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Global Health Pathology Research: Purpose and Funding

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SYNOPSIS

Like in all areas of science, it is important for funders and investigators of pathology to work together to develop a well-designed, well-executed clinical research agenda. In the first section of this chapter, we discuss how the NIH peer-review process applies to global health pathology research projects. Then, we present an illustrative sampling of NIH funded projects with performance sites in low and middle-income countries with two examples focused on cancer and anatomic pathology. Finally, we relate the research agenda to overarching strategic recommendations for enhancing global pathology.

Keywords

Pathologist; global health; cancer research; funders; accurate diagnosis

Introduction

Peer reviewed research funding is highly competitive: it is incumbent upon the investigators to demonstrate the value, relevance, and impact of their proposals. At present, the practice of both pathology and global health are evolving rapidly. Funders and investigators need to work together to define a well-designed, well-executed clinical research agenda that will

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DISCLOSURE STATEMENT

All authors work for the National Cancer Institute

generate a sustainable, powerful field of clinical research. Pathology clinical practice ranges from laboratory medicine to anatomic pathology, microbiology, transfusion medicine, and molecular diagnostics. In this era of precision medicine, diagnostic pathology plays a pivotal role in accrual to clinical trials. Areas of research include basic biological investigation through translation of current automated tests to new practice settings.

Pathologists become interested in global health for a variety of reasons, and perusal of the table of contents of this volume demonstrates their range of motivation. These include altruistic volunteerism, education of the next generation of practitioners, sampling a comprehensive cross-section of human genetic diversity, and acquiring biospecimens for basic research. Likewise, funders of global health have varying priorities. These priorities range from investigation of basic biology to scaling interventions that will reach the world's most disadvantaged citizens. It is beyond the scope of this chapter to debate the relative value of these underlying motivations – in fact there is value in each of these approaches. The goal here is to improve communications among all interested parties to generate the evidence needed to advance our understanding of human biology and to improve the human condition.

The Center for Global Health¹ (CGH) of the National Cancer Institute² (NCI) at the National Institutes of Health³ (NIH) was formed in 2011 to catalyze global cancer research. CGH addresses the NCI's commitment to strengthen global cancer research, build a global cancer research community, and foster the translation of research results into practice. From CGH's inception, pathology and laboratory medicine have played a pivotal role in global clinical research by contributing to an accurate diagnosis, monitoring the effects of therapy; and providing precise input into disease surveillance systems⁴. Over the past five years, the center has supported the intersection of pathology and global cancer research in many ways. CGH has funded grants, contracts, and supplements to support new and enhanced diagnostic technologies. Additionally, CGH has supported training the next generation of practitioners, hosted strategic planning sessions for pathology, and held workshops to increase the profile of pathology practice in low resource settings.

This chapter summarizes our experience to date and outlines future directions for pathology research. The NIH has a long history of working with the scientific community to generate funding announcements and many of the 27 NIH Institutes and Centers pursue international projects. Peer reviewers use a well-defined set of criteria to work together to identify meritorious proposals.

- **Section I** will discuss how the NIH peer-review process applies to global health pathology research projects.
- **Section II** will present an illustrative sampling of NIH funded projects with performance sites in low and middle-income countries (LMIC's) with two examples focused on cancer and anatomic pathology.
- **Section III** will relate the research agenda to overarching strategic recommendations for enhancing global pathology.

Section I: Applying NIH review criteria to global pathology research

Performing research in international settings presents many opportunities for ingenuity. Access to facilities, equipment, communications, information technology, supplies, support staff, ethics review boards, demographic data, vital registration data, and baseline epidemiologic information can be challenging. Inclusive, intellectual partnerships among high income country (HIC) investigators and those working in local LMIC communities can not only address these challenges but can also refine and improve scientific hypotheses and assure relevance to local patient populations. For example, CGH funded a partnership of Tanzanian and U.S. investigators to document the high burden of esophageal cancer. Pathologists, epidemiologists, and clinicians worked together to elucidate geographical biological variation of esophageal cancer in East Africa. This collaboration has generated new hypotheses on disease causation⁵.

Many funders, including the NIH, have predominantly domestic mandates. Agency leaders ask, “why not do this study in your home setting?”. Experienced global health researchers must pre-empt this question. Credible rationales focus on the scientific question being asked. For example, is there a higher burden of an uncommon disease; are there rare genetic variants or environmental exposures that warrant conducting research outside the US. Although social justice, humanitarian need, and interest in foreign locale are all motivations for individual global health engagement, the NIH responds to clear, convincing, scientific rationale for working in any population, foreign or domestic. It is the responsibility of the investigator to effectively justify why the research project should be based at a foreign site. All NIH funding announcements include five major review criteria: significance, investigators, innovation, approach, and environment. Meritorious applicants weave their structured justification for working internationally into these established review criteria.

1. Significance

There must be a scientific premise driving the proposal. Testing the premise should lead to new scientific knowledge, new technical capacity, and/or impact clinical practice. It is important to relate the proposed study to the purpose of the funding opportunity described in the purpose and background sections of the Funding Opportunity Announcement (FOA). Table 1 highlights examples of significance statements from NIH FOAs in various topic areas.

Please note that the above funding announcements involve broad areas of science. The following comments highlight how pathology fits into these topic areas.

- **Research Training:** The Fogarty International Center¹¹ is the major source of research training support for LMICs. Fogarty priorities have included medical education for primary practitioners, educators, and for both international and domestic junior researchers. To date, pathologist participation has been infrequent.
- **Research Capacity:** FOA’s specifically addressing research capacity such as Planning for Regional Centers Excellence in Non-Communicable Diseases in LMIC’s (RFA-CA-15-007)⁷ are relatively uncommon. While this announcement

specifically mentions accurate diagnosis, most funding announcements address specific scientific questions.

- **Biological Questions:** Accurate tissue diagnosis is needed in many studies performed in global settings. Scientific reasons for studying populations in low resource settings include variations in disease epidemiology by geography, population genetics, differing exposures and risk factor burden. Sampling human genetic diversity enables investigators to study rare diseases and to identify new genetic drivers. Some investigations require patient populations naïve to current treatments or with higher burdens of advanced disease.
- **New Technologies:** There is interest in developing innovative, frugal technologies for diagnosing and monitoring diseases. Given the high performance of current pathology practice in the U.S. and a reluctance to streamline practice unless the highest standards of diagnostic accuracy can be met or exceeded, it is sometimes necessary to test new devices or strategies in lower resource settings. Ethical considerations related to trials in LMIC's are addressed in good clinical practice guidelines and there is a growing experience in performing trials in these settings¹². An example of this type of program is the NCI program "Cancer Detection, Diagnosis, and Treatment Technologies for Global Health (UH2/UH3) (RFA-CA-15-001)⁹.
- **Health systems, scalability of interventions, and program science:** International policy makers need data to establish norms and standards. Some funders concentrate on bringing interventions to scale for underserved populations. Demonstrated best practices are needed by all parties interested in advancing global health. Evidence is needed on cost effectiveness, affordability, integration of systems, and improving communication and coordination of effort in both research and clinical care. Funders concentrating on scaling programs are reluctant to invest in extensive research data acquisition. Well-conducted research studies can indicate a narrower set of key performance indicators of quality, process indicators to monitor efficiency, and most importantly, metrics to assess the impact of the outcome. Implementation science research is a systematic tool to assess multidimensional interventions and can be a highly effective way to translate scientific evidence into practice (Figure 1). Pathologists can play a key role in designing systems and assessing impact in this field.

2. Investigator(s)

Principal Investigators, collaborators and other researchers must have the skills, knowledge, and resources necessary to carry out the proposed research project¹⁴. Pathologists most-often contribute to basic science research by developing and applying leading-edge technology to diagnostics¹⁵ and by joining a team of investigators with complementary expertise. Successful clinical research projects are aligned with other medical services and ongoing patient care.

Team science is clearly a trend in the performance of research. Working across geography, cultures, and economic resources adds an additional dimension to team work. Inclusion of

experienced global health practitioners on the research team improves the likelihood of successful research project completion. Furthermore, these investigators are familiar with the scientific needs of the local community and have earned the trust of the local population. Pairing investigators from LMIC's with those from greater resourced universities is increasingly prevalent. It can be an explicit requirement, such as in the NCI RCRE Program⁷, or it can often be part of the training mission of the academic partners¹⁶. Fulfilling partnerships between paired investigators are built on clear, agreed on, upfront expectations of benefit, such as publications, presentations, and future collaborative grant applications¹⁷. Furthermore, mutually fulfilling partnerships include clear delineations of budgetary and other in-kind resource control¹⁷. Full participation of international investigators enables research to advance more quickly and is to the long-term advantage of all.

A clearly reasoned approach to leadership, governance, and organizational structure is a crucial element of peer review for complex projects. Study sections reviewing global health projects are particularly careful to look for evidence of the scientific productivity among the proposed partners. Meritorious applications specify realistic governance structures including strategies for dealing with differing expectations of co-investigators.

3. Innovation

Meritorious applications challenge current paradigms in research or practice. In our experience, grading innovation in global health FOA's has been challenging for peer reviewers and reaching consensus has engendered some debate. Proposals based on performance of current pathology techniques in new settings are not sufficiently innovative. Global Health Pathology Research must include making new connections and applying novel solutions to existing problems. Applying current methodology to an LMIC setting in and of itself is insufficient. Innovation related to new techniques or instrumentation may be apparent to reviewers, but innovation based on translating known interventions to new settings must be clearly justified by the applicant. The Center for Translational Science at the National Heart Lung and Blood Institute¹⁸ addresses these issues in implementation science by sponsoring workshops and has released a translational science FOA, T4 Translational Research Capacity Building Initiative in Low Income Countries (TREIN) (U24) (RFA-HL-17-003)¹⁹. Again, this support is relatively uncommon.

4. Approach

Addressing potential problems, proposing alternative strategies, and offering benchmarks of success are all required elements of successful applications, domestic or international. Peer reviewers and funders are attentive to the pitfalls of working abroad and expect a premeditated plan to deal with not only scientifically warranted adjustments but also the realities of logistics, politics, and environment on research programs. The anticipated duration of a research project influences risk assessment of possible delays. Such delays need to be weighed when measuring the duration of the project, current financing, and the anticipated start of follow-on programs.

5. Environment

Environment includes both scientific and physical resources favoring success. Institutional support, partnership strengths, and access to facilities are usual elements. Importantly, unique features of the scientific environment including subject populations and collaborative partnerships can be emphasized. The NCI's Regional Centers of Research Excellence RFA announcement included several cues investigators should consider when preparing applications with international components. These prompts include:

- Will the scientific environment in which the work will be done contribute to the probability of success?
- Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed?
- Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?
- How will the institutional support contribute to the success of the RCRE planning grant?⁷

Additionally, the NCI-designated Cancer Centers Program is a signature program of the US NCI. The physical space supported by these Centers is described here:

Physical Space: Centers are more successful in establishing an identity if they have a distinct physical location. Not all members of the Cancer Center need be physically located in facilities controlled exclusively by the Center; however, location of members across program areas (basic laboratory; clinical; and prevention, control, and population-based science) in close physical proximity enhances shared use of resources and facilitates scientific interactions. Even if proximity is impossible, Center shared resources and other services should still be reasonably accessible to all members, including consortium members.

In your application, briefly describe the physical facilities dedicated to cancer research, Center shared resources, and administration. Indicate how the Center facilitates access to shared resources and other services (i.e., Clinical Protocol and Data Management). Discuss any plans for expansion.²⁰

Having reviewed scoring methodology, Section II will review a sample of currently funded NIH research.

Section II: Landscape of NIH Funded Global Pathology Research in LMIC's

1. Overview of Global health programs and Partnerships

As reviewed in the previous section, there are many reasons for US universities to expand their portfolios and conduct research in low and middle income countries. Establishing efficient, equitable, and sustainable partnerships with international institutions is essential to the production of the best science in LMICs⁴. In 2016, the Center for Strategic and International Studies (CSIS) conducted a study of the global health partnerships of 82 North American Universities and 44 international partnering institutions. The goal of this study

was to examine the benefits and characteristics of successful partnerships²¹. Their data demonstrate that in general, these partnerships were mutually beneficial, and that most partnerships had an equitable arrangement. The largest perceived benefits were seen in education and research. Collaborations among research institutions were the most frequently reported activity among North American universities and international partners.

Academic twinning programs provide a two-way transfer of expertise and skill. For example, when pediatric oncologists in low-resource and high-resource settings are twinned, these teams of committed health care professionals are perfectly poised to develop and implement locally appropriate treatment protocols. Furthermore, all patients have an increased access to treatment. Working together, implementation of locally appropriate protocols and an increased access to care contribute to an overall increase in childhood cancer survival rates²².

For international institutions, partnerships were less successful with respect to health impact, policy development, and advocacy. The data show some unevenness around decision making, lack of bidirectional funding, and publication authorship. In general, the study found that global health partnerships are perceived as beneficial for both North American universities and international institutions.

According to the CSIS survey, funding was one of the most important factors for program success. Research funding can come from many different types of organizations such as universities, government, non-governmental organizations (NGOs), private donors, or foundations. A strength of NIH funding is explicit guidance for budget allocation among investigators and institutions. This alignment of budget, roles, and responsibility allows for transparency and accuracy of task ownership. The survey found that international research agencies such as the NIH was the second most important source of funding for international institutions and was deemed a very important or essential source of funding by the majority of North American universities (Figure 2). Below we examine this relationship in more detail by analyzing the contents of the NIH research portfolio in cancer and anatomic pathology.

2. Portfolio Analysis of NIH funded Cancer Research in LMIC's

The Mission of the US NCI is to coordinate the National Cancer Program. This Program conducts and supports research, training, health information dissemination, and other cancer-related programs. It provides research grants and cooperative agreements to coordinate and support research projects conducted by universities, hospitals, research foundations, and businesses throughout this country and abroad. To enhance survival and improve patients' quality of life requires evidence-based clinical protocols, and the NCI is one of the largest funders of evidence-based clinical research. To illustrate the contribution one dedicated funder can make, we examined the NCI's investment in global cancer research over time.

Figure 3 shows a comprehensive analysis of the NCI-supported extramural research portfolio between FY 2008 and FY 2014. Importantly, the total number of NCI-supported

extramural cancer research projects both domestically and in LMICs remains relatively constant.

The NIH uses three main grant mechanisms to implement its scientific agenda: training, research, and cooperative agreement.

- NIH training grants provide the protected time and research budget for postdoctoral, post-medical, and early-stage faculty members to develop into independent investigators.
- NIH research grants support a discrete, specified, circumscribed project
- NIH cooperative agreements support discrete research projects that are conducted between extramural and intramural NIH researchers and program staff

The sophistication of the research question, the local environment, and the scientific maturity of the investigators all contributes to the choice of grant mechanism. Figure 4 shows the distribution of NCI-supported extramural cancer research projects by World Health Organization (WHO) region.

An example of research conducted as part of a training grant in Africa was a project conducted by Dr. Akwi Asombang, a gastroenterology Fogarty fellow from the Washington University School of Medicine. Fogarty Fellows and Scholars²³ are carefully chosen participants invited to conduct yearlong research projects in low-and middle-income countries. During Dr. Asombang's fellowship in Zambia, she demonstrated that eating fruits and vegetables year-round was protective against gastric cancer. She documented this observation by measuring urinary isoprostanes, which are biomarkers of oxidative stress²⁴.

Research grants addressing specific cancers are a recurring source of global health support when the distribution of malignant neoplasms is not uniform across the country or region. Some diseases such as virally-induced cancers have geographic and environmentally associated incidence patterns. Figure 5 shows the distribution of the NCI-supported extramural research programs in LMICs by anatomic organ site for FY 2008–2014. Research topics include contributions from environmental exposures, infectious agents, and unknown biological variables. As pathologists join global research teams, their expertise in diagnosis and staging will ensure that accurate data is available to advance our understanding of human biology.

3. Portfolio Analysis of NCI Pathology Research in LMIC's

The NCI supports a modest program of pathology-related research specific to LMICs. In 2017, the NCI anticipates supporting approximately 35 pathology-related cancer research projects. These grants run the gamut from etiological studies of gastric cancer to culturally appropriate screening and diagnosis cervical cancer screening programs. Figure 6 shows the distribution of projects by research area.

The distribution of projects shows that there are opportunities to engage in research currently, especially as a member of an investigational team. One of the NCI-supported research projects was designed to improve the pathological diagnosis capabilities of

lymphoproliferative disorders diagnostic at Kamuzu Central Hospital in Lilongwe, Malawi²⁵. Through this joint research project, investigators discovered a high concordance between real-time diagnoses in Malawi and final diagnoses in the United States. This high concordance rate demonstrates the value that strong, local pathology services provide to real-time clinical care and research in LMICs. In the next section, we will discuss how these scientific pursuits help to meet the overarching strategic goals for strengthening global pathology.

Section III: Challenging Pathologists to Think Strategically

All research occurs within a system of scientific investigation, teaching, and patient care delivery. Given the complexity of pathology systems and the many points for improvement suggested in this volume, it is important to relate any proposed investment of time, talent and funds in research to the needs of the larger system. In May of 2016, the NCI convened a group of international experts in pathology and global health to outline a strategy for supporting pathology. At the time, many organizations were engaging in international initiatives in research, clinical instruction, communication, and telepathology. Building on years of advocacy, the first ever Chapter on Pathology in *Disease Control Priorities edition 3*²⁶ was in preparation, the WHO Geneva was preparing *Priority Medical Devices for Cancer Management*²⁷ including equipment standards for pathology labs, the International Committee on Cancer Reporting was increasing the availability of evidence based synoptic reporting²⁸ and the NCI had funded several new contracts and grants specific to pathology in LMICs. The experts' recommendations fell into broad categories. They are summarized below with remarks pertinent to the research agenda.

Leadership

Historically, high impact medical institutions from high income countries have developed a triad of research, teaching, and clinical care. The concentration of medical skills, scientific investigation, and a significant number of trainees has led to increased system productivity. Internationally, medical schools are often smaller with fewer faculty members and limited research capacity. An engaged research community can strengthen these institutions and as discussed, pathology is a key component of research and quality care.

Advocacy

Specific to pathology, evidence of improved clinical outcome related to accurate diagnosis and careful patient laboratory monitoring is needed. Pathology and laboratory medicine are longstanding foundational elements of medical practice in the U.S. and Europe and many components predate rigorous cost effectiveness analysis. Introduction of "best buy" medical interventions in developing countries as guided by the WHO and international funders require more specific data on patient impact and cost related epidemiological measures such as disability adjusted life years²⁹. Beyond documenting an economic case for current pathology practice, investigating pathways to streamline diagnosis and to measure the relationship between precision and efficiency are of interest to clinicians, public health practitioners, and policy makers in both high resource settings as well as LMICs.

Training and Education

Producing more investigators and scientifically prepared clinicians is of immediate importance to pathologists. Research in optimizing workforce development is an area of applied research widely appreciated in the global health community. An important part of systems research is identifying efficiencies in task shifting, task sharing, and supporting optimal performance of practitioners dependent on data generated by pathologist and clinical laboratories.

Quality Assurance and Communication

Improving access to data both for research and clinical care is an area of interest in all settings, independent of income. Standardizing descriptive language, establishing interoperability of databases, and making information accessible to clinicians, investigators and policy makers is a shared priority. Including performance improvement in data management at the level of laboratory information systems, clinical medical records, and surveillance systems such as cancer registries offers opportunities to demonstrate the key role of pathologists in collaborative endeavors.

Technology Development and Translation

The Affordable Cancer Technology program for LMICs³⁰ is the largest funded portfolio within the Center for Global health, NCI. The explosion of point of care technology, such as molecular diagnosis using lateral flow devices and rapid evolution of genomic precision medicine are alluring areas for investigators hoping to bring new tools to address LMIC disease burden. The involvement of experienced pathologists in developing and implementing these tools in clinical practice is self-evident.

Experienced pathologists, especially those with field experience in lower resource settings, also remind us “to look before you leapfrog” [Modupe Kuti, personal communications] since new technology can have unintended consequences and translation to new practice environments and new populations is often more challenging than predicted by the prototyping experience. Pathologists have an important role both as investigators and clinical practitioners in validating new technologies and judging their suitability to local practice needs. The combination of technical expertise and clinical judgement is paramount in guiding changes in practice; involvement in all phases of technology development and translation to human use is perhaps the greatest responsibility of a pathologist.

Conclusion: Pathologists and the path to an era of accurate diagnosis and evidence based care in LMICs

Pathologists have made great progress in educating investigators, clinicians, and patients on the importance of correct diagnosis and monitoring data. Given the complexity of modern research and care, the demand for accuracy will only increase. Pathologists are fundamentally positioned to contribute to basic biological knowledge, to increasing accurate and efficient diagnostics, to enhance cost effective practice, and to shape healthcare policy. The opportunities found in the developing world should be regarded as new windows to formulate provocative questions and to address the burden of disease for all the world's

population. Innovative research by pathologists can add to progress in global health by embedding accurate diagnosis and precise lab monitoring as a cornerstone of scientific research and practice.

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KEY POINTS

- Pathologists are fundamentally positioned to contribute to basic biological knowledge, to increasing accurate and efficient diagnostics, to enhance cost effective practice, and to shape healthcare policy.
- Scientific rationales for international research projects include: the local preponderance of disease, rare genetic variants, and/or unique environmental exposures. Well-conducted research studies include performance indicators to monitor quality, efficiency, and impact. Peer reviewers expect a deliberate plan to accommodate the realities of conducting international research.
- Improved communications among researchers and funders will help generate the evidence needed to advance our understanding of human biology and improve the human condition.
- Pathologists should think strategically about how their investigations fit into a larger agenda to address the needs of the health system.

Figure 1. Getting from Scientific Evidence to Public Health Practice: Role of Implementation Science Research. *From* Sivaram S, Sanchez MA, Rimer BK, et al. Implementation science in cancer prevention and control: a framework for research and programs in low and middle-income countries. *Cancer Epidemiology, Biomarkers & Prevention* 2014;23(11):2273–2284; with permission.

Figure 2.

Importance of various funding sources (North American academic institution survey). *From* Muir JA, Farley J, Osterman A, et al. Global Health Programs and Partnerships: Evidence of Mutual Benefit and Equity. *A Report of the CSIS Global Health Policy Center*. March 2016. Available at: https://csis-prod.s3.amazonaws.com/s3fs-public/publication/160315_Muir_GlobalHealthPrograms_Web.pdf; with permission.

Figure 3.
NCI Supported Extramural Research, FY 2008 – 2014

Figure 4.
NCI-supported extramural research projects by WHO region

Figure 5.
NCI Supported extramural research by anatomic organ site for LMICs for FY 2008–2014,
projects can be coded for more than one organ site

Figure 6. NCI supported research related to pathology in 2017, by research area

Table 1

Significance statements from select NIH FOAs

FOA	Topic	Significance
PAR-16-279 “Fogarty HIV Research Training Program for Low-and Middle-Income Country Institutions (D43)” ⁶	Research Training	“Over the years, some of the most important recent scientific advances in HIV/AIDS... have been facilitated through partnerships with LMIC scientists. Many of these partnerships have been supported by the FIC research training programs. Continued investment in training strengthens research at LMIC institutions and addresses the ongoing HIV epidemic. FIC research training programs are part of the solution to achieve an ‘AIDS-Free Generation.’”
RFA-CA-15-007 – “Planning for Regional Centers of Research Excellence in Non-communicable Diseases in Low and Middle Income Countries” ⁷	Research Capacity	“Many region of the world have untapped potential and research capabilities. To develop a plan that will coordinate the basic, translational, clinical, and population science research for Non-Communicable Diseases (NCDs) in these regions will generate the evidence needed to advance our understanding of human biology.”
PAR-15-093 – “Basic Cancer Research in Cancer Health Disparities (R01)” ⁸	Biological Questions	“These research project grants will support innovative studies designed to investigate biological/genetic bases of cancer disparities”
RFA-CA-15-001 – “Cancer Detection, Diagnosis, and Treatment Technologies for Global Health (UH2/UH3)” ⁹	New Technologies	“To conduct projects that adapt, apply, and validate existing or emerging technologies into a new generation of user-friendly, low-cost devices. To develop assays that are clinically comparable to currently used technologies for imaging, in vitro detection/diagnosis, prevention or treatment of cancers in humans living in LMICs.”
PAR-16-238 – “Dissemination and Implementation Research in Health (R01)” ¹⁰	Health Systems, Scalability of Intervention, and program science	“To identify, develop, test, evaluate and/or refine strategies to disseminate and implement evidence-based practices (e.g. behavioral interventions; prevention, early detection, diagnostic, treatment and disease management interventions; quality improvement programs) into public health, clinical practice, and community settings.”