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Clinical prediction rules: new opportunities for pharma

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Clinical prediction rules (CPRs) are important tools in the development of an evidence-based, personalized medical system. This article compares CPRs to other medical information tools, giving solvent examples of their clinical application and potential to increase efficacy and efficiency, as well as their utility in drug development. The primary focus is on the potential of CPRs to define the most effective level of generalization, predictably and reproducibly identifying homogenous groups of subjects (based on outcome) in heterogeneous and undifferentiated trial populations. This potential can be met if CPR construction integrates three elements: the identification of variables both within and outside the disorder that affect outcome and the mapping of relevant human physiome types based upon identifiable trait and reactionary patterns.

Introduction

The era of the 'blockbuster drug model' is ending, and the development of personalized pharmaceutical systems is on the rise. Clinical prediction rules (CPRs) are a valuable new tool and are helping to move medicine from 'trial and error' treatment to more accurate, individually targeted and reproducible methods. CPRs are built on sets of simplified, empirically derived and clinically validated rules leading to actionable decisions that are highly correlated to clinical outcome. When properly designed, CPRs remove the inter-patient variability that confounds clinical trials and treatment decisions by defining homogenous groups of patients that will respond in a similar manner to a given treatment, thus emerging as pragmatic tools that will play a lead part in defining a new era of personalized medicine, both in clinical practice and in drug discovery and development.

Throughout this article, we will demonstrate the evolutionary advantage CPRs bring to both clinical practice, where they aid in the refined differentiation of diagnosis and treatment decisions, and drug development, where they enable the pharmaceutical industry to truly partner with medical providers and actually name the clinical subpopulations that will either benefit or be at risk of adverse events from the drug under study.

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Definition, development and validation of CPRs

In one of the earliest descriptions of CPRs, Wasson defined their purpose as tools or rules that help 'reduce the uncertainty inherent in medical practice by deciding how to use clinical findings to make predictions' [1]. In an often-cited 1997 paper by Laupacis, a CPR is defined as a 'prediction-making tool that includes three or more variables obtained from the history, physical examination, or simple diagnostic tests and that either provided the probability of an outcome or suggested a diagnostic or therapeutic course of action' [2]. CPRs are developed by 'applying statistical techniques to find combinations of predictors that categorize a heterogeneous group of patients into subgroups of risk' [3]. CPRs are also referred to as 'clinical prediction guides' and differ from best practice guidelines and evidence-based guides in that they are exclusively evidence-based and empirically validated through clinical trials. Other related terminology includes 'clinical decision rules' (CDRs), which have been described as direct decision-making devices that have been widely validated in a variety of populations, implying a higher level of validation and a greater proven impact on clinical decision-making [4]. For the purpose of this paper, we

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TABLE 1

Differentiation between practice guidelines and clinical prediction rules

Best practice guidelines	Preliminary clinical prediction rule	Broadly validated clinical prediction rule
Consensus-based	Evidence-based	Evidence-based
Expert opinion	Retrospective analysis Mathematical modeling	Empiric validation Impact analysis
Scientific data support	Small prospective trials Single or multiple settings Inform clinical decision-making	Large prospective trials Varied population settings Alter clinical decision-making Econometric impact

include CDRs in the general discussion of CPRs, despite the important difference in validation. Table 1 lists and briefly differentiates these related constructions.

The primary purpose of any CPR is to enhance the accuracy of clinical practice, which might include improving diagnostic accuracy, understanding prognostic differences for individual patients, suggesting a treatment choice or helping a clinician predict the utility of a given test. CPRs can thereby enhance clinical decision-making, either directly, by suggesting a course of action, or indirectly, by refining a diagnostic group according to prognosis.

One good example of a CPR is the prediction rule to determine the need for respiratory isolation in patients suffering from tuberculosis (TB) [5]. This CPR is composed of a variety of factors, including symptoms (significant weight loss, malaise, weakness, night sweats and shortness of breath), epidemiologic factors (recent immigrant, institutionalization and history of exposure to TB), physical findings (presence of fever and lung examination findings) and test results of the Mantoux test and chest X-ray. These factors are weighted according to predictive importance, then the combined analysis guides the determination of whether to place the patient in isolation. A well-designed CPR will divide a group of diagnostically identical patients (those with TB, e.g.) into specific groups with different treatment or prognostic outcomes (contagious versus non-contagious, e.g.).

The CPR development process has been covered in depth in other reviews (see Ref. [3] for a particularly accessible walk-through), but a brief summary here will help frame the rest of the discussion. At the most general level, developing a CPR consists of the following three steps: (i) derivation of the rule itself based on literature review or retrospective analysis of treatment outcomes, (ii) validation of the rule through prospective or retrospective clinical trials and (iii) assessment of whether the CPR has any impact on clinical decision-making behavior and outcomes in larger populations over time [6].

Derivation of the CPR

In 1998, Randolph suggested that data used in the development of CPRs are called prognostic factors and might come from patient history, physical examination, laboratory results or radiologic tests [3]. This initial set of potentially predictive clinical indices is commonly defined by a panel of experts in the diagnostic area being considered. Once a patient population representative of the eventual CPR target population has been chosen and the predefined data gathered, computation of the rule itself proceeds via numerous types of mathematical techniques that can quantify the magnitude of risk associated with any particular predictor variable and discard predictors that are redundant or irrelevant. Regression analysis is a commonly used methodology in the construction of CPRs, but discriminant analysis [7], recursive partitioning analysis [8], neural networks [9] and others have been used [10]. The prognostic factors with the highest predictive capacity are then assigned a relative value and assembled into a CPR that can be applied quickly by medical providers. The finalized CPR will require the input of a small number of clinical indices and will then output some form of probability determination for the outcome of the decision or likelihood of the response, displayed as a simple score on an analog scale or as a percentage probability that might reflect anything from improvement in morbidity or lower mortality to higher adverse effect risk or greater economic benefit. The actual form of the tool can range from a simple decision tree to an algorithm requiring multiple inputs and complex computation. For example, in the TB CPR previously mentioned, the clinician simply sums up the total of all the individually weighted prognostic factors, which then predict the need for patient isolation based on comparison with a preset cutoff.

Validation of the CPR

Although all CPRs relate a set of prognostic factors to the likelihood of a certain outcome or diagnosis, optimal CPR tools have scientific evidence for three essential elements: validity, usability and impact (Box 1). CPRs gain validity through prospective trials in diverse patient populations, thereby obtaining sufficient weight of evidence to suggest a positive impact on actual clinical practice. The CPR must then be shown to positively impact the outcomes in the treatment decision-making process for which it was designed to be considered fully validated and worthy of widespread use in clinical practice. Large prospective trials of CPR application in clinical settings compared with the outcomes of clinician decision-making without the CPR will reveal the gross clinical impact of the rule, whether measured in economic savings, improvements in clinical outcomes or accuracy of diagnosis. Eventual uptake and clinical use of the CPR will ultimately depend on the veracity of these development and validation steps, as well as the efficacy of the tool, its ease of use and economic feasibility, and the value it brings to the clinical decision-making process by predictably defining outcome-based subpopulations.

Although many CPRs have been developed for clinical use, such as the TB example above, there are also good examples available of those relevant to drug development and marketing. Table 2 lists further examples of recently published CPRs that are relevant both

BOX 1

Key CPR quality features

Features that enhance CPR design and likelihood of implementation.

Features related to condition and diagnosis

- High patient volume for the condition
- Significant severity of condition
- Inefficient use of resources (lab tests, hospitalization, and so on) using current decision-making process

Features related to treatment

- High inter-provider variability in current treatment practice
- High inter-patient variability of treatment

Features of rule development

- Medical provider participation in rule development
- Includes all significant clinical variables
- Multiple, large validation studies

Features improving uptake by the end user

- Previously unmet clinical need
- Positive treatment decision rules (help make correct decisions to treat patients who need it)
- Simple application and availability to clinician
- Improves efficiency of decision-making process
- High sensitivity and specificity of the rule
- Significant impact on outcome for efficacy or adverse effects
- Significant impact on medical economics

to clinical use and to the drug development and post-marketing process. The Adjuvant! tool, for example, analyzes clinical features of breast cancer including known age, estrogen receptor status, comorbid conditions, histological grade, tumor size, number of nodes examined and number of nodes positive to estimate the overall survival, breast-cancer-related survival and recurrence-free rates. In addition, the tool can predict ten-year morbidity and mortality according to four variations of hormonal treatment and six variations of chemotherapy, and combinations of these. The tool's predictions were studied prospectively for ten years in more than 4000 patients, and the findings showed that the CPR was within 1% of actual outcomes across the board [11].

Overall, the number of high-quality and broadly validated CPRs is on the rise. A 2005 meta-analysis of 163 current CPRs showed 69 had scientific merit [4]. Figure 1 illustrates the trend in CPR derivation, validation and impact analysis over a 20-year period.

CPRs value add

Although best practice guidelines form much of the current template for diagnosis and treatment decisions, CPRs represent an important step in reliably predicting outcomes for different subgroups within a diagnostic population. Current diagnostic decision-making tends to include multiple types of patients within most diagnostic groups, although over time, these often become subcategorized. Diabetes mellitus, for example, was simply divided into juvenile or adult onset types for many years. Now we have prediabetes; Type 1, broken into immune-related and other causes; Type 2, broken into secretory defect and insulin-resistant types; and more than 11 types that have been linked to specific genetic defects [18]. However, even diabetic patients in a precisely defined category with shared genetic markers differ because they exist at different points along the continuum of the disease depending on their diet, exercise, comorbid conditions and other factors. These phenotypic dissimilarities are the source of inter-patient variability, which confounds both clinical trials and treatment results.

It is precisely this phenotypic diversity, however, that lends itself to refined differentiation through CPRs, which can incorporate a wide array of phenotypic, metabolic and genetic markers into a simplified tool predicting novel diagnostic subpopulations, which might, in turn, be correlated to specific treatment outcomes. For this reason, CPRs can be used to define inclusion criteria for phase II and III prospective trials by correlating subpopulations within the trial to treatment efficacy or adverse event risk, thus raising the likelihood of successful development.

Economic impact of CPRs

A few studies of CPRs have examined the economic impact of the tool in a clinical setting. In 2000, a study by Marrie *et al.* [19] on a community-acquired pneumonia decision-making CPR demonstrated an 18% reduction in hospital admissions and a 1.7-day reduction (over a 6.1-day average) in hospitalization duration and intravenous antibiotic use. In a multicentered trial across the USA, the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) was tested in 10,689 patients, demonstrating improvements in ability to determine which patients could be safely discharged to home and which patients needed coronary care unit (CCU) admission, without affecting morbidity or mortality. If implemented nationwide, the ACI-TIPI could result in 204,000 fewer hospitalizations and 112,000 fewer CCU admissions, for a total saving of $728 million annually [20].

One of the best-studied CPRs is the Ottawa ankle rule, which is used to predict which patients with ankle injury require an X-ray,

TABLE 2

Clinical prediction rules designed to predict drug treatment effects

Category	Parameters	Refs
Breast cancer	Adjuvant! Tool predicts survival and recurrence for adjuvant chemotherapy	[11]
Warfarin	Predictors of warfarin treatment needs in patients with atrial fibrillation	[12]
Psychosis	Predictors of response to different antipsychotics for first psychotic episode	[13]
Sjogren's syndrome	Predictors of successful response to Cevimeline treatment	[14]
Alzheimer's disease	Radiographic predictors of response to Donezepil treatment	[15]
Adverse effects	Clinical predictors of Coumadin-related bleeding in outpatients	[16]
Adverse effects	Predictors of ACE-inhibitor-related cough development within six months	[17]

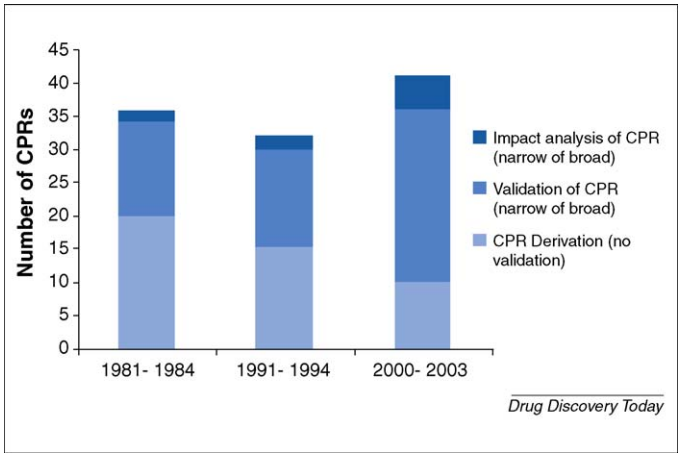

FIGURE 1

Evaluation of CPRs published in four medical journals (*New England Journal of Medicine*, *Journal of the American Medical Association*, *British Medical Journal* and *Annals of Internal Medicine*) evaluated according to quality and validation level of study. On the basis of data from Refs. [1,2,4].

based upon physical examination findings. More than 30 studies, representing 15,000 patients in multiple settings, have demonstrated a sensitivity of almost 100% for fractures of the ankle and mid-foot, with an overall reduction in the number of radiographs performed of 30–40% [21]. An economic impact analysis estimated savings of $18–90 million annually in the USA with the full implementation of this rule [22].

As CPRs become more broadly studied, their applicability to treatment decisions is likely to be advocated, or even dictated, by both third-party payment systems and governmental regulatory systems as an opportunity to increase cost effectiveness and quality of care delivered. Such implementation of CPRs would probably impact pharmaceutical sales by correlating the diagnostic subpopulation to improved outcome with that drug. This correlation enables evidence-based marketing and preferred status of these treatments within the reimbursement tier system.

Pharmaceutical development using CPRs

A well-developed CPR determines the optimal level of generalization, defining homogenous subgroups that either benefit from or are harmed by a particular treatment decision. These types of CPRs represent a small and underdeveloped but highly meaningful departure from current medical practice and clinical trial design process. The pharmaceutical industry has a vested interest and the financial power to create a substantial breakthrough in the development of these tools and thereby take an important step toward evidence-based, personalized medicine.

CPRs can help optimize drug development and marketing by providing the following: correlation of diagnostic subgroup to positive treatment outcome, identification of diagnostic subgroup to accurately predict adverse responders, and inclusion of all variables that accurately and reliably identify patients within the subgroups of interest (for use by clinicians when prescribing). Most drug trials use currently accepted general diagnostic criteria for the inclusion of test subjects. Diagnostic usefulness is related to the ability to determine the optimum level of generalization across a population with similar clinical features that will produce a group of patients with similar prognosis and response to treatment. Using CPRs to define the effective level of generalization for drug trials will create new diagnostic criteria that reflect therapeutic outcome similarities.

Current pharmaceutical trial design measures many parameters to help create rudimentary forms of a CPR, usually limiting the analysis to factors related to the disease under study such as characteristic features of pathology, associated laboratory tests, demographic parameters, recognized epidemiologic factors and potential genetic markers. Analysis of outcome based on all of the measured parameters is then conducted to determine whether any subgroups preformed better on treatment or were tied to adverse events.

When clinical trials for drug development fail to demonstrate efficacy or have high frequencies of adverse events, a systematic data-mining exploration is undertaken in which all the intake variables are reviewed and analyzed for any possible trending or subgroup identification. These variables tend to include everything from demographics to comorbid conditions to metabolic and genomic markers tied to the disorder under study. This type of data dredging can lead to breakthroughs using adaptive trial design and subsequent relabeling to get new drug approval when all signs pointed to failure. This type of relabeling represents a rudimentary form of CPR in that it ties a newly identified diagnostic subgroup to a treatment outcome that differs from that expected for the larger diagnostic group as a whole.

Dendreon, for example, developed Provenge (APC8015) as a monoclonal antibody vaccine for metastatic prostate cancer. After an initial failure to demonstrate efficacy in all patients, Dendreon researchers used enrichment criteria to select a subgroup of prostate cancer patients with Gleason scores of 7 or less. This subgroup, based upon severity of pathology, showed improved drug efficacy compared with the general group that included patients with more severe disease [23].

However, the short-sighted limiting of data analysis to known factors within the disease excludes potential confounders outside the known 'box' of the disorder under study. These factors include currently unknown aspects within the disorder and characteristics of the patient that lie outside the disorder but impact pharmacokinetics and pharmacodynamics because of the complex web of genetic and metabolic interactions. These unmeasured factors are the basis of inter-patient variability within a diagnostic category. Ideally, development of well-designed CPRs begins with the inclusion of all relevant variables early in the process, whether or not they seem to be related to the disease under study. Once gathered, the variables are then systematically analyzed or evaluated for relevance. Occasionally, drug development will stumble upon one of these unrecognized variables when an astute researcher notices an unusual trend within the treatment response group. These occurrences, now considered simple anomalies, can move a failing compound to considerable success, as exemplified by the Eli Lilly drug, Prozac (fluoxetine). Lilly repositioned fluoxetine from its original status as an antihypertensive drug to another failure as an antiobesity compound to its eventual blockbuster success as an antidepressant [24].

New technologies have been employed to build on these types of successes. Information management companies have dramatically increased their power to analyze such data points using electronic data capture (EDC) and analysis systems. Higher

powered computer applications have enabled the entry of electronic personal diary information from trial subjects and many more data points at trial entry to be evaluated for possible correlation to treatment outcome.

Although this EDC approach is clearly a step forward, there are two potentially fatal flaws: the failure to look outside the disorder under study and the production of background noise.

Despite capturing many more data points for study, EDC systems still rely upon initial trial design to establish the parameters for data capture. These parameters are selected based upon current knowledge of the compound under study and the disorder under treatment, but the problem lies in the limitations imposed by our current notion of diagnosis.

A new diagnostic system

Diagnosis today is typically a discrete and binary 'yes or no' process: you either have hypertension that requires treatment or you do not. This failure to account for the continuum of health and disease often fails to recognize different types of patients along a spectrum. As in the example of Provenge above (i.e. lesser severity associated with better outcome), recognition of the continuum of a disorder can be crucial to accurately identifying effective treatment targeting in clinical trials.

This continuum of disease, or inter-patient variability, within a clinical trial is a key confounder of outcome and can directly threaten success when its investigation is limited to parameters linked directly to the disorder or demographics. Human beings, however, are complex organic systems with many cross-linked and interdependent metabolic variables owing to differences in inheritance and epigenetic factors controlling gene expression under different environmental exposures. Capturing the essential aspects of inter-patient variability requires complex, dynamical system modeling of the disorder and the treatment.

For CPRs to correlate sufficiently to treatment outcomes, they must adequately define the continuum of a disorder, which, in turn, forms the basis of a new diagnostic categorization. Three elements are required to define inter-patient variability: the identification of all variables within the disorder that affect outcome, the identification of all variables outside the disorder that affect outcome and a 'roadmap' of human physiome types based upon reproducible trait patterns to exclude the background noise inherent in such complex systems.

Genetics alone will adequately describe inter-patient variability only in those disorders related to genes of major effect (Herceptin, e.g.). When multiple genes of minor effect are at play within a disorder (as in most diseases), downstream measures must be used to effectively capture all relevant system characteristics that influence treatment outcome. Metabolomics, in which the identification of variations in metabolites helps capture intermediate phenotypes that respond differently to the same treatment, has developed from this need. For example, a variant of the B1 adrenergic receptors is associated with a considerable improvement in response to treatment with carvedilol in patients with congestive heart failure [25].

Still further downstream from the genes, some researchers have looked at comorbid conditions to help define subdiagnostic groups that show variable treatment outcome. Eli Lilly, for example, has recently marketed Strattera for attention-deficit disorder patients who have a comorbid reading disability. What becomes apparent is that factors outside the traditional boundaries of the disorder can affect treatment outcome and, therefore, confound trial outcomes. For example, variants of the cytochrome P450 system can alter pharmacokinetics considerably, adding a large degree of variability to treatment outcome in certain populations.

Inclusion of all factors relevant to drug treatment outcomes is only possible at the whole-system level of an individual patient. Capture of contributing genetic factors, variations in expression of those genes under differing environments and interaction of other metabolic systems on the pathologic and pharmacologic process can produce the full picture of the phenotype of interest for the disorder and drug treatment under study. Initially, a wide assay of all trait development can be gathered through historical accounting of all physiologic responses to all environmental changes within each patient. A multivariate analysis can then identify those traits that have high frequency within the diagnostic group. Finally, component analysis of different sets can be used to define the boundaries and associated groupings of the relevant complex traits that tend to have high prevalence in the population.

Because the human physiome is so complex, this approach would have to capture every possible physiologic trait during a trial. Using EDC and electronic analysis, this becomes feasible; however, this approach leads to mountains of information and the inherent noise leads to unreliable and inaccurate associations. The essential prerequisite to deploying such a dynamical systems approach is to create a 'phenotype roadmap' that reliably maps out the characteristics or traits of importance found within the diagnostic population under study. Such a map would link the key phenotype identifiers to produce groupings of traits that accurately define diagnostic subpopulations of patients that have similar responses to environmental factors in general and to the drug treatment specifically.

Future personalized pharmaceutical systems

Development of the 'phenotype roadmap' would necessarily include all known genetic and metabolic variables of significance to the diagnosis under study. Additional data points would be drawn from historical variations in response to a spectrum of environmental factors. Because drug treatment represents a direct environmental influence on individual physiology related to the disorder of interest, previous treatment outcomes in response to various therapeutics can add additional clarity. Identification of the common pattern of traits associated with historically shared environments between subjects within the diagnostic category will define the effective level of generalization necessary to define each relevant phenotype.

Once the roadmap of phenotypes is defined for the diagnostic category under study, drug treatment outcomes can be mapped to each of the subgroups in a retrospective manner. Test subjects belonging to those phenotypes with the best response to treatment and those with highest probability of adverse effects can be identified. A novel CPR can then be defined using phenotype characteristics shared by the newly identified subdiagnostic groups that occupy the best outcome section of the bell curve.

CPRs developed in this manner will define the inclusion criteria during phase II and III drug development. The CPR defines the homogenous population, creating a more accurate 'diagnosis' that

becomes part of the labeling criteria for the compound. This technology will closely match patient phenotype to probably treatment outcome, adding a high degree of certainty to treatment decision-making and predictability to clinical outcomes. Partnering with clinicians in the CPR development process to identify and effectively label truly homogenous patient treatment groups will enhance medical provider buy-in to this process and increase the likelihood that practice patterns will shift accordingly. CPRs can be instrumental in differentiating same class compounds to guide clinicians to the 'right' patients for that treatment. CPRs used in this manner could also identify the subgroup characteristics of those patients at highest risk of adverse effects, enabling their appropriate removal from the treatment population and lessening the risk for black box labeling by the FDA.

Limitations in CPR development and utilization

There are some important limitations that affect the development and utilization of CPRs, as mentioned throughout the text. However, rather than being a detriment to progress, these issues should be recognized as areas where crucial changes could improve the potential impact of these tools.

First, development of a CPR and corresponding determination of clinical impact and efficacy is rightfully seen as a time- and resource-intensive process. For one thing, derivation of a CPR demands a broad initial exploration of data, resulting in a highly complex data set for analysis. This requirement, in turn, increases the initial study population size required for statistical analysis. In addition, for the finalized CPR to be valid over a wide, highly demographically variable population, the initial selection of subjects must be of similar heterogeneity, further increasing study size. Finally, a CPRs reliability as a tool to inform and improve clinical decision-making will require multiple confirmatory studies that show efficacy over a broad population. Any tools that can streamline the list of initial variables to consider or refine the initial size and scope of the study population would effectively lower these hurdles.

Second, it is notable that predicting individual outcomes, as opposed to predicting aggregate outcomes within subpopulations, requires a more complex initial study, exacerbating the first limitation. However, CPR development that is aimed at predicting outcomes in aggregate subgroups of relatively homogeneous patients (versus the entire heterogeneous population of interest) represents not only a less demanding initial study but also an end product that is of the required scope for enhancing clinical trials in the pharmaceutical industry, where it is not individual outcomes but rather subpopulation outcomes that are of interest. A third, and related, area of limitation involves the difficulties imposed on CPR development by patient phenotype complexity. As people age, comorbid diseases might make determining their susceptibility for a certain outcome or diagnosis more difficult. Although an individual or group might be at low risk when considering genetic makeup, comorbidities such as obesity, cholesterol level, blood pressure and diabetes might themselves impose increased risk, and a given CPR might not have the statistical power to detect these interactions and make successful predictive models. However, this limitation – again – depends on the size and scope of the initial trial; larger sample sizes have the benefit of more easily capturing these complex interactions. Advances in the ability to understand global patient phenotypes would help address this limitation by targeting data acquisition to those factors that are needed to differentiate such complex phenomic interactions.

Finally, physician willingness and ability to utilize the finalized CPR, even if it has proven benefit, can be a limitation. For example, there is evidence that physician utilization of a new tool is inversely proportional to the difficulty of the skill acquisition involved. The more easily it is applied, and the less training that is required, the more probably any tool is to be used by a physician. Here, the burden is on developers of CPRs to define the minimal necessary attributes (and, thus, the simplest CPR) to predict outcomes. In addition, developing systems within the office setting that lead to easy implementation of the CPR and clear differentiation of benefit in efficacy and efficiency should be part of the developer's focus. Physician reimbursement, cost containment and satisfaction of practice are other issues that might affect CPR use. The potential for CPRs to aid in prescribing the right drug the first time, however, should not only lessen patient dissatisfaction but also increase physician effectiveness and satisfaction.

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