# Introduction

International comparisons show that the United States spends much more on health care and has poorer health outcomes than other advanced economies.[[1]](#endnote-1), [[2]](#endnote-2) While many important issues are involved in such comparisons, improving outcomes and resource use are key goals in the US and throughout the world, now and in the future.

A key intellectual milestone in health care in the 20th century was the recognition that clinician experience alone as a guide to decision making is often misleading because differences in outcomes may reflect differences in pre-treatment status rather than treatment effects. This recognition is the foundation for evidence-based medicine as ‘… the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.’ [[3]](#endnote-3)

A second milestone was the Institute of Medicine’s 2007 conclusion that an ongoing “learning health system” (LHS) was needed to “generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care.” [[4]](#endnote-4),[[5]](#endnote-5)

This paper focuses on these initiatives, discusses their status, barriers to progress, and proposes a set of requirements and methodology for a project and a plan to accelerate progress.

# Current Status

More than 40 years ago, a cardiologist could type patient characteristics into Duke University’s cardiac database and see three-year survival curves for comparable patients treated with medical versus surgical therapy for coronary artery disease.[[6]](#endnote-6) More than 30 years ago, evidence-based medicine became the paradigm for clinical decision-making worldwide.[[7]](#endnote-7) But today, while there are many examples of progress, clinicians are all too often forced to make educated guesses. Fragments of evidence must be pieced together like pieces of a jigsaw puzzle to make “evidence-based” recommendations. [[8]](#endnote-8), [[9]](#endnote-9) Guidelines are typically developed for the “average” patient with a single condition, making them difficult to apply to those with multimorbidity or unique circumstances.[[10]](#endnote-10), [[11]](#endnote-11) Additionally, the evidence base is often incomplete, with few if any high-quality studies for many clinical decisions.[[12]](#endnote-12) As a result, clinicians must integrate limited evidence with their own expertise and patient values to provide truly individualized care.[[13]](#endnote-13), [[14]](#endnote-14) Evidence also is fragmented across disease-specific guidelines, forcing clinicians to synthesize disparate recommendations when treating complex patients, potentially risking polypharmacy and adverse interactions.[[15]](#endnote-15)

Similarly, almost twenty years after its initial launch, the LHS model is not yet a fully operational, end-to-end reality at an institutional level. Some health care systems have implemented some of its elements, but achieving a true, continuously improving LHS across entire healthcare systems is still a work in progress. It is, still, more of an aspirational model.[[16]](#endnote-16), [[17]](#endnote-17), [[18]](#endnote-18)

# Barriers

How can we make learning health systems and evidence-based health care an everyday reality rather than something that is always fifteen years to twenty into the future, as has been the case for nuclear fusion? Unlike the case of nuclear fusion, the barriers are not technological. The necessary technologies already exist and have been demonstrated in many settings.

Electronic health record (EHR) data is being generated and aggregated at scale. Every day, thousands of healthcare institutions generate vast amounts of EHR data. This data is increasingly being standardized and aggregated into common data models like OMOP and PCORnet, making it readily available for research and analytics.[[19]](#endnote-19), [[20]](#endnote-20) Large-scale datasets from these networks have already enabled observational studies, comparative effectiveness research, and predictive modeling at unprecedented scales.[[21]](#endnote-21) Over the past two decades, more than 31,500 EHR-based studies have been published globally.[[22]](#endnote-22) Additionally, major research and commercial networks house hundreds of millions of unique patient records.[[23]](#endnote-23), [[24]](#endnote-24) These figures show data availability is not a primary barrier to making a learning health system an everyday reality.

Analytic capability also is not a primary barrier. A broad range of advanced statistical and machine learning methods have been developed for use with EHR data. Causal inference techniques, such as target trial emulation and inverse probability weighting, enable researchers to derive real-world evidence that can complement randomized controlled trials.[[25]](#endnote-25), [[26]](#endnote-26) Machine learning models have been used with EHR data to support risk prediction and improve diagnostic accuracy.[[27]](#endnote-27) All-by-all analysis has emerged as a powerful approach to discover novel associations between clinical variables, enabling large-scale hypothesis generation across the full spectrum of coded medical concepts.[[28]](#endnote-28) Additionally, distributed model-building has been demonstrated in selected use cases thereby reducing security risks associated with centralized pooling of multi-institution data.[[29]](#endnote-29), [[30]](#endnote-30), [[31]](#endnote-31), [[32]](#endnote-32), [[33]](#endnote-33)

What then might be the barrier to progress? The key barrier might well be the “research mindset,” a mindset that dominates the field. To be clear, this way of thinking has been enormously successful. But building a learning health system that can support everyday clinical care across the entire range of health problems and health care is a different task than answering a research question for publication.

To the best of our knowledge, all existing work to support evidence-based medicine and learning health systems involves answering discrete, highly specific research questions. Medicine involves a high degree of specificity. If attention is not paid to minute details, clinical care and study conclusions could easily be wrong. *One-at-a-time research is essential for successful, timely, and on-budget completion of many projects*. But if you need to build the capability to answer thousands or hundreds of thousands of questions, the one-at-a-time approach is exponentially more costly, more time consuming, and will ultimately fail.

This tendency to focus on one-at-a-time research is further reinforced by the history and culture of modern medicine. Over the past hundred years, medical practice, medical literature, and medical research have developed as a complex web of many disease-specific or specialty-specific communities, each with their own language and set of concepts. That approach was optimal until recently. There was little need for standardizing concepts, vocabularies, and methodologies across diseases, organ systems, or specialty domains when the output of research was embodied by text on paper or presentations at conferences and used primarily by specialized practitioners and researchers. There was no need to make concepts and metrics “interoperable” prior to the advent of EHRs and large databases integrating clinical data on millions of people encompassing a comprehensive set of health problems and clinical modalities.

Now, we risk creating an unmanageable, unknowable, and costly “Tower of Babel” with the flood of information made possible by new technology, unless we develop analytics that are use-case, and condition and treatment agnostic. Moreover, as has always been true, patients can have any set or combination of illnesses, risks, and treatments, and so analytics or research findings must fully account for such situations. This can be achieved by only building an analytic system from the ground up in a use-case, condition, and treatment agnostic manner.

Of course, clinical issues are highly specific. But rather than having different data structures or concepts for different clinical domains, unique characteristics of illnesses and treatments can be fully represented by patient-specific values that populate rows and columns in a set of condition-, treatment agnostic data structures, concepts, and methodologies. This, in turn, will support mass-production of clinically valid inferences based on application of knowledge to real-world clinical situations.

# Requirements for a Comprehensive Health Care Analytic System

“Patients, doctors, nurses, payers, public health officials, and other government agencies all need better, more timely … information if we are to improve. To make a measurable impact, applied clinical analytics must inform these decisions and processes on a mass scale whenever and wherever needed. That is why we need *an ongoing health care analytic system*.[[34]](#endnote-34) EBM and LHS must be transformed from goals into a working analytic system that can be used and relied upon in everyday care as a trusted source of evidence.

For such a system to be trusted, it must be fully transparent, easily understandable, auditable, and fully validated. Methodologies and data sources must be subject to peer review. And it must be based on methodologically sound statistical and causal inference methods.[[35]](#endnote-35), [[36]](#endnote-36), [[37]](#endnote-37) Moreover, as an ongoing learning system, the analytic system must be easy to maintain and update to incorporate new knowledge, new concepts, new data, and new medical technologies.

While artificial intelligence (AI) can play a role, AI cannot be the main foundation of the system simply because AI by itself cannot create evidence. Evidence can only be sourced from randomized clinical trials or observational studies that use proven methods to control sources of bias.[[38]](#endnote-38)

Note that the system must be based on conceptual framework and data model that enables the system to provide internally consistent and methodologically sound answers for a comprehensive range of questions. Otherwise, the resulting complexity will result in a “Tower of Babel” that cannot be readily understood, audited, and maintained.

To have maximum impact, the system must be designed to provide evidence-based answers for the myriads of questions that arise in everyday patient care and in improvement initiatives at organizational, community, or system-wide levels. Supplementary Appendix 1 sketches out a compact set of broader, more abstract, high-level questions that serve as templates for more specific, detailed questions that must be answered, and shows how these questions can be answered, using the concepts, methodologies, components, and data structures described in this paper. This appendix also describes how these capabilities can be incrementally enhanced.

# Conceptual and Analytic Frameworks

To improve outcomes, we need to understand how and why suboptimal care and suboptimal outcomes occur. For this, we need an updated and expanded version of Donabedian’s “structure, process, outcome” (SPO) paradigm[[39]](#endnote-39). Two major changes are included in this version.

The new version of Donabedian’s 1966 framework incorporates a broader range of “actors” by including patients, families, communities, provider organizations, health insurers, government, and others, a broader range of actions, including self-care by patients and families, and finally a broader range of root causes, including social factors that impact on a patient’s self-care and ability to access clinical care. The range of relevant actors (and actions) varies depending on the context and health problems involved. (For example, in an ICU, the primary actors are the ICU team. At the other extreme, for most preventive care and care for chronic conditions, patients and families must take the lead since they spend 99% of their time outside the doctor’s office—at home, work, or elsewhere. For other contexts and problems, other actors and actions are relevant, for example home health nurses for at home care or public health agencies for communicable disease.)

This new SPO framework also adds a “generic process of care model,” that specifies a sequence of high-level steps that must be completed successfully on a timely basis for optimal outcomes. The list is intended to be complete and comprehensive as a high-level outline for all health problems. The specific actions required for a process step vary by health problem, and some steps may be unnecessary for some problems, but not for others. By standardizing the architecture of care processes, this generic model enhances transparency as to what is being required in complex guidelines, facilitates their automated application to clinical data, and facilitates analytics to identify and develop new best practices and standards of care. (See )

We also need a framework for understanding modeling output in causal terms. Modern causal theory provides this guide by classifying covariates based on how they influence causal relationships—whether by confounding, mediating, or modifying effects—and provides formal criteria to distinguish among them, guiding proper adjustment strategies. [[40]](#endnote-40), [[41]](#endnote-41), [[42]](#endnote-42) (Supplementary Appendix 5 for further details.)

# Key System Components

For a comprehensive system, hundreds, if not thousands, of explanatory, causal, and predictive models must be mass-produced on a methodologically sound, comprehensive, and internally consistent basis. How can this be done? *The key is to combine observational data with ‘machine-readable’ clinical knowledge to build data files that anticipate, standardize, and automate SPO-based analysis and modeling*.

The *’analytic patient history’* is one of three key system components. This history is a set of data tables that integrates clinical knowledge with observational data and serves as input for automated model building. One set of tables tracks changes in a person’s health problems while a second set maps all care for a health problem (including self-care) into a sequence of process of care steps with an identified “best practice” for each (if known). Together these tables can identify all variances between actual and recommended care and the resulting health impact for *each problem and step.* A thirdset of tables identifies patient- and clinician-related factors (“root causes) that are barriers to optimal care. When used together these tables can identify the root causes responsible for suboptimal processes that result in suboptimal outcomes. (See Supplementary Appendix 6, “Analytic Patient History”.)

Categories of suboptimal outcomes that can be identified include: (1) new conditions that could have been prevented, (2) symptoms, or disabilities resulting from an illness or injury that could have been shortened in duration or better controlled, (3) acute exacerbations or progression in disease stage that could have been prevented, and (4) complications of illness or treatment that could have been prevented. Categories of suboptimal resource use include: (1) care required due to preventable adverse outcomes, (2) costlier treatments when safer, equally effective alternatives exist, and (3) care with little or no benefit. The data tables also help identify (1) diagnostic delays and errors and (2) cascading complications and their impact on health and resource use.

Through this approach, a comprehensive set of avoidable adverse outcomes can be identified at a patient, cohort, or population level along with causative suboptimal processes and patient and clinician-related root causes. This information, in turn, can be used to identify care improvement priorities and “corrective interventions.” Moreover, the resulting data set would be well-organized to accelerate the development of new best-practice standards to fill the highest priority gaps. (See for further discussion on prioritization.)

*A set of ‘machine-readable’ clinical knowledge is a second key component.* Four types of knowledge *relationships* are needed for constructing the analytic patient history: *causal* (e.g., pneumonia can cause sepsis), *recognized use* (e.g., a chest X-ray can be used to diagnose pneumonia), *principal / supporting service* (e.g., anesthesia is a supporting service for surgery), and *clinical best practice* (e.g., routine use of some type prophylaxis to prevent venous thrombosis after hip replacement).

While some limited resources exist, we are unaware of a publicly available resource that encodes these relationships in machine-readable form that is both systematic and comprehensive.[[43]](#endnote-43) This gap can be rapidly filled by mining observational data to develop a comprehensive list of 'candidate relationships.' These can then be reviewed for completeness and validity using large language models on a mass production basis. In our previous studies (unpublished data), we have developed and tested this approach. Causal discovery methods can also be used. Additionally, relationships can be validated by an expert review process akin to Wikipedia's crowdsourced editing model.

Indeed, providing a comprehensive and publicly accessible set of clinical knowledge relationships would be a key deliverable for a project to build the proposed comprehensive health care analytic system. This knowledge database would be linked to other components of the system and would thereby allow identification of key knowledge gaps, and their systematic prioritization of closing identified gaps in terms of potential favorable impact on health outcomes and resource use.

We further envision that this knowledge repository would include additional categories of relationships between concept pairs, such as semantic relationships, and would also include classification of covariates using the typology developed as part of modern causal theory. (See for further details on the proposed knowledge repository.)

*A third system component is a set of automated processes that build a comprehensive set of causal and predictive models* needed to improve outcomes on an individual and systematic basis.

# Accelerating Progress

The OMOP common data model has similarities[[44]](#endnote-44)

To follow

# Next Steps

To follow

# Conclusions

To follow

# Supplementary Appendix

## Analytic Capability Requirements

# Supplementary Appendix

## Process of Care Models

**Process Steps for a New or Ongoing Health Problem**

* Initial access to care
* Diagnosing the problem (testing and /or referral, if needed)
* Identifying the cause of the problem
* Recommending and planning treatment, educating patients
* Carrying out treatment (by clinician or patient at home)
* Follow-up, monitoring, and re-evaluation, if needed
* Screening and prevention of complications
* Continuing or revising treatment, if needed
* Rehabilitation or restoration, if needed

**Process Steps for a Complex or High-Risk Treatment**

* Pre-treatment evaluation and planning -
* Evaluation and tests to confirm need and optimal approach for treatment.
* *Evaluation and tests to assess operative risk due to unrelated co-existing conditions.*
* Intra-treatment care -
* The principal component of the treatment itself, e.g., coronary artery grafting
* Supporting components of the treatment itself, such as anesthesia, facility services, or supplies
* *Tests, monitoring, and supportive care to manage* ***expected adverse effects*** *of treatment.*
* *Tests to identify our services to prevent potential treatment complications.*
* Post-treatment care -
* Evaluation and tests to monitor and manage recovery.
* *Post-op care of expected adverse effects of treatment, such as care of post-op pain or surgical wounds.*
* *Tests to identify our services to prevent treatment complications.*
* Rehabilitation for restoration of function

# Supplementary Appendix

## Prioritization

# Supplementary Appendix

## Clinical Knowledge Repository

|  |  |  |  |
| --- | --- | --- | --- |
| Supplementary Appendix  **Comprehensive List of Covariate Types** | | | |
| **Covariate Type** | **Definition** | **Representation** | **Example (All Related to Heart Disease O)** |
| Direct Cause | has a direct causal effect on the outcome. | Z → O | Smoking (Z) directly increases the risk of heart disease (O). |
| Indirect Cause via a Mediator | affects the outcome only through a mediator. | Z → M → O | A sedentary lifestyle (Z) leads to weight gain (M), which in turn increases the risk of heart disease (O). |
| Mediator | transmits the effect of another cause on the outcome. | X → Z → O | High blood pressure (Z) mediates the effect of high sodium intake (X) on heart disease (O). |
| Moderator | modifies the strength or direction of X on O | X → O, modified by Z | Older age (Z) correlates with longer duration of risk factor exposure (e.g., high cholesterol), making cumulative damage more relevant for heart disease (O). |
| Confounder | affects both the exposure and the outcome, creating a spurious association. | Z → X and Z → O | Dietary habits (Z) influence both physical activity levels (X) and heart disease risk (O), potentially confounding the relationship between exercise and heart disease. |
| Collider\* | is caused by two or more independent causes; can introduce bias if adjusted for. | X → Z ← O | Genetic predisposition (Z) is influenced by both family history (X) and environmental factors (O). Adjusting for Z can create a spurious association between X and O. |
| Independent Cause | affects the outcome but is unrelated to other variables in the model. | Z → O, but Z ≠ X | Air pollution (Z) independently increases heart disease risk (O) but is unrelated to dietary sodium intake (X). |
| Proxy Variable | is correlated with an unmeasured cause of the outcome but has no causal effect | U → Z, U → O | Waist circumference (Z) is a measurable proxy for visceral fat (U), which is the true cause of heart disease (O). |
| Instrumental Variable | affects the exposure but has no direct effect on the outcome | Z → X → O  (No direct Z → O path.) | Genetic variation (Z) influences cholesterol levels (X) but does not directly cause heart disease (O). Used for causal estimation. |

Supplementary Appendix

**The analytic patient history**

**Health –** health adjusted life expectancy reflecting impact of health problems on longevity and daily well-being at a given point in time

**Health risk** – probability of a new illness based on known risk factors, such as probability of coronary disease based on risk factors

**Condition** – a distinct illness or injury, with start and end dates, potentially life-long

**Reported diagnosis** – set of initial and subsequent “working” diagnoses and “correct” final diagnosis for a condition

**Condition sub-episode** – a significant change in a condition over time reflecting a change in condition control, acuity, or stage

**Clinical observations, test results, self-reported outcomes related to a condition**

**Condition-related symptom or complication** - a symptom or a new illness or injury caused by a condition, such as sepsis caused by pneumonia

**Process Step – a high-level step in the process of care for a health problem, includes one or more units of care, and supporting services**

**Health problem** – a health risk, condition, condition phase, symptom, disability, or complication affecting longevity or daily well being

**Treatment episode –** a multi-day unit of care with all supporting services, such as all pre-, intra-, and post- care for a surgery or a course of chemotherapy

**Inpatient stay or ambulatory encounter** – a unit or care that includes all facility and professional services provided during the stay or encounter

**Intervention** – a subunit of care provided during an inpatient stay or encounter including all component services, such as a cardiac stress test

**Service or medication** – a service or medication that corresponds either to the principal service or a supporting service of an intervention

**Treatment-related symptom or complication** - a symptom or complication caused by a treatment

**Person –** demographics and socioeconomic characteristics that increase risk or a new illness or injury or impair self-care or access to clinical care

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AI-generated content may be incorrect.A black and white screen with white lines

AI-generated content may be incorrect.

Add table showing factors that increase the probability of sepsis

Supplementary Appendix

**Structure of Relationship Tables Used to Assemble Analytic Patient History**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **dx co-occurring with lupus** | **co-occurrences** | **lift** |  | **dx co-occurring with lupus** | **co-occurrences** | **lift** |
| cv - raynaud's syndrome | 868 | 15.4 |  | cv - pulmonary embolism | 1,641 | 1.4 |
| cv - other arteritis | 789 | 10.2 |  | eye - other keratitis | 1,044 | 1.4 |
| blood - hypercoagulable state | 1,474 | 7.6 |  | eye - dry eyes | 802 | 1.3 |
| ms - extremity - other arthropathy | 23,232 | 6.9 |  | endo - thyrotoxicosis +/- goiter | 1,143 | 1.3 |
| gu - nephritis - in other diseases | 690 | 5.1 |  | bh - adjustment/stress | 5,032 | 1.3 |
| gu - nephritis / nephrosis | 10,803 | 4.6 |  | cv - thrombophlebitis - deep - le/nos | 13,600 | 1.3 |
| gi - hepatitis - other chronic | 534 | 4.0 |  | cv - chronic cor pulmonale | 1,516 | 1.2 |
| blood - acquired hemolytic anemia | 716 | 3.7 |  | endo - goiter - non-toxic | 2,705 | 1.2 |
| ns – migraine | 9,383 | 3.0 |  | endo - hypothyroid – primary | 4,417 | 1.2 |
| ns – myopathy | 1,812 | 2.9 |  | id - candida – other | 1,615 | 1.2 |
| blood - primary thrombocytopenia | 586 | 2.6 |  | cv – endocarditis | 1,170 | 1.1 |
| skin - other skin conditions | 134,310 | 2.6 |  | gi - peritonitis - nec/nos | 930 | 1.1 |
| ms - joint - other arthropathy | 33,319 | 2.3 |  | bh - depression/affective ds | 116,790 | 1.1 |
| blood – neutropenia | 2,528 | 2.2 |  | id - other bacterial id | 12,208 | 1.0 |
| cv - other pericardial disease | 1,215 | 2.1 |  | blood - anemia - nec/nos | 9,884 | 1.0 |
| resp - pulmonary fibrosis | 803 | 2.0 |  | blood - other white blood disorders | 518 | 0.9 |
| eye - other eye inflammation | 936 | 1.9 |  | gu - other ureteral disorders | 2,988 | 0.9 |
| ms - elbow – enthesopathy | 740 | 1.8 |  | gu - chronic renal failure | 29,810 | 0.9 |
| ms - bone - other bone / cartilage | 21,987 | 1.7 |  | id – sepsis | 15,351 | 0.8 |
| blood - anemia due to chronic illness | 744 | 1.7 |  | endo – malnutrition | 5,560 | 0.8 |
| ns – epilepsy | 7,690 | 1.5 |  | gu - acute renal failure | 5,668 | 0.7 |
| blood - other coagulation defect | 818 | 1.5 |  | ns – encephalopathy | 2,112 | 0.7 |
| skin - dermatitis – nos | 1,161 | 1.5 |  | eye - macular degeneration | 6,573 | 0.7 |
| blood - thrombocytopenia – nos | 803 | 1.4 |  | ms - hip – fracture | 2,664 | 0.7 |
| cv - pulmonary embolism | 1,641 | 1.4 |  | bh - organic mental ds | 32,525 | 0.5 |

Supplementary Appendix

**Statistics and machine learning can semi-automate relationship table build**

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