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Perspective

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Computer clinical decision support that automates personalized clinical care: a challenging but needed healthcare delivery strategy

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ABSTRACT

How to deliver best care in various clinical settings remains a vexing problem. All pertinent healthcare-related questions have not, cannot, and will not be addressable with costly time- and resource-consuming controlled clinical trials. At present, evidence-based guidelines can address only a small fraction of the types of care that clinicians deliver. Furthermore, underserved areas rarely can access state-of-the-art evidence-based guidelines in real-time, and often lack the wherewithal to implement advanced guidelines. Care providers in such settings frequently do not have sufficient training to undertake advanced guideline implementation. Nevertheless, in advanced modern healthcare delivery environments, use of *eActions* (validated clinical decision support systems) could help overcome the cognitive limitations of overburdened clinicians. Widespread use of *eActions* will require surmounting current healthcare technical and cultural barriers and installing clinical evidence/data curation systems. The authors expect that increased numbers of evidence-based guidelines will result from future comparative effectiveness clinical research carried out during routine healthcare delivery within learning healthcare systems.

Key words: clinical, clinicians, computers, decision-support, automated clinical care, closed-loop

INTRODUCTION

Evidence-based guidelines currently address a small fraction of the patient care decision-making quandaries that clinicians encounter. Overburdened, unfettered clinicians in the absence of guidelines deliver opinion-based care reflecting their variable levels of understanding, their biases, their backgrounds, and their personal foibles. Clinician treatment decisions/actions vary widely.[1–5] Even when relevant best-of-care recommendations for patients do exist, unwarranted variation in clinicians' decisions and actions impair care delivery,[1,6–8] when they fail to use applicable guidelines.[9,10] Patients only receive recommended care about 50% of the time.[5,11–13] This can lead to costly inefficiencies in care delivery,[14,15] delayed care, and patient morbidity and mortality These, in part, reflect the dangers of lack of standardization that characterize poor process control.[16–18] Eliminating unwarranted deviations from evidence-based care is thus a fundamental clinical challenge.

We recently discussed barriers (both technical and cultural) that impede consistent evidence-based care delivery and reviewed obstacles to the implementation of learning healthcare systems.[19] We concluded that replicable expert clinical decision-support systems (CDSS) called "*eActions*," based on either physiological models or production rules, were a desirable solution.[19] While the previous publication described CDSS that can produce replicable clinician actions (*eActions*), it did not forcefully advocate for automating personalized clinical care (precision medicine[20]) with *eActions*.[19] This manuscript presents the case for the adoption of *eActions* to automate care where possible.

Well-designed CDSS can improve both the safety and efficiency of care and patient outcomes, but they are not widely used, even though electronic health record (EHR)-based automation of some tasks[21–30] can unburden clinicians by diminishing their workloads.[31] Challenges to their use include economic, cultural, and technical impediments.[32–35] Two critical objectives for improving care involve (1) increasing adherence to relevant guidelines and best evidence when they are available and (2) developing additional guidelines for clinical situations not yet adequately addressed.

RATIONALE FOR ADOPTION OF *eActions*

In situations where established guidelines and a useful evidence base do not exist, carefully reasoned, mindful clinician variation can contribute new insights. Examples of this occurred during the coronavirus disease 2019 (COVID-19) pandemic.[36] However, individual clinician decision-making is commonly associated with mindless[32,36] or unwarranted variation (deviations from best practice, not based on evidence or patient preference),[37,38] and associated with waste, morbidity, and mortality.[2,39–45] Even specialists claiming to follow the best evidence do not consistently do what they say.[46–51] Unwarranted variation introduces noise, both random and systematic, into EHR system data. Regardless of its source, variations in clinical practice contribute to EHR data that can appear erratic ("noisy") when viewed in aggregate. Such noise can impair the ability of modern information systems to generate high-quality data capable of supporting clinical investigations and improvements in clinical practice, and impairs our ability to achieve a learning healthcare system.

EHR noise is produced by corrupt, inaccurate, outdated, or biased data that commonly exhibit unexplainable and unwarranted variation[3–5,19,37,38,52] reducing the signal-to-noise ratio for important clinical data and events.[53–55] Noisy EHR data result not only from clinician performance (unwarranted,[2–5,32,36–39,41–45,52,56–60] or mindless,[32,61] in contrast to mindful[19,32,36,62,63] variation) but also from clinical information systems designed without due consideration for the downstream dependencies of CDSS. Unwarranted variation in clinician decisions and actions can be produced by conflicting clinician opinions or biases, inaccurate laboratory data, vague interpretations of images, and other sources. Both "big data" and "deep learning" have been proposed as solutions to this challenge.[31,64–69] However, data quality is often more important than data quantity.[70,71] The validity of machine learning, including deep learning, is limited by the validity of the learning data it uses.[71–73] While machine learning has been successful in multiple applications,[74,75] it has not yet realized its clinical potential.[31,69,71–73,76–81] Some of its most successful applications are in image interpretation (see Appendix in Ref.76) but even imaging results can be misleading due to data noise.[71] In certain contexts, machine learning models currently return only approximate results that are often reasonable. Importantly, approximate results, whether from clinical guideline applications or image interpretations, are not adequately detailed to provide personalized clinical care (or precision medicine[20]) CDSS instructions.[74,77,79] Accordingly, any CDSS produced by machine learning can reflect random and systematic EHR noise,[3,4,19,37,38,52] in part due to poor clinical process control[16–18] induced by unwarranted clinician variation. This noise may be subtle and difficult to identify.[71] Successful applications of machine learning CDSS have used population predictive analytics for condition surveillance coupled with careful incorporation into clinical workflows. These efforts rely heavily on frequently overburdened clinicians to determine appropriate courses of action after being alerted by the CDSS model output.[74,77,82] This differs from replicable, closed-loop systems that provide specific personalized care for individual patients and simultaneously unburden clinicians.[21,23–25,83–98] Promising recent reports highlighted the potential value of techniques such as reinforcement learning to create closed-loop CDSS. These approaches still await rigorous prospective clinical trial evaluation.[99,100]

We characterize *eActions* as complex, highly evolved, and validated expert systems that manage a specific clinical task or condition. *eActions* generate multiple, replicable, decisions based on relevant data inputs. We chose the name *eActions* to emphasize replicable clinician actions. We contrast patient-specific replicable actions with decision aids (common clinical guidelines, protocols, and machine learning) that merely deliver replicable generic messages to clinicians, such as "give influenza vaccine to eligible patients each September." Clinicians considering such general, "high-level" recommendations must often collect and consider additional patient-specific information and introduce additional logic before deciding upon a specific action for each patient. Replicability occurs when the decision-making process leads different clinicians to take the same actions for different patients whenever the patients' contexts and clinical information match.[101–113] To test if a clinical care or research method is replicable, one can ask, "Is the advice from the decision-support tool theoretically capable of being executed automatically?" If not, it requires supplemental clinician judgment (additional input data or CDSS logic) at the point of decision-making and will not lead to replicable clinician actions because of unwarranted variation among healthcare decision-makers.[2–5,32,36–39,41–45,52,56–60]

Specifically, *eActions* return detailed, personalized clinical care (precision medicine[20]) recommendations for individual patients. By contrast, other types of CDSS tools provide often reasonable but only approximate recommendations that do not lead to replicable personalized care decisions and actions. We summarize the contrasting attributes of different clinical decision support systems (CDSS)

in Table 1. While not a comprehensive literature review, Table 1 should help clarify important distinctions between *eActions* that return detailed personalized clinical care (precision medicine[20]) decisions and actions for individual patients, from other CDSS tools that cannot do so. Replicability of clinician actions (interventions) enhances the scientific validity of both experimental and observational studies.

Two modes of *eActions* implementation exist. In the first, open-loop *eActions* present each decision to clinicians for approval.[9,29,107,109–111,113,116,121–125] In the second, closed-loop *eActions* directly and automatically control therapy—they remove the decision from the clinician.[21,23–28,83–86,88–92,95–98,126–129] Results from initial *eActions* developed by the group at LDS Hospital (Salt Lake City, USA, using an open-loop CDSS[101,103–105,114]) illustrate the potential for improved clinical research and care. These *eActions* generated personalized mechanical ventilation care instructions, displayed on bedside computer terminals (Figure 1). These open-loop instructions were accepted by bedside clinicians 95% of the time.[101,103–105,107,111,114,123–125] Furthermore, closed-loop control (automated care) can also be reasonable and practical in specific settings.[21,23–25,83–98] A mechanical ventilation closed-loop controller evaluated in a randomized controlled trial reduced clinician burden and was safe.[130] Importantly, a compelling, quasi-experimental comparative effectiveness clinical trial of closed-loop mechanical ventilation, generated through routine clinical care of COVID-19 pandemic acute respiratory distress syndrome (ARDS) patients, produced results favoring closed-loop control, while also unburdening clinicians.[97]

We present herein our argument for the targeted use of automated, closed-loop *eActions* in personalized care, as a fundamental objective of both clinical care and clinical research. Examples include closed-loop control of ventilator weaning and specific treatments for Type 1 diabetes mellitus.[94,96,98,117] Support for our argument includes the following:

1. *eActions* satisfy CDSS evaluation requirements.
2. *eActions* fit within clinical informatics models.
3. *eActions* use can produce study results that are more scientifically rigorous and valid.
4. *eActions* use will identify those clinical decisions that can be automated, differentiating them from those that cannot, only if initially designed to function as closed-loop (automated) CDSS.

eActions satisfy CDSS evaluation requirements[131]

First, we should distinguish therapeutic from diagnostic CDSS. Therapeutic *eActions* return personalized best evidence-based care for patients, once a diagnosis has been made, or a clinical task specified.[9,19,101,105–113,115,132,133] The diagnosis or specified clinical task establishes a clinical context that enables the initiation of a therapeutic process.[128] As articulated by others, diagnostic CDSS is inherently more challenging.[34,134–137] Previous workers have had difficulty capturing a physician's complex patient understanding with a CDSS tool[137] and artificial intelligence has not yet realized its promise to properly assist clinician decision-makers.[80] In contrast, for therapeutic *eActions*, it is possible to capture the way clinicians manage clinical tasks or problems. This is achieved through knowledge engineering with multiple clinicians,[106] coupled with implementation, iterative refinement, and validation in multiple clinical settings in which the specific clinical task or problem-focused *eActions* are intended to be used.[106,131,135] These are well-supervised clinical settings that can function as human outcomes research laboratories[106] (Figure 1). This approach assures validation and safety in all sites in which *eActions* are implemented. *eActions* thus meet effective CDSS implementation requirements.[138]

System-wide Information Technology (IT) "top-down" CDSS solutions are unlikely to produce positive outcomes[34] and can even lead to harm.[139] By contrast, a narrow focus on the clinical problem at hand is a prerequisite for success in an advice-giving CDSS. *eActions* embrace an interprofessional clinician and patient problem-centric strategy[140] in concert with Abraham Maslow's problem centering research imperative (see Chapter 16 in Ref.141) echoed by others (see pp. 543–4 in Ref.142) CDSS-based *eActions* are not information technology-focused, but rather provide tools to address specific clinical problems. *eActions* only require the decision-making information that expert clinicians need and currently use for the specific clinical problem or task.[19,102,106,108]

eActions fit within clinical informatics models

Friedman's "fundamental theorem" of biomedical informatics requires a synergy between clinician-users and computer applications, with clinician users being the most important source of information.[136] To be successful, the outcome of this synergy must exceed the outcome achieved by the unaided clinician (Fig-Figure 2).[34,136,137,149] *eActions* comply with this "fundamental theorem" by capturing the detailed and comprehensive information clinicians use to make decisions.[102,106,108]

Our previous work demonstrated how *eActions* instructions at LDS Hospital (Salt Lake City, UT, USA)[101,103–105,112,114,150] (Figure 1) and elsewhere[9,107] led to more uniform patient management and lower tidal volumes, within the safety limits of accepted mechanical ventilation (Figure 3). *eActions* reduced unwarranted variation in care, thereby reducing both random and systematic (bias) EHR noise.[151–159] *eActions* must therefore increase the signal-to-noise ratio[53–55] of EHR data[55] and outcomes (Figure 3), improving the "Knowledge to Performance" limb of the proposed learning healthcare cycle (Figure 4),[68,160] reflecting a common conceptual model (see pp. 28, 667, and 786 in Ref.161). The *eActions* for mechanical ventilation of ARDS patients[101,103–105,112,114,150] provided a foundation for the mechanical ventilation protocol developed and used by the ARDS Network in a groundbreaking randomized clinical trial.[162]

eActions use can produce study results that are more scientifically rigorous and valid

The quality of scientific data depends on methodological replicability for validating research results—a long recognized[163] core requirement of rigorous science[164–167] and a clinical research ethical imperative.[168] Methodological replicability is achieved by *eActions* that utilize detailed and comprehensive input data.[19,169] Replicability is not achieved by more general evidence-based guidelines currently provided to clinician decision-makers.[170–174] Consequently, *eActions* increase the scientific rigor of clinical studies.[3,4,37,38,52]

Joining 4 strategies reflected in Table 2 would enhance the population of a robust EHR with valid and largely noise-free data, enabling the development of a rigorous learning healthcare system. For example, *eActions* can enable distributed, replicable, evidence-based clinical care and research methods.[101,105–113,115] This would lead to more robust explanatory trial results, more scientifically robust multi-institutional trials, and could replace some pragmatic comparative effectiveness clinical trials.[108,190] After completion of a trial, *eActions* have been immediately introduced into usual care[110] and

Table 1. Attributes of usual guidelines, protocols, and machine learning that contrast those of *eActions*: CDSS examples that demonstrate and clarify distinctions between *eActions* that return detailed personalized clinical care decisions and actions from the other CDSS tools that provide only approximate and often reasonable recommendations that cannot lead to replicable personalized care decision and actions

Decision-support tool	Replicable?	Description	Model		Needs added clinician logic	*eActions*		
			Rule	Physiol		Yes	?	Auto
Mechanical Ventilation for ARDS patients[9,101,103–105,107,114].	Yes	Production rule-based protocol generating decisions for starting, stopping, and adjusting FiO_2, PEEP, mode of ventilation, arterial blood gas testing sampling, and waiting times. Multisite validation with iterative refinements following capture of clinician reasons for declining any returned personalized medicine instruction. The *eActions* if-then logic fills approximately 50 pages of paper flowsheets. Used clinically as an open-loop CDSS for >30 years at 3 hospitals in Utah (~2200 patients) and one in Texas. It was successfully used in 2 patients for ~850 h as a closed-loop controller.	X			X		X
Mechanical Ventilation[115].	Yes	This was a short-term (6 h) open-loop CDSS management study.		X		X		
Iron Lung Mechanical Ventilation[83]	Yes	These investigators and clinicians used closed-loop control to manage iron lung mechanical ventilation for 2 poliomyelitis patients.		X		X		X
Weaning Mechanical Ventilation[91]	Yes	These investigators and clinicians managed mechanical ventilation weaning in children using the SmartCare/PS option of the Evita XL mechanical ventilator (Dräger-werk AG & Co. KGaA). .				X		X
Mechanical Ventilation[21]	Yes	These investigators managed inspired oxygen to maintain arterial oxygenation in low-birth-weight infants.	X	X		X		X
IV Insulin: ICU blood glucose[109,110116]	Yes	These investigators and clinicians used *eActions* to personalize care orders for starting, stopping, and adjusting IV insulin, blood glucose testing, measurement and waiting times, IV glucose, and nutrition. Developed and validated over several years and implemented in multiple institutions in adult and pediatric ICUs.	X			X		
IV insulin to control ICU blood glucose[98,113,117]	Yes	These investigators and clinicians used *eActions* to personalize care orders for blood glucose management in RCTs of children.		X		X		
Sepsis[111]	Yes	eActions produced higher compliance and lower mortality in Sepsis and Septic Shock patients than did a paper-based protocol with the same rules. Both were more favorable than published outcomes after usual care.	X			X		
Post Operative Left Atrial Pressure[85]	Yes	These investigators and clinicians managed 8500 consecutive cardiac surgery postoperative patients with a physiological model for controlling left atrial pressure with automatic control of blood infusion and vasodilating agents by closed-loop feedback control. They managed other postoperative care with a rule-based CDSS.	X	X		X		X
Clinical Guidelines	No	Generally, a consensus circumscribed set of if—then—else statements, based on a very limited set of input data that fail to lead to replicable clinician actions. For example, if a diabetic patient has not had an HbA1c test in the last 6 months, then order an HbA1c test. Or if a treatment is employed, like a diet in a hospitalized patient, the recent ESPEN Hospital Nutrition Guideline recommends "reevaluation 5 days after hospitalization."[118] In contrast to the preceding general guideline statements, the Heart Failure Guideline, arguably the most mature and scholarly of clinical guidelines, provides more detailed recommendations but			X			

(continued)

Table 1. continued

Decision-support tool	Replicable?	Description	Model		Needs added clinician logic	*eActions*		
			Rule	Physiol		Yes	?	Auto
		these also fail to lead to replicable clinician actions. For example, Diuretic and Decongestions Strategies in Patients with Heart Failure and Pharmacological Treatment for HFrEF recommend: "For patients with HF and congestive symptoms, addition of a thiazide (eg, metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high-dose loop diuretics to minimize electrolyte abnormalities," and "In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value."[119]						
Common Clinical Protocols	No	These are usually paper-based and generally consist of a circumscribed set of if—then—else statements based on a very limited set of input data. "Try to return to FIO2 = 0.4 and PEEP = 5 as soon as possible," a recommendation from an old book of ICU protocols, is an example of a protocol return that fails to lead to replicable clinician actions. Similarly, a more recent recommendation for oxygen: "Oxygen has to be given cautiously with monitoring as uncontrolled high-flow oxygen can lead to respiratory depression and worsening hypercapnia in type 2 respiratory failure. . .," or for Noninvasive Ventilation: "To control pH and pCO2-manipulate the minute ventilation, the respiratory rate and tidal volume, consider NIV for extubation in selected cases."[120]			X			
Machine (Deep) Learning[74,77,79]	No	Machine learning CDSS currently return only approximate results that are often reasonable, like clinical guideline recommendations are reasonable. However, approximate results, whether from clinical guidelines application or from image interpretations, are not adequately detailed to provide personalized medicine CDSS instructions.			X			
Renal Dialysis	?	Potential clinical challenges that we expect can likely be managed with a future *eActions*					X	
Anesthetic dosing	?	Potential clinical challenges that we expect can likely be managed with a future *eActions*					X	

Rule: rule-based model; Physiol: physiological-based model; Needs bedside clinician logic: Decision-making clinician must supply missing data or logic not found in the decision support system; ?: uncertain if decision support tool is replicable or qualifies as an *eActions*; ARDS: acute respiratory distress syndrome patients.

have become foundations[9,107,111] of additional quasi-experimental or more rigorous comparative effectiveness trials.[123–125,191–193] This contrasts strikingly with the longstanding extended delays characteristic of translation of research results to clinical practice.[5]

eActions use will identify those clinical decisions that can be automated, differentiating them from those that cannot, only if initially designed to function as closed-loop (automated) CDSS

Automated (closed-loop) personalized clinical care has been a difficult concept to accept by those engaged in healthcare delivery.[1,6,7,19,31,69,143] Our *eActions* strategy does not assume all clinical tasks/decisions can be automated.[194] Only by capturing the information detail that would theoretically enable automated functions can we identify those clinician decisions and tasks able to be automated. Necessary details of a task may only become clear when the CDSS is executed in the intended clinical environment.[34] This has been one justification for the required iterative refinement and validation of *eActions* in the intended clinical use environments.[102,105–108,111,195] Significantly, *eActions* need not be perfect to justify *eActions* use. Clinicians aided by *eActions* need only produce more favorable clinical outcomes for each specific clinical task *or* problem than do unaided clinicians.[131,136,137]

We believe the evidence we cite strongly supports our argument that the best CDSS strategy for distinguishing those clinical tasks that can be fully automated using *eActions* from those that cannot is to undertake the same detailed work on evidence and logic for all clinical tasks being considered for *eActions*. The results of this process will make it clear that some *eActions* are implementable as closed-loop CDSS[21,23–30,83,85–92,95–98,126–129] and some are not.

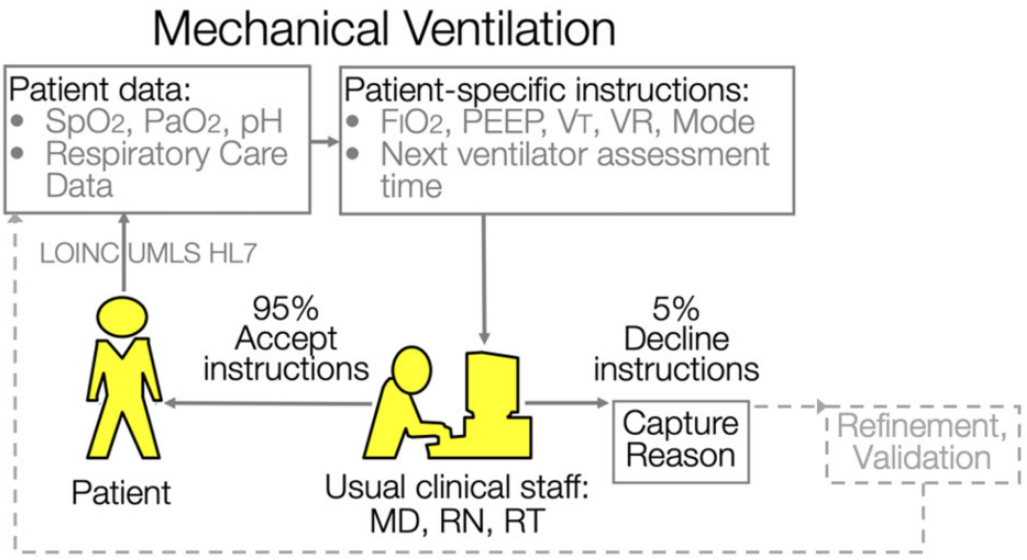

Figure 1. Iterative refinement (indicated by ————) and clinical implementation strategy[105,106] for an open-loop mechanical ventilation *eActions* clinical decision support system (CDSS)[9,29,107,109–111,113,116,121–125] that provides personalized medicine care instructions. SpO2: pulse oximetry; PaO2: arterial oxygen partial pressure; pH: arterial pH; FIO2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; VT: tidal volume; VR: ventilatory rate; MD: physician; RN: nurse; RT: respiratory therapist. Clinicians accepted *eActions* instructions 95% of the time and declined *eActions* instructions 5% of the time.[105,106] Clinician reasons for declining instructions were captured by *eActions*. Quantitative distributions of VT are presented in Figure 3. Information Technology Communication Standards include, but not limited to: LOINC: Logical Observation Identifiers Names and Codes; UMLS: Unified Medical Language System; HL7: Health Level Seven, a standard for exchanging health information between medical applications. Modified from Ref.[104]

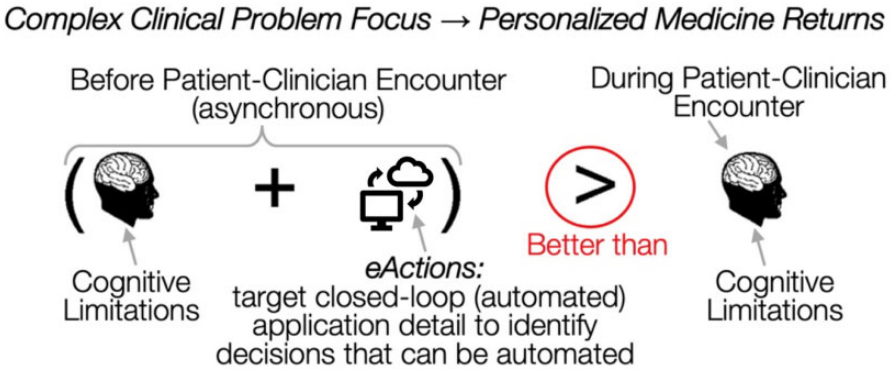

Figure 2. Modified from Ref.[136] eActions CDSS, operating as a Web service, focus on complex clinical problems to deliver personalized medicine returns tailored to the individual patient's needs at the time of execution. Friedman's "fundamental theorem" of biomedical informatics requires only that the clinician, with her/his cognitive limitations,[32,36,81,102,108,143–148] aided by the computer CDSS (eActions), produces a clinically important outcome more favorable than that produced by the unaided clinician.[131,136,137] eActions need not be perfect, but only better than the unaided clinician. The information captured by knowledge engineering and embedded in eActions occurs asynchronously, before the patient-clinician encounter.[106] During the patient-clinician encounter, eActions provide what amounts to a consultation that delivers evidence-based clinical decisions and actions. The "Computer Screen←→Cloud" icon indicates a Web-service communication strategy.

Maintenance and curation of *eActions* will be challenging but should be manageable with allocation of adequate resources. To keep *eActions* data and logic updated and reliable, a yet unexplored formal process for continuous curation seems necessary. Our anticipated structure and flow of this formal process are outlined in Figure 5.[19,31,69] We foresee that each *eAction* focused on a specific clinical problem/task will be curated by a separate multi-institutional committee. Each committee would be tasked and resourced to provide continual iterative refinement and assessment of clinical outcomes. Curation would comply with national policies for best practices to improve both use of CDSS and health care decision-making. Widespread use of *eActions* will require transparency and shared learning. Transparency in the development, testing, and implementation processes should support and accelerate *eActions* adoption. Users of *eActions* should be able to review the clinical logic that generated any clinician action and be able to review the oversight results of *eActions* effectiveness.

Curation of multiple copies of *eActions* on different vendors' cumbersome EHR platforms would be an irresolvable technology maintenance nightmare. Consequently, we suggest that *eActions* should operate as platform-independent Web-services, based on a standard, shared data model and interchange format that ensures syntactic and semantic interoperability, to enable effective and efficient curation of the *eActions* logic and performance.[142,161] Signifi-

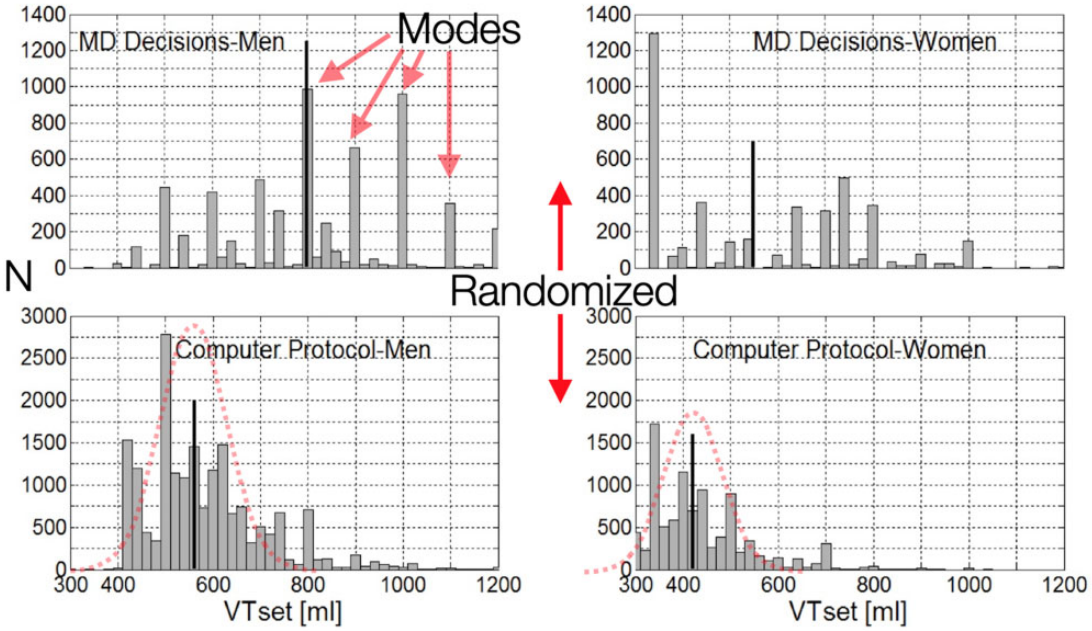

Figure 3. Distribution of set Tidal Volume (VT set [ml]) in physician-controlled (MD Decisions) and *eActions* controlled (Computer Protocol) groups (unpublished RCT data from Ref.[105]) from the same study depicted in Figure 1. *N*: number of VT set (ml). Vertical black bars = group means. The tidal volume setting (VTset [ml]) distributions in the *eActions* controlled (Computer Protocol) group more strongly reflect the random contributions of physiologic and other variability that are expected to have a Gaussian distribution (superimposed red dots) than those of the MD Decisions groups. Modes indicate step changes of 100 ml, a reflection of noise introduced by MD Decisions.

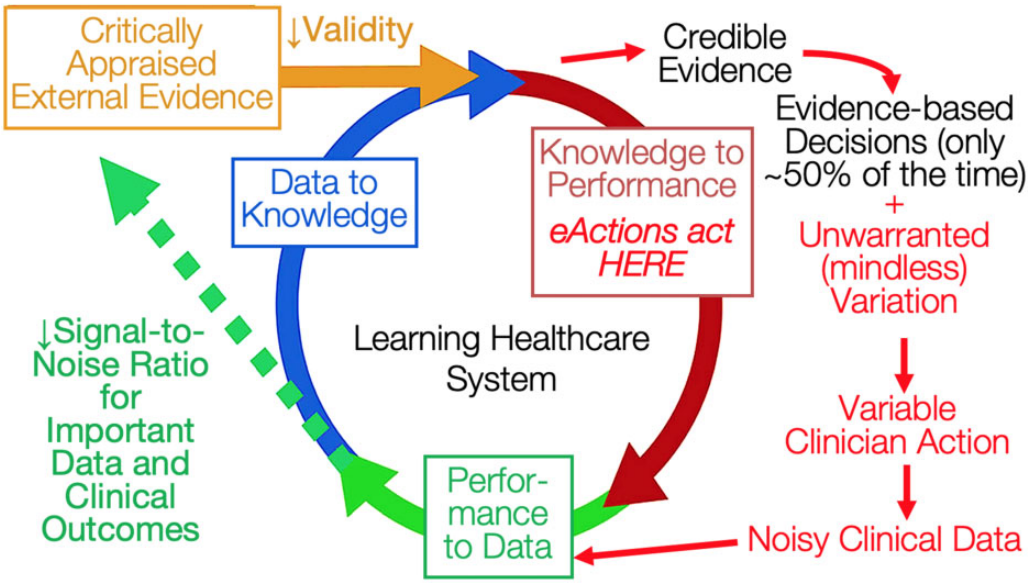

Figure 4. Conceptual learning healthcare system model modified from Friedman et al[68,160] and reflecting a common conceptual model (see p. 28 in Ref.161) EHR data are noisy and degraded reducing signal-to-noise ratio[19,55] for important data and outcomes, and therefore reducing both precision and validity of "Critically Appraised External Evidence." *eActions* focus on clinician performance and reduce EHR noise by reducing unwarranted,[2–4,32,36–39,41–45,52,56–60] or mindless,[32,61] in contrast to mindful[19,32,36,62,63] variation, improving the "Knowledge to Performance" component of the learning healthcare system model and secondarily improving the Performance to Data and the Data to Knowledge limbs, since all 3 limbs are tightly linked.[68] This will increase the signal-to-noise ratio for important clinical data and outcomes and should increase the validity of "Critically Appraised External Evidence," leading to more "Credible Evidence" for "Evidence-based Decisions."

cant obstacles exist to the implementation of "external to the institution" remote clinical services. These include maintaining the privacy of transmitted patient information, maintaining bi-directional feedback connections among participating sites so discovered erroneous recommendations can be rapidly reported from peripheral sites and alternatively recognized "centrally" at the remote service provider. Regardless of origin, errors must be dealt with rapidly and effectively to ensure patient safety. The ability to identify patients who may have been affected by "bugs" in remotely hosted *eActions* will be of utmost importance. Sites hosting remote

Table 2. Four strategies for advancing a learning healthcare system

Strategy	Bottom-up clinical problem-centric	Top-down system-centric	Efficacy trials	Effectiveness trials	Replicable method	Reference
Information Technology standardization		X				175–181
Embedded clinical investigation	X	X		X		182–184
Multiple simultaneous interventions	X			X		185–189
eActions CDSS or other replicable-evidence-based strategies	X		X	X	X	101,105–113

The citations are not an exhaustive literature review but support our conclusions. For example, *eActions* are "bottom-up" (designed and led by clinicians trying to solve a clinical task/problem), enable both effectiveness and efficacy clinical trials, and are replicable clinical care/research methods.

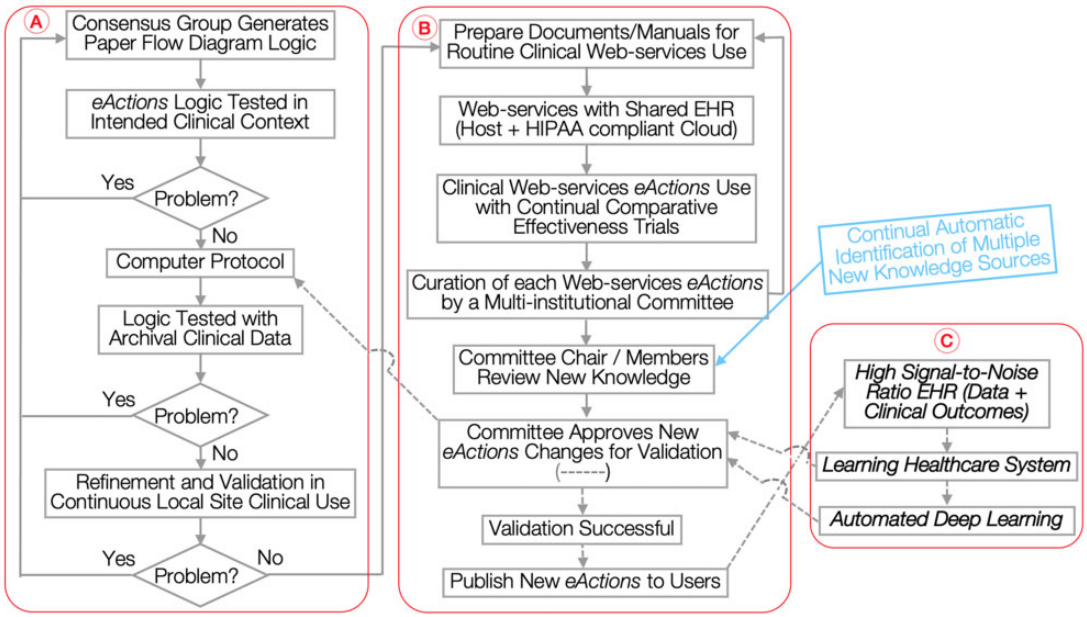

Figure 5. (A) Development, iterative refinement, and validation of *eActions* at the local development site (modified from Refs.[101,150]). (B) Anticipated Web services *eActions* implementation and distribution with iterative refinement and validation of *eActions* directed by the chair and members of each multi-institutional committee responsible for each specific clinical *eActions* curation. (C) Anticipated Learning Healthcare System with continual, iterative learning enabled by the high signal-to-noise ratio of EHR data populated with *eActions* clinical care. We envision curation to include continual outcome analyses (length of stay, survival. . .) to accommodate any change in *eActions* or in databases (eg, coding). We envision use of web-services *eActions* to require participation of all institutions, practitioners, and patients in ongoing curation (comparative effectiveness research) and requiring links to the Host EHRs to allow assessment of the outcomes.[226–228] Refusing to participate would preclude clinical use of *eActions*.[227] We do not expect this will be a problem if *eActions* produce a significantly better clinical outcome, than is realized with unaided clinicians or with other forms of "usual care." New knowledge or changes returned from C (Learning Healthcare System) lead the multi-institutional committee members to first approve for validation (B), then send to Computer Protocol in A, for the process to flow down A, then return to B (Prepare Documents. . .), flow down to "Publish New. . .," and then go to C (High Signal-to-Noise) in an iterative loop without end.

eAction services must be fully uninterruptible and crash-proof. Similarly, network connectivity between clinical sites and remote *eAction* service providers must be error-free and uninterruptible. Interruptions in network connectivity can be just as serious as life-threatening software bugs. Healthcare institutions relying on closed-loop remote service-based *eActions* will put patients at risk if services "downtimes" are not recognized immediately and effective downtime procedures are not implemented rapidly and safely.

With the momentum and requirement to learn faster and better (eg, COVID-19 provides an example[196,197]) extending the admittedly difficult development of *eActions* in collaboratives that rely on a shared or synthetic data infrastructure across health systems is desirable. This will expand the problem space (clinical challenges and tasks) that *eActions* can address and will engage smaller healthcare organizations that cannot resource their own embedded learning systems. This could address concerns that most care in the United States occurs in small-to-medium sized hospitals and clinics that lack adequate informatics personnel and expertise. These challenges could include issues that benefit from n-of-1,[198–201] micro-randomized,[202,203] or novel decentralized[204] clinical trials, as well as from traditional randomized controlled clinical trials (RCTs)[151] and quality improvement strategies.[36,205–208]

LEARNING HEALTH SYSTEMS FOR DEVELOPING AND TESTING NEW GUIDELINES/*eActions*

The conceptual model of the learning healthcare system of Friedman et al proposes an iterative learning cycle involving EHR and other data, knowledge, clinician performance, and external critical ap-

praisal (Figure 4).[68,160] Learning healthcare systems and *eActions* are mutually complementary activities. In the absence of guidelines and consensus for many healthcare delivery topics, proposed learning healthcare systems can provide data to support creation and validation of new guidelines and *eActions*, both within an institution and at the national level. Such learning systems will work best with valid and precise data, but EHR data are noisy and degraded.[3,4,19,37,38,52] In contrast, data generated by *eActions* can enable rigorous explanatory clinical trial results and complement other major efforts to achieve a learning healthcare system, both "bottom-up" and "top-down" (Table 2). "Bottom-up" approaches include rule-based eActions,[9,19,101,105–112] model-based *eActions*,[113,115,132,133] comparative effectiveness studies of multiple interventions simultaneously (master protocols,[185] platform trials,[186–188] and combinations of adaptive platform trials with pragmatic point-of-care trials,[189] and adaptive intervention trials[209]) "Top-down" IT-based efforts include system-centric or administration-centric efforts to standardize information exchange or work processes and focus on multiple standardization strategies (Table 2).[175–181] Recent investigations have combined some "bottom-up" and "top-down" efforts and have been embedded in routine care processes, sometimes within the EHR.[182–184,210–212]

Results from RCTs remain a reference standard for many clinical care and research questions. However, RCTs are costly, time- and resource-consuming, cannot address all pertinent clinical areas of uncertainty because of resource limitations,[174,194,213–218] and impact clinical care slowly and incompletely.[5] As a complement and addition to needed RCTs, many clinical questions and challenges could be effectively addressed with valid study designs in a learning healthcare system with data generated through routine clinical care.[31,149] These questions and challenges could theoretically be rigorously studied in a learning healthcare system with comparisons of different care strategies using comparative effectiveness, quality improvement, quasi-experimental, and even RCT strategies that could avoid large cost and time consumption. Such studies could be conducted if best evidence-based clinical care methods were consistently applied in routine clinical care. Results from this care would reduce random and systematic (bias) noise and populate EHRs with more valid data. However, EHRs have not yet met such expectations.[31,69,159,219,220]

Ongoing continuous quality improvement efforts within a learning healthcare system could use *eActions* as their foundation. As critical care increasingly evolves to deliver phenotypic-based therapy (personalized medicine), *eActions* could facilitate adherence to protocol for studies enrolling large numbers of patients at multiple institutions. Thus, *eActions* use provides a basis for clinical discovery and advances through thoughtful modifications that can be tested. This would lead to enhanced replicability of clinical care and research. This all depends on obtaining credible, internally valid study results (best evidence) that are then applied consistently by clinicians in usual care. This contrasts with allowing variable decision-making and actions, hoping to find a better solution by chance, a real but infrequent route to progress. This need for credible evidence-based care has been highlighted by widespread exaggeration and hyperbolic behavior that characterize discussions of the current COVID pandemic.[196] This behavior evokes images of the poor process control that results from responding to system noise rather than to credible representative data.[16–18,197] We aver that joining automated *eActions*[97,130,221] with the comparative effectiveness clinical studies in a learning healthcare system such as the groundbreaking studies conducted at Vanderbilt University Medical Center (Nashville, TN, USA)[182,210–212] could significantly enhance our ability to achieve an effective learning healthcare system based on routinely acquired clinical care data.

Table 3. Impact of decision support tools on clinician decision-making burden

		Clinician unburdened?		
Decision support tool type	Clinician use	Little	Moderate	Maximal
Clinical Process[16–18,41]	Common	X		
Guideline[10,17,41]	Low	X		
Common paper or computer protocol	Common	X		
Open-loop *eActions*[9,29,101,103–105,107,109–111,113,114,116,121,122]	∼95%		X	
Closed-loop *eActions*[21,23,25,83–98]	∼100%			X

eActions consistently link personalized medical decision-making with best evidence, even though *eActions* algorithmic data and logic are based on population evidence, clinician protocols from accepted best practice, results from RCTs, and meta-analyses.[9,19,101,105–113,115] When *eActions* cannot accommodate a particular patient state, the input data, and associated logic are incomplete. Accordingly, clinicians must then supplement such data and logic gaps of the *eActions*. For this reason, it is essential during CDSS development, validation, and subsequent clinical use, to capture the bedside clinician's reasoning for not following every declined *eActions* instruction.[106] This enables modification of detailed elements of the algorithm, with the potential to eventually achieve closed-loop control, the ideal development target for the CDSS, though closed-loop control will not always be possible.[19] While the feasibility of *eActions*, including closed-loop implementation, is clearly established, the evaluation of clinical problems and tasks for which *eActions* in either closed- or open-loop application would be desirable has been sparse. Substantial work invested in clinical guidelines and ordinary protocols (including pharmacy drug-drug interaction CDSS), neither of which are replicable methods of care or research, does not inform this issue. The fraction of applicable clinical problems or tasks is currently unknown but, in our view, likely sizeable. Even if only 10% of clinical activities accommodate *eActions*, that would represent ∼$410 billion in US national annual healthcare expenditures.[222,223] Widely applicable scalability remains to be demonstrated.

We expect most comparative effectiveness clinical research[224,225] questions in the future to be addressed within learning healthcare systems,[169,190] as part of routine healthcare delivery with *eActions*,[226–228] if *eActions* CDSS can be successfully scaled and broadly applied.[167]

DISCUSSION

Whenever relevant and feasible, patient care and clinical studies should be guided by well-designed *eActions* that enable interprofessional clinical teams[229,230] to consistently link decisions and actions to best evidence.[55,231] This will both maximize the probability of desired individual and population clinical outcomes, and address the tension between individual patient and population care.[232]

Clinical care is delivered in a complex and dynamic system.[230,233] Clinical decision-makers are cognitively limited[32,36,46,48,234–238] and commonly overwhelmed with both information and clinical tasks.[32,36,81,102,108,143–148] Within that system, unintended consequences and errors are well documented[239–245]—likely reflecting domain-independent general human limitations.[246] Despite the advancement of clinical guidelines and protocols, clinical practice remains a process that largely lacks systems-engineering input and design.[9,247–249] Insights generated from even the most detailed *in silico* simulators of health systems and human biology have not yet, to our knowledge, been translated to wide-ranging practice changes nor have such holistic mathematical models been subjected to rigorous, prospective evaluation.[250–252] Unburdening clinicians, expediting care including emergency care, and enabling all clinical team members to practice at their maximum skill level will be most effectively accomplished by automating some evidence-based care tasks (Table 3).[21–30,78–87]

Many clinicians and investigators with different views will likely object to our arguments for *eActions* use in clinical research and care[253–256] described in this Perspective manuscript. These different views have focused on diverse issues that include: hazards of EHRs with frequent, often irrelevant, system-generated disruptions,[257–259] ethical challenges,[260,261] the potential for overuse of automated CDSS,[262] potential CDSS bias,[263] and the potential to make some clinicians obsolete,[264,265] a fear linked to concern about deskilling.[266–269] Deskilling appears to be an unavoidable consequence of civilization's advance (see p. 42 in Ref.270, p. 29 in Ref.271) and is certainly apparent in the changing medical landscape of the past 60 years. These issues have merit and deserve our attention. However, with respect to *eActions*, they are largely distracting because they are equally applicable to the decisions and actions effected by unaided clinicians. Rather than using these distractions to dismiss *eActions*, we assert it is more important to focus on the question implicit in Figure 2: "Does clinician behavior aided by albeit imperfect *eActions* lead to more favorable healthcare outcomes?"

Automated *eActions* (where possible) have been only sparsely evaluated in clinical settings[21,83,85,91] and are disruptive innovations.[272] They are responsive to the call for new care models[5,117] including changes in academic centers.[118] Disruptive innovations are not likely to be encouraged by mature medical institutions, including professional societies.[273–276] *eActions* work best when advanced by clinician-led interprofessional teams.[229,230] They will have to address multiple regulatory barriers.[31,69,231] We cannot expect politicians and regulators to take the lead[275]—nor should they. Politicians and regulators typically follow healthcare changes; they do not lead them.[277]

SUMMARY

All pertinent clinical questions have not, cannot, and will not be addressable with costly time- and resource-consuming controlled clinical trials. We expect most comparative effectiveness clinical research questions in the future to be addressed within learning healthcare systems, as part of routine healthcare delivery using evidence-based care. EHR data noise and overburdened clinician cognitive limitations are barriers to providing accurate evidence to a learning healthcare system. Reducing EHR data noise and unburdening clinicians will be most effectively accomplished by automating some care tasks and removing these decisions and tasks from the clinician's workload. Automated *eActions* (validated clinical decision support systems) would help achieve a learning healthcare system. Widespread use of *eActions* will require surmounting current healthcare technical and cultural barriers and installing a clinical evidence/data curation system.

Widespread and scaled implementation of *eActions* entails significant future work. Clinical experts must identify new healthcare guidelines based on data gleaned from learning health systems (and other mechanisms). Local and national clinical committees must determine which clinical problems and tasks are amenable to open- and closed-loop *eAction* solutions. Healthcare system vendors must evolve current, relatively inflexible and proprietary EHRs into systems that can be modified to collect and rapidly externalize patient data in standardized format in order to support the implementation and evolution of *eActions*. Fundamental to all of this is rigorous testing of *eActions* and evaluation of *eActions* impact on important clinical outcomes.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of this work, revised the drafts critically for important content, approved the final version, and are accountable for the arguments contained therein. The following authors participated as investigators in the development and validation of *eActions* described in cited works: Alan Morris, Michael Lanspa, James Orme, Jr, Terry Clemmer, Lindell Weaver, Frank Thomas, Colin Grissom, Ellie Hirshberg, Thomas East, Carrie Wallace, Michael Young, Mary Suchyta, Dean Sittig, Michela Bombino, Eduardo Beck, Katherine Sward, Shobha Satsangi Phansalkar, Gordon Bernard, Taylor Thompson, Roy Brower, Jonathon Truwit, Jay Steingrub, Duncan Hite, Douglas Willson, Jerry Zimmerman, Vinay Nadkarni, Christopher Newth, Jacques Lacroix, Kang Lee, Bennett deBloisblanc, Dean Sorenson, Anthony Wong, Peter Haug, Ulrike Pielmeier, Stephen E. Rees, Dan S. Karbing, Steen Andreassen, David Schoenfeld, Derek Angus, and Michael Pinsky.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

No new data were generated or analyzed in support of this Perspective manuscript.

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