelling scientific questions that create the knowledge for sustainable implementation (Table 1) [26]. For each category, key challenges and recommendations from panelists and workshop participants were summarized. The following section describes 7 major themes that emerged.

evident. The ultimate outcome will be to improve health care outcomes through improved health care delivery and health policy while potentially contributing to better social policies beyond the health sector—policies that strengthen health diplomacy and contribute to social justice and better opportunities for all individuals. For example, a women’s group community mobilization intervention has been found to be a highly effective (and cost-effective) approach to improve newborn survival in rural Bangladesh [27]. This philosophy is aligned with the Gates Foundation statement that every life has equal value [28].

In order to address urgent needs in limited resource and capacity environments, initial efforts need to focus on developing capacity, infrastructure, and skill sets to 1) assess public health and clinical care systems, 2) identify local health priorities, and then 3) develop a strategic T4 research agenda. A strong T4 research team in place with a keen understanding of strengths and limitations of the local health system and what is possible in the short and long run will be critical success factors.

Theme 2: Partnerships for successful T4 research.

T4 research teams must partner with those who actually implement treatment—that is, public health and clinical care services providers. At the country level, partnering with the Ministry of Health, and Ministry of Finance, along with government units and private sector partners providing public health and clinical services, will be necessary. These partners provide insight into country-specific high-priority health issues as well as the opportunities and challenges to address them. Research teams also can include international institutions with expertise and commitment to T4 research. In addition, studying complex interventions with facets embedded at multiple levels of the health care system and the community requires designs developed by broad interdisciplinary research teams that are familiar with specific challenges at each of the intervention levels. These research teams can engage patients, families, health care and public health providers, health care and public health systems staff, and population level policy makers and be mindful of country cultural norms. This is *not* a traditional research team. Members and partnerships often include those who may not have worked together previously and, therefore, may not be familiar with others’ work or priorities. This collaborative approach requires key partners to move beyond their traditional training and work across disciplines to realize win-win common goals. Team members bring understanding of the local context and provide insights on what proven-effective interventions might be acceptable, feasible, adaptable, and sustainable and that address country-specific high-priority local health issues. Brokering these partnerships will be a critical success factor and must be explicitly addressed.

Other partnerships might include philanthropies such as the Clinton Foundation, Bill and Melinda Gates Foundation, and Wellcome Trust along with the private health

care industry and the private business sector’s social responsibility philanthropies. Developing and maintaining linkages with academia is critical to ensure a robust research community that can respond to calls for innovative investigator-initiated proposals, support training and capacity-building efforts, and provide key insight into emerging opportunities and strategic directions. Finally, creating new or reinforcing established partnerships with global institutions such as WHO, the World Bank, and regional development banks will be needed.

Theme 3: Platforms and consortia to foster T4 research.

NHLBI and NIH global health investments have led to the development of some research platforms and consortia that may potentially facilitate initial T4 research efforts. Exploring the utility of entities including the NHLBI/UnitedHealth Group’s Global Health Centers of Excellence Program [29], the Global Alliance for Chronic Diseases [30], the Global Alliance for Clean Cookstoves [31], the Medical Education Partnership Initiative [32], and Human Health and Heredity (H3) Africa [33], as platforms for research will be key first steps. Although these platforms are currently used to conduct research efforts that are focused on earlier translation stages (e.g., discovery science and clinical trials), in contrast to T4 research as defined earlier, they may prove adaptable with suitable support.

Global programs with established infrastructure within low- and middle-income countries may provide leveraging opportunities. One example is the U.S. President’s Emergency Plan for AIDS Relief Program, which has a highly developed chronic care delivery system for human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients [34]. Successful delivery of long-term ongoing antiretroviral treatment has resulted in impressive life expectancy gains—so much so, that aging and risk factors for heart and lung diseases are now more common in the HIV populations and need attention [35]. The President’s Emergency Plan for AIDS Relief footprint is largely in high HIV/AIDS burden, and low-income countries may prove a good venue for T4 collaborations within the HLBS research arena. Another example is the GREAT (Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, and Transfer of knowledge) Project, a joint special program with 3 U.N. institutions focused on child health along with WHO and the World Bank. GREAT is integrating WHO recommendations into national guideline adaptation processes to expand access to effective practices [36]. The key goal of GREAT is to use evidence-based clinical practice guidelines to transfer high-quality evidence about maternal and perinatal health to stakeholders across the health care system.

Challenges for long-standing global health institutions when moving forward with T4 research agendas will include the following: balancing the focus on scientific rigor and scholarship and avoiding drift into nonresearch

program implementation and blanket advocacy activities; understanding that low-income country senior researchers and mentors are often overcommitted; and understanding that technical support and governance infrastructure may be weak due to chronic underfunding and low staffing. Getting the right balance within a consortium will require a keen understanding of the context where activities and operations are occurring and a comprehensive understanding of skill and resource needs.

Theme 4: Building a cadre of T4 researchers. Global health settings often experience shortages in skilled research staff, yet these personnel will be expected to make progress with any research efforts. These deficiencies in skilled staff extend across all disciplines—including T4 research—and need to be addressed. T4 research training currently is limited in the United States and abroad. A strategy to build an interdisciplinary, skilled research community in the United States and globally is needed. The National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, NHLBI, the NIH Office of Behavioral and Social Sciences Research, and the U.S. Department of Veterans Affairs support the Training Institute for Dissemination and Implementation Research in Health [37]. The Training Institute for Dissemination and Implementation Research in Health and other courses/workshops deliver instruction to improve skill sets for conducting T4 research in health care and community settings. The training also emphasizes creating partnerships with multilevel, transdisciplinary research teams and developing research designs, methods, and analyses appropriate for T4 investigations that often include multilevel interventions (e.g., clinical, community, policy). The Fogarty International Center joins with various NIH Institutes to support the Global Health Scholars and Fellows program that trains U.S. doctoral and post-doctoral fellows in global health, and this program may be amenable to investigators with interest in T4 research. Several existing training programs (e.g., NIH training and fellowship grants) might also consider innovative methods of encouraging T4 and global health research for young investigators.

Another example of a domestic program training model with an intense track and high-quality output is the Centers for Disease Control and Prevention Epidemic Intelligence Service Program [38]. In the 2-year program, early stage public health professionals are immersed in didactic and experiential training focused on public health and epidemiology. This model has also been exported to several countries and adapted to the local context and needs. Availability of distance learning is increasing from high-income country universities.

NIH and NHLBI's research training and career development portfolios need to be strengthened to encourage and support early stage investigators as they develop T4 research skills. Training and capacity building for T4 research—research that cannot wait for the next generation

of researchers—will need to occur simultaneously as T4 research efforts unfold. Finally, roles for the National Center for Advancing Translational Sciences [39] and for programs such as Medical Education Partnership Initiative [32] will continue to emerge and provide opportunities.

Theme 5: Creative and sustainable support strategies for T4 research.

The support and funding for global health research—especially for NCD—is continuously evolving, yet optimizing future returns on investments will need to consider new and sustainable funding models. High-income countries commonly support global health research as do some middle-income countries [40]. Due to the recent global financial recessions, some countries may have reduced their global health research investment, regardless of their wealth status. Yet, with the rapid pace of globalization and interconnectedness, global science is increasingly becoming important. However, support for global health resources will likely receive more domestic scrutiny, especially during difficult fiscal times, and solid rationales that link them back to domestic health challenges and opportunities for science and to U.S. investigators and institutions will likely be needed. Middle-income and especially low-income countries may also have little budget flexibility during financially difficult times. Innovative financial arrangements, cofunding, in-kind support, and other creative fiscal strategies can be explored. A general assumption is that low-income countries will need mostly outside financing. Therefore, an emphasis on the sustainability of these efforts in times of fiscal austerity will be essential if research in low-income countries is to flourish during and after financial recessions.

Similar to high-income countries, middle-income country research funding, especially in upper-middle-income countries, may adopt models with adjustable levels of matching financing. High-income country bilateral and multinational research projects of mutual benefit can consider domestic funding of domestic components.

Addressing compelling scientific questions

Theme 6: Developing high-quality methods and metrics.

The complexities of T4 research demand both creative and innovative study methods that can be applied in real-world settings as well as high-quality metrics that can accurately and reliably assess research achievements and accomplishments. Methods such as randomized community designs lend themselves better to larger scale complex interventions than do individual randomization—a methodology now embraced by some institutions [41]. Modeling big data that can elucidate complex associations between policies and outcomes may help inform study designs and intervention development. Integrating business and entrepreneurial strategies into interventions can be explored. Typically in global health efforts, health care systems often struggle with getting supplies transported

with proper handling in a timely fashion to where the need resides. At the same time, some businesses and industries—working in the same context—have created successful models to distribute their products to all corners and every village regardless of the logistical challenges. Inexpensive technologies such as cell phones and point-of-care technology for diagnosis and care management can be integrated into the existing context-specific health care system framework. Finally, team-based care is an important care delivery strategy and can be a high-priority element for interventions. This will ensure optimal utilization of human resources that have been built from investment in health care for communicable diseases. An example is the use of HIV counselors who have expertise in health education on lifestyle and behavioral change to prevent HIV infection. They can be trained to provide health education on lifestyle modification to reduce the risk of NCD.

Even with good study design, neutral study results may be common and yet can provide useful information. Using T4 research outcomes including factors such as acceptability, fidelity, sustainability, and costs—even when faced with a neutral study—will lend insight into why a study generated neutral results and will help inform future efforts [42].

Developing and strengthening metrics will be critical. The National Academy of Medicine (formerly the Institute of Medicine) and National Research Council have recommended that NIH and other research-funding agencies support development of more refined analytic methods and study designs for cross-national health research [7]. These methods can include innovative study designs, creative uses of existing data, and novel analytical approaches to better elucidate complex causal pathways that might explain cross-national differences. Rigorous study design may include T4 standard research metrics along with population-level impact direct measures (e.g., morbidity, mortality) and intermediate measures (e.g., blood pressure reduction) to demonstrate clear outcomes and define success.

Measuring the ultimate impact of T4 research remains a major challenge. Peer-reviewed scientific publications as a metric may fall short. Innovative studies yielding new knowledge that potentially can make important contributions may not always garner attention among peer-reviewed high-impact journals nor among the broader scientific and researcher community. New collaborations and further refinement of study methods and metrics will enhance understanding across disciplines of the importance and impact of T4 research for improving population health.

Theme 7: Addressing health inequities. Health inequities exist, regardless of country income status, and opportunities to address them are currently available. The underlying drivers of shorter life expectancy and poorer health are not well understood, yet the recognized ones are largely similar across the globe. The role of social determinants, though well recognized, remain a challenge

to address. A strategic approach for initial research efforts might be studying groups at high risk for poor outcomes for which proven effective interventions are available but delivery is lagging. For example, among sickle cell disease patients in high burden regions, simple interventions such as penicillin prophylaxis to prevent fatal pneumococcal septicemia, are often lacking, and rheumatic heart disease patients often are not receiving antibiotic prophylaxis [43,44]. Effective implementation of either of these treatments could deliver short-term improvements in major outcomes such as mortality. Testing implementation of contextually adapted evidence-based clinical care guidelines for common diseases with large burdens—such as hypertension, asthma, and chronic obstructive pulmonary disease—are important topics. “Best buy” interventions have been developed by international agencies and promoted as affordable and feasible [45]. With shortages in human resources in health common across low- and middle-income countries, using alternative delivery models staffed by personnel with skills similar to community health workers has been successful and may be explored along with task shifting some primary health care provider duties to pharmacy and nursing staff.

Although health gains have occurred in recent decades within the United States, many high-income peer countries, as noted, have done better and are outdistancing the United States [6]. Within the U.S. population, a pattern of health inequities across racial/ethnic, new immigrants, socioeconomic strata, and urban and rural regionals remains common. The lagging U.S. performance for many health indicators and pervasive health inequities remains a major challenge. Likely rooted in the quality and access to care and variation in social determinants within the U.S. population, comparative national studies examining implementation challenges and natural experiments from policy variation across and within countries may prove helpful in elucidating these patterns. Thus, effective and innovative T4 research is also urgently needed within the United States and across peer high-income countries.

DISCUSSION

Past and current NIH and NHLBI leadership support engagement in global health research. More recently, the Institute of Medicine [7] and the Council on Foreign Relations [10] have called for the United States to continue active engagement in global health, and to increase technical assistance and support for research, especially for NCD. Moving forward, NHLBI can take lessons learned and build, adapt, and tailor efforts on past and ongoing investments. In an effort to obtain lessons learned for multiple stakeholders in the global health arena, the NHLBI held a global health Think Tank meeting that provided a venue for broad perspectives and inputs to help create an overall strategy, set a direction, and operationalize some initial research efforts. New skill sets, research teams, partners, and stakeholders in the NHLBI research

community will be needed. These new elements will help catalyze the T4 research agenda and synergize within and across NHLBI, NIH, and the entire research community.

New paradigms for global health research are unfolding. First, a compelling agenda is being developed for multilateral high-income country T4 research. Not unlike previous and ongoing transnational clinical trials that address research questions of common interest, such transnational research can enhance study populations' size, which may be inadequate within a single country, and can promote sharing of common resources allowing for more return from scarce research dollars. Second, a new tailored approach to low- and middle-income country institutions where capacity can vary from minimal/limited to near/equal to that of high-income country institutions is needed. Tailoring efforts to low- and middle-income countries considers the "6 Cs": *customizing* appropriately for country-income level, *context-specific* to the local environment, *capacity building* foci, *country-driven* priorities, and finally, targeting *critical challenges*, and *compelling questions* for high-priority HLBS health issues [46].

Building a future cadre of T4 researchers skilled and equipped to navigate the global health challenges in a networked manner is critical. The goal is to build in-country T4 capacity that can identify and prioritize the local health issues and conduct high-quality research within the local context. The in-country research cadre can then build regional and global collaborations with both peer countries and with high-income country institutions. This effort aligns with the NIH and NHLBI's commitment to develop and foster a robust T4 biomedical research workforce capable of tackling today's challenges.

CONCLUSIONS

The time is ripe for focused investment in T4 translation research both in the United States and abroad. As the Institute of Medicine recently affirmed, reducing the burden of cardiovascular and other chronic diseases worldwide—especially in low- and middle-income countries—is an achievable goal [47]. The deliberations of this Global Health Think Tank provided valuable insights and guidance in the development of NHLBI's strategic global health research agenda. These recommendations are aligned with NHLBI's Strategic Visioning [17] and can help take on the important challenge of translating research into practices to maximize population health impact in the United States and abroad.

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