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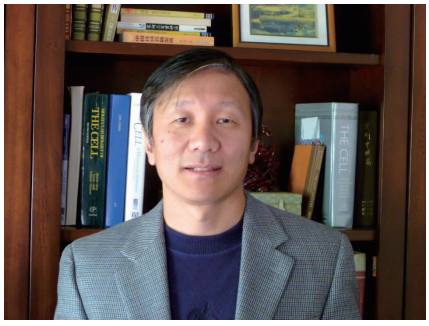
Monograph



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Editorial note: *Translational medicine research is the science to overcome research gaps among all interested parties to advance the bench-to-bedside translation. This review introduced the establishment of the Duke Translational Medicine Institute (DTMI) and its function: to bridge translational gaps between basic science researchers and clinicians, academe and industry, health care system and community, wealthy and less-developed nations. This article could provide the model of the translational medicine research of Duke to China and push the development of translational medicine research of our country.*

Translational medicine at Duke University

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1 Introduction of the Duke Translational Medicine Institute

Duke is proud of her long history of excellence in clinical research. Duke Databank for Cardiovascular Diseases was established in 1969 [1]. The Duke Clinical Research Institute (DCRI), leading clinical research and practice, was officially established in 1996[1]. To overcome research gaps among all interested parties to advance the bench-to-bedside translation, the National Institutes of Health (NIH) in the US launched "Roadmap" by then NIH director Dr. Elias Zerhouni in 2003[2]. Duke was among the first few institutes to champion translational medicine. To best serve the Duke research community, the Duke medical system established the Duke Translational Medicine Institute (DTMI) with a Clinical and Translational Science Award (CTSA) from the NIH in October of 2006[3] and with additional support from the University. The total budget for the DTMI exceeds $600 million over (the first) five years[4].

DTMI is now the academic home for the clinical and translational research community at Duke. It is an integrated support structure that provides resources and training and facilitates collaborative research in clinical and translational research. The mission of DTMI is to transform clinical and translational research at Duke, to encourage faster, more efficient translation of new scientific discoveries into clinical practice, to promote measurable improvements in community health and global health, and to make "personalized" medicine a reality. DTMI encourages team science by joining multidisciplinary investigators and industrial-model project management, while providing investigators with easy access

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to emerging technologies and methodologies.

2 Organization and framework of DTMI

By bridging disciplinary and scientific boundaries, the Duke Translational Medicine Institute strives to accelerate the translation of new discoveries into effective therapies and clinical care. The DTMI includes the following entities that span the translational and clinical research continuum [3] (Fig. 1). The DTMI has expanded from its original "three pillars" [4] to today's "five pillars" infrastructure [3, 5]. The five branches of DTMI support different stages of the translational effort[6].

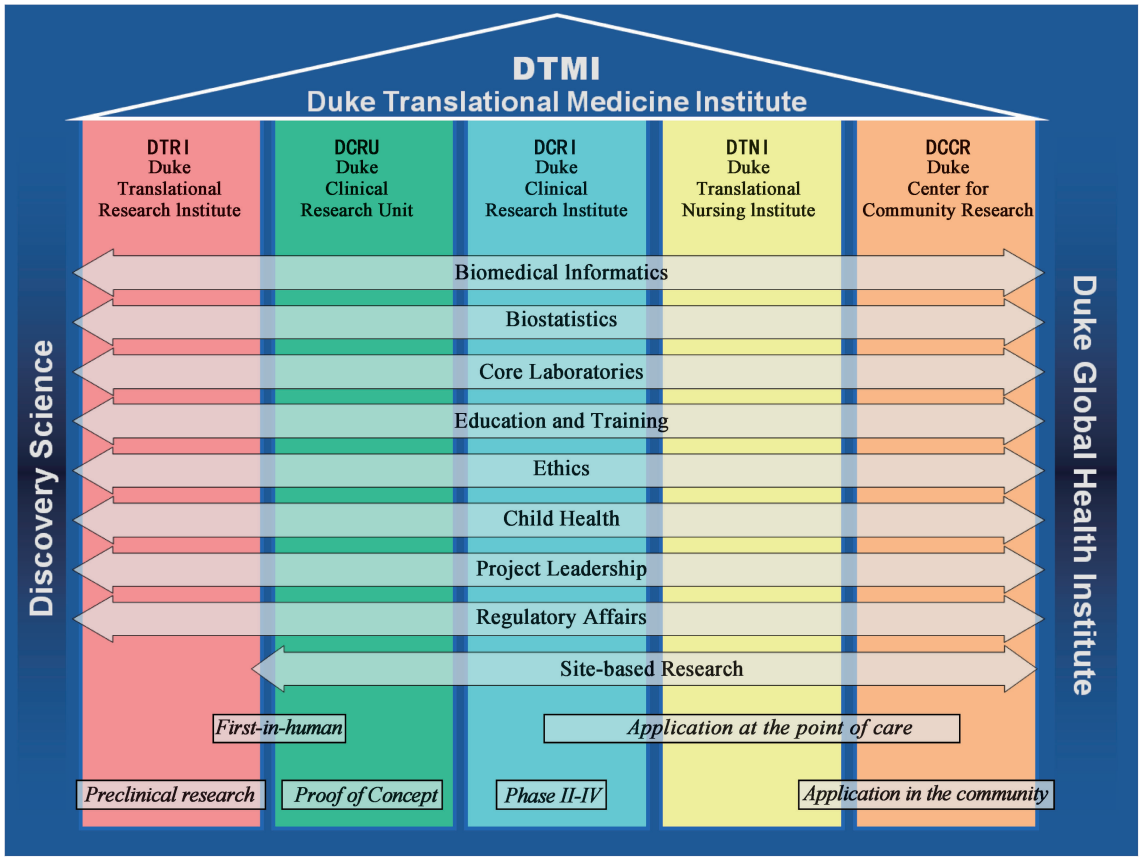

Fig. 1 Framework of DTMI

The DTMI consists of five "pillars": the Duke Translational Research Institute, the Duke Clinical Research Unit, the Duke Clinical Research Institute, the Duke Translational Nursing Institute, and the Duke Center for Community Research. Providing support for each of these pillars are a number of research support core resources. Figure adapted with permission from https://www.dtmi.duke.edu/about-us/organization.

The Duke Translational Research Institute (DTRI) fosters collaborations between basic scientists and clinical researchers to rapidly and effectively invent, develop, and test new drugs, diagnostics, and devices for human use. DTRI supports a variety of specialty technical research cores such as a DNA bank and tissue repository, synthetic organic chemistry, imaging, and proteomics. DTRI currently provides funding to 28 projects to enable Duke investigators to access these specialty core services to address specific questions in their translational research projects.

The Duke Clinical Research Unit (DCRU) provides infrastructure support to sponsors and investigators for early phase and proof-of-concept research studies, including testing new drug candidates and other cutting-edge therapies and seeking to identify and validate novel biomarkers. DCRU has a 13 000 – square-foot pediatric unit featuring 16 beds, and a 17 000 – square-foot adult unit including 30 beds. The DCRU has experience across therapeutic areas and pulls from the broad expertise of Duke's translational faculty.

The Duke Clinical Research Institute (DCRI) is the largest academic research organization (ARO) in the world and coordinates global multicenter clinical trials and outcomes research, integrating the expertise of a premier academic medical center with the operational capabilities of a full service contract research organization. The DCRI is known for conducting groundbreaking multinational clinical trials, managing major national patient regis-

tries, and performing landmark outcomes research. DCRI research spans multiple disciplines, from pediatrics to geriatrics, primary care to subspecialty medicine, and genomics to proteomics. The DCRI currently has 1 100 employees, of whom 224 are faculty[1]. The DCRI enlists more than 5 000 investigators in 3 592 sites over 64 countries to carry out scientific investigations. DCRI has completed more than 730 phase I-IV clinical trials, registries, and outcomes and economic studies, enrolled over 1 127 000 patients [1, 7] (Fig. 2). The DCRI has published more than 5 500 publications in peer-reviewed journals, of which about 20% were high impact [1] (Fig. 3).

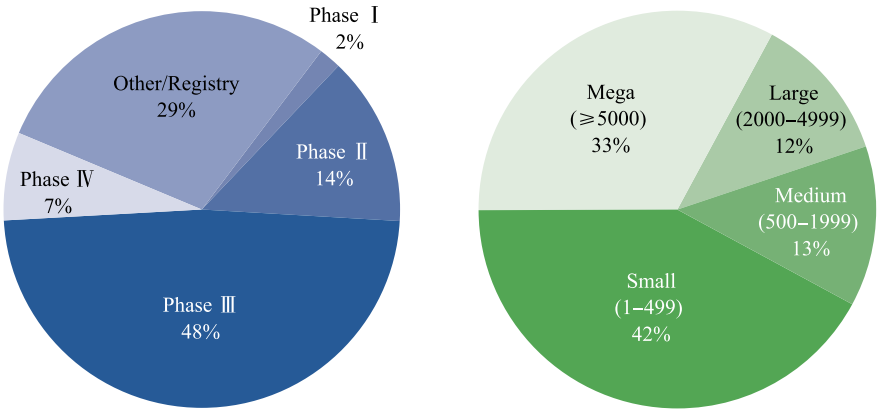

Fig. 2 Trials experience of Duke Clinical Research Institute by phase and size

The DCRI conducts trials in all phases, predominantly phase III. In terms of size, about 45% are registrations over 2000. The data were adapted with permission from DCRI annual report (2010) [1]

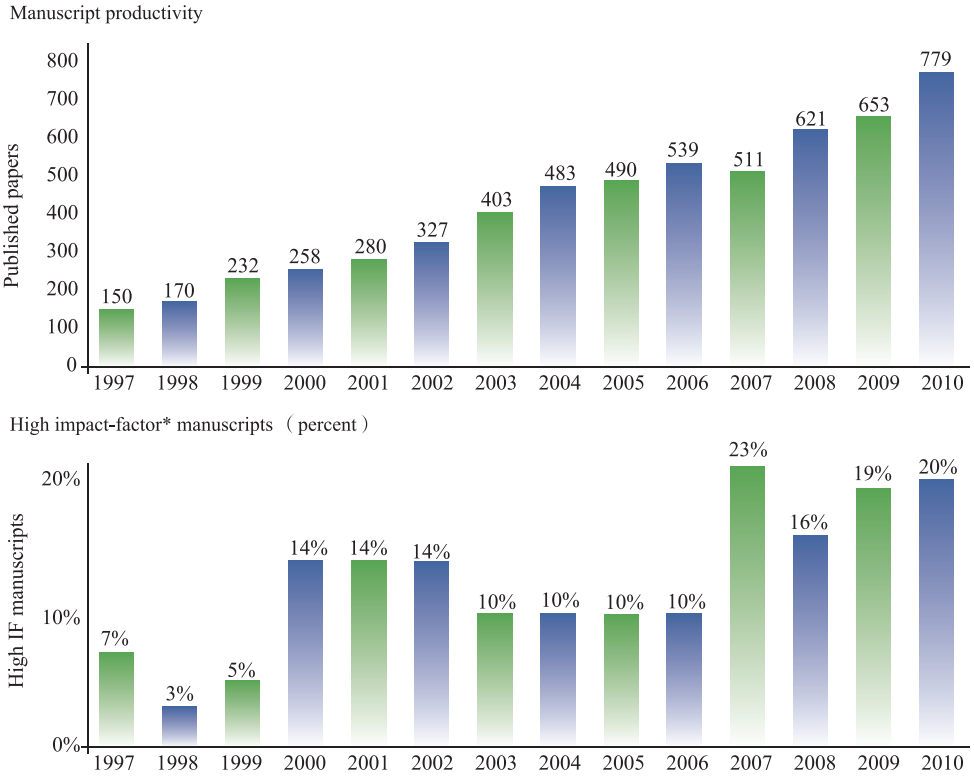

Fig. 3 Publications of Duke Clinical Research Institute

The DCRI published a great number of research articles on trials, about 20% of which were with high impact factors. The data were adapted with permission from DCRI annual report (2010) [1]. *Manuscripts published in journals with an impact factor greater than 10.0 (<2% of all indexed journals).

Building on over 40 years of experience in innovative approaches to analyze the impact of various therapies on patient outcomes, the ARO offers full clinical trial services as well as substantial resources dedicated to outcomes research and assessments, clinical database design and management, and medical education [7].

The model of ARO at Duke thrives on a direct connection between the outcomes and the patient's bedside, as study results change clinical practice and new clinical methods improve patients' results, stimulating more scientific concepts to turn into protocols and restart the cyclical process. Independent interpretation of study results offers additional credibility [7].

The Duke Translational Nursing Institute focuses on generating evidence at the point of care and fostering the implementation and adoption of effective practices across the continuum of care delivery. The DTNI addresses key scientific activities facilitating the transfer of knowledge into clinical application.

The Duke Center for Community Research (DCCR) fosters engagement among community members, agencies, practices, and academicians in order to transform research and practice, and demonstrably improve the health of our community [4]. The DCCR works with communities to better understand their concerns, and to find ways to move proven technologies and therapies more quickly out into community practice so that they improve health, especially of under-represented minorities. The DCCR leverages the talent of the academic research community to collaboratively create a training, research, and liaison system that will effectively and systematically involve the community in clinical and translational research training, priority setting, participation, and follow-up [4,6].

The Duke Global Health Institute (DGHI) was established in 2006 to reduce health inequalities locally and internationally[4]. Recognizing that many global health problems stem from economic, social, environmental, political, and health care inequalities, DGHI brings together interdisciplinary teams to solve complex health problems and to train the next generation of global health scholars [8]. The DGHI has collaborations with many countries in the world, such as Mexico, Haiti, Kenya, Tanzania , Sri Lanka, India, Singapore [9], Thailand, and China. The DGHI aims to become a world-recognized authority in global health and to make significant contributions to the prevention and treatment of health problems, thereby reducing health disparities in vulnerable and underserved populations around the world.

3 DTMI core resources

The DTMI provides supporting infrastructure as core resources to the investigators in the Institute[5].

The Biomedical Informatics Core empowers investigators to be leaders in the impending global effort to redefine human disease by using combined clinical and molecular profiling and to measure changes in health status across multiple dimensions as a routine function of biomedical informatics. The core provides systems and platforms to accelerate the translation of research, methodological developments, and clinical data query and standard.

The Biostatistics Core provides services and training in biostatistics and computational biology. Biostatistics is becoming increasingly important in medical research, training, and in the translation of research findings into practice, as the practice of medicine becomes increasingly evidence-based and the wealth of information within medical and genomic databases grows dramatically. The Core includes a team of statistical faculty and staff with diverse and extensive experience in the design, conduct, and analysis of clinical trials and other biomedical research projects. The core provides consultation and assistance with statistical issues in the design and analysis of research projects.

The Regulatory Affairs Core provides leadership and facile infrastructure support for investigators specially designed to accelerate the pace of translational research projects while protecting the quality and integrity of the research process and the safety of human subjects. The core provides strategic program development, investigational new drug (IND) and investigational device exemption (IDE) preparation and maintenance support, regulatory program development and maintenance, and training.

The Research Ethics Core identifies ethical, legal, and policy issues encountered in carrying out clinical translational science and applies that science in practice, as well as identifies options to address those issues. The Core provides education to the research community about ethical issues in research and conducts empirical, hypothesis-driven studies on research ethics.

The Training and Education Core supports the development of the next generation of interdisciplinary research leaders. It recognizes the need to create a smoother continuum of clinical and translational research education that spans pre-doctoral years to the crucial early faculty years and incorporates training that facilitates translation of basic and clinical sciences discoveries to the bedside and to the clinic[5].

The Child Health Research Core provides support to pediatric clinical and translational research to make evidence-based therapeutics available to children.

4 The cycle of translational medicine

The DTMI has developed a model, the cycle of quality, from generating evidence to inform policy (Fig. 4) [5, 10]. In this model, the discovery of fundamental biological, physical, and social constructs are conducted by scientists based on their scientific curiosity rather than an externally planned direction. Once a discovery is made, it undergoes a development cycle including extensive preclinical applied research before it can be developed as a treatment with plausible human benefit. The early translational steps are critical in promoting the bench-to-bedside translation, since the laboratory discoveries are often tested in limited situations such as in simple systems, either cell or animal models, without determining toxicity or "off-target" effects. Therefore, quality of discovery limits the translation from the laboratory to human studies. Upon entering clinical studies, evidence is gathered in human experiments, and assessments are made about the intervention's value. These evaluations continue after the treatment is clinically available [10].

The human trial system must be improved, since some of the current trial enterprises lack common standards and adequate infrastructure in academe for developing and maintaining an intellectual discipline. Clinical practice guidelines have evolved as the prevalent mode for defining professional standards for disease prevention and management. When findings from these guidelines reach a level of definitive evidence in a quantifiable context, the guidelines can be translated into performance measures that are then used to quantify the degree to which best practices are followed by practitioners, practices, hospitals, health systems, communities, or countries[10]. The final outcomes feedback to scientific discovery.

In a recent article, the leaders of the Duke Health System and the DTMI emphasized the importance of academic health science centers (AHSCs) to improve health locally and globally[11]. The discovery-care continuum represents such a pathway, in which scientific discovery can be put into practice to improve patient care [11] (Fig. 5A). To achieve transformation, two distinct translational gaps must be overcome. The first is the gap between a scientific discovery and its clinical translation (from bench to bedside); the second is the gap between expert acceptance of the application and its broad adoption in practice by local and global communities (from bedside to population) [11, 12]. The old model of medical research is fragmented, both internally and among their external partners (Fig. 5B). Each institution has its own incentives, which are often not aligned, resulting in inefficient systems of research, health-care delivery, and finance. An experiment in organizational transformation is in progress at Duke Medicine, which has aligned research and care delivery by developing a matrix organization and establishing inter-related institutes, including the Duke Translational Medicine Institute and the Duke Global Health Institute[11] (Fig. 5C). These flexible systems bridge translational gaps and encourage propagation of several types of knowledge along the discovery-care continuum.

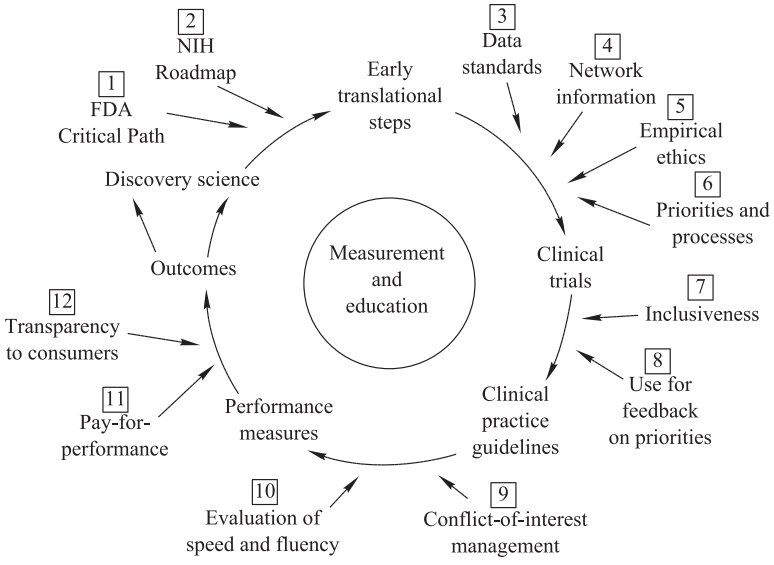

Fig. 4 The cycle of translational medicine

The figure depicts the steps from early scientific discovery, early translational steps, feeding into clinical trails, suggestions of clinical practice guidelines, accountability measures, and the final outcomes feedback to scientific discovery. Figure adapted with permission from Reference [10].

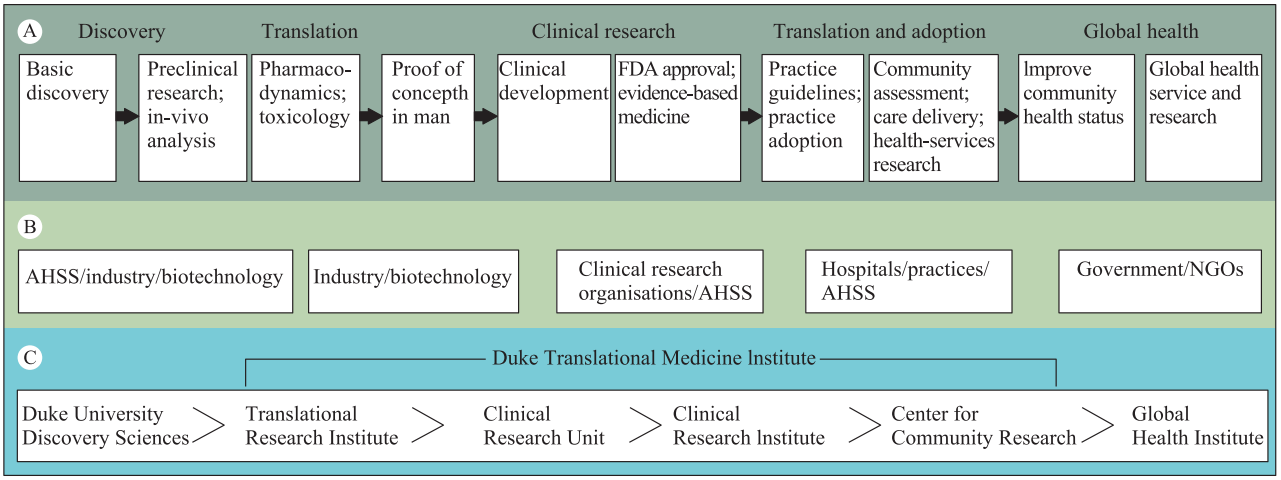

Fig. 5 Academic health science systems as integrator

(A) The discovery-care continuum, including discovery science, preclinical and clinical research, adoption in practice, and global uptake; (B) current fragmented organizational structure of the clinical research enterprise; (C) Duke Medicine model: a continuous, intercommunicated discovery-care model. FDA, US Food and Drug Administration. AHSS, Academic health science systems. NGOs, non-governmental organizations. Figure adapted with permission from Reference [11].

5 Integrated model of academic health science systems (AHSS)

Recently, Duke Medicine leadership emphasized the evolution of the academic health science centers (AHSCs) further into academic health science systems (AHSSs) [11]. AHSC is defined as a specific location where patients receive care (e. g., a medical campus), whereas AHSSs are thought of as integrated health-care delivery systems that not only include the traditional medical centre but also a network of community hospitals and practices[11, 13]. AHSCs play an important role in improving health locally and globally while also supporting economic development in the USA as well as the other countries. However, AHSCs should create not only novel drugs, devices, and other technologies, but also new ways of deploying broad, inexpensive preventive and treatment strategies among populations. AHSCs are ideally poised to become system integrators that are capable of bridging these translational gaps, thereby greatly reducing delays and inefficiencies between discovery and global adoption. These system integrators do not replace industry or non-academic providers; rather, they improve the capacity to develop and deliver new treatments by filling the spaces between academic discovery, science, industry, and the general health care delivery system. Dr. Dzau (Duke Medicine CEO) and Dr. Califf (DTMI director) at Duke championed the establishment of AHSSs[11,13]. AHSS should meet global challenges through planning, engagement, and innovation that combine traditional academic activities with entrepreneurial approaches to health care delivery, research, and education, including international public-private partnerships.

Duke Medicine includes the Duke University Schools of Medicine and Nursing, the Duke University Health System (Duke University Hospital, Duke Raleigh Hospital, Durham Regional Hospital, Duke Clinic, and Duke Children's Hospital and Health Center), and related organizations[14]. To transform health care, Duke evolves AHSC further into an academic health science system (AHSS) [11, 13]. According to this model, care delivery at AHSSs should be vertically integrated to develop a continuum from community care to tertiary care, helped by effective clinical information systems (Fig. 6). Ideally, each AHSS has missions, resources, and standards that are shared by the system to improve the way in which it helps patients and communities[11]. To catalyze the needed transformation, AHSSs focus on organizational structures, external partnerships, research translation, models of care delivery, new educational models, and information technology. As AHSSs develop, effective communication and collaboration with external stakeholders increases in importance. AHSSs should engage in flexible arrangements, including public-private partnerships and the strategic cultivation of external resources[11,15]. Partnerships should focus on filling specific gaps and should cross geographic and functional boundaries.

Many barriers exist to the creation and implementation of effective integrated care models[12, 16]. AHSSs will need to work with communities to support program development, implementation, assessment, and dissemination to overcome such barriers. Despite these challenges, promising examples of innovative care models exist. Through partnerships with the state of North Carolina and

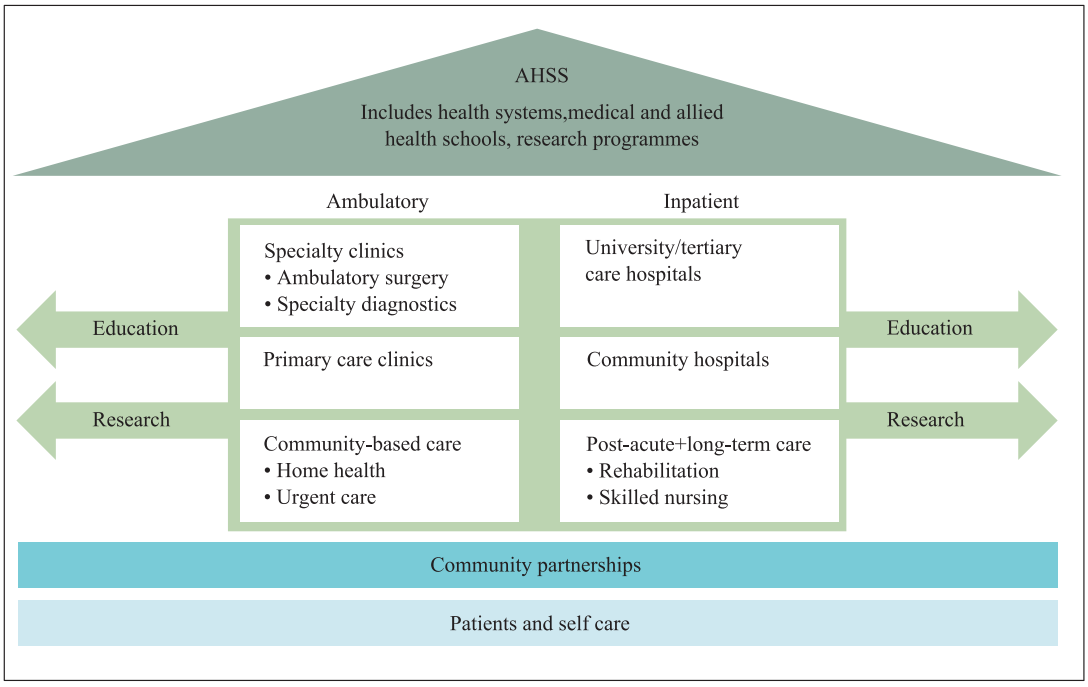

Fig. 6 Framework of AHSS

Academic health sciences system (AHSS) as a vertically integrated care-delivery system. Figure adapted with permission from Reference [11].

various community groups, Duke Medicine currently participates in a primary-care case management program (Community Care of North Carolina) that resulted in substantial Medicaid savings for the state of North Carolina and the Federal government, and has created a home-based care program for at-risk elderly people, reducing inpatient expenses for participants by 68% while improving health outcomes[11]. In addition to Duke Medicine, several AHSSs have expanded their presence in the global medicine programs[13]. However, one should recognize that there are risks associated with global medicine activities on financial, organizational, political, legal, and reputation levels[13]. To minimize these risks, the mission should be stayed focused, and durable partnerships between public and private sectors should be actively engaged.

6 Duke and China

The Duke model has gone through from simple sample banks and clinical databases to today's whole blooming academic health science system to integrate all the interested parties in the discovery, care provider, policy making, and elimination of disparities in the world. This has provides an example from which many health system can learn. In China, the talk of translational medicine has just started. To provide quality care to the one-sixth of the world population, China has long way to go to transform her health system, and China's health systems can learn from Duke's experience. On the other hand, the medical education and health care system are very different from those in the US [17]. China must adapt to the new way to transform the systems to achieve these goals.

7 Conclusions

With 40 years of excellence in clinical research, Duke Medicine now champions the integrated academic health science system. The establishment of DTMI has set an example that medical research, care delivery, and global health can be integrated into one system. The system aims to bridge translational gaps between basic science researchers and clinicians, academe and industry, health care system and community, wealthy and less-developed nations. One important consequence of DTMI's work is that the boundaries among organizations conducting research become blurred. Great translational research requires talented people, but true success comes from teamwork in which the value of individual contributions is enhanced and multiplied through collaboration and the pursuit of shared goals. We hope that the DTMI can be modeled in China.

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