THE NETWORK FOR EXCELLENCE IN HEALTH INNOVATION

An Evolving Landscape: Comparative Effectiveness Research, Outcomes Research and Health Care Innovation

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Authors:
Thomas E. Hubbard, Vice President of Policy Research

Erin Bartolini, Program Director

Rebecca Paradis, Health Policy Analyst

Sarra Sabouri, Health Policy Intern

Editor:
Larry Bernard, Senior Director of Communications

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Looking Back: Expansion of CER in the United States and Its Impact on Innovation

Five years after Congress approved a major infusion of new funds for comparative effectiveness research (CER) via the American Recovery and Reinvestment Act, and four years after enactment of the Affordable Care Act and the creation of the Patient Centered Outcomes Research Institute (PCORI), the landscape of outcomes research in the United States health care system continues to shift. The shift may create significant new opportunities for valuable innovation in U.S. health care, but as yet, longstanding barriers and challenges to innovation that pre-date the period remain unresolved.

In NEHI's initial examination of the intersection of CER and innovation five years ago, concerns about the potential impact of an expanded CER program on innovation focused primarily on two areas.

First, there was a concern that a new CER program could be directly linked to technology adoption and reimbursement policies, in a relationship similar to that of health technology assessment (HTA) organizations in many European health systems. As it was finally enacted, the Affordable Care Act (ACA) did not create such an HTA-style organization, but instead created a new organization (PCORI) that is (a) focused on the generation and dissemination of new research, as opposed to making recommendations or decisions based on this research; (b) independent and multi-sectorial in governance, and; (c) patient-centered in its orientation, that is designed to answer questions of importance to patients, questions both clinical and non-clinical.

A second and related concern was broader and more difficult to quantify. By expanding the field of comparative effectiveness research in the U.S., there were concerns that standards of evidence for the validation and adoption of innovations would change. Indeed for CER proponents this was the whole point of expanding CER, to shift standards of evidence toward greater proof

of value – a fundamental theme of the movement in U.S. health care toward value-based decision-making and value-based payment.

Changes in standards of evidence pose a unique challenge to innovator biomedical companies. Companies face long lead times for development of products and when standards of evidence change while development and approval is still in process unanticipated delays and costs may ensue. “Downstream” changes in standards, such as changes in the standards of regulators or even the standards of payers and providers further downstream, can create uncertainty that will slow or freeze up further development and research of new products.

At this juncture, more downstream changes may be in the offing. This may create more uncertainty and more risk for innovation, but these changes could yield real benefit to innovation as well. The objective of this NEHI Issue Brief is to outline the nature of these changes and the potential implications, positive and negative, for valuable innovation in U.S. health care.

The upside potential essentially is this: The confluence of rapidly accumulating patient data available for research (in electronic health records, patient data registries, clinical trial datasets and in other forms), and of continued work in innovative, non-traditional methods of statistical analysis, hold the promise for faster research that can yield findings at smaller population levels (if not at the patient-specific level) and at higher levels of statistical confidence. For innovators, the promise is one of quicker, more accurate findings of clinical effectiveness that will reveal more valid measures of value for innovations such as new drugs, devices, and procedures.

At least three inter-related dynamics are helping to drive research and application of new findings: the rise of risk-bearing physicians and providers who represent an audience for findings of comparative effectiveness and of outcomes data more generally; expanded support for comparative effectiveness research in both the public and private sectors (albeit within limits such as those noted above); and the continued development of robust infrastructure for capturing and evaluating electronic health information. Each of these three dynamics is evidenced in the case examples presented below.

While these trends may promise a generation of research that produces findings more precisely targeted to individual patient needs, they do portend continued shifts in standards of evidence for the validation and adoption of innovation – and therein lies a risk. Whether changes in standards yield the best possible results for patients will depend on whether standards are developed and applied consistently and in a timely manner, and whether resulting processes to evaluate innovations keep pace with changes in science and technology.

PCORI at Year Four: Broad Mandate, Broad Agenda

The Affordable Care Act (ACA) created a new entity in PCORI that both expanded the organization's mission beyond a strict focus on CER, and also broke new ground by stipulating that PCORI governance be broadly representative of U.S. health care stakeholders, including patient advocates and industry representatives. The new organization was named the Patient Centered Outcomes Research Institute, as if to accentuate the point that PCORI's mission would range beyond CER.

Several provisions from the ACA and from the subsequent PCORI strategy are especially noteworthy:

- PCORI's sponsorship of comparative outcomes research is focused squarely on comparative clinical effectiveness. As such, PCORI's remit is not analogous to many European health technology assessment (HTA) programs that conduct cost effectiveness studies for purposes of coverage and reimbursement decisions. By extension, the Centers for Medicare and Medicaid Services (CMS) is prohibited from using cost-effectiveness as a basis for Medicare policy and is subject to statutory limitations on how it uses comparative clinical effectiveness research.

- PCORI is directed to undertake a broad research agenda that not only focuses on comparative analysis of discrete therapies, devices, and procedures, but directs PCORI to compare entire care protocols, entire modes of delivery, and even entire distinct systems of health care delivery. Here again, PCORI's agenda is much broader than the "drug vs. drug" or "device vs. device" studies historically associated with European HTA agencies.

- The PCORI Board of Governors made a substantial investment in distributed research networks through the creation of the National Patient Centered Outcomes Research Network (PCORnet) that will be enabled to conduct ongoing outcomes research on patient data routinely collected at points of patient care including hospitals and clinics. As of year-end 2013, PCORI invested nearly $94 million in 11 clinical research networks (CRNs)and 18 networks organized around patient volunteers and data shared by patients (Patient Powered Research Networks, or PPRNs).

- The ACA directs PCORI to make a substantial investment in activities that will expedite dissemination of medical and health services evidence so as to improve patient care more rapidly. PCORI also enjoys substantial discretion to invest in infrastructure (such as the development of research networks) that will accelerate the conduct of outcomes research.

- The ACA directly stipulates the creation of the PCORI Methodology Committee, a panel of experts charged with a mission to set priorities for investment in, and validation of, statistical methods for health-related data analysis. The overarching goal is to support

data analyses that yield safe and clinically useful findings for health care practice from methods that serve as a practical alternative to prospective Randomized Clinical Trials (RCTs).

- Finally, PCORI's lifespan is statutorily limited. Unless reauthorized, PCORI authorization and dedicated funding will expire in 2019. While it has a broad agenda, it will have less than a decade to demonstrate its impact.

According to research conducted by the California Healthcare Institute (CHI) dedicated a little over a third of its funding to straightforward CER studies that compare two or more health care interventions.[1] The remainder has been directed to methodology studies, dissemination-related research, and investments in data and analytic infrastructure such as its new PCORnet.[2]

"PCOR" as a PCORI Priority: Much of the non-CER investment represents a commitment to the "PCOR" concept for which PCORI is named. PCOR is largely focused on three objectives:

1. Establishing research study objectives (such as endpoints) that are derived directly from patient input and patient health care goals as expressed by patients themselves; (patient-reported outcomes, or PROs, are examples);

2. Improving scientific rigor around the collection and analysis of patient-reported data and data on patient goals; and

3. Development of research on patient engagement and improving the ability of patients to manage their own health care.

PCOR as a field can overlap but is not synonymous with CER, since patient-centered outcomes studies do not necessarily have to be comparative. Moreover, as a relatively new or undeveloped field, the PCOR research agenda will be one that will require prospective research, as much of the PCOR agenda requires the development of new tools and approaches for patient involvement. Thus the PCORI agenda extends beyond a pure focus on CER, as CER was generally conceived prior to the organization's creation.

Example: Patient-Powered Research Networks

One element of the current PCORnet strategy is the creation of "Patient-Powered Research Networks" (PPRNs), networks of patients with similar conditions who share their health data, their experience with treatment, and information on their clinical outcomes and quality of life with peers so as to directly inform research and the development of treatments and care protocols.[3]

The PPRN movement promises to have a direct influence on innovation. For example: Since its formation in 2006, the PatientsLikeMe community of ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease) patients have pooled their data to conduct analyses that demonstrated ineffective and potentially harmful use of two proposed new drugs and one off-label use of an existing drug. This kind of rapid, real time evaluation of results could lead to more highly targeted and effective research, clinical trials, and ultimate application of innovations. However, as PatientsLikeMe has acknowledged, it could also create unintended consequences, including inducement for clinical trial subjects to abandon trials prematurely – all pointing toward the need for greater development of rapid, effective patient-centered research practices that will enable the most effective participation of Real World patients.[4]

Outside PCORI: An Expanding List of Approaches, Players and Users of Outcomes

Developments transpiring outside of PCORI's program may portend the greatest implications for health care innovation in the U.S.

A Continuing Role for Health Technology Assessment

Health technology assessment (HTA) continues to influence payment and reimbursement decisions around the globe. European health care systems continue to rely on HTA agencies such as the United Kingdom's National Institute for Health and Care Excellence (NICE) and Germany's Institute for Quality and Efficiency in Health Care (IQWIG) for decisions on clinical and cost effectiveness, which in turn have substantial impacts on the pipeline for development of new products in many countries, including the U.S., since they influence the size of the global market for innovations.

Comparative studies conducted in the U.S. (from the National Institutes of Health [NIH], the Agency for Healthcare Research and Quality [AHRQ], and others) continue to inform serious debates about the adoption of various technologies, ranging from proton beam therapy for prostate cancer[5] to a long-running debate over the utility of drug-eluting stents for treatment of cardiovascular diseases.[6]

Example: Health Technology Assessment and Proton Beam Therapy

Health technology assessment studies are playing a major role in a series of decisions by public and private payers throughout the country regarding reimbursement of prostate cancer treatment by proton beam therapy (PBT). As of year-end 2013, Blue Shield of California and Aetna were reported to have dropped coverage of PBT for prostate cancer treatment, and Cigna was reported to have similar action under review.[7] Studies cited in validation of the action include retrospective studies of clinical and patient quality of life outcomes, supported by NIH and AHRQ. Systematic reviews of published evidence on PBT use are now under way on behalf of the Washington State Health Care Authority.[8]

Payers Take a Bigger Role in the Health Care Analytics Industry

The U.S. health care analytics market has grown substantially in recent years as improvements in health information technology (HIT) tools and infrastructure have improved capabilities, and the shift toward performance-based or outcomes-based payment has accelerated demand. U.S. health insurers are now playing a bigger and more direct role in the industry, based on their control of patient claims data and their access to related data such as pharmacy, laboratory and EHR data. The country's two largest private sector insurers (United Healthcare and WellPoint) both own analytics firms (Optum and HealthCore) that have access to the insurers' data (more than 109 million and 36 million covered lives respectively). These firms are strengthening the analytical capabilities of the insurers in support of coverage and reimbursement policy, including policies on value-based benefit design and formulary coverage decisions that directly influence adoption of new therapies and diagnostics. Pharmaceutical and medical device firms have proven to be major customers of insurer-owned analytics firms.

Example: WellPoint and AstraZeneca

In 2011, AstraZeneca Pharmaceuticals announced a "Real World Evidence Collaboration" in alliance with HealthCore, the data analytics firm wholly owned by WellPoint, the nation's second largest health insurer. The alliance facilitates research on WellPoint claims datasets, related pharmacy, lab and other clinical datasets available to WellPoint, and pharmaceutical trial data from AstraZeneca. The stated objectives of the alliance include research to determine improved endpoints for patient care, as well as research on overall treatment protocols and delivery modes that will reduce total costs of health care. The alliance has also sought partnerships with public agencies to conduct population health management analysis to support improved health and total cost of care management: The first such partnership is with the State of Delaware and the Delaware Medicaid program.[9]

Hospitals, Health Systems and The Learning System Model

For the last decade or more, the potential power of "learning health care system" capabilities in the U.S. has emerged as a pathway for simultaneously improving patient outcomes while reducing costs. The overarching goal is to incorporate continuous analysis and improvement of care and care processes based on emerging evidence and outcomes data. A major Institute of Medicine panel on Learning Health Care systems has noted that "emerging tools like computing power, connectivity, team-based care, and systems engineering techniques – tools that were previously unavailable – make the envisioned transition possible, and are already being put to successful use in pioneering health care organizations."[10] This trend has been accompanied by the parallel growth in policies that place provider organizations (hospital systems, integrated delivery systems, and so on) at financial risk for the clinical care they deliver, which has in turn fueled demand for data infrastructure and reporting that allows providers to manage their clinical and financial performance against specified metrics.

Organizations that are most likely to take the lead in learning health care system approaches are organizations with prior experience with, and an installed base of, patient data (such as EHRs). Highly integrated health care systems and academic health centers are at the forefront of the learning system movement. Systems such as Intermountain Health Care and the Veterans Health Administration (VHA) are frequently cited for their utilization of patient EHR data and advanced analytics to assess patterns of care within their own hospitals and clinics and, in some instances, to revise their own internal standards of care and care protocols as a result. Continuous, coordinated use of data and analytics within these systems is emerging as another alternative process for the use of evidence in medical decision-making.

Example: Standardized Clinical Assessment and Management Plans (SCAMPs)

SCAMPs are an alternative to clinical practice guidelines (CPGs). They emerged originally from pediatric hospitals seeking to leverage internal patient data to proactively redesign entire pathways of care, tailor care to the individual characteristics and needs of patients, reduce unnecessary practice variation, and optimize use of hospital resources and the overall cost of care. The inventors of the SCAMP approach at Boston Children's Hospital describe SCAMPs as a complement to comparative effectiveness research. Care plans are designed within the hospitals through a physician-led, multi-part process that begins with an assessment of current literature and may be enhanced with a retrospective study of current practice in the hospital. A treatment algorithm is created to guide care of patients eligible for SCAMP treatment, with appropriate provisions for physician override. As of 2013, almost 50 SCAMPs were in place in hospitals in nine states and Washington, D.C., covering a wide range of both pediatric and adult medical conditions.[11] Funding for SCAMPs development thus far has come from donated time, hospital resources, and philanthropy.

Collaborative Research Networks Also Represent a Growing Resource for Outcomes Research Used for Decision-Making

Collaborative or networked organizations could also prove to be more powerful sources of research as patient data accumulates. Several major clinical registries built on collaborations (such as the American College of Cardiology's [ACC] National Cardiovascular Data Registry [NCDR]), were created long before the enactment of the ACA or the creation of PCORI, but the acceleration of healthcare information technology (HIT) adoption since the enactment of the 2009 HITECH Act is expected to significantly increase the volume of data available for analysis, as well as the resources devoted to development of the tools and infrastructure that will enable the research. Collaborative networks administered or governed by professional societies such as the ACC or the American Society of Clinical Oncologists (ASCO, now the proprietor of the CancerLinQ network) represent a vehicle for the nation's specialty societies to expand their role in defining standards of care, a role they have often played by promulgating clinical practice guidelines (CPGs).

Investment in collaborative research data networks is a major element in PCORI's strategy, evidenced by the creation of PCORnet that will be managed by the Harvard Pilgrim Healthcare Institute. The Harvard Pilgrim group already serves as manager of the Food and Drug Administration's (FDA) Mini-Sentinel drug safety surveillance network as well as the NIH Health Care Systems Research Collaboratory. Thus, the governance structure created through Harvard Pilgrim could represent a means to achieve coordination and harmonization of standards and methods for outcomes research that is pertinent not only to clinical (post-market) practice, but to biomedical research and regulatory approvals as well.[12]

Example: CancerLinQ –The Learning Intelligence Network for Quality Cancer Care

CancerLinQ is a project of the American Society of Clinical Oncology, the professional society for U.S. cancer physicians. The Society's expressed goal in creating CancerLinQ is to create an "HIT-enabled rapid learning system" that will provide oncologists with real time clinical decision support for care of individual patients that meets ASCO-supported quality goals. CancerLinQ functions as a data network that draws individual patient data from participating clinical sites. Network proof of concept was achieved with the collection of breast cancer data for over 100,000 patients in 2012. ASCO expects the network to be available for general use in 2015.[13] Funding for the project thus far has been provided through private philanthropy.

Data from Clinical Trials – A Potential New Factor

Finally, a new factor in the expanding landscape of outcomes research is the potential availability to academic researchers of data from proprietary clinical trials conducted by pharmaceutical companies for purposes of regulatory approval.

Efforts to open up access to clinical trial data are rapidly gaining speed in the Europe and the U.S. The European Medicines Agency (EMA) is expected to rule in 2014 on a new policy for "pro-active" release of clinical trial data submitted to the EMA by pharmaceutical firms seeking authorization to market drugs in European Union member countries served by the EMA.[14] The EMA policy may well set a *de facto* international standard for public access to clinical trial data at the level of the individual patient. Both the European and American pharmaceutical trade associations (the EFPIA and PhRMA) have proposed alternatives to the current EMA proposal, and as of this writing two large pharmaceutical companies (GlaxoSmithKline and Pfizer) have announced their intention to provide public access to their trial data largely along lines proposed by PhRMA.

Example: Johnson & Johnson pharmaceutical trial data and YODA

In January 2014, Johnson & Johnson announced that it would make clinical trials data from its Janssen pharmaceutical companies available for independent research through a new arrangement with the Yale School of Medicine and its Yale Open Data Access (YODA) project. Researchers will apply for access through YODA, and access will be granted to non-commercial researchers who file a specific research proposal. Research findings must be made public. YODA's work will be supported by Johnson & Johnson.[15, 16]

Major Challenges Remain Unresolved in the Quest to Use New Data and Methods to Spur Innovation

Notwithstanding the excitement generated by the surge of data collection and analytics, coined "Big Data," some fundamental and longstanding challenges remain.

Methodological Challenges

While sources of patient data, improving infrastructure for research, and the arrival of fresh approaches such as PCOR are fueling excitement over the applications of outcomes research, the field as a whole continues to face serious challenges in standards and methodology. Effective methods must not only be developed, but also validated and widely used across the field if they are to influence health care decision-making and provide clear signals to health care innovation. The challenges include:

The problem of "dirty data": One great strength of prospective research remains the fact that data needs can be identified in advance and collected according to rigorous, pre-specified, and validated standards. Routinely collected patient data rarely meets such standards. Most patient data has been collected to serve immediate clinical and business needs, not for research purposes. Often there is significant variation in the categorization of data, the structure of reported data, and also the methods of soliciting and recording data. In order to ensure that data is valid and usable or to make competing datasets comparable, analysts must manually review and cull through data, which introduces an additional element of potential error and uncertainty. Making use of existing data requires workarounds in statistical methods, and devising the workarounds requires funding, effort, and experimentation to validate their use: in other words, a further expansion of the health care system's outcomes research agenda. Standards for the collection of new patient data need to be harmonized to assure that the data can be efficiently analyzed according to recognized principles.

Improving methods of analysis: It is widely accepted that new statistical methods must be devised and validated in order to generate useful analysis of existing patient data. The ACA recognized this by stipulating creation of the PCORI Methodology Committee. The oft-cited "gold standard" of analysis remains prospective RCTs of relatively homogenous patient pools, which tend not to be reflective of the pool of patients that will receive care in typical clinical settings. Statistical methods that allow for retrospective randomization of real life patients are not as yet backed by the same kind of expert consensus that supports RCTs, nor are statistical methods that yield precise, valid estimations of the clinical impact of health care interventions among populations of heterogeneous, Real World pools of patients.

Lowering barriers to collaborations for sharing data and improving methods: Barriers to collaboration inhibit development of consensus on methods. Many of the barriers are technical, but others are financial and competitive.

As a technical matter, lack of interoperability of electronic health records (EHRs) remains perhaps the single biggest barrier to advanced use of EHRs and the exchange of patient data for both clinical and research purposes. Technical flaws in protecting the privacy of patient data also inhibit greater patient support for the sharing of patient data for research purposes.

From a business standpoint, the sustainability of health care data exchanges remains a critical financial barrier, as all but a few of the emerging health data exchanges have negotiated a business model built on recurring funding. While some leading provider organizations are now willing to share data within clinical research networks in the hope of deriving clinically useful information, not all providers are convinced; ownership of data remains proprietary and the use of it is a competitive issue for some provider organizations.

For all these reasons, leading clinical researchers indicate that data sharing and collaborative research across research networks will continue to necessitate negotiation among provider

groups and creation of workaround strategies that would allow organizations to engage in research without sacrificing their control.

The Impact of Real World Evidence will be limited until methods challenges are overcome: Innovations in analysis, in the creation of research networks and the accumulation of massive amounts of patient data, are already generating useful findings for health care practice in the U.S.[17] But consensus among methodology leaders consulted by NEHI suggest that the impact of "big" patient data will be limited until the challenges outlined above are resolved, or at least until all stakeholders reach consensus on a pathway to resolving major methodological problems. Until then, several experts convened by NEHI in 2013 suggested that existing retrospective patient data is still mostly useful for "ruling things out, not ruling things in."

For example, some current analysis of big datasets is generating information on safety signals from the Real World use of medicines and devices, which may impact product labeling as well as provide useful information for practitioners at the point of care. But analysis with current methods and data is less useful in pinpointing the clinical effectiveness of interventions as tied to specific endpoints and patient outcomes. Thus current analysis can be useful in generating hypotheses of causality, but not for demonstrating causality itself. This is an extremely valuable result in its own right, and a potential boon to innovation, but a result that will still feed a need for prospective research. That would include RCTs, thus contributing a further demand on the health care system's outcomes research agenda that will stretch existing resources.

Utilization Challenges

As NEHI appraised the potential impact of expanded CER in 2009 we noted that "the accumulation of experience (with early stage utilization of innovations) is perhaps the most important dynamic of innovation from the standpoint of CER policy."[18] Early utilization of innovations frequently points the way to the true value of innovations for patient health as innovations are utilized among real patients in Real World settings. Moreover, as we observed in 2009, "new technologies frequently find their best, highest value use ... in combination with other products or procedures, often as a result of utilization with varying combinations of treatments carried out over time."[19] Payers have frequently proven reluctant, if not resistant, to fully cover and reimburse innovations that lack practical demonstrations of value. This results in a longstanding dilemma: how to demonstrate the value of innovations if they are not adopted and evaluated.

With the expansion of CER activity in the U.S. and other forms of outcomes research such as PCOR, the problem of how to create clear standards of evidence and clear standards of early adoption and use will intensify. The ongoing shift in payment policy toward value-based and globally-budgeted care will likely become major factors.

Accountable Care Adds a New Twist to the Challenge of Utilization: The advent of Accountable Care Organizations (ACOs) adds new twists to the dilemma of innovation adoption. Many of the earliest adopters of the ACO model are also organizations that tend to be the earliest adopters

of innovations, if not the actual inventors of those innovations: namely, academic health centers and many of the most highly integrated health care delivery systems. Under the ACO model these organizations face global budget caps that intensify the pressure they will feel to cost-justify the adoption of innovations. As it happens, many are also among the earliest adopters of HIT and represent the provider organizations that are most likely to generate their own patient data and conduct their own analytics to decide what interventions work best for their patient populations in their unique care settings. Some ACOs have begun to do precisely that.

At this early stage in the development of ACOs, experts are reluctant to predict how the ACO model will influence the adoption of innovations. The ACO model should create bigger demand for innovations that enable ACOs to achieve reductions in overall medical spending (Total Medical Expenditure) for patient populations, such as innovations that streamline care, enhance care coordination, enable prevention, and assist patient self-management.

On the other hand, since the ACO model shifts financial risk to the provider organization, the ACO has a stronger incentive to apply greater scrutiny to high-cost capital expenditures (such as those supporting new surgical units, or new imaging systems) and high cost new therapies and interventions (such as new drugs and devices). This represents a potential role change for academic health centers that are early-stage adopters of the ACO model, as academic health centers historically have been the places where innovations in acute care, such as surgical techniques and use of experimental new drugs, are often tried out first, and where the ability to train physicians on leading-edge innovations is often seen as a competitive necessity for medical education. Analysts such as Professor Michael Porter of Harvard Business School also point out that repeated utilization of new innovations in academic health centers or other leading-edge institutions often creates the learning curve on which practitioners perfect methods of utilization which lead, at least in some instances, to reduced costs of utilization over time.[20]

Meanwhile, provider organizations that have adopted the ACO model are now increasingly grappling with adoption of bundled payment strategies as well, responding to payer demands that episodes of acute care such as surgeries be packaged in highly efficient and cost effective new configurations. As provider organizations respond to bundled payment demands they will engage in what is essentially a form of comparative effectiveness analysis and determine which combination of interventions and tasks will satisfy patient care quality and outcome goals at prices that payers are willing to offer. Bundled payment plans will thus create yet another variable in the innovation adoption process, and one likely to be felt in organizations such as academic health centers that are traditional early adopters of innovations.

Shifts in Payment Increase the Need to Redefine Collaboration Among Providers, Payers and Life Science Firms

The shift toward value-based and budgeted payment in the U.S. is once again raising issues about how and when life science firms may collaborate with health care payers and health care providers. As noted above, some U.S. health insurers are positioning themselves as data and

analytic resources for pharmaceutical companies, as witnessed by the WellPoint/Healthcore relationship with AstraZeneca.

The ability of pharmaceutical companies to present data back to health insurers for consideration in coverage and payment decisions remains highly circumscribed by the FDA, particularly as it relates to communications about off-label uses of products. However as organizations (such as ACOs, networks of providers, networks or registries, etc.) increasingly gear up to conduct their own research on their own data – and on uses of pharmaceuticals and medical devices that may or may not confirm to FDA labels – life science firms feel an increasing disadvantage. Research on off-label uses remains particularly intense in areas where there are high levels of unmet medical need, such as cancer and psychiatric disorders.

The need for clear rules of the road on industry communication with payers and providers has also intensified with the move by pharmaceutical companies to open up access to previously proprietary clinical trial data for research by third-party researchers.

Numerous industry organizations and analysts have called for more formal agreement – and FDA guidance – to establish strong standards of good communication among industry, payer, provider and patient groups, including standards for transparency in reporting and adherence to good research practice. As health care providers take on increasing risk, through payment arrangements such as bundled payment plans, life science firms may even be called upon to provide expertise, or even serve as partners with health care providers seeking to find the most efficient possible uses of drugs and devices – thus further increasing the need for new principles of transparent, ethically appropriate and effective collaboration.

Example: The High Value Healthcare Collaborative

The High Value Healthcare Collaborative is a network of 19 health care systems joined to share data, conduct joint analysis on common health care conditions with a high cost impact on system costs, and to rapidly disseminate and adopt findings. The Collaborative is organized and administered by the Dartmouth Institute for Health Policy and Clinical Practice, which hosts the data infrastructure for the network. Initial study projects have focused on hip and knee surgeries, diabetes care, and improvement of sepsis control. The Collaborative's founders believe that research from the collaborative network will prove to be more rapidly performed (due to the network's electronic data infrastructure) and its findings more rapidly adopted (because analysis will be done across diverse, national settings, thus enhancing generalizability). Initial funding for the network has been provided by the collaborating health care systems, although the Collaborative is also the recipient of a $26 million CMS Innovation Center grant for a project to employ "Patient Family Activators (PFAs)," staff specifically trained to assist patients and their families with health care shared decision-making (SDM), and deployed throughout the member organizations of the High Value Healthcare Collaborative.

Summary: A Shift in the Traditional Paradigm of Evidence Adoption

Growth in patient databases, Big Data analytics and research networks raise a number of important questions for health care innovation. One very important question is how growth in Big Data or Real World Evidence research will change the way the U.S. health care system translates research findings into clinical practice. The historical paradigm (often observed in the breach) is one in which an accumulation of clinical data, mostly from one-off or short-term research studies, contributes to an evidence base that is periodically reviewed, with findings synthesized and recommendations converted into practice guidelines or other clinical advice, ordinarily by bodies such as professional societies that act on behalf of their profession.

There are exceptions to the paradigm that pre-date the ACA/HITECH and Big Data era (such as the VHA's extensive Quality Enhancement Research Initiative), but the emerging alternative paradigm is one in which any organization that can command a suitable volume of patient data and has the analytical capabilities suited to the task can perform their own analysis, drive their own conclusions, and put them into practice. Analysis can be conducted at any level that makes sense for its users: at the level of the individual health care system (e.g. Intermountain Health Care), a collaboration of similar health care systems (e.g. the High Value Health Care Consortium managed from Dartmouth Medical School), a network of specialists (e.g. the American Society of Clinical Oncologists' CancerLinQ), or networks run by patients themselves (e.g. PatientsLikeMe).

The promise of this decentralized trend in outcomes research is that it will create faster, cheaper clinical findings that reflect the characteristics of actual patient populations (Real World Evidence) and, because it was derived close to the point of care, will be applied to practice much more quickly than the oft-cited 17 year-to-adoption pattern made famous in successive Institute of Medicine reports.[21]

The positive news for health care innovation is that faster, cheaper analysis could lead to faster, cheaper findings that will allow for improvements in innovations and, when necessary, earlier termination of investments not likely to win regulatory approval or practitioner adoption (or what the firm of PriceWaterHouseCoopers recently termed "fast, frequent, frugal failure." [22]

For health care innovators, the more daunting prospect is that a proliferation of new evidence-generating initiatives, reaching down to the level of individual health care systems, will create greater uncertainty at least in regard to the type of innovative products and services that health care systems purchase, including medicines, medical devices, information systems, and so on. Variability among individual health care systems, in terms of the decisions that they make in deciding "what works best" among their unique patient population as treated in their own unique settings, may create some uncertainty for innovator biopharmaceutical and medical device companies as they work to develop new products and navigate regulatory and reimbursement pathways. Although the clinical practice guidelines or best practice recommendations promulgated by groups acting at the national level may present some

challenges for these developers, such recommendations do provide well-established, clear targets for innovators to aim at. The proliferation of decision-making processes down to the provider level could create many smaller targets that rely on underlying data that may not be collected and analyzed in ways that are exactly comparable from one provider organization to the next.

What Happens Next?

The expanding agenda for U.S. outcomes research, including evolving advances in data collection and analysis, and research methodology, is itself an innovative force in U.S. health care that is already generating useful research that could shape health care policy and decision-making in coming years. The bigger question for the cause of valuable innovation in U.S. health care is whether the landscape will evolve in directions that foster innovation and if the process can be accelerated, especially under current conditions.

First, the expansion in the outcomes research field is creating a lengthened "To Do" list of tasks. Standards and methods for data collection and analysis need to be developed, validated, and broadly accepted in order to influence health care decision-making and to send clear signals to innovators at all levels of the system. In many cases, the development and validation of methods to study existing patient data (old data) will have to be achieved through prospective study (new data), including RCTs. Considerable investment will need to be made in standards, methods and infrastructure before the use of routinely collected data fulfills the promise of faster, cheaper, and clinically relevant analysis for decision-making. Assuring transparency in how real-world data are used, and the underlying methods employed, also will foster accountability for high-quality research.

Second, the growing ability of health care delivery systems (including ACOs) or networks administered by medical specialty societies may spark innovations in health care delivery but may also create multiple targets for "upstream" innovators or innovators outside those networks to aim at as they develop new technologies or other innovations. Greater transparency of decision-support tools and evidence-based decision-making within new payment models will create clearer targets for innovators and a more level playing field for innovation. So far, PCORI has shown itself to be sensitive to this dilemma by entrusting the central administration of its new PCORnet network-of-networks to the same entity (the Harvard Pilgrim Healthcare Institute) that manages the FDA Sentinel network for drug safety network and the NIH Research Collaboratory. This centralization of coordinating power could be a practical way to promote a harmonization of standards and methods among outcomes researchers that also harmonizes the conduct of research useful for upstream biomedical research and FDA licensing purposes, as well as for use in daily health care practice.

Nevertheless, resources are limited. While the PCORI budget is often characterized as a major expansion of federal research funding, its annual operating funds are roughly equivalent to the

10th or 11th largest institute at the National Institutes of Health.[23] The NIH itself has faced a declining level of support in real dollars for more than a decade. Meanwhile, health care data exchange at the local level is still hobbled by the lack of sustainable funding for exchange construction and operation, while health care systems face the cost control constraints imposed by global or capitated budgeting. Pharmaceutical and medical device companies also face constraints in their ability to fund outcomes research, as investment time horizons in these industries have grown shorter and shorter.

Finally, progress could be hampered if major priorities for research and analysis are not set and shared more widely. Many observers (NEHI included) urged PCORI to focus intensively on major disease states with high unmet patient needs and major cost impact on the U.S. health care system, and to craft strategy to move research quickly into findings and dissemination.[24, 25] PCORI now faces some criticism that its investment strategy is too diffused to create a real impact on health care decision-making and health care spending in the near term.[26]

Conclusion

Five years ago, the U.S. expanded federal support for comparative effectiveness research amid a fractious debate over how new research might be used to ration patient access to innovations and reduce patient care. Five years later, there has been a notable shift from what was conceived as traditional CER to health outcomes research that is more broad in scope and striving toward meaningful, patient-centered research. This shifting landscape creates the potential for new forms of research and burgeoning volumes of patient data that may create faster, cheaper and more precise ways to deliver highly effective care to patients.

These advances in data and evidence also create some challenges. Big Data has not eliminated longstanding challenges in standards and methods, nor has it addressed the dilemma of allowing Real World demonstration of innovations in a health care environment where cost pressures can inhibit real world demonstration of innovation. Additionally, standards of quality measurement (including quality of life), as collected both within the clinical trial framework and in Real World clinical practice, are evolving and must be better aligned with patients' needs and values. Moreover, while the decentralization of research capabilities may prove to be a "thousand flowers blooming" episode that sparks innovation in research and analysis, it may also break up the traditional paradigm of evidence adoption in U.S. health care that has provided some level of certainty, however imperfect, that guides upstream innovation. Thus the continuing shift in the outcomes research landscape may merit a system-wide reexamination of research priorities and development of new consensus on a path forward, similar to the process that pre-dated the creation of PCORI and the expansion of U.S. outcomes research under the Affordable Care Act.

Key priorities moving forward include:

- Clarifying policy on access to emerging real world data sets for purposes of conducting comparative effectiveness and health services research. Policies that promote broader access to all qualified researchers, while affording appropriate protection to patient confidentiality and resolving any legitimate concerns over commercially sensitive data, , will accelerate the emergence of "Big Data" as a solution in health care.

- Promoting transparency in communication and use of CER and real world data. Transparency will help ensure that analyses are scientifically sound and clinically valid, and encourage work that provides an empirical basis for findings that identify the value of innovation, including innovations that address the individual patient's needs and preferences.

- Greater strides in defining and measuring value in ways that recognize the variability in treatment effects among patients, as well as encompass new definitions of value such as non-traditional and even on-clinical measures that pertain to patient quality of life, patient preferences and other measures of patient-centered care.

- Promoting the development and use of high quality data and sound research methods in new CER that relies on electronic claims and clinical data.

Advancing these priorities gives the best opportunity to ensure that the shifting landscape of comparative effectiveness research allows for innovation to take hold and flourish in the health care system.

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