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Transforming Medicine: A Manifesto

Integrating “best practices” with “alternative” methods to determine which therapies benefit patients the most

by Stuart Kauffman, Colin Hill, Leroy Hood & Sui Huang

American medicine is in desperate need of transformation, regardless of the vested interests that may challenge its reform. Lives, health,

resources and our morality are at stake. One of us—Kauffman, an MD biologist—watched his wife, Elizabeth Kauffman, fall through the cracks that splay, known but unseen, across our wider medical practices. Elizabeth had pancreatic adenocarcinoma, a terrible cancer, and was not likely to live longer than the year that she did survive with such courage, grace and generosity. We, the authors of this article, came together in part through our efforts to help Elizabeth. We started meeting in October 2012, when she was in treatment at the University of Washington Medical Center.

There were two drivers of our early conversations. First, we discussed how Elizabeth fell through the cracks in Western medicine, between oncology’s “best practices” protocol and its slightly off-center “alternative” counterpart, which includes experimental approaches. Physicians with off-mainstream perspectives often are viewed with contempt by established medicine and are routinely hounded by their local and state medical boards. Dismissed by the establishment as deviating from best practices, their work lies in a therapeutic grey zone, widely referred to as alternative medicine. This grey area is entirely within the perimeter of rational science, yet is not embraced by best-practice medicine. It exists because best-practice medicine is a subset and not the absolute equivalent of good, useful, rational medicine. The effective components of alternative medicine need to be united, in new and integrative ways, with best-practice medicine, whose central pillar is evidence-based medicine.

Maneuvering through Mountains

That brings us to the second driver of our conversations, now more academic, which is the limitations of the randomized clinical trial (RCT), our field’s gold standard, which provides, well, the evidence for evidence-based medicine. In a study in 2012, Maggie Eppstein, of the University of Vermont, Stuart Kauffman and their collaborators used a carefully designed mathematical model and computational simulations to compare RCTs to an alternative approach called team learning. This approach generates new treatment combinations based on current success data and opinions of those hospitals with the best result, about which of the 100 treatment factors to alter at each point in time.¹ In particular, they compared the methods for establishing the optimal treatment protocol, which consists of 100 features—practices, types of interventions and so on—and typically varies from institution to institution. Team learning is now organized into qualitative improvement collaboratives (QIC), composed of groups of several care providers who exchange accounts of their experiences and discuss how to optimize the treatment protocol without the blinded pooling of all the data into a large, multi-center study.



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The results from the study Eppstein and her colleagues conducted depended on the complexity of the procedure. Engineers and biologists often liken an optimization process to walking on a landscape, where every position represents, in our case, a particular therapeutic combination of procedures, and the elevation at that position reflects the success rate of the procedure. Optimization involves finding the highest peak. Depending on the complexity of the problem, the landscape topography can vary. If the problem is simple, the individual features of the procedure do not interact with each other but act independently, as “mono-causal” factors that contribute to the good outcome; then the landscape has a single peak, like Mount Fuji. Here optimization is simple: Move in the direction of steepest incline. In more complex tasks, the features of the treatment depend on each other, and mathematically this results in a landscape that is rugged, with multiple peaks separated by plateaus and valleys—more akin to the Rocky Mountains. Here, simply moving in the direction where the terrain goes uphill will not bring the walker to the highest peak, and there is no guidance of direction in flat regions between the peaks. One can easily get stuck on the top of a small hill, far from the highest peak.

In their simulations of the Mount Fuji-like scenario, Eppstein and her colleagues found that the RCT performed better, especially when a larger number of patients were involved. But intriguingly, it beat QIC only by a small margin. With a smaller number of patients and a Rocky Mountain-like landscape—indicating multi-causality—QIC outperformed RCT. As multi-causality increased, RCTs failed even more dramatically. Thus, team learning, which may cost less than RCTs and uses nearly anecdotal data, can lead us to better care protocols in complex environments, especially where the RCT’s evidence-based, brute-force statistics become inappropriate. So we need better methods with multi-causal statistics.

Testing New Techniques

Do we think that biology and medicine involve multi-factorial causality? The answer is almost always yes. These results suggest that RCTs throw away some or even vast amounts of clinically relevant data. No one knows how much.

We randomize a study, divide the patients in control and treatment groups in a blinded fashion to eliminate confounding factors, which we suspect but cannot pinpoint. For instance, if we know that gender might affect the outcome, we make sure that both groups will have the same number of male and female patients. Such controlled stratification cannot be applied to the thousands of possible factors that influence the outcome when we do not know what those factors are. Consequently, randomization neglects the vast space of information about causal factors that likely differ between individuals and might interact with each other, thereby leading to a multi-causal effect on the outcome, such that randomization might not average away these causative effects. Moreover, randomized trials produce results that apply to a phantom “average” person, whom a given individual is unlikely to resemble with respect to every possible characteristic that might impact the disease or response to treatment.

It gets even worse. Only drugs that pass phase-III RCT trials, in which efficacy is demonstrated in a larger number of patients, can be FDA approved. Only such drugs can become part of the hospital best-practice formulary. Once on the formulary, the hospital faces sanctions, even loss of accreditation, for failing to follow best practice as hallowed by RCTs. But best-practice doctors—typically highly trained, of high integrity and good intent, aiming to be “scientific” and not let in charlatans—are confined to best-practice medicine both by professional ethics and because they will most likely not be insured should they stray. Furthermore, in the name of best-practice medicine based on a now outdated reliance on RCTs, off-center, skilled doctors are harassed, pay exorbitant legal fees defending their rights to practice and carefully explore outside the box, or may even lose their licenses. The healthcare establishment scoffs at their off-center ideas.

In the nether-regions near the inferno of pure charlatanism lies alternative medicine, often founded on merely anecdotal accounts—not unlike the team learning above—and held in contempt. What can we do?

Alternative medicine lacks the reassuring endorsement that the label “evidence-based” confers, and hence, is abhorred by mainstream medicine. But it is as rational and rigorous as any mainstream philosophy that relies on the scientific method. “Evidence” may be overstated; the evidence in evidence-based medicine is obtained through randomization and averaging over heterogeneous populations,

just to neutralize our ignorance, and thus is almost guaranteed to not fully apply to a specific person. Evidence-based medicine would work if we were all clones of each other. Evidence-based procedures will work in a given patient to the limited extent of how much her thousands of relevant characteristics match those of the theoretical “mean” patient. But how much does she depart from that average?

'Omics Options

We are entering an era in which we can measure those factors that RCTs have considered dark matter in the information space of patient-specific traits and have randomized away. We can determine the multi-causality network of each individual patient. The arrival of the 'omics technologies—genomes, epigenomes, transcriptomes, proteomes and metabolomes—is about to shine light into this dark matter of patient-specific causality. This offers an opportunity to unite the “unscientific,” but patient-focused alternative medicine with the “scientific,” evidenced-based best practices, or one-size-fits-all medicine. The fact is that the thousands of patients who participate in clinical trials differ from one another both genomically and environmentally, and the assumption that they are equivalent is patently false. For each patient, the 'omic analyses generate a virtual data cloud of billions of data points. These can be used to analyze the individual patients, and those who share interesting features, like response to a given drug, can then be aggregated into groups that will respond uniformly. In a sense, N=1 experiments—those that include only one person—are performed, and the patients with shared features are aggregated.

Personalized medicine strives to exploit precisely the information that is randomized away in RCTs by studying one thousand patients or more. Instead of the false certainty obtained by neutralizing patient-specific variation in studies that include as many people as possible, personalized medicine seeks, ideally, a full molecular profiling of an individual patient. The technology is here, and the knowledge of how the human system functions is improving rapidly, such that the collected data cloud around each individual patient can serve as the basis of informed decisions. Thus, the dimensionality of measurements, which captures the multi-causality revealed by team learning and the conscious abnegating of randomization, warrants the personalized approach. The prerequisites for this approach are high-dimensional measurements that leave no or little unaccounted-for factors that would have to be randomized, and mechanistic knowledge that allows predictive models based on the high-dimensional data obtained for each individual.

In November 2012, as Elizabeth was getting worse, a careful study at the Moffitt Cancer Center in Tampa, Florida, demonstrated that in some solid tumors, the cells in the acidic areas grew faster than those in the more alkaline areas. There is a known biochemical basis for this preference of tumor cells for lower pH and, thus, for a mechanistic rationale for alkalization as a way to curb tumor growth. Treatment with mere sodium bicarbonate slowed the growth in the acidic areas in animal experiments. But not all tumors are equally sensitive to alkalization. If we had measured Elizabeth's tumor-cell metabolome, an analysis soon to be available in the clinic, this could have revealed whether her tumor could be suppressed by controlled alkalization. When told of these preclinical data, the in-the-box oncologist dismissed alkalization therapy for lack of RCT evidence. Still, Elizabeth received intravenous cesium chloride, a powerful alkanizing agent, under another doctor's care, and it may well have extended her life several months. We will never know. The N=1 experiment was never permitted.

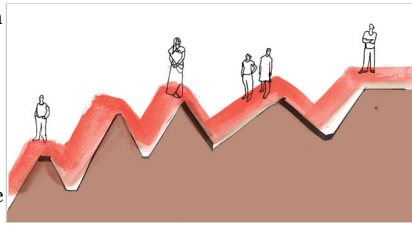
1. Eppstein, M.J. et al. PLoS One (2012). doi: 10.1371/journal.

Pathways To Improvement

To reveal more options in our search for advanced treatments of disease, we recommend the following changes:

1. Explore real clinical-fitness landscapes, empirically treated with combinations of candidate therapies, to see how often the landscapes are multi-peaked.
2. Search other fields for alternative ways to empirically search clinical-fitness landscapes.

3. Use various search engines and data from empirical clinical-fitness landscapes to build ensembles of putative single- and multi-causal models of disease processes that can be tested in simulations.



4. If true mechanisms of causality cannot be determined, we must study how to optimally treat patients in the absence of detailed knowledge. For example, can we better treat with single drugs for single targets or with combinations of drugs aimed at many points in complex regulatory networks?

5. Urge the US Food and Drug Administration to preserve its accumulated wisdom but very carefully widen its scope beyond RCTs.

6. Consider foregoing phase III trials and moving to phase IV trials, where defined patient populations, perhaps identified by the N=1 experiment defined above—with coordinating supervision—begin to generalize team learning and test treatments with multi-factorial causality. This empowers all of us to be part of a global medical learning system.

7. Build very high-dimensional “state spaces” of thousands of pieces of environmental, genetic, epigenetic and physiological data—so-called big data—and follow hundreds or thousands of patients to define “health” and “diseased” areas in these huge state spaces to move toward personalized medicine.

8. Begin a slow careful integration of in-the-box, near-the-box and alternative medicine to broaden our information and exploration bases.

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