The Quickening Pace Of Medical Progress And Its Discontents

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AGAINST THE BACKDROP of current controversies over drug pricing and access to new medical breakthroughs is a transformation in the relationship between basic science and the practice of medicine. The pace at which fundamental discoveries of basic science are being uncovered is accelerating, as is the speed at which medical practice is being transformed by these inventions. Metamorphic changes are sweeping a wider breadth of clinical areas more regularly than at any time in the history of science. Creative destruction is an increasingly prominent feature of modern medical practice.

This acceleration in the translation of basic science into practical treatments, and the resulting waves of transmutable change in medical practice, stands in stark contrast to the longer sweep of medical history. It's this pace of the modern medical advance, perhaps as much as issues related to the cost of the new treatments, which are creating the challenges being cited by elements of our healthcare delivery system in maintaining access to these opportunities.

Those delivery systems have evolved to finance the entry of gradual or episodic changes in medical practice. They certainly were not engineered to match an environment where therapeutic areas are repeatedly transformed, or embrace a period where better insight into the biological basis of disease would create the opportunity to suppress or cure once intractable diseases.

The historical context for how medical care has evolved as a result of new findings of science and technology is worth revisiting not only to frame the intense change that characterizes modern drug innovation and its impacts on medical practice, but also its challenges. The current environment stands apart from any pervious period of rapid medical progress. These opportunities also bring with them a novel set of challenges for payers, creating imperative for new coverage arrangements that can embrace the pace of scientific change.

To see how much the connection between scientific discovery and its corresponding impact on medical care has changed, begin with the earliest discovery of basic science that bent the trajectory of medical practice -- the discovery of the germ theory of disease, that tied illness to microorganisms.

This concept was first proposed in the mid 16th century and gained widespread credence through a long series of follow on discoveries. But it wouldn't be until the 19th century that hand washing was first introduced into medical care as a way to prevent disease, when Hungarian physician Ignaz

Philipp Semmelweis proposed in 1847 that maternal death could be sharply cut when obstetricians washed their hands with chlorinated lime solutions.

Seammelweis produced studies showing that antiseptic techniques reduced maternal deaths rates that hovered as high as 40% down to 1%. But doctors bristled at his suggestion that they had to start washing their hands, and they rejected his concepts. Semmelwies was hobbled by the fact that he couldn't offer a plausible scientific reason for his observations. He was committed to an asylum in 1865, and died 14 days later after guards beat him.

So it wasn't until Louis Pasteur confirmed the germ theory in the 1860s and a few years later, Joseph Lister began introducing sterile techniques into surgery that the findings firmly impacted medical practice. The experimental methods, laboratory tools, and scientific insights were finally at hand to not only explain how germs caused disease, but also explain how they could be controlled to the benefit of patients. It only took 300 years.

It wouldn't take this long the next time to turn a pivotal finding of science into something of practical benefit to patients. This is a key point. The history of science reveals that the period of time between a central discovery and its translated benefits is being continually compressed as science advances. The pace of the consequent change in medical practice was accelerated. There appears to be a compounding effect to scientific knowledge. Each major advance in science creates a base of knowledge and enabling tools that make it easier to translate subsequent discoveries into practical treatments.

Consider the firming of our understanding of immunology, and the creation of drugs based on these discoveries. One of the most profound efforts to harness immunology as a way to target disease was through the creation of monoclonal antibody drugs. The idea was to use replicas of our body's own immune cells as vehicles to target specific illnesses like cancer, and use antibodies to disable or destroy the disease causing cells.

Paul Ehrlich first proposed this basic concept of a "magic bullet" that could target disease-causing cells at the beginning of the 20th century. He postulated that a compound could be engineered to selectively target and destroy a disease-causing organism by delivering a toxic payload. By the 1970s, it became understood that certain B-cell cancers all produced a single type of antibody. This insight was used to manufacture antibodies experimentally. But it still wasn't possible to produce antibodies specific to a desired target and Ehrlich's full vision could not be realized.

The comingling of these two findings – targeting an element of disease and using a tailored antibody to achieve this -- would still require an additional discovery, made in 1975. That was when Georges Köhler and César Milstein pioneered the fusion of cancerous B-cell lines to invent immortal cells that were able to reliably manufacture carefully derived antibodies that targeted disease-related cells. By 1986, scientists used this approach to develop the first antibody drug called OKT3 that prevent the rejection of transplanted organs.[1] [2]

Yet the drug was still a crude creation in many respects. It was a reproduction of a mouse antibody, not the human equivalent of that protein. That limited its effectiveness, and also increased its propensity for side effects.

It wasn't until 1988 that Greg Winter and his team at the University of Cambridge pioneered the techniques to "humanize" monoclonal antibodies, making them part human, and part mouse,[3] [4] and it wasn't until 1997 that the

first "humanized" antibody drug Zenapax would hit the market. It still took another five years for the first fully human antibody drug to reach patients, a medicine for inflammation and arthritis called Humira.

It was almost thirty years since scientists had first started making some fundamental discoveries about these immune cells that antibodies could be reliably used as drugs, and almost 100 years since such targeted drug therapies were first envisioned. Today antibody-based drugs comprise six of the 15 top-selling medicines and represent some of the most impactful therapies used in the treatment of cancer and many other diseases.

This brief and selective history epitomizes the changing pace of medical progress. It took 300 years for the discovery of germ theory to find its way into new antiseptic treatments and clinical practices that changed the contours of medical care. But it only took a mere thirty years for our modern scientific work on immune cells to translate into the development of some of the most transformative and efficacious drugs in the annals of medical science.

Now consider the year 2003, when the mapping of the human genome was declared complete. It wasn't long before we were hearing laments from some critics about the enormous sums of money we sunk into new tools and methods for understanding the genetic and protein basis for disease, and the alleged dry hole of tangible benefits – in the form of new drugs -- to show for these investments. Most of the new drugs, it was said, were incremental advances. "Me-too" therapies that chased established approaches for attacking the biology of disease and offered only marginal advantages over older drugs.

Contrast that refrain against the prevailing views today. The debate over new drugs and their costs has shifted from one of drugs that offered too little benefits and shouldn't be widely used in lieu of cheaper alternatives, to concerns that breakthroughs are so plentiful, and medically transformative, that we're challenged to finance their widespread delivery to patients.

Gene therapy seemed like a high-risk, if not elusive concept when it was seriously advanced in the 1990s, and the initial of a wave of gene therapy biotech companies was first funded. Just twenty years later, there's a plethora of advanced gene therapy based drugs in development. Some are on the cusp of regulatory approval. These approaches offer legitimate opportunities to essentially cure some of the most debilitating inherited disorders, including devastating blood disorders like Sickle Cell Disease.[5] Right now, there are almost 400 ongoing gene therapy clinical trials that are labeled as active registration studies and being conducted under the FDA's supervision.[6]

The construct holds true for an array of new scientific platforms, from gene editing, to cell-based therapies, to profoundly new ways of manipulating immune cells to target cancers. Today, science is being translated into practical treatments for patients at a breakneck speed. The results are so convincing, and the benefits so seductive, that the resulting treatments face efficient routes through regulatory agencies, and are readily and widely adopted across clinical practice. Many of these new drugs are based on technologies that were discovered or affirmed in only the last decade. The scientific route from pioneering discovery to new drug, once traversing centuries, and recently spanning decades, now is measured in years, and in some cases, just months.

What's the point? Simply that the pace of progress between the revelation of some basic scientific datum about disease, and its translation into

a practical therapy that impacts medical practice has been considerably compressed as a result of better science and a base of understanding that enables progress to build on itself. The period of time between the uncovering of some fundamental scientific finding that underpinned a medical advance, and the realization of the corresponding advance in the form of a new drug or medical technique that improves the health of patients, is being continually hastened. Moreover, the platforms and approaches that we're using today to discover new treatments are so integral to biological systems that the resulting therapeutics often has profound impacts on progression of disease.

This compression in time between the discovery of profoundly new science, and its payoff in the form of transformative new treatments, is one of the triumphs of our modern drug discovery. It's a reflection of the advances in drug development made over the last few decades as biopharma companies adopted better discovery tools and methods for tailoring molecules. It's also a result of better sharing of information that improves learning environments, enabling findings to be more widely shared, teams of researchers more tightly connected, and capital more readily available at a lower cost.

But perhaps most significantly, it's also a consequence of a deeper understanding of the molecular basis of disease that has pushed us past an inflection point where accumulating knowledge is leading to accelerating efficiencies in translating basic science into practical therapies.

This experience brings to the fore todays underlying challenges of delivery and access when it comes to breakthrough drugs. It isn't just a matter of cost. It is a function of the bounty of rich new science that is changing the practice of medicine and the nature of disease at a pace never witnessed in human history. Moreover, the new treatments are targeting such fundamental aspects of disease that they are having a transformative effect on illness. This only intensifies the imperative to approve new treatments quickly, adopt the briskly, and make them available to properly indicated patients on a wide basis.

But our healthcare delivery system wasn't conditioned to this pace of rapid change because such profound and wide scale advances were never before realized. Our payment systems were conditioned to financing the cost of foreseeable expenses that increased at predictable rates. Where the treatment of specific diseases underwent transformative changes in the achievable outcomes, raising costs, these opportunities were not the normal course.

Today they are become the standard, especially when it comes to unmet medical needs, which has been the focus of the new innovations. The technologies that are altering the long-term trajectory of disease also pull some of the later costs forward, even if the innovations reduce costs in the long run.

This new expectation requires an investment mentality when it comes to reimbursement for breakthrough new drugs. But our reimbursement models, as they exist today, are not adapted to these constructs. In some cases, government rules stymie the changes that need to occur.

In many cases, the impact of the new technologies promise to offset their costs when one considers all the downstream benefits in terms of future economic savings, reduced morbidity, and increased productivity. But the current financing models can't bake into the current outlays these longer-term economic returns. The challenge is that the financing arrangements have not been established to accommodate the financial rewards of discontinuous

advances that alter a disease trajectory, even if these kinds of transformative changes are the sort of technological improvements that we all seek.

The transformative science underlying today's new medicines also means that more of the drugs are aimed at mechanisms of disease, and are more likely to cure disease, or sharply alter its course. Many of these drugs are not being targeted to the normal bell curve distribution of a disease, but the smaller tails of outliers who are not well addressed by conventional therapies.

Under these terms, the cost of the research and risk taking can't be recouped over many years. More of it needs to be baked into upfront costs, since more of the drugs are bending the morbidity curve and changing long-term treatment patterns and their resulting costs. The benefits, not only in terms of lower long term costs, but also reduced morbidity and higher productivity from affected patients, is realized incrementally over many years as patients enjoy improved survival. The cost of treating disease, which was once amortized over many years and sometimes the life of a patient, must be recognized sometimes in full, up front, when a treatment doesn't just temporize a condition, but aims to cure or alter its trajectory.

In other spheres of commerce, where a high upfront cost is incurred for a good whose benefits are realized over many years, financial intermediaries have created financing schemes to deal with the economic lumpiness. Credit allows costs to be amortized over the useful life of a good or service.

Similar credit facilities could be offered by health plans to the parties that are taking on the long-term financial risk of paying for medical care; the self-insured businesses, the capitated providers, or government programs. Health plans could play an important role in servicing these agreements. By financing technology through credit agreements, premiums increases as a consequence of wide adoption of a costly new technology could be smoothed.

These credit facilities could also be securitized into debt instruments that could be sold or traded. They have a stream of revenue associated with them, and variable risk that might be associated with the continued success of the treatment that is being funded, just like other credit facilities that have similarly been securitized into tradable instruments. If government authorities want efficient ways to ease adoption of a technology for some groups, they could subsidize or guarantee the interest associated with these instruments.

New approaches to paying for curative therapies through credit facilities might require a change in accounting rules so that those paying for a treatment over time don't have to recognize all the costs up front anyway, and reserve against these liabilities. Some will also worry that financing schemes will only serve to make it easier for drug makers to charge high prices. This misses an important opportunity. Such amortization approaches will also make it easier for those paying the bills to embed look backs into these contracts that tie continued payments to measures of outcomes and performance. These provisions might actually make it easier for those holding the risk to avoid full accounting recognition at the outset of the agreements. The full re-payment of the credit facility wouldn't be assured under these conditions. It would depend on clinical outcomes that health plans could help track and measure. Under these circumstances, accounting rules might not require the full liability to be recognized up front, but instead, taken as the credit facilities is paid down.

These approaches could facilitate more opportunities for governance over how the prescriptions of new drugs are impacting patients over time. The health insurers and the pharmacy benefit managers would seem to be uniquely positioned to serve as intermediaries to these financing arrangements, creating a new business line in offering financial services as an enterprise solution.

Yet the biggest impediment to these opportunities may not be market hesitance but policy obstacles. Government rules like Medicaid best price rules, and Medicare's Average Sales Price reporting requirements, as well as other forms of implicit and overt government price controls and mandatory rebating, all serve to prevent experimentation with how drugs are priced. But novel payment arrangements might break apart the usual charges, to spread them out over time, and price therapies by a course of treatment rather than for each discrete vial. These rules get in the way of schemes to amortize drug costs.

The challenges we face in adopting breakthrough technologies, and making sure patients have access to them, isn't merely a matter of price. It's a question of disruption to the existing models of reimbursement and delivery.

We are going to need to reconstruct how we pay for new technology to embrace the quickening pace that characterizes today's destructive innovation in medicine. To make sure that the resulting breakthroughs continue to reach patients requires us to have an approach to financing medical care that's as modern and imaginative as the drugs that are being invented.

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