Generating Knowledge from Best Care:
Advancing the Continuously Learning Health System

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In this Perspective, the authors aim to facilitate the growth of learning health environments by highlighting strategies and examples of operational and research collaborations within delivery system settings in the United States. Informed by empirical data, conceptual literature, and authors' experiences, the paper explores barriers to successful research and operational collaborations within the current health care context, as well as strategies that various health systems have used to move further toward the goal of continuous learning.

Specifically, the authors highlight activities by the National Academy of Medicine (NAM) (1) and the Patient-Centered Outcomes Research Institute (PCORI) to engage various stakeholders, specifically health executives, in the evidence-generation process; present an overview of collaborative activities that have resulted from these initiatives, including the findings from two research projects designed explicitly to explore the priorities, decisions, and analytic needs facing health executives at the delivery-system level as they consider further transitioning to a learning health system; and finally offer a series of priorities for actions (see Box 1) and corresponding case examples, to demonstrate strategies for generating knowledge from care. While all types of research are essential to continuous learning, this Perspective focuses on those evidence-generating activities that are designed explicitly to be conducted within the care delivery system, embedded within the practice of routine care, and whose findings are used to impact the clinical enterprise.

It is the authors' intention that this paper will add to the emerging body of knowledge around learning health systems while also serving as an actionable blueprint for institutions interested in transforming to a continuously learning system.

An Opportunity for Collaboration

In 2014, operational leaders in Kaiser Permanente (KP) Colorado resolved to reduce missed appointments in their primary care clinics. While these leaders considered simply initiating telephone and text-message reminders throughout the delivery system, KP's commitment to evidence-based practice led them to collaborate with researchers from their organization to implement a strategy that could simultaneously meet operational need, improve quality, and lead to generalizable knowledge. They initially randomized patients to receive, or not to receive, telephone and text-message reminders at 1 of their 27 primary care clinics and then

PAPER CONTENT OVERVIEW

replicated the randomized intervention at a second clinic. In both the pilot and replication sites, rates of missed appointments declined significantly, while appointment cancellations increased. The intervention increased appointment access by 17-38 slots per week at each site. Based on this evidence, the intervention was then disseminated to all primary care clinics in the system. Perhaps most telling, the intervention fostered an ongoing collaboration between operational leaders and researchers to further refine the reminder process and to better understand the characteristics of members missing appointments (Steiner et. al., 2016). This

BOX 1
Transforming to a Learning Health System: Priorities for Action (2)

- Emphasize the bidirectional relationship between health operations and research;
- Participate in networks and relationships that facilitate a faster, more relevant research process and better use of finite resources;
- Embed learning activities (especially pragmatic clinical trials, systems/management studies, and quasiexperimental studies) within delivery systems;
- Involve a broad range of stakeholders;
- Prioritize training for stakeholders while identifying and increasing opportunities for learning; and
- Focus on implementation and dissemination of results.

Note: The Priorities for Action are the authors' opinions based on their knowledge of the literature and professional expertise. The Priorities of Action do not necessarily reflect the opinions of the authors' organizations or of the National Academy of Medicine.

example of evidence generation and dissemination—as well as the additional examples provided throughout this paper—is illustrative because it is relevant to the priorities of a delivery system, engages both operational and research leaders, and exemplifies the possibilities of a continuously learning health system.

In a continuously learning health system, as defined by the NAM Learning Health System Series, "science, informatics, incentives, and culture are aligned for continuous improvement and innovation, *with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience*" (italics added) (2). This vision calls for mutually productive, meaningful partnerships between researchers and those responsible for delivering health services.

To transform into a learning health system, the authors believe that the knowledge used by delivery systems must be generated by a research enterprise that is fully integrated, with researchers embedded in the system itself, and operations and clinical professionals helping to identify key questions. Additionally, a learning health system will advance by facilitating a variety of embedded learning activities (especially pragmatic clinical trials and quasiexperimental intervention studies) (3, 4), within delivery systems. These embedded learning activities require collaboration between various stakeholders at all stages of the knowledge generation cycle, from identification of the problem to devising and testing solutions and then finding ways to implement and refine them. It is also the authors' viewpoint that, while there are examples of successful research and operational alignment and integration—many of which have been highlighted below—widespread progress to reach these goals continues to face numerous barriers.

Current Health Care Context

Overcoming barriers requires an understanding of the current health care context. In particular, health delivery systems are operating within an environment that increasingly demands continuous improvements in the quality, outcomes, and systems of care under increasingly tight margins. Enormous amounts of data are generated to meet these requirements. Data are generated as well for other ongoing activities within health systems such as administration, care delivery, care improvement, performance transparency, registries, patient-powered research networks and online forums, and consumer genomic databases. Yet, the vast majority of the data are not captured for broader systematic (i.e., research) learning, creating a missed opportunity. As demonstrated by the examples highlighted throughout this paper, enhanced linkage of the research enterprise to care delivery, and of care and operational challenges to research questions, can increase the relevance of research questions and findings, accelerate knowledge transfer, and lead to care and outcome improvement. For example, as demonstrated by Harvard Pilgrim Health Care (see Box 2), there is great value in understanding what type of care works (or does not work) (Greene, et. al., 2012), for whom, and under which circumstances.

Despite the promise of embedded learning activities, barriers to operational and research collaboration remain. A dearth of research studies is not the problem.

BOX 2
Learning What Does Not Work is Equally Important

Harvard Pilgrim Health Care attempted to improve performance on an important Healthcare Effectiveness Data and Information Set indicator, renewal of first dispensing of antidepressants, by reminding the prescribers shortly before the prescription renewal date. Interrupted time-series analysis provided compelling evidence that the practice had no effect on adherence as measured by dispensing of a refill. It was a surprise to health plan leadership, which discontinued the program.

Source: Bambauer, K. Z., A. S. Adams, F. Zhang, N. Minkoff, A. Grande, R. Weisblatt, S. B. Soumerai, and D. Ross-Degnan. 2006. Physician alerts to increase antidepressant adherence: Fax or fiction? Arch Intern Med. 166(5):498-504.

Even with the thousands of randomized clinical trials (RCTs) and clinical studies published yearly, a lack of evidence exists to inform clinical decisions made by providers and patients (Bracken, et. al., 2014; Patsopoulos, 2011), clinical practice guidelines are often based on low-quality evidence (Level C: 48% of ACA/AHA guidelines in one study) (Tricoci, et.al., 2009), and translation of research into practice continues to take far too long (Slote, et. al., 2011).

Barriers to Continuous Learning

The path toward continuously learning faces numerous barriers in part because clinical and research systems have been developed and maintained separately from one another in personnel, agenda setting, data infrastructure, and funding.

Lack of Generalizability

Research studies often do not reliably generate evidence that is generalizable for clinical decision making. The use of strict inclusion and exclusion criteria restricts a broader clinical population from participating in studies. In 2003, Masoudi and colleagues demonstrated that only a minority (13% to 25%) of persons with heart failure in clinical practice would qualify for enrollment in clinical trials (Masoudi, et. al., 2003). Similarly, studies demonstrate that a majority of persons with asthma would be ineligible for selected randomized clinical trials (Travers, et. al., 2007; Herland, et. al., 2005). Most individuals with psychiatric disorders would not qualify for clinical trials of medications or psychotherapy (Blanco, et. al., 2008; Okuda, et. al., 2010; Hoertel, et. al., 2012). The Food and Drug Administration (FDA) has also produced a white paper that reported that patients with serious but common conditions, such as psychiatric and cardiac diseases, were frequently excluded from evaluations of new medicines (FDA, 2011). Although there are ongoing efforts to develop statistical methods to validly extrapolate results from clinical trials to general populations of individuals with the target disorder, much work remains to be done in this area (Cole, et. al., 2010; Blanco, et. al., 2016). As such, even when lengthy clinical trials are completed, clinicians may not feel that study results can be applied to their own, often more complex, patient populations.

Limited Relevance

Current research findings are not consistently relevant to the broader population, business strategies, and immediate needs facing decision makers at the delivery system level. Within the current health context, investigators and funding agencies often identify research priorities on their own, rather than working with health executives, payers, clinicians, and patients to define questions or to provide input for the design or conduct of research studies. Front-line clinicians are not trained, nor do they have time, incentives, or funding, generally, to engage in evidence-generation activities, and they are typically overlooked during development of research priorities. Furthermore, the outcomes and questions being assessed are not the most pressing clinical questions for practicing clinicians. For example, a systematic review evaluating treatments for depression concluded that few studies provided data on the long-term effectiveness of treatment, the functional status of patients, or the outcomes of patients treated in typical practice settings (Mulrow, et. al., 1999). The absence of longer-term follow-up and typical practice settings is not unique to depression treatment—more the rule than the exception—but these characterize questions that both clinicians and patients most want answered.

Investigators, clinicians, operational leaders, and health executives have few incentives to collaborate on research priorities or enhance the applicability of results. Investigators are encouraged to seek grants and publish findings but are not evaluated on the impact of their findings in changing practice. Furthermore, promotion committees are not designed or inclined to reward either impact or collaboration, both of which can potentially slow down research completion. Operational leaders and health executives may see most research studies as expensive and interfering with current operations and patient care, while offering uncertain and distant knowledge that may not benefit them directly.

Inconsistent Taxonomy

While all types of research are crucial to continuous learning, this Perspective specifically focuses on activities that can be conducted within the care delivery system, by design both embedded within the practice of routine care and intended to influence the clinical enterprise. Yet, the authors recognize that even the term "research" covers many kinds of activities and means different things to different stakeholders. For instance, research to health system leaders could mean "narrowly focused operations research that addresses an immediate question and may or may not generalize outside my institution," while funding leaders might define research as "implementing protocols to test hypotheses that may or may not lead to changes in clinical care after several more years of investigation." When working toward collaboration, there is a risk of talking past one another.

Competing Priorities

Health systems are operating within tight margins and need desperately to identify means of generating revenue and controlling costs. Most have been organized on a fee-for-service basis, meaning that additional tests and procedures contribute positively to their financial bottom line. Better care is not always cheaper or reimbursable, and what is most lucrative is not always best care. Using the traditional models of research, the knowledge generated from studies may be important to health, but they may not be implemented due to competing incentives. Health system chief executive officers (CEOs) face an abundance of competing demands and increasing data. Amidst competing demands, CEOs may not see or understand how research could provide a return on investment, especially when research competes with what many health system CEOs experience as unlimited demands for funding. The funding provided by a grant may be a fraction of the revenues that could be generated through clinical care and the salaries that are allowed from grants may be considerably smaller than those of the participant clinicians, thus requiring the institution to subsidize one way or another a portion of the salary of those clinicians.

Additionally, within the current environment, funders do not routinely fund researchers to move to the implementation stage. When making funding decisions, funders do not necessarily ask for a plan for who would authorize the integration of findings if appropriate and whether those stakeholders are part of the project team.

NAM Partnerships to Advance Continuous Learning

To respond to the ever-evolving health environment, and to further explore the potential of operational and research collaboration, the NAM partnered with PCORI in 2014 to develop a two-session workshop titled "Health System Leaders Working Towards High-Value Care Through Integration of Care and Research" (IOM, 2015). The goal of the project was to engage health system leaders as essential partners in the development of research that aligns with the pace and priorities of health delivery centers and systems. The first workshop convened health care system leaders and researchers to discuss activities and opportunities. The second workshop convened health system CEOs considering strategic priorities and approaches to implementation. Foundational to the workshop was the idea that continuous and seamless assessment of the effectiveness and efficiency of care is basic to a continuously learning health care system, and constant integration of what was learned is central to a continuously improving one.

The 2014 workshop resulted in multiple outcomes:

- Two independent research initiatives (described in Boxes 3 and 4);
- The development of the NAM Executive Leadership Network;
- A follow-up 2016 NAM/PCORI meeting that engaged additional health leaders, policy leaders, and researchers interested in practice-embedded research; and
- A new PCORI funding opportunity through its National Patient-Centered Clinical Research Network (PCORnet), which brings together health systems from across the country into Clinical Data Research Networks (CDRNs) and offers a standard way of organizing and aggregating data to facilitate multisite research.

See details of each initiative below. Each of these activities highlights an increasing interest and willingness of health executives to engage in the evidence-generation process. The authors believe that achieving a continuously learning health system depends on a well-informed and equipped cadre of stakeholders, including health care system leaders, who have patient-centered values and motivation, aligned interests, and levers for making progress, and can benefit directly from a better synergy of effort through collaboration.

Research Studies

A survey of health care executives

In consultation with the NAM and a small group of PCORnet awardees and stakeholders, the Group Health Research Institute (GHRI) conducted a survey in between the 2014 NAM workshops to "explore the benefits and challenges of integrating research into practice from the perspective of C-suite leaders . . . and from the perspective of persons engaged in developing Clinical Data Research Networks (CDRNs) and others attending the first NAM workshop" (Johnson, et. al., 2014). Key findings from the survey are presented below (see Box 3).

Interviews with Health Systems

At the conclusion of the 2014 workshops, researchers from the Johns Hopkins Berman Institute of Bioethics, in consultation with the NAM, identified and interviewed leaders from U.S. health care institutions engaged in a transition toward learning health care. The goals of this project were to explore how institutional leaders in "learning health care" transformed their health care systems or institutions to proceed further

BOX 3
Integrating Research into Health Care Systems: Executives' Views

Introduction: In partnership with the NAM and PCORnet, researchers from GHRI conducted a survey with leaders from U.S. health care institutions on the benefits and challenges of integrating research into practice.

Method: Forty-nine participants responded to the survey in 2014. Twenty-three respondents had a C-suite role.*

Key Findings:

- Health care leaders believe integrating research with clinical care could have many benefits, including identifying questions that support organizational performance goals, using data to drive decision making, enhancing reputation and connections, and improving patient care.
- Respondents saw the speed and focus of research as "out of sync" with fast-paced changes in the delivery system because
    - The questions that research studies address and the measures that are available often do not provide enough detail to support decision making;
    - The pace of traditional research lags so far behind the real pace of change that results are often outdate by the time the studies are completed; and
    - Meshing research designs with daily clinical practice and subsequently disseminating findings into work flows requires significant planning and shared commitment among researchers, providers, and leaders.
- Patient engagement is a cornerstone of creating care that patients prefer and research results that matter to them.
- Participants were interested in guidance on minimizing the impact of research on clinical operations.
- Executives find value in knowledge generation, when it
    - Identifies questions that support organizational performance goals,
    - Uses data to drive decision making,
    - Enhances reputation and connections, and
    - Improves patient care.

** For a full list of participating organizations, please see Johnson K, Grossmann C, Anau J, Greene S, Kimbel K, Larson E, Newton K. Integrating Research into Health Care Systems: Executives' Views. Discussion paper. Washington, DC: Institute of Medicine; 2014.*

along the path to becoming learning health care systems, and then to document the nature and extent of ethical and regulatory challenges they faced in this transformation (Morain and Kass, 2016). Key findings from the interviews became the impetus for the development of this NAM Perspective and are presented below (see Box 4) and discussed throughout the remainder of this piece.

Executive Leadership Network for a Continuously Learning Health System

The NAM Leadership Consortium for a Value & Science-Driven Health System developed the *Executive Leadership Network (ELN) for a Continuously Learning Health System* to facilitate the cooperative engagement, communication, and leadership of health system executives to accelerate individual, organizational, and system-wide capacity and progress for health care that continuously learns and improves. Network participants advise on the issues, strategies, and returns from continuous learning capacities that simultaneously support operational decision making, performance improvement efforts, and the generation of better evidence—including rapid-cycle learning efforts,

BOX 4
Common Elements for Health Care Systems Seeking to Become a Learning Health Care System: Results from Interviews with 25 Health Systems

Introduction: In consultation with the NAM, researchers from the Johns Hopkins Berman Institute of Bioethics interviewed leaders from U.S. health care institutions engaged in a transition toward learning health care.

Method: Twenty-nine leaders from 25 health systems were interviewed between 2014 and 2015.*

Key Findings

- Systems change only when leadership is committed to the learning health system (LHS) model; without a culture committed to LHS it is hard to be successful.
- Successful institutions have identified strategies for ongoing discussions about challenges and potential solutions among operations, clinicians, and researchers.
- Rapid growth is occurring in unstructured data collection, but there is limited capability to analyze and use these data.
- There are also challenges in use and sharing of data to support learning activities.
- There are a number of financing challenges, related to transition from fee-for-service reimbursement to quality- and value-based reimbursement mechanisms. This transition requires enhanced process and cost understanding as well as enhanced data collection.
- As pressure mounts relating to clinical reimbursement, there are challenges in securing internal commitments, external funding, and time for clinicians.
- There is a lack of available skilled individuals who possess the unique combination of clinical and clinical management experience, health services research, and systems engineering. To solve that issue, incentives and messaging need to improve.
- It is difficult to manage competing priorities, such as prioritizing among different learning activities and weighing learning activities against other needs.
- There are regulatory challenges that are barriers to learning, such as ethics/Institutional Reveiw Board (IRB) oversight; quality or improvement priorities set by regulatory requirements or insurance companies that constrain ability to target quality priorities to community- or institution-level needs; and antitrust laws that can obstruct collaboration and care coordination.
- Common strategies for transformation include
    - Strong leadership committed to a LHS model,
    - Training leaders and staff for continuous improvement and why it is important to the quality of the organization,
    - Setting a limited number of organizational priorities,
    - Internal transparency of quality metrics so that all players are accountable, and
    - Building on existing strengths and priorities.

** For a full list of participating organizations, please see Morain, SR, Kass NE. Ethics issues arising in the transition to learning health care systems: Results from interviews with leaders from 25 health systems. eGEMs (Generating Evidence & Methods to improve patient outcomes) 2016; 4(2): Article 3. doi: http://dx.doi.org/10.13063/2327-9214.1212, available at http://repository.edm-forum.org/egems/vol4/iss2/3* patient data sharing across entities, focus and harmonization of measurement activities, ethical framework and IRB streamlining for evidence development from the care experience, and improving the implementation of reliable clinical decision support tools.

2016 Accelerating Clinical Knowledge Generation and Use Meeting

In a January 2016 meeting, *Accelerating Clinical Knowledge Generation and Use* (5), the NAM and PCORI convened health system leaders and researchers to explore strategies to improve linkages and synergy among health care organizations with related interests and to consider questions and demonstration projects that PCORI might support to advance the field. Participants worked to identify compelling questions on system performance, measurement, and operations that might be answered from structured and routinely captured care delivery data, and provided input on the priority of the questions and standardized data needed; explored communication strategies to help improve linkages, synergy, access to information, and progress among health care organizations with related interests; characterized core clinical data elements and system characteristics necessary to generate usable knowledge in real time, including use of PCORI's common data model; and considered demonstration projects that PCORI might support, along with approaches for expanding strategic priorities.

The Health Systems PCORnet Demonstration Project

Another key initiative was the development of the PCORI Health Systems PCORnet Demonstration Project, which is designed to "provide the CDRNs participating in PCORnet with an opportunity to test their capacity to conduct collaborative research with health systems leaders across the network" (6). According to its funding announcement, the Health Systems PCORnet Demonstration Project will have the following objectives and guidelines:

- The project will be of interest and add value to multiple health systems.
- The project must include at least two health systems that span two or more CDRNs.
- The project will leverage PCORnet data resources.
- Topics will be rated as priority by the CEOs and systems leaders, and their input will be included in the PCORI Funding Announcement responses.
- Proposed projects will be identified, vetted, and involve iterative review and discussion among researchers, clinicians, and health systems leaders.
- Projects may be comparative, may be descriptive, or may evaluate the utility of new data sources for addressing specific questions of health systems leaders.
- The project will pay particular attention to the needs of a learning health care system to optimize decisions made by health systems, care providers, and patients and their families.
- The project may involve linkage to administrative claims data.
- The project will evaluate the impact of the research on PCORnet's capacity to support collaborative research and extend the breadth of PCORnet's shared tools and resources using PCORnet infrastructure.

In Step 1 of the Health Systems PCORnet Demonstration Project, which occurred between June 2015 and January 2016, each participating CDRN implemented stakeholder engagement processes within their networks to prioritize a set of health system–oriented research topics to inform the Step 2 funding announcement described above. By aligning with PCORnet researchers and utilizing the PCORnet data infrastructure, these projects are designed "to identify and prioritize a set of data-driven research activities of high interest to health systems and clinicians."

Priorities for Action

To enable the engagement of well-informed and equipped stakeholders and successfully transition to a learning health system, the authors propose a cultural shift in the practice of research and operations, in which research priorities also come from clinicians, evidence-generation activities are embedded, collaboration is rewarded, funding agencies support research whose results can be readily applied in routine clinical settings, evidence-based clinical and operational improvements are reimbursed by payers, and research findings inform clinical decisions and improve health outcomes. Reaching these goals requires a concentrated effort from leadership at the national funding and policy-making levels, from multistakeholder teams in delivery systems, and from those designing and providing education at our nation's medical and research institutions. It also requires that health systems come to view continuous learning as helpful to their mission and bottom line.

The authors have identified a number of key priorities for action, with the belief that they will foster the growth of learning health care environments, including

- Emphasizing the bidirectional relationship between health operations and research: research is more relevant that is responsive to key clinical and operational challenges, and those able to consider how findings can be incorporated into clinical or operational protocols should be part of teams;
- Participating in networks and relationships that facilitate a faster, more relevant research process and better use of finite resources;
- Embedding learning activities (especially pragmatic clinical trials, systems/management studies, and quasiexperimental studies) within delivery systems, which allows learning to be more relevant and more generalizable; it also sets processes that are more easily replicable for the long term;
- Involving a broad range of stakeholders: patients and clinicians may be best situated to identify their highest priority unanswered questions, operations managers will know which operational challenges are most central, and researchers can consider how to best answer these questions and in ways that can appropriately be generalized back to the functioning clinical and operational systems;
- Prioritizing training for a variety of stakeholders while identifying and increasing opportunities for learning; and
- Focusing on implementation and dissemination of results; considering how results will be translated into implementation should be considered when learning projects are planned, with key operational stakeholders at the table to ensure the design facilitates future implementation.

Additionally, realizing that there are a number of examples of successful partnerships, the authors looked across health systems to highlight both research- and process-specific case examples that demonstrate these priorities for action. It is our intention that the proposed priorities for action, as well as the compilation of case examples, will add to the emerging body of evidence around learning health care while also serving as an actionable roadmap for institutions interested in transforming to a continuously learning system.

Underlying all of these priorities, and demonstrated repeatedly throughout the case examples, is an essential commitment to culture change. Transformation to a learning health system requires the development of a culture committed to continuous learning. A key finding from the Johns Hopkins research study (described in Box 4) is the importance of top leadership communicating the culture of the institution and representing a commitment to a learning health system as an organizational priority. Leaders must be instrumental in communicating a commitment to learn and then asking "how" to implement new opportunities for evidence generation rather than "whether" to implement them, and in developing an environment committed to multistakeholder engagement and innovation. Transformation also requires a culture of collaboration among clinical leaders, operational administrators, and researchers. While all three groups have much to gain, each must also adapt to the legitimate needs and expectations of the others. At their best, learning health system projects and programs must blend the timeliness and relevance expected by clinical/operational leaders with the rigor required by researchers. The topics chosen for learning health system projects should both improve care and contribute to scientific knowledge. Inevitably, compromises between these expectations will be necessary. Such compromises can only be made in a culture of trust, which in turn requires an investment of time, financial, and emotional capital. A collaborative culture is slow to build and easy to squander. Therefore, all partners in a learning health system must take a long-term, strategic perspective. If a group of leaders can navigate the obstacles and instill such a culture in their organization, it can provide a uniquely productive and professionally satisfying haven for its participants and can serve as a model to others.

Enhanced Bidirectional Relationship Building

As described above, within the current health context, the two activities of clinical operations and research operate in largely separate environments with different (and at times competing) players, funding streams, incentives, and priorities. The authors believe that research can move more quickly once research interests are aligned with operations. Likewise, operations will be more evidence based and thus the quality of care improved once operations stakeholders are engaged in the development of research priorities and their needs and strategies are reflected in the research agenda.

To build these relationships requires that health executives promote the benefits of integration, including ideas related to seamless integration of research and practice, and that they create structures, funds flow, and processes, and allocate time and resources, to those collaborations. Of key importance in relationship building is that leaders work to overcome barriers related to competing priorities between researchers and clinicians, and they collaborate to build an environment that promotes transparency, as well as opportunities to ask questions together, to develop innovative solutions to health care delivery and population health problems, and to build synergistic and productive partnerships. By working through this process, researchers, clinicians, and leaders should discover mutual interests, leading to an environment that values and rewards collaboration through new models for tenure and promotions and shared financial rewards. In the process-specific case examples below, one medical center, Wake Forest Baptist Medical Center (see Box 5), uses a shared strategic commitment to "becoming a Learning Healthcare System" and a centralized fund-

BOX 5
Case Example:
A Shared Vision and Bottom Line: An Example from Wake Forest Baptist Medical Center

Background

Wake Forest Baptist Medical Center (WFBMC) operates as an integrated structure, in which revenues of approximately $2.3 billion annually from clinical activity, contracts and grants, endowments, tuition, and intellectual property are combined into a common bottom line. This approach allows coordinated strategic planning for clinical, research, and educational programs and distribution of shared resources.

The Learning Health Care System Transformation

The 2017-2019 strategic plan was designed with the intention of "becoming a Learning Healthcare System" as the overarching theme and developed by faculty and staff from the School of Medicine, Health System, Basic Science and Clinical Departments, and administration. The strategic plan

- Includes financial performance and quality metrics goals and
- Describes the development of destination clinical programs that are directly linked to the growth of basic and translational research programs as well as associated clinical trials activity.

The Details

- The WFBMC strategic plan prioritizes interactions between clinical service lines, clinical trials activity, and research groups in six specific strategic areas (cancer, aging/Alzheimer's disease, diabetes/obesity, cardiovascular disease, pain/addiction, and regenerative medicine).
- Incentives, such as increased funds that flow to both basic and clinical departments, as well as to clinical service lines and integrated practice units, and increased faculty compensation, are designed to achieve combined clinical and research goals, including increased patient care activity, improvement in metrics relating to patient care quality and satisfaction, enhanced clinical trials enrollments, and growing extramural funding in these strategic areas.
- Funding was provided for the establishment of a new Center for Health Care Innovation, focused on developing innovative approaches to major population health issues and tested in individuals and communities served by the medical center.
- Budgeting for both capital and operations over the 3-year period covered by the strategic plan provides for recruitment of faculty and staff as well as investment in infrastructure designed to enhance growth of revenues from research and clinical activities specifically tied to the areas targeted.

What Makes This Transformation Possible?

- Culture of continuous learning communicated from top leadership
- Investment in infrastructure

ing flow to align clinical, research, and educational programs, while Johns Hopkins School of Medicine's institution-wide vision of a learning health system (see Box 6) is communicated across its system to align clinicians and researchers.

Networks for Evidence Generation

Another approach to aligning research at the health delivery system is through the participation of health systems in multi-institutional networks that allow a faster, more relevant research process and better use of finite resources.

A number of interconnected networks exist, both within single institutions and among multiple health systems that are designed to foster the development and conduct of evidence-generation activities across institutions. Examples include PCORnet, the National Patient-Centered Clinical Research Network;

BOX 6
Case Example:
Institutionalizing the Learning Health System: Lessons from Johns Hopkins University School of Medicine

A Systemic Vision of Continuous Learning

The Johns Hopkins University School of Medicine (JHM) learning health system (Pronovost, et. al., 2015b) is realized through four aims:

1. Declaring and communicating goals broadly across the health system and with each vertical entity within it.
2. Creating an enabling infrastructure by providing project management, analytic, technical, and research expertise.
3. Engaging clinicians and connecting them in peer learning communities: JHM has 40 clinical communities based on geographic location (hospitalist unit), topics (transfusion), and service line (heart failure). Each community achieves its purpose within a shared organizational framework that addresses four categories: patient safety (which represents internal risks), performance on externally reported measures, patient experience, and value. Communities include clinicians and applied researchers, but, thanks to the support of the enabling infrastructure described above, basic and clinical researchers are being integrated as well. An underlying theme in the learning health system is precision measurement. Too often precision medicine or learning refers narrowly to sequencing genes. Armed with data, supported by an analytics platform, the clinicians and researchers in the clinical communities broadly apply precision medicine in their work to solve problems and achieve our purpose.
4. Implementing a transparent reporting system that is modeled on the JHM finance structure and ensures accountability. Clinical communities and hospitals regularly present data through dashboards. Accompanying the data is an explicit accountability plan, built on the cascading fractal model—division directors meet with department directors, department directors meet with hospital leaders, and hospital leaders meet with health system leaders and trustees.

Putting the Vision into Practice

The institution's vision for continuous learning is demonstrated within the Armstrong Institute for Patient Safety and Quality, a collaborative effort with faculty from 18 disciplines from over 8 schools (Pronovost, et. al., 2015).

- The Armstrong Institute developed a goal to improve annual aggregate performance in seven process-of-care measures that performed below the goal of 96% in 2011.
- The JHM Board of Trustees and the Johns Hopkins Health System created a transparent, four-level accountability plan to monitor hospital progress across the seven measures. This plan, as well as the sustainability plan implemented after a hospital maintained at least 96% on core measures for 4 months, ensured that hospitals had the support necessary to maintain good results.
- The Armstrong Institute utilizes a "fractal infrastructure." Each "fractal" houses similarly skilled groups of people, as well as similar resources and goals:
    - A vertical stream of accountability ensures that responsibility is delegated efficiently and transparently.
    - Horizontal connections between communities allow for communication, support, and idea sharing.
    - The heads of 13 councils (e.g., Quality Analytics Council and Quality and Safety Council) comprise the Armstrong Institute Executive Committee, which is responsible for overseeing patient care quality at all institutions housed within Johns Hopkins Medicine.
    - Hospital staff is integrating into this initiative.
- Of the five hospitals involved, five received at least one Delmarva award for Quality Improvement in Hospitals and three received the Joint Commission Top Performers on Key Quality Measures program award.
- All five hospitals showed improvement in percent of patients who received recommended process of care.

the National Institutes of Health, Health Care Systems Research Collaboratory, National Center for Advancing Translation Sciences; Big Data to Knowledge Initiative and Precision Medicine InitiativeTM Cohort Program; the Health Care Systems Research Network [formerly known as the HMO Research Network and which includes topical research networks in cancer (Cancer Research Network) and mental health (Mental Health Research Network) among others], and the FDA Sentinel initiative. Through these efforts, multi-institutional collaborations are studying aspirin dosing, bariatric surgery outcomes, and the use of antibiotics in children, to name a few. Box 7 provides two examples of multistakeholder research prioritization efforts from the PCORI Health Systems PCORnet Demonstration Project, while Box 8 demonstrates a multi-institutional pragmatic study led by the Hospital Corporation of America.

BOX 7
Case Example:
A New Type of Evidence-Generation Team: Two Examples of Executive and Researcher Partnerships

In Step 1 of the PCORI Health Systems PCORnet Demonstration Project, which occurred between June 2015 and January 2016, each participating CDRN implemented stakeholder engagement processes within their networks to prioritize a set of health system–oriented research topics to inform the Step 2 funding announcement described above.

Example 1: The **Research Action for Health Network (REACHnet)** is 1 of 13 CDRN members. REACHnet is managed by the Louisiana Public Health Institute (LPHI) and includes the following partner health systems: (1) Ochsner Health System, (2) Baylor Scott & White Health, (3) Pennington Biomedical Research Center/Louisiana State University, (4) Tulane University Schools of Medicine and Public Health/Tulane Medical Center (HCA), and (5) Partnership for Achieving Total Health, a supporting organization of LPHI that administers the Greater New Orleans Health Information Exchange among a network of community-based clinics and hospitals. REACHnet includes clinical data on over 1.7 million active patients in Louisiana and Texas.

In Step 1 of the Health Systems PCORnet Demonstration Project, REACHnet engaged a total of 30 patient, health system leader, researcher, clinician, and payer stakeholders through the following methods in order to successfully meet the project's objectives.

1. Preliminary interviews: Developed a potential topic list and interviewed health systems stakeholders to discuss priorities.
2. Meeting 1 (initial discussions): Convened Health Systems Demonstration (HSD) stakeholder designees (health system C-suite and payer leadership) for review of the topics. Care coordination was prioritized, with the following specific considerations: (1) primary care provider assignment and (2) triangulation of data from health systems, health plans, and the Office of Public Health to analyze utilization trends and intervention efficacy.
3. Meeting 2 (broad prioritization): HSD stakeholders convened. Care coordination was discussed and the group brainstormed other topics more aligned with REACHnet resources. A matrix was developed reflecting 11 prioritized topics and the potential domains across which their efficacy could be assessed.
4. Meeting 3 (patient engagement): The REACHnet Community Health Advisory Board (patient board) met to provide feedback on the 11 prioritized topics. They prioritized (1) assessment of relationship between health literacy and readmissions; (2) effects of end-of-life care/palliative care, use of chemotherapy, and discharge planning in oncology patients on outcomes; (3) relationship between PCP-driven care coordination and pain management; and (4) the effect of postdischarge follow-up on patient satisfaction and outcomes.
5. Meeting 4 (final prioritization): An expanded set of HSD stakeholders (patients, health systems leaders, payer representative, clinicians, and researchers) convened to further refine the prioritized topics. The following three topics were prioritized through a scoring process:
   - Examine patterns of health care utilization 1 year prior to mortality to better understand the comparative effects of advanced illness management/end-of-life care on outcomes and resource utilization.
   - Evaluation of the effects of multiple factors on weight loss maintenance after initial weight loss success (e.g., post-bariatric surgery).
   - Compare the influence of postdischarge follow-up and encounter patterns postdischarge (e.g., time to follow-up, method of follow-up) on patient health outcomes.
6. Survey (final prioritization refinement): HSD stakeholders were given a Research Question Refinement Survey to provide additional feedback regarding the three prioritized topics.
7. Meeting 5 (prioritized topic deep dive): HSD stakeholders convened to conduct a thorough analysis of each of the three prioritized topics.

BOX 7 continued

Example 2: The New York City Clinical Data Research Network (NYC-CDRN) "brings together 22 institutions—including health systems, medical colleges, patient engagement organizations, research institutions, health information exchanges, and government agencies—that have agreed to share data, develop common tools and services, and support patient-centered collaborative research."* To develop and prioritize its research questions, the NYC-CDRN implemented the following approach to meeting the project's objectives, which included in-person meetings with various stakeholders as well as a series of interviews.

First Stage

- The project team iteratively identified, specified, and refined priority topics by
    - Studying the existing literature,
    - Reviewing PCORI's guidance on health system improvement priorities, and
    - Interviewing more than 19 health system "content experts" (i.e., administrative directors and managers), senior health services researchers, as well as patient representatives using the PCORI engagement rubric.

Second Stage

- In consultation with each site's Principal Investigator (PI), the project team identified health system executives and patient representative interviewees who could provide expert feedback on the use cases.
- People were carefully selected who had personal and/or professional experience in key topics such as complex medical needs, mental health issues, information systems, and quality improvement.
- A total of 39 people were interviewed.
- Each interviewee received a package of materials for the interviews, including (a) a slide deck and one-pager introducing PCORnet and the NYC-CDRN, (b) an interview guide, and (c) use case descriptions.
- The interviews provided essential information to inform the development of the NYC-CDRN and PCORnet.
- The interviewees provided their priorities for data-driven insights, offered feedback on existing use cases, and proposed new use cases.

Final Stage

- The project team assessed the proposed projects for
    - Value and relevance to health systems,
    - Suitability with PCORnet's unique assets,
    - Technical and operational feasibility, and
    - Scientific merit.
- The project team then engaged researchers to refine the proposals.
- Based on this process, the following research questions were prioritized

1. Can a risk adjustment model that incorporates claims, clinical, and socioeconomic data more accurately predict high utilization than existing claims-based risk adjustment models?
2. How are co-occurring behavioral and physical health conditions associated with utilization and quality outcomes?

**Note: See http://www.pcori.org/research-results/2015/new-york-city-clinical-data-research-network.*

Embedded Learning Activities

Embedded learning activities in health care delivery systems can be greatly facilitated by six attributes, summarized as "right team, right question, right design, right data, right analysis, and right interpretation" (7) :

- *Right team.* Systems should assemble teams of operational/clinical experts, patients, and researchers with diverse perspectives and skill sets. These teams should operate under the sponsorship of supportive executive leaders who are committed to incorporating rigorously derived, local evidence into their decisions.
- *Right question.* These teams should propose research questions that are clear, answerable, of high operations and/or clinical priority, and actionable. Leaders should be able to define a course of action that would result from any plausible answer to a good question. For example, if the question involved the effectiveness of a new clinical strategy or approach to delivering care, leaders should anticipate how the program can be disseminated if it is effective, and should be willing to terminate it or modify it if not.
- *Right design.* The design of a data analysis or evaluation must balance multiple competing constraints such as the urgency of a decision, the level of confidence necessary to make that decision, and the costs and feasibility of collecting data to answer the question. Within those constraints, the design should be as rigorous as possible. Obser-

vational data analyses should consider issues of data quality, as well as missing data, and should account for the well-known biases that can affect the interpretation of observational analyses such as comparative effectiveness studies. Studies of interventions should incorporate rigorous designs, and consideration should be given to the use of randomization to conduct pragmatic trials.

- *Right data.* Research in a learning health system must take advantage of the rich clinical data provided by electronic health records, augmented by administrative data and clinical information from laboratory, imaging, pharmacy, and other sources. Researchers should invest the time to understand the provenance of the data, and its biases and limitations.

BOX 8

REDUCE MRSA: How a Multihospital Study Impacted Practice and Policy

Background: Health care–associated infections are a major cause of preventable injury and death in hospitals. Methicillin-resistant Staphylococcus aureus (MRSA) is a major cause of these infections. The Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE MRSA) trial evaluated methods to prevent these infections in intensive care units.

Intervention: A multi-institutional pragmatic study to compare three competing evidence-based practices in use clinically to determine “best” care. The study was conducted through the use of a cluster-randomization (by hospital) trial design and included an aggregate of 43 hospitals; 74,356 patients; and 282,803 patient-days. The three practices included (a) screen and isolate: screen every patient and implement barrier isolation, if MRSA positive (n.b., mandated by law in nine states at the time of the trial); (b) targeted decolonization: screen, and if MRSA positive, isolate and decolonize; and (c) universal decolonization: discontinue screening for MRSA and decolonize all patients on admission to ICU (Septimus, et. al., 2016; Huang, et. al., 2016); Huang, et. al., 2013).

Results

- Universal decolonization reduced all bloodstream infections by 44% and MRSA by 37%.
- For every 99 patients decolonized, 1 bloodstream infection was avoided.
- Universal decolonization also reduced the frequency of false-positive (contaminated) blood cultures (Septimus, et. al., 2014)
- Universal decolonization was cost saving, compared to the other two strategies (Huang, et. al., 2014)
- The findings contributed to a new standard for reducing bloodstream infections in intensive care units (ICUs).
- Policy:
    - Universal decolonization is a recommended strategy in hospitals/populations with unacceptably high MRSA rates despite implementation of basic prevention strategies (Calfee, et. al., 2014).
    - Demonstrated that state-mandated screening was expensive and inappropriate.

REDUCE MRSA is notable not only for its outcomes, but for its methods

- Speed: 43 hospitals allowed evaluation of impact on a low-frequency, high-morbidity outcome in 18 months;
- Implementation: By nurses and infection prevention professionals during routine patient care;
- Setting: Occurred in community hospitals across the country;
- Relevance: Study answered real-world questions, in real-world environments, that generalize to real-world situations. Dissemination to 95 additional hospitals (136 ICUs) resulted in a 23% decrease in a related measure, central line associated blood stream infections.
- Dissemination to other settings facilitated via online toolkit (Agency for Healthcare Research and Quality, 2013).

What made the REDUCE MRSA Study Possible?

- Partnership of public, private sector, and academia;
- Host Organization (HCA) commitment to infection prevention, learning health care, and providing a platform;
- Contribution of logistical and organizational resources;
- Financial Investment: high-quality delivery science is very efficient, but not free. Belief in clinical, societal, scholarly, and financial return on investment;
- Randomization sometimes necessary, and cluster randomization well suited to pragmatic research and comparative effectiveness; and
- Interconnected, interoperable (EHR) health information.

- *Right analysis.* Analytic approaches should be as sophisticated as the constraints of the process allow. Researchers may be particularly helpful in areas such as applying advanced, multivariate techniques to the analysis of observational data, accounting for hierarchical data structures (patients nested within clinician practices, in turn nested within clinics), and accounting for potential sources of bias in patient selection.
- *Right interpretation.* The results of these analyses should be conveyed to decision makers and patients in a format that is interpretable and actionable. In conventional research, the findings of a multiyear clinical trial must often be condensed into one or two figures and a few data tables. Similar parsimony should apply to the presentation and interpretation of findings from embedded research.
- *Right action.* This step is the culmination of all the preceding "rights" and reinforces the expectation that, in a learning health system, knowledge should lead to interventions. These interventions should be evaluated rigorously, so that their outcomes can inform the next round of increasingly relevant and sophisticated questions.

Box 9 highlights an embedded research study within Mount Sinai Health System (MSHS)—an interrupted time-series design for evaluating an intervention for restricting intravenous acetaminophen use, which has implications for administrative costs and prescription behaviors between groups within the hospital.

BOX 9
Case Example:
Embedded Learning at Mount Sinai Health System

Background: Although widely used, the utility of intravenous (IV) acetaminophen relative to its price is still controversial; the wholesale acquisition cost per vial increased from $12.43 in 2013 to $35.40 in 2014. Therefore, its use is subject to restrictions in hospitals nationwide.

Intervention: To study the effectiveness of the approach to limit IV acetaminophen ordering at Mount Sinai Health System (MSHS) (a >1,000-bed, tertiary-care, urban, teaching hospital). From June 2014 onward, electronic ordering was restricted to (1) specific services, (2) only NPO patients ("nil per os," which means nothing by mouth), and (3) placed orders only active for 24 hours except for palliative care.

Analysis: A segmented regression analysis assessed immediate changes and changes over time in ordering behavior while controlling for baseline trends. Analyses were also stratified by (1) type of ordering provider, (2) top 30 most frequent prescribers versus others, and (3) type of orders.

Results:

- Before restrictions, IV acetaminophen use increased sharply, with residents and anesthesiology providers ordering the most.
- IV acetaminophen orders briefly decreased only to increase again.
- There was no change in ordering among residents while others did demonstrate changes.
- The restriction affected the top 30 prescribers while not affecting less frequent prescribers.
- "Once every 6 hours" orders greatly decreased after the restriction, while "once" orders increased and "once every 6 hours AS NEEDED" did not change.

Conclusions: Overall, the restrictions did not affect long-term IV acetaminophen prescribing behavior. The results, however, provide useful insights into the groups to target (residents, nonfrequent prescribers) as well as additional changes in the electronic ordering of IV acetaminophen, e.g., changing the default order from "once every 6 hours" to "once every 6 hours AS NEEDED" or even to just "once."

What Makes This Study Possible?

- Commitment and resources from MSHS for developing a research institute for health care delivery science (I-HDS) dedicated to achieving the "triple aims";
- Outreach of I-HDS members to departments of pharmacy and medicine, MSHS leadership, and president's office representative assigned for reducing cost; and
- Teamwork approach at I-HDS that was effective for engaging multiple stakeholders, performing the research (data analysis, presentation locally/nationally, surveying the pharmacists, and publication with all engaged stakeholders), and advocating for a needed cultural change at multiple meetings.

Involve a Variety of Stakeholders

A successful learning environment involves shared strategies, linked activities, and the involvement of stakeholders from throughout the health care system, each representing different departments, disciplines, and perspectives. By actively involving a variety of stakeholders, systems can increasingly demonstrate the value of operational and research collaboration,

BOX 10
Case Example:
New Collaborations: Group Health's Impact on Opiod Policy and Research

Background: Starting in 1996, the use of chronic opioid therapy was promoted as a safe and effective treatment for chronic noncancer pain, setting in motion an increase in the use of opioid analgesics for chronic pain in community practice. In 2007, with limited evidence available, the Group Health Research Institute (GHRI) initiated a program of research to evaluate risks associated with increased use of opioids for chronic pain and ultimately discovered that people taking opioids for noncancer pain at higher doses experience a markedly higher drug overdose rate than patients on lower doses.

Through research initiatives and partnerships with policy makers, health executives, clinicians, and community members, Group Health (GH) and GHRI played an important role in (a) evaluating risks associated with increased use of opioids for chronic pain, (b) developing national recognition of the harms, and (c) identifying and evaluating practical steps to address the epidemics of opioid addiction and overdose.

Multistakeholder Interventions

- **Practice change:** GH implemented major risk reduction initiatives which were a national model in its Integrated Group Practice to lower risks associated with high-dose opioid prescribing for chronic noncancer pain. Partnerships between primary care leadership, expert pain clinicians, and the quality improvement department led to defining standard practices, an online educational program, alerts and decision support in the GH EHR, and developing care plans for persons using opioids for noncancer chronic pain. By 2010, around 80% of all persons using these medications had a pain management agreement in their medical record, rates of urine drug testing were markedly increased, and average daily opioid dose prescribed was substantially reduced.
- **Advocacy:** GHRI helped found a national organization, Physicians for Responsible Opioid Prescribing (PROP), to advocate for more cautious and selective prescribing of opioids for chronic noncancer pain. PROP filed a citizen's petition with the FDA calling for changes in labeling of opioid analgesics to clarify the lack of evidence regarding their safety and effectiveness for long-term use for chronic pain.
- **State and federal partnerships:**
  - GH clinicians and researchers worked with the state of Washington to establish new guidelines promoting safer use.
  - The FDA mandated large-scale postmarketing surveillance studies to assess risks of addiction and over dose among chronic pain patients using extended-release opioids. GHRI researchers helped design these studies and are participating with other Healthcare System Research Network research centers, the Department of Veterans Affairs (VA), and a Practice-Based Research Network, in carrying them out.
- **Dissemination:**
  - In 2010, GHRI researchers published the first study showing that, among patients receiving chronic opioid therapy, risks of opioid overdose were markedly increased among patients receiving high doses, findings soon replicated by other research groups. This paper was accompanied by an editorial co-authored by the Deputy Director of the White House Office National Drug Control Policy calling for changes in current opioid prescribing practices (McClellan and Turner, 2010).
  - In 2015, recommendations from an opioid safety summit organized by GHRI for more cautious and selective opioid prescribing were published in the *BMJ* (Deyo, et. al., 2015). GHRI advised the Centers for Disease Control and Prevention in its development of dissemination strategies for its recently released guideline for opioid prescribing for chronic pain.
  - In a 2016 editorial in *Medical Care* (Von Korff and Franklin, 2016), GHRI researchers outlined steps that could be taken to stem these epidemics.

What Made the Interventions Possible?

- Multistakeholder partnerships
- Embedded research
- Organizational commitment to change

and increase the likelihood that research and operational priorities align.

To involve a variety of stakeholders will require looking beyond the traditional research environment and beyond traditional research activities to involve patients and other key stakeholders (e.g., advocates, community leaders, clinicians, board members, health executives, payers, and policy makers). GHRI researchers, who have a history of collaborating with clinicians and unit leaders (Buist, et. al., 2016), partnered with the community and policy makers (see Box 10) to increase national attention of the prescription practices of opioid analgesics for chronic pain. This work illustrates the potential for learning health system work to generate important and currently ongoing public policy and research efforts as well as to generalizable knowledge. Box 11 is an example of clinician leadership in evidence generation and practice at Intermountain Healthcare.

BOX 11
Case Example:
Clinicians as Partners in the Learning Health System

Background: It remains a challenge to implement what's learned within the field into health care delivery. To address this challenge, a clinician-led multistakeholder initiative was created at Intermountain Healthcare in order to develop Shared Baseline "Lean" protocols. Development teams were formed to (1) identify a high-priority clinical process; (2) build an evidence-based best practice protocol; (3) blend it into clinical workflow; (4) embed data systems to track (a) protocol variations and (b) short- and long-term patient results (intermediate and final clinical, cost, and satisfaction outcomes); (5) demand that clinicians vary based on patient need; and (6) feed those data back (variations, outcomes) in a Lean Learning Loop in order to constantly update and improve the protocol.

Development teams consist of

- Team leader
    - respected physician leader, in active practice
    -functionally a knowledge expert
- Core work group
    - knowledge experts
    - build initial Care Process Model
    - provide academic detailing, run referral clinic
    - geographically based
- Front-line clinicians
    - physicians, nurses, clerks, techs, etc.
    - first-level review; keep knowledge experts grounded
    - two-way street: fundamental knowledge up, ownership down
    - geographic representation
- Staff support: flow charter, statistician, data manager, clinical ops administrator

Managing clinical knowledge:
It became the Development Teams' responsibility to build and maintain the Care Process Model.

Initial development stage:

1. Generate initial evidence-based best practice guideline (flowchart).
2. Blend the guideline into clinical workflow (standing order sets, clinical flow sheets, checklists, action lists, etc.).
3. Design variation, outcomes tracking system (feed patient registries).
4. Design patient and professional education materials.
5. Deploy, test, and validate in actual care delivery.

Maintenance Stage

6. Keep the Care Process Model current (protocol variations + patient outcomes; core experts: new research findings; improvement suggestions).
7. Core experts: academic detail front-line teams (Clinical Learning Days).
8. Core experts: run the referral clinic (last step in treatment cascade).
9. Core experts: manage specialist care managers.

BOX 11 continued

Clinicians are offered multiple opportunities to engage in the initiative:

- Really interested? Serve on Development Team
  - About 3 to 6 hours per month
  - We'll pay for your time (we'll make you whole for time lost from practice)
- Somewhat interested? Respond when we circulate
  - We really want is your expertise/ownership (but no $$ compensation)
- Just too much/way too busy? Just practice
  - Every time you vary you are criticizing the guideline

Benefits of the protocols to patients and clinicians:

- Clinical development teams produced 115 protocols that cover 80% of the care.
- Protocols yielded better outcomes and knowledge generation, transparency, lower costs, higher productivity, and improved real-world knowledge:
  - Lower health care costs, e.g., Intermountain's total operating costs down 13%
  - Clinical effectiveness research embedded in routine practice

Every patient generates knowledge:

- Fifty-eight longitudinal patient registries representing about 80% of all inpatient and outpatient care delivered within Intermountain
- About 3 petabytes (thousand terabytes) of storage
- Primary use: routine clinical management (justifies operational expense)

2015-2016 learning production:

- ~150 on the heart and maternal/child health areas
- Total of 390 peer-reviewed publications for the Intermountain system in 2015, and 239 in 2016 (to date)

Prioritize Training

Among the challenges identified by respondents in the Johns Hopkins University's interviews with health executives (see Box 4) was that the traditional model of medical training fails to prepare clinicians for the evidence-driven, team-based approach needed for a successful learning health care system. As previously argued by Catherine Lucey, the goal of medical education should not be to produce physicians; it should be to improve the health of patients and populations (Lucey, 2013). Respondents to the interviews noted the importance of education in "system sciences," reinforcing similar arguments in the literature of the need for physicians working in complex health systems to have knowledge and understanding of health care financing, population health, quality improvement, informatics and health care technology, and team-based care (Gonzalo, et. al., 2015). Box 12 below demonstrates how the University of Michigan is working to educate on system sciences and formally integrated the concept of continuous learning within its medical institution.

The authors believe that, while it is important to train the next generation of clinicians and researchers, in a continuing learning system everyone needs training. Health systems should also prioritize training for stakeholders already within their employ.

Focus on Implementation and Dissemination of Results

One of the motivators for developing this Perspective was the agreement among its authors that, while there are examples of institutions engaged in continuous learning, there are few mechanisms for scaling and spreading these best practices within and between health systems. Implementation and dissemination of the lessons learned from the practice of care, and its impact on cost, better practices, and generalizable knowledge, should be a priority among health executives, clinicians, researchers, and patients.

The transformation to a continuously learning system is critically dependent on dedicated resources and a commitment to sharing, adopting, and sustaining these best practices. A number of the examples above include implementation and dissemination strategies,

BOX 12
Case Example:
Training the Next Generation in Continuous Learning

Background: The Department of Learning Health Sciences (DLHS) was initially created in the University of Michigan Medical School in May 2014, as a transformation of the Department of Medical Education. The Health Infrastructures and Learning Systems (HILS) program was officially approved as a formal degree-granting program in mid-January 2016. The decision to transform the Department of Medical Education to a Department of Learning Health Sciences was critical and involved stakeholders both within the University of Michigan Medical School as well as a large and growing group of individuals and agencies outside the University. Transforming the department was important in aligning an academic department with the mission of learning health systems.

Motivation for Change: There is a growing awareness that health systems, both in the United States and globally, are under considerable stress, in part because of the rapid growth in new information and need to integrate new forms of knowledge, but also due to constant flows of innovation and information required to provide treatment and manage care (Bernstein, et. al., 2015). HILS is designed to link communities and infrastructure needs with skills to support full learning cycles. Courses enable students to

- Understand and conduct research to help build infrastructure in health systems and
- Receive deep learning in key points of a learning health cycle, including conceptualizing a problem; extracting data to support problem solution; applying principles of data aggregation and analytics; transforming data to knowledge; representing and storing knowledge; and managing behavior change at individual, organizational, and societal levels.

The program grants both Ph.D. and M.S. degrees. A total of five Ph.D. students and one M.S. student are enrolled for the first cohort beginning fall 2016. Graduates will be skilled in applying data science principles and techniques to problems in health and health care systems, both nationally and internationally. It is expected that graduates will work in academic settings across many different kinds of departments but also in the health care industry, building systems and system features to enact learning health systems at scale.

including peer and research networks. The networks are important conduits for putting research evidence into daily clinical practice.

As health systems and researchers embark on embedded activities, they should simultaneously reach out to external funding sources to identify or create opportunities for collaborative support. This is again why the involvement of multiple stakeholders is crucially important—a supportive board member or health executive may be able to make a particularly compelling case to external funders. Additionally, consideration should be given at the beginning of a study to intervention and implementation strategies, including ongoing funding for services and the development of new partnerships once the original research funding is no longer present. Box 13 demonstrates how the VA continues to expand, communicate, and successfully implement its primary care–mental health integration program throughout its system.

Conclusion

As illustrated throughout this piece, the transformation to continuous learning requires several key components. It requires strong leadership, one that both signals a cultural change and demonstrates a commitment to multistakeholder collaboration. Interviews with C-suite executives and institutional leaders suggest that if there are not commitments from the top, change will be difficult, and once commitments are in place, strategy and choice of specific projects must reflect the thinking of multistakeholder teams, be deliberate and limited in priorities at any one time, and build in systems for implementation and translation once done. Second, it requires engagement of health executives, academic leaders, and research institutes to create the necessary physical and cultural infrastructure, provide financial incentives, and offer professional rewards for partnerships. Third, successful transformation depends on local teams of clinicians, operational front-line leaders, and researchers who identify problems that matter to them and to their patients, begin a shared process of solving those problems, and disseminate solutions.

The learning health system is increasingly recognized as critical to improve the quality of patients' care, to be efficient in what is provided, to increase the justice of care, and to use research as a tool to improve quality and operations, rather than risk it being viewed as an end in itself. As the authors have demonstrated above, multiple institutions across the United States are addressing the structural, leadership, and collaborative elements necessary to move closer toward transforming to a continuously learning system. They are creating models and examples from which we can all learn. That institutions are working to test models to improve is important and we can and must continue to identify which models work or do not work to help all institutions continue on the path.

BOX 13
Case Example:
The VA's Primary Care—Mental Health Integration Program

Background: As one of the largest single employers and a trainer of mental health clinicians, notably psychologists and clinical social workers, the VA has led several initiatives to scale up and spread effective collaborative care models for mental health conditions in primary care settings. Its signature initiative, primary care–mental health integration (PC-MHI), was initiated by the VA in 2007 (Post, et. al., 2010) to spread evidence-based integrated care for depression, posttraumatic stress disorder, and substance use in VA primary care settings, particularly for patients with mental health symptoms who often present to primary care first.

Intervention: PC-MHI is based on findings from several RCTs, including groundbreaking studies in the VA (e.g., Translating Initiatives in Depression into Effective Solution, the TIDES study) showing that integrated collaborative care models when delivered via care management (e.g., team-based proactive management of patients in primary care, self-management support in mental health symptoms, and consultation with specialty mental health providers) can improve physical and mental health outcomes. TIDES and similar follow-up studies funded through the VA's Health Services Research & Development (HSR&D) and the VA's Quality Enhancement Research Initiative programs also showed successful implementation of integrated collaborative care models in lower-resourced and rural VA sites. Since TIDES, the Well-being among Veterans Enhancement Study (WAVES) demonstrated further implementation of the TIDES collaborative depression care program in smaller VA sites, the Cost and Value (COVES) study provided the business case for the program to VA clinical managers, and the ReTIDES focused on development of implementation tools. These "water studies," as they came to be known, were also complemented by research on the development and implementation of the Behavioral Health Lab, a computerized mental health outcomes assessment tool for routine primary care (Tew, et. al., 2010), all of which culminated into the PC-MHI program in 2007, which provided national organizational and leadership support to scale up and spread of integrated mental health collaborative care nationally.

Results: PC-MHI programs are required at larger VA primary care venues, and combine colocated collaborative care and care management functions to support providers within medical homes (Patient Aligned Care Teams) in treating common mental health conditions.

Through September 2015, 355 (96 percent) of these 370 venues (VA Medical Centers and large Community-Based Outpatient Clinics) have integrated mental health programs, and 7.3% of all primary care patients at these sites were directly served during fiscal year 2015.

Notes

1. Formerly the Institute of Medicine (IOM)
2. See https://nam.edu/programs/value-science-driven-health-care/learning-health-system-series/.
3. "Pragmatic clinical trials (PCTs) test clinical interventions (e.g., treatments, diagnostic tests, and delivery strategies) that are widely used in practice and for which there is often clinical equipoise. Similar to traditional explanatory trials of novel therapeutics, PCTs use randomization to decrease selection bias. In contrast, PCTs rely on extant data sources (e.g., electronic medical records [EMRs]) and test interventions that can be implemented with minimal research infrastructures. Thus, PCTs have drawn interest as vehicles for decreasing the cost of clinical research and for creating learning health systems, which, as articulated by the Institute of Medicine, seek to generate new knowledge as an integral by-product of the delivery experience. However, realizing this vision for PCTs will require innovative approaches for engaging clinicians, improving the efficiency of subject recruitment, improving

the reliability of EMR data, and new paradigms for the regulatory review of low-risk trials to decrease unnecessary hurdles to practice-based knowledge generation" (Rosenthal GE. 2014. The Role of Pragmatic Clinical Trials in The Evolution of Learning Health Systems. *Transactions of the American Clinical and Climatological Association.*125:204-218.).

4. "Although PCTs are often a gold standard for determining intervention effects, in the area of practice-based research, there are many situations in which individual randomization is not possible. Alternative approaches to evaluating interventions have received increased attention, particularly those that can retain elements of randomization such that they can be considered "controlled" trials." (Handley, M. A., D. Schillinger, and S.Shiboski. 2011. Quasi-Experimental Designs in Practice-based Research Settings: Design and Implementation Considerations. *J Am Board Fam Med*. 24(5):589-596). These quasiexperimental design approaches—the interrupted time-series design, the stepped-wedge design, and a variant of this design, a wait-list crossover design—are gaining popularity.
5. The *Accelerating Clinical Knowledge Generation and Use* meeting agenda and summary are available at https://nam.edu/event/accelerating-clinical-knowledge-generation-and-use.
6. See http://www.pcori.org/sites/default/files/PCORI-PFA-2016-Health-Systems.pdf.
7. The attributes are part of the framework used for promoting the learning health system in Kaiser Permanente-Colorado. See http://kpco-ihr.org/Press/newsletter.html.

References

Agency for Healthcare Research and Quality, Universal ICU Decolonization: An Enhanced Protocol. September 2013, Rockville, MD. http://www.ahrq.gov/professionals/systems/hospital/universal_icu_decolonization/index.html.

Bernstein, J. A., C. Friedman, P. Jacobson, J. C. Rubin. 2015. Ensuring public health's future in a national-scale learning health system. *Am J Prev Med*. 48:480-487.

Blanco, C, A. N. Campbell, M. M. Wall, M. Olfson, S. Wang, and E. V. Nunes. 2016. Towards national estimates of treatment effectiveness for substance use. *J Clin Psychiatry*, in press.

Blanco, C, M. Olfson, R. D. Goodwin, E. Ogburn, M.R. Liebowitz, E. V. Nunes, and D. S. Hasin. 2008. Generalizability of clinical trial results for major depression to community samples: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 69(8):1276-1280.

Bracken, M. B., B. Djulbegovic, S. Garattini, J. Grant, I. Chalmers, A, M. Gülmezoglu, D. W. Howells, J. P. A. Ioannidis, and S. Oliver. 2014. How to increase value and reduce waste when research priorities are set. *Lancet.* 383:156-165.

Buist, B, E. Chang, M. Handley, R. Pardee, G. Gundersen, A. Cheadle, and R. Reid. 2016. Primary care clinicians' perspectives on reducing low-value care in an integrated delivery system. *Perm J.* 20(1):41-46.

Calfee, D. P., C. D. Salgado, A. M. Milstone, A. D. Harris, D. T. Kuhar, J. Moody, K. Aureden, S. S. Huang, L. L. Maragakis, and D. S. Yokoe. 2014. Strategies to prevent methicillin-resistant S*taphylococcus aureus* transmission and infection in acute care hospitals: 2014 update. *Infect Control Hospital Epidemiol.* 35:S108-S132.

Cole, S. R. and E. A. Stuart. 2010. Generalizing evidence from randomized clinical trials to target populations: The ACTG 320 trial. *Am J Epidemiol.* 172(1):107-115.

Deyo, R. A., M. Von Korff, and D. Duhrkoop. 2015. Opioids for Low Back Pain. *BMJ*. 350:g6380.

Food and Drug Administration (FDA). White Paper: Inventory of Clinical Trials Protocols and Clinical Study Data. http://www.fda.gov/downloads/drugs/developmentapprovalprocess/conductingclinicaltrials/ucm309552.pdf (accessed March 2016).

Gonzalo, J. D., P. Haidet, K. K. Papp, D. R. Wolpaw, E. Moser, R. D. Wittenstein, and T. Wolpaw. 2015. Educating for the 21st-Century Health Care System: An Interdependent Framework of Basic, Clinical, and Systems Science. *Acad Med.*

Greene, S. M., R. J. Reid, E. B. Larson. 2012. Implementing the learning health system: From concept to action. *Ann Intern Med.* 157:207-210.

Herland, K, J. P. Akselsen, O. H. Skjonsberg, and L. Bjermer. 2005. How representative are clinical study patients with asthma or COPD for a larger "real life population of patients with obstructive lung disease? *Respir Med.* 99(1):11-19.

Hoertel, N, Y. Le Strat, C. Blanco, P. Lavaud, and C. Dubertret. 2012. Generalizability of clinical trial results for generalized anxiety disorder to community samples. *Depress Anxiety*. 29(7):614-620.

Huang, S. S., E. J. Septimus, K. Kleinman, J. Moody, J. Hickok, T. Avery, J. Lankiewicz, A. Gombosev, L. Terpstra, F. Harford, M. Hayden, J. Jernigan, R. Weinstein, V. Fraser, K. Haffenreffer, E. Cui, R. E. Kaganov, K. Lolans, J. B. Perlin, and R. Platt.2013. Targeted versus universal decolonization to prevent ICU infection. *New Engl J Med.* 368:2255-2265.

Huang, S. S., E.J. Septimus, M. K. Hayden, K. Kleinman, J. Sturtevant, T. R. Avery, J. Moody, J. Hickok, J. Lankiewicz, A. Gombosev, R. E. Kaganov, K. Haffenreffer, J. A. Jernigan, J. B. Perlin, R. Platt, R. A. Weinstein. 2016. Effect of body surface decolonization on Bacteriuria and Candiduria in intensive care units: An analysis of a cluster-randomised trial. *Lancet Infect Dis.* 16(1):70-79.

Huang, S. S., E. J. Septimus, T. R. Avery, G. M. Lee, J. Hickok, R. A. Weinsten, J. Moody, M. K. Hayden, J. B. Perlin, R. Platt, and G. T. Ray. 2014. Cost savings of universal decolonization to prevent intensive care unit infection: Implications of the REDUCE MRSA trial. *Infect Control Hospital Epidemiol.* 35(S3):S23-S31.

IOM (Institute of Medicine). 2015. Integrating research and practice: Health system leaders working toward high-value care: Workshop summary. Washington, DC: The National Academies Press.

Johnson, K, C. Grossmann, J. Anau, S. Greene, K. Kimbel, E. Larson, and K. Newton. 2014. Integrating Research into Health Care Systems: Executives' Views. *Discussion paper.* Washington, DC: Institute of Medicine.

Lucey C. R. 2013. Medical education: Part of the problem and part of the solution. *JAMA Intern Med.* 173:1639-1643.

Masoudi, F. A., E. P. Havranek, P. Wolfe, C. P. Gross, S. S. Rathore, J. F. Steiner, D. L. Ordin, and H. M. Krumholz. 2003. Most hospitalized older persons do not meet the enrolment criteria for clinical trials in heart failure. *Am Heart J*. 146(2):250-257.

McClellan, T, and B. Turner. 2010. Chronic Noncancer Pain Management and Opioid Overdose: Time to Change Prescribing Practices. *Ann Intern* Med.152(2):123-124.

Morain, S. R. and N. E. Kass. 2016. Ethics issues arising in the transition to learning health care systems: Results from interviews with leaders from 25 health systems. eGEMs (*Generating Evidence & Methods to improve patient outcomes*). 4(2): Article 3.

Mulrow, C. D., J. W. Williams Jr, M. Trivedi, E. Chiquette, C. Aguilar, J. E. Cornell. 1999. Treatment of Depression: Newer Pharmacotherapies. Rockville, MD: Agency for Health Care Policy and Research; AHCPR publication 99-E014.

Okuda, M, D. S. Hasin, M. Olfson, S. S. Khan, E. V. Nunes, I. Montoya, S. M. Liu, B. F. Grant, and C. Blanco. 2010. Generalizability of clinical trials for cannabis dependence to community samples. *Drug Alcohol Depend.* 111(1-2):177-181.

Patsopoulos, N. A. 2011. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci.*13:217-224.

Post EP, Metzger M; Dumas P; Lehmann L. Families, Systems, & Health, 2010; 28(2): 83-90.

Pronovost, P. J., C. G. Holzmueller, N. E. Molello, L. Paine, L. Winner, J. Marsteller, S. M. Berenholtz, H. J. Aboumatar, R. Demski, and C. M. Armstrong. 2015. The Armstrong Institute: An academic institute for patient safety and quality improvement, research, training, and practice. *Acad Med*. 90(10):1331-1339.

Pronovost, P. J., C. M. Armstrong, R. Demski, T. Callender, L. Winner, M. R. Miller, J. M. Austin, S. M. Berenholtz, T. Yang, R. R. Peterson, J. A. Reitz, R. G. Bennett, V. A. Broccolino, R. O. Davis, B. A. Gragnolati, G. E. Green, and P. B. Rothman. 2015b. Creating a high-reliability health care system: Improving performance on core processes of care at Johns Hopkins Medicine. *Acad Med.* 90(2):165-172.

Septimus, E, J. Hickok, J. Moody, K. Kleinman, T. R. Avery, S. S. Huang, R. Platt, J. Perlin. 2016. Closing the translation gap: Toolkit based implementation of universal decolonization in adult intensive care units reduces central line associated bloodstream infections in 95 community hospitals. *Clin Infect Dis.*

Septimus, E. J., M. K. Hayden, K. Kleinman, T. R. Avery, J. Moody, R. A. Weinstein, J. Hickok, J. Lankiewicz, A. Gombosev, K. Haffenreffer, R. E. Kaganov, J. A. Jernigan, J. B. Perlin, R. Platt, and S. S. Huang. 2014. Does chlorhexidine bathing in adult intensive care units reduce blood culture contamination? A pragmatic cluster-randomized trial. *Infect Control Hospital Epidemiol.* 35(S3):S17-S22.

Slote, M. Z., S. Wooding, J. Grant. 2011. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med.* 104: 510-520.

Steiner JF, Shainline MR, Bishop MC, Xu S. 2016 Reducing Missed Primary Care Appointments in a Learning Health System: Two Randomized Trials and Validation of a Predictive Model. *Med Care.* 54(7):689-96.

Tew J, Klaus J, Oslin DW. The Behavioral Health Laboratory: building a stronger foundation for the patient-centered medical home. Fam Syst Health. 2010 Jun;28(2):130-45. doi: 10.1037/a0020249

Travers, J, S. Marsh, M. Williams, M. Weatherall, B. Caldwell, P. Shirtcliffe, S. Aldington, and R. Beasley. 2007. External validity of randomized controlled trials in asthma: To whom do the results of the trials apply? *Thorax*. 62:219-223.

Tricoci, P, J.M. Allen, J. M. Kramer, R. M. Califf, S. C. Smith. 2009. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA.* 301(8):831-841.

Von Korff, M, and G. Franklin. 2016. Responding to America's Iatrogenic Epidemic of Prescription Opioid Addiction and Overdose. *Med Care.* 54(5):426-9.

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