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COMMENTARY

The fast route to evidence development for value in healthcare

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ABSTRACT

Over the past 30 years, our greatest accomplishments in advancing understanding about the safety, effectiveness and value of healthcare interventions have been achieved through the availability and accessibility of health insurance claims for large populations and, more recently, access to pockets of electronic health records that can be linked to information on expenditures, outcomes and patient experience. Although useful, this data lacks clinical detail and patient relevance. Going forward, we need qualified data networks that understand their data, have a research administration in place to evaluate requests, obtain institutional review and transfer data – all on a timely basis. The mecca of health information will be networks with comprehensive electronic health records that are able to collect and link supplementary data collected from clinicians, tissue banks, etc., and/or directly from patients, including information on quality of life and other patient-reported outcomes. A combination of data collected from clinicians, patients and health systems will provide details about treatment use, patient characteristics and health outcomes that are not consistently available in a patient's medical record, including whether prescriptions were actually filled, and if patients were hospitalized or had other costly healthcare that may not have been reported to their network doctors. We need a simple process to serve as a gateway to identify qualified research partners, the types of data each has access to, and how to work with them. The best partners will have established processes for contracting, prompt and informed institutional review, and data integration including supplementation from patients, clinicians and others, as needed, to support evidence generation that is more nuanced than simply choosing treatments based on how the average patient would respond.

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Introduction

It seems that nearly every week there are new reports about drug companies asking high prices for life-saving drugs or for drugs that dramatically improve quality of life. Consider, for example, a new drug which is expected to be a blockbuster, like the drug under development for psychosis related to Parkinson's disease[1]. How can we assess its value in terms of exactly who benefits, under what circumstances, and how much it is worth? "For most of medicine's history. . .physicians have been forced to approach prevention and treatment of disease based on the expected response of an average patient because that was the best that could be done"[2]. Considering the cost of developing and approving new medicines and the economic pressure on health systems, there is a new urgency to support more nuanced evaluations of care pathways and to provide treatment guidance for various subgroups and situations of special interest. There is also a longer horizon of focus, including risks and benefits that may not be evident for some time.

As biopharmaceutical and device manufacturers awaken to the realization that market adoption depends on more than regulatory hurdles and pricing, their interest increases in finding relatively quick, affordable approaches to providing evidence that will satisfy the needs of clinicians, patients, payers and health systems. We need access to large population-based data to support nuanced decision-making for patients with various characteristics that can make treatment challenging, such as for the elderly and very young as well as those with comorbidities or rare diseases. Many think that the solution lies in using "big data", as if the sheer quantity of observations were sufficient to provide robust and relevant enough information for all stakeholders and situations.

The most tried and true big data solutions have come from using health insurance claims and electronic health records, largely from ambulatory care settings. Since the 1980s, health insurance companies, particularly in the United States (US), have collected and made available uniform electronic data on covered services and medical products, including medications provided through out-patient pharmacies. Services and prescriptions can sometimes be linked, subject to privacy and data use agreements, which allows evaluation of drug safety and effectiveness, including the outcomes according to various types of medical care. Although limited by a dependence on billing codes that do not provide much clinical information, health insurance claims have real value

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because of the systematic scrubbing and vetting procedures applied before an insurer will provide payment. We can consider claims data a blunt tool, in that they can be useful for detecting big effects, like major safety issues that result in hospitalization or use of other expensive medical procedures, and crude measures of effectiveness such as the number of hospitalizations and length of stay after outpatient treatment for a medication intended to reduce such events.

More recently, electronic health records for large ambulatory care practices have become available in the US, in large part because of the governmental incentives provided to digitize medical records systems[3,4]. Companies that produce and support electronic health record systems, and the health systems themselves, are developing infrastructures for re-use of this data for research purposes due in part to altruism but also in an effort to monetize this sizable investment. Although there are good resources for ambulatory care data in many geographic regions, it is generally difficult to find out what else happened to a patient outside of a physician's individual practice, including information about treatments administered in infusion centers, hospitals and other locations where care may be provided. Information about continuity of care from hospital discharge through outpatient management, particularly for long term outcomes, is critical.

It is also important to recognize the role of patient-reported outcomes (PROs) in evaluating the health impact of different treatments through added insights that are otherwise not measured, either clinically or through health claims data. PROs enable measurement of the effectiveness of treatments beyond traditional endpoints such as survival or other objective endpoints of disease progression or resolution. Understanding the impact of treatment and clinical encounters on domains of health that are by definition patient-perceived, and hence patient reported, can improve individualized clinical management of patients and populations.

Key challenges for today

We recognize that aging populations and the increased prevalence of chronic diseases are straining healthcare systems. Policy makers and payers aim to control costs by requiring evidence of value and comparative effectiveness. European and US regulators are becoming more receptive to approving label extensions based on non-interventional studies using existing data, such as expanding approvals to broader age groups[5,6]. Patients have changed as well – they have become more empowered, better informed, and more invested in their health and well-being. Patient perspectives on value can also differ significantly from those of payers and healthcare practitioners, often integrating considerations beyond clinical outcomes. As a result, we are starting to see healthcare evolve toward a more patient-centric delivery model, a paradigm shift that is gaining some recognition from policy makers, payers, and the pharmaceutical industry. The FDA has led, for instance, nearly 20 disease-specific meetings to characterize and prioritize the impact of diseases on patients' lives through its Patient-Focused Drug Development Program. The movement towards patient-centricity has led some to advise biopharmaceutical companies to follow this "necessary revolution" or be left behind:

> "If pharmaceutical companies are to forge effective relationships with other key healthcare stakeholders, they need to be much more than a supplier and really understand the needs and expectations of their customer groups. They must partner with organizations that are addressing the major issues of cost, outcome and care, and become a more integral part of the health ecosystem."[7]

We need access to comprehensive and granular information on treatments and outcome information in large populations, with a focus on outcomes that are meaningful to clinicians and patients and which can guide effective treatment and health policy. For example, while drugs often receive market authorization based on changes in intermediate biomarkers in the pathway of disease, such as reducing low density lipoproteins which contributes to plaque buildup and leads to a narrowing of the arteries, patients are asking for information about how these treatments will affect their quality of life now and for how long. Payers want to know whether such treatments will avoid or delay expensive medical care. In oncology, for example, the balance between the quantity and the quality of the life remaining to be lived becomes paramount, since side effects of certain chemotherapeutic drugs can far outweigh the benefits, even when the benefit is prolonged survival. The EuroQol-5D[8] and Health Utility Index[9] measures have attributed a value to certain health states to be considered to be "Worse than death", as is the case for instance with prolonged coma[10–13].

Researchers are asking where they can find potentially relevant data sets to address these more nuanced questions, like which types of patients will benefit and in what situations[14]. Although networks of linked electronic health data and administrative claims are already a core foundation of the evidence structure, how they are organized and accessed is the challenge at hand. Some advocate large scale government-funded solutions, like the Sentinel Program for drug safety surveillance which links various networks that all use a common data model. There are also newer networks like the Patient Centered Outcome Research Network in the US and others in development to address issues not well served now, such as the paucity of uniform data available for medical devices[15]. Although these are costly undertakings, they offer a relatively rapid approach to evaluating safety signals in large populations, and a mechanism for more detailed evidence support for drug safety. However, these networks operate through gatekeepers and access is challenging, even for well recognized researchers. A more fruitful approach would be to develop a system where data network partners become qualified by virtue of their data, and experience, and willingness to use a common contract for data sharing.

There are three criteria that should qualify networks as potentially useful research partners. They must:

1. be knowledgeable about their data and network,
2. have a research administration team in place that will evaluate research requests, obtain institutional review

and approval, arrange for research contracts and secure data transfer(s) and
3. have a track record showing their ability to provide agreed-on data within a reasonable time frame.

A broad research contract could be created that would establish basic terms and conditions for these research partners. These contracts would include key provisions that address important issues such as the purpose for which data would be used, whether aggregate or patient-level data would be provided, if these data would be made available for a single purpose or for multiple purposes, if the data are to be used for a journal or regulatory submission, whether the providing institution would be given the opportunity to review and comment prior to any such submissions, etc., and the all-important waivers of liability.

There are some good examples of large data sharing partnerships with governance committees and processes for sharing and analyzing data, like the Biomarkers Consortium[16]. But other well intentioned collaborations have simply failed under the weight of their infrastructure. For example, Frances Collins has talked about the National Children's study, a program funded by the National Institutes of Health which folded after a $1.2 billion dollar investment, as "a Christmas tree with every possible ornament placed on it"[17]. While all research programs benefit from infrastructure and scientific depth, they are often inflexible and can be resistant to address new issues as they arise.

A light-touch approach could be developed for qualifying partners, whether through an independent certification body or simply by demonstration and attestation on the part of research entities. An accessible directory of well characterized research partners that may be engaged quickly and with confidence would facilitate their use. Distinguishing features of the best networks will be those that offer an integrated and comprehensive clinical and patient-centered picture. These networks will consist of electronic health records (EHR) that can be supplemented with data collection from clinicians, tissue banks, laboratories, etc. and/or directly from patients, including information on the quality of life and other patient-reported outcomes, and can link these data with health insurance claims. The supplementary data collection from clinicians and patients will provide detailed information about treatment use and patient characteristics that are not always consistently available in a patient's medical record. The addition of health insurance data allows evaluation of whether prescriptions were actually filled, not just prescribed, and whether patients were hospitalized or had other costly healthcare events that may not have been reported to their main doctor (general practitioner, specialist, or whoever is included in the particular research network).

This mecca of evidence can be accomplished right now in some countries, with appropriate informed consent and protection of privacy, but a lack of familiarity with this process and an overabundance of caution about potential threats makes such research activities cumbersome at best, with unpredictable processes and no guarantees of success. For example, a recent study that was conducted through a public–private partnership in the EU was delayed almost a full year because of administrative issues relating to legal control of data, protection of privacy and issues relating to obtaining informed consent for an Internet-based study of volunteers who offered to provide information about medication use and lifestyle practices during pregnancy. Although concerns about protecting patients and the privacy of their data are inarguably important, their right to reliable information about risks and benefits of medication use during pregnancy is also important. In this particular study, a substantial portion of the funding period for study conduct was spent trying to wrangle solutions that were particularly complicated in this new frontier of Internet-based, multi-country, public–private, multi-institutional collaborative research[18].

Nonetheless, social media shows us that millions of people with varying incomes and personal experience welcome the opportunity to share information about health issues and to contribute systematic information about themselves. We see well organized examples like PatientsLikeMe and Sharecare.com where patients provide personal health information in a de-identified manner. We also are seeing systematic direct-to-patient research being undertaken in the field of drug safety, without any direct, study-driven clinician engagement. For example, in the Internet-based pregnancy study mentioned above, the intent of this pilot study was to evaluate whether patient-reported data on medication use was reliable enough to be used for research. This study showed that consumers can be reasonably good reporters about their prescription medication use, as was validated by comparison with national prescription data and a sample of electronic medical records. Women also reported information that would not be available through tradition resources, such as use of non-prescription medicines, herbal and complementary medicines as well as alcohol, tobacco and recreational drugs. Respondents even told investigators when they decided not to take a medication that had been prescribed to them[19].

Consumers cannot be expected to report as if they were clinicians. For example, reporting whether a pregnancy resulted in a live birth or still birth is relatively straightforward, in contrast, say, to describing the clinical features of an adverse birth outcome. In some instances, however, patient-reported information can provide valid and reliable outcomes, even without clinician input. In patients with rheumatoid arthritis, the patient-reported version of the Disease Activity Score in 28 joints (DAS28), for instance, was found to be at least as reliable as physician-, nurse-, or US-derived DAS28, except for the detection of synovitis[20].

It is also important to keep in mind that volunteers for direct-to-patient studies, and possibly for any research that does not provide any "free" treatments or services as would be received in clinical trial, attract people who are likely to be well educated, on the whole, and who earn enough money to allow them the time to participate in studies. So non-interventional research results generally reflect the treatment risks and benefits experienced by people who can afford access to healthcare. Participants in direct-to-patient studies, in particular those that require data gathering longitudinally, are known to be reflective of the most engaged patients. They also require a minimal level of health literacy, and

a basic, accurate understanding of their medical conditions. Although this clearly poses limitations in terms of generalizability to under-served or vulnerable populations, many important questions about safety and effectiveness, derived from observations in more affluent subjects, may also be applicable to them. Nonetheless, it is important to keep in mind that underserved and vulnerable populations may only have access to selected health services and health systems that will not participate in large research consortia due to budgetary limitations, and these people may not have internet access or use devices that can directly provide data to clinicians, like wearables. Thus separate approaches will be needed to fully understand safe and effective treatments for some vulnerable populations.

Conclusion

We see healthcare systems and private entities starting to reap the benefits of research based on their patient data collected via real world, routine care. The more we are able to identify relevant and accessible data partners that have reliable processes for collaboration including contracting and data sharing, the easier it will be to draw sound conclusions about treatment value and relevant outcomes for various groups of interest. The best research partners will be those that have established processes for access to electronic health records and integration, and can support direct data collection from clinicians and patients. Experienced researchers with access to these tools will be able to generate relatively quick and reliable information to help us gain a better understanding of clinical, patient and treatment factors that predict favorable health outcomes from the perspective of patients, clinicians and health systems.

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