research by optimizing data sharing, controlling costs, saving time, educating the general public, and facilitating translation of new discoveries. There are strong natural incentives for both public and private stakeholders to participate in such an initiative. Initial funding could come from funding agencies or disease-group consortia who wish to exploit this resource to address specific research questions or to promote the use of data from unique communities. Individual research projects could then fund the sequencing and data interpretation. The scale of the DDP could be large. The genomic community would stand to benefit from an effective DNA-procurement system analogous to what is now a highly organized national organ-procurement system for transplants. We believe that the educational efforts of the DDP could act as a catalyst to bring about what has long been anticipated: a new societal approach to genomic research and personalized medical care.

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Integrated Efficacy to Effectiveness Trials

RM Califf[1,2]

Experts in clinical research, therapeutic development, and comparative effectiveness are continually frustrated in their attempts to fit the square peg of therapeutic development into the round hole of clinical trials. Trials can be optimized to provide signals in highly controlled experiments or to estimate an intervention's effect in poorly controlled real-world settings, but not both simultaneously. Selker and colleagues propose a continuum that creates a smooth transition from controlled experiments to real-world, real-time studies within a single mechanism.

The "efficacy-to-effectiveness (E2E)" approach described in this issue of *Clinical Pharmacology & Therapeutics* by Selker *et al.*[1] describes a new paradigm for therapeutic development that is both consistent with current thinking and sensible from a conceptual standpoint. It is also timely, as our current system for developing and testing new medical technologies is clearly on an unsustainable trajectory.[2] Drug developers face dire challenges within an environment where investment in new therapeutics is jeopardized by sharply rising costs of development—an escalation that has grown particularly acute for later-phase clinical trials. Advocacy groups understandably want swift access to potentially useful therapies and a better understanding of the comparative safety and effectiveness of technologies. Clinicians seek to narrow the range of uncertainty in their recommendations. And payers and health systems would prefer to pay only for therapies that provide a favorable balance of risk and benefit.

All these factors were reflected in the report of the special subcommittee of the President's Council of Advisors on Science and Technology (PCAST) in 2012.[3,4] Prompted by an exodus of high-paying pharmaceutical and biotechnology jobs from the United States,[5] the PCAST subcommittee included industry executives, academic leaders, government and policy experts, and patient advocates. Fundamentally, the committee recommended a more continuous approach to technology approval in which the level of uncertainty is continuously narrowed by a series of studies and permission for marketing occurs earlier in the cycle but is accompanied by a robust commitment to continuous postmarketing evaluation.[3]

In the E2E model,[1] the developmental path for a novel technology starts with an efficacy study designed to optimize detection of a signal for a favorable benefit/risk balance. Once this initial hurdle is cleared, the trial would evolve through a carefully planned, systematic process into a comparative effectiveness trial. This trial would be conducted in a population that represented the breadth of the technology's intended use and would have a duration and sample size adequate for informing its rational use in practice. The eminent sensibility of these proposals is unsurprising

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given the experience and collective wisdom of this group of authors, who span academia, industry, and the regulatory world. However, despite its conceptual appeal, the E2E construct presents significant challenges that must be surmounted before it can be applied in practice.

Contrary to current practice

Selker and colleagues appropriately raise the issue of motivation for industry sponsors to assume the risk of effectiveness trials as part of a continuum with efficacy. The metric typically used for industry funding is *net present value* (NPV), a calculation that compares the financial investment in a trial to the revenue generated over the life cycle of the project.[6] Under the current market system, however, the height of the regulatory hurdle before regulatory approval is a major determinant of NPV. After marketing, unless there is substantial demand for a comparative effectiveness trial, a very high level of confidence in a correspondingly high probability of successful demonstration of superiority is needed to meet the NPV required. Even when there is certainty of superiority, a trial with an alpha level of 0.05 and a beta of 0.90 essentially has a 10% chance of failing to show superiority where it actually exists and a 5% chance of a false-positive finding for the comparative therapy.

The rational application of NPV in this market environment, then, has led to a regime in which phase II and phase III trials are typically constructed to optimize the signal for benefit in restricted populations, whereas market expansion occurs through a combination of widespread off-label use and specifically targeted, industry-funded postmarket trials and registries. In other words, avoiding the direct answer and using marketing to create marketplace momentum with carefully designed niche studies wins the NPV comparative contest.[6] If E2E is to displace the current system of therapeutic development, we will need to carefully consider how incentives are structured within this space.

Investment approaches

A further impediment to adopting the E2E model arises from the ways that investment typically occurs in medical product development. Because phase III programs typically cost hundreds of millions of dollars, investors understandably agree to fund to specific milestones. Data are then aggregated to present a composite picture of a technology's clinical value to patients and providers and its financial value to investors and manufacturers. Then, another decision is made about the next tranche of investment. Amid this complex mix of data, opinions, and prognostications about future trends in therapy, epidemiology, and market competitors, many potentially useful therapies are developed for indications that maximize financial return rather than human benefit—or are shelved entirely. One example of this dynamic is provided by the history of the drug eflornithine. Originally developed as a chemotherapy agent, eflornithine was found in the mid-1980s to be a curative treatment for African trypanosomiasis (sleeping sickness).[7] However, the agent, which was both expensive and difficult to manufacture and store, languished as an orphan drug and supplies were nearly exhausted when regulatory approval for a potentially lucrative cosmetic indication in 2000 allowed large-scale production to resume for both applications.[8] Agreeing to the E2E approach would commit investors and companies to expansive trials in situations where pausing for reflection and recalculation might tend to suggest different directions.

Technical considerations for data collection and analysis

Even if the investment issues can be sorted out, significant technical issues remain. During the efficacy phase of therapeutic testing (late phase II and early phase III), little is known about the safety and off- and on-target effects of the new technology. Detailed record keeping is necessary, and, for understandable reasons, regulatory agencies are extremely concerned about the accuracy and completeness of the information collected. This leads to expensive, redundant data-collection systems and extensive use of monitoring, coupled with complex systems of auditing and error correction.[9] Successfully navigating a transition from this type of data collection, reporting, and monitoring system to the type needed to support feasible large-scale effectiveness trials will not be simple.

What about these predictive models?

Another facet that emerges from the E2E plan is Selker and colleagues' advocacy for the routine use of modeling based on clinical trial data so as to estimate the balance of risk and benefit for individuals and groups of patients. Although this is a laudable goal on the path to integrating personalized medicine with population health, it is somewhat tangential to the main thrust of their argument. Nevertheless, the E2E approach would produce the type of data needed to construct models that could be used as predictive instruments for decision support in practice.

Reasons for guarded optimism

As noted above, implementing the E2E scheme would require significant changes to the policies and procedures that govern the conduct of clinical trials. Just a few years ago, this would have seemed impossible, but two major new initiatives offer hope. The NIH Health Care Systems Research Collaboratory ("the Collaboratory"; https://www.nihcollaboratory.org/about-us/Pages/default.aspx) is seeking to demonstrate that large-scale trials can be embedded into integrated health systems, taking advantage of electronic health records to conduct effectiveness trials at a fraction of the cost typical of similarly sized studies. In addition, the Patient-Centered Outcomes Research Institute is constructing a national patient-centered clinical research network (PCORnet) that will bring together patients, providers, administrators, and researchers with the intent of conducting numerous comparative effectiveness trials at a lower cost and providing reusable infrastructure for trials and outcome studies (http://www.pcornet.org).

The fact that these and other complementary efforts are beginning to address the inefficiencies and shortcomings of our research systems is reason for guarded optimism. For the immediate future, the chief challenges will be (i) understanding and mastering the complexities of collecting and sharing data in clinical practice

while ensuring the quality needed to draw reliable research conclusions and (ii) replacing the prevailing view of practice and research as separate activities with a "learning health system" methodology that incorporates research into practice as a routine element of clinical care. These changes will require significant adjustments to the ethical frameworks that span the spectrum of learning activities, from quality improvement to interventional research involving new therapies.[10]

Conclusion

Selker and colleagues have articulated a vision that is consistent with our evolving understanding of therapeutic development. Before this vision can become a reality, numerous practical and conceptual barriers must first be overcome. However, revolutionary clinical research methods that are now being piloted have the potential to help make E2E a reality.

CONFLICT OF INTEREST

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In Vitro Prediction of Clinical Drug Interactions With CYP3A Substrates: We Are Not There Yet

DJ Greenblatt[1]

In 1973, Malcolm Rowland and associates described an approach to predicting clinical pharmacokinetic drug–drug interactions (DDIs) using an inhibition constant determined *in vitro* (K_i) together with anticipated inhibitor exposure *in vivo* ([I]). Despite numerous modifications and refinements of the core model over the following 40 years, we still have not achieved a predictive paradigm having accuracy sufficient to justify bypassing all, or even most, clinical DDI studies in the course of drug development.

The use of *in vitro* data to anticipate, predict, or explain clinical pharmacokinetic drug interactions was first described by Rowland and Matin in 1973, in the context of the inhibition of tolbutamide clearance by coadministration of sulfaphenazole.[1] The core of the model was what is now commonly termed "[I] over K_i"—the ratio of inhibitor exposure *in vivo* ([I]) divided by an *in vitro* inhibition constant (K_i) that reflects (in reciprocal fashion) the quantitative potency of the inhibitor. The more [I] exceeds K_i, the greater is the $[I]/K_i$ ratio, and the greater is the probability and/or magnitude of a clinical pharmacokinetic DDI caused by the perpetrator's (e.g., sulfaphenazole) inhibition of clearance of the victim (e.g., tolbutamide). Rowland and Matin at that time also pointed out the importance of f_m—the fraction of the dose metabolized via the target pathway—as a modulator of the predictive validity of the $[I]/K_i$ ratio.[1]

Clinical and scientific interest in DDIs intensified in the late 1980s and

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