

Comprehensive Health Care Reform and Biomedical Innovation

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Acknowledgement: I thank Marc Tessier-Lavigne for helpful discussions regarding the organization of drug discovery activities in the industry and for assistance in putting together the Technology Development Chart.

To be sustainable, comprehensive health care reform will have to address health care inflation. There will have to be concerted efforts to control costs. There are many possibilities for savings, including reducing administrative costs, doctors' salaries, and drug prices. While these changes can generate substantial savings, they are one-time savings; once the cost of administration, salaries, or drugs are lowered, the savings are absorbed into the system. Prices cannot decline forever.

Sustainable cost control requires changing the rate of *growth* of health care costs over time. As countries become richer they are likely to spend more on health care as a proportion of GDP. Therefore, over time, health care costs will—and should—probably increase faster than growth in the GDP. However, over the last 3 decades, health care costs in the United States have increased 2.8% per year more than overall economic growth. This seems excessive by all comparisons. For any health care reform to be sustainable, the increases in health care costs should probably not be zero, but somewhere between zero and 1% increase over economic growth.

A major driver for health care cost increases is technology—drugs, devices, surgical procedures, and other interventions. This includes the development, adoption, and diffusion of new technologies. Research and development on new drugs and devices raises costs because newer is usually more expensive. For example, drug eluting stents are more expensive than bare metal stents. In the case of drugs, a new drug on patent may replace an older drug whose price will decline when it goes off patent. The adoption of technologies by more doctors also raises overall costs. They treat more patients with the condition. Finally, and probably most importantly, costs rise most when technologies are used for a wider range of patients, especially patients who have less clear cut clinical

indications for the intervention. In these cases, a new drug or medical technology may be developed for people with specific clinical indications. As physicians become more comfortable using the drug or technology, they then prescribe or apply it to more patients who may not fit the clinical indications for which the drug or technology was proven safe and effective or who are not as sick and in whom the intervention produces—or is likely to produce— fewer benefits. For instance, after their introduction, about 1 million drug-eluting stents were implanted per year, with 60% of them implanted in patients whose coronary occlusions were different from the occlusions in which the stents were proven safe and effective. In these patients, there was an absence of data indicating that the drug eluting stents provided any clinical benefits over bare metal stents.

Cost control in comprehensive reform cannot merely examine health care costs in isolation, but must consider the costs relative to the benefits and whether spending on health care could displace other expenditures. Expensive drugs that prevent hospitalizations or shorten nursing home stays may be costly from the health care perspective, but could be cost-effective and reduce costs overall. Thus, assessments of costs should be from the societal perspective.

Serious cost control under comprehensive health care reform will have to tackle these three technology drivers—the development, adoption, and diffusion of new technologies. How might that be done?

Technology Assessment and Controlling Technology Driven Costs

It is likely that any comprehensive reform proposal will create some type of technology assessment organization because it provides an essential foundation to controlling

technology-driven costs. Yet by itself, technology assessment does not do anything to control costs. It needs to be linked to some process for determining coverage of services, reimbursing physicians, or altering care processes. Nevertheless, technology assessment provides information essential for these cost control interventions. Without this information, changing coverage, reimbursement, or care processes could be ineffective, costly, or even produce harm. Information from technology assessments is critical to making these cost control interventions effective in reigning in costs without undermining health outcomes.

How this technology assessment process would be structured—whether based on Britain’s National Institute for Clinical Excellence (NICE), Blue Cross and Blue Shield’s Technology Evaluation Center (TEC), or some other technology assessment model— is unclear. At a minimum, this organization is likely to be empowered to make comparative effectiveness determinations for commonly used technologies. This would exclude considerations of cost and simply evaluate how well different interventions achieve some clinical endpoint. Structured more expansively, this technology assessment organization could be empowered to include costs in explicit cost-effectiveness determinations.

Apart from the types of assessments performed, the technology assessment authority of this new organization might be expanded in two other ways. First, it might have the authority not just to review existing data, but to actually sponsor and/or conduct clinical studies on technologies to determine their effectiveness and risks of technologies. This would require substantial funds, but would also expand the range of technologies and interventions that are evaluated rather than focusing solely on treatments for which

data already happened to exist. It would drive the creation of substantially more data to make more of medicine “evidence-based.”

Second, we must consider how these evaluations are linked to coverage or reimbursement decisions. One possibility is for there to simply be no formal link between the technology assessments and coverage or reimbursement decisions. The technology assessment could be “advisory” and constitute one of multiple elements of information used by payors or insurance companies. Alternatively, as in Britain and Israel, there might an explicit link between the technology assessments and coverage decisions. That is, the technology assessments might determine whether a technology is covered by insurance at all, covered but with different copayments, covered with the development of new evidence, or linked to reimbursement to providers.

Summary of Variations on Technology Assessment

Variations	Spectrum of Options
Types of Assessments	Comparative effectiveness to cost effectiveness
Types of Data	Existing research to newly sponsored clinical trials
Type of Links to Coverage or Reimbursement	Advisory to explicit link

Interventions to Control Technology-Driven Costs

In a cost conscious health delivery system, the information developed from technology assessments can be linked to 3 different ways of influencing practices: 1) Insurance Benefit redesign; 2) Provider reimbursement redesign; and 3) Care system redesign.

Type of Intervention	Options	Other Aspects
Insurance Benefit Redesign	Cost sharing	
	Mandated specific interventions	
	Reference pricing based on cost	
	Reference pricing based on cost-effectiveness	
Provider Reimbursement Redesign	Cut provider payments and reimbursements	
	Pay for Performance	
	Bundled Reimbursement	
	Risk Shifting	
Care System Redesign	Disease Management	
	Lean Production	

Insurance Benefit Redesign

Under a comprehensive health care reform plan, it is likely that insurance benefits packages would change. A traditional method of insurance benefit change is cost sharing through co-payments regardless of a technology's cost, effectiveness, or medical indication. This is what is commonly done today through say 20% co-payments regardless of the intervention. This seems a blunt instrument, currently exists, and does not seem to have any effect on restraining technology adoption or diffusion.

Another possibility is mandate of specific interventions that have been proven effective, cost effective or even cost savings. This would obviously create guaranteed and substantial demand for the intervention. Since this would be done after development of an intervention and would probably constitute a special action, it is hard to see how any manufacturer could use this to guide research and development decisions.

A new potential change is reference pricing. Much like tired pharmacy benefits in which costs to patients for certain classes of drugs (eg generic drugs) are lower than other

drugs in the same therapeutic class, insurance premiums or co-payments could be linked to the price of the medical technology. Thus insurance companies or health plans could pay for the least costly intervention with limited or no co-payment or deductibles.

Individuals who preferred more expensive interventions for the same condition would have to pay for the more expensive interventions.

Another option is for the reference price to be determined by how cost-effective the interventions are. Some interventions may be more expensive but overall provide a better value because the health outcomes are better. When there are several different interventions available for a particular condition, insurance might cover the most cost-effective intervention with no co-payments or deductible. If patients wanted—or are prescribed—the less cost effective intervention they would have to pay more, up to the added incremental costs of the treatment. For instance, there are four different types of radiation for early stage prostate cancer (see Table). They vary tremendously in cost. Existing studies do not suggest a significant difference in survival. The studies suggest a small, 10%, difference in the rate of GI toxicity, mainly rectal bleeding.

Type of Radiation	Approximate Cost	Late Moderate to Severe GI Toxicity	GU Toxicity	Impotence
3-D Conformal Radiation	\$11,000	12-14%	15%	36-39%
Brachytherapy	\$15,000			
IMRT	\$42,000	4%	15%	36-39%
Proton Beam	Over \$50,000			

With reference pricing, insurance companies might pay the entire cost for 3-D conformal radiation, but if patients wanted one of the other treatments they would be required to pay more—up to the full incremental cost— for the more expensive treatments.

Reference pricing would provide financial incentive for patients to prefer high-value interventions, those with lower cost for the same benefit, while discouraging use of expensive or low-value, marginal interventions.

Provider Reimbursement Redesign

Today, about 80% of physicians are paid some form of fee-for-service, whether directly or through a PPO arrangement. In the current system, the main mechanism for adjusting provider reimbursement is by untargeted, across the board fee reductions. This has been the traditional approach by Medicare, and is urged by some health care reforms such as the Physicians' Working Group for a Single Payer Plan. Unlinked to a technology's cost, effectiveness, or the appropriateness of the intervention, it seems not to have had any restraining effect on the use of technology. It is also a failed mechanism for cost control.

In a reformed system focused on cost control, reimbursement is likely to shift in several potential ways. First, there is likely to be expansion of pay for performance (P4P) arrangements and a decrease in strict fee-for-service reimbursement. In these circumstances, physicians and other providers will receive bonuses or some other special payment based on achieving process measures, adhering to guidelines, or realizing favorable patient outcomes. Thus, the providers might get an extra payment for a patient with a myocardial infarction if they complied with all guideline requirements such as

prescribing aspirin and a beta blocker, and providing educational, nursing, and other interventions for changes in diet and physical activity. Similarly, providers might get extra payment for ensuring diabetic patients have their hemoglobin A_{1c} checked, or for having the patient's hemoglobin A_{1c} within a specified range or for not having the patient admitted to the hospital over some specified time period.

Pay for performance is supposed to encourage both use of technologies proven to extend life or enhance quality of life, and adherence to processes that are linked with improved outcomes. Depending upon how it is structured, P4P is likely to encourage use of low cost technologies or high value technologies.

A second, more substantial re-formulation of reimbursement would be bundling of payments, such as implementation of episode-based payments. In this case, providers would be paid not for individual services or activities but for a bundle of activities and services related to a health care episode. For instance, once a woman has a suspicious mammogram and a positive biopsy for breast cancer, then there might be a single payment for the subsequent treatments including surgery, radiation treatment, chemotherapy, follow-up office visits, and a follow-up mammogram related to breast cancer treatment. Similarly, if a person has a myocardial infarction, there might be a single episode payment to physicians and hospital for all interventions to treat the actual infarction as well as for 6 months after the initial acute event. This bundling of payments would encourage integration of care among physicians and hospitals. It would also give providers an incentive to minimize the use of costly interventions. By linking payment for both acute care and care beyond an acute episode, episode based payment might provide incentive not just to reduce immediate costs by, for example, shorter hospital

stays, but for more cost-effective interventions over an extended period. In selecting drugs for a woman's chemotherapy, for instance, physicians would have an incentive to use the cheapest proven combination.

Still a third redesign of reimbursement entails various strategies to shifting more risk to providers. This might entail paying physicians a flat annual fee to manage patients with chronic conditions as well as a slight additional fee that is less than full costs for specified events, such as hospitalizations. This additional fee would serve as a way to risk adjust for uncontrollable events or very high cost patients but it would be low enough not provide an incentive to use high cost services. The shift of more risk to the providers would give them an incentive to use lower cost, high value services and discourage the "let's try anything" approach.

A final possibility is for insurers to pay providers to care for a patient with a chronic condition with a payment based on the actuarial determination of optimal care. The health care provider could charge patients for additional services or more costly interventions. This way, the negotiation over the more costly interventions would be directly between patient and physician. This may induce less costly interventions, although it may also be that patients will associate high cost with better care and be willing to pay for it.

Care System Re-Design

Another approach to focus on improved quality of care and lower costs are disease management strategies, especially for chronic conditions. These entail the development

and implementation of a whole package of evidence based services for patients with chronic diseases requiring substantial services—patients with congestive heart failure, COPD, or diabetes for instance. Much of the focus in this strategy is on optimizing medications and keeping patients taking their medications, adhering to their diets and exercise programs, etc. This management is intended to save money by preventing acute care hospitalizations. By substituting cheaper education and visiting nurse interventions for expensive acute hospital stays, disease management might save money and improve outcomes. The existing data on disease management approaches are very limited; there are only a few studies which are not of the best quality. These data have not consistently demonstrated significant cost savings from such disease management interventions. These programs might save money by reducing use of marginal technologies and the high technology interventions used in hospitals.

The Impact of Cost Control Strategies on Biomedical Innovations

These various cost control strategies aim to constrain the use of technologies that are of marginal value, that is do not produce added benefits worth the incremental costs. A fundamental question is: How will implementation of any of these cost control strategies affect the development of biomedical technologies? Will they reduce the influx of funds supporting new biomedical technology companies? Will they reduce the amount of research and development conducted by biomedical technology companies? Or will they shift the types of research and development projects pursued by biomedical technology companies? Will such cost control techniques encourage more personalized medicine? Will they encourage the search for more “blockbuster” drugs?

Drug Development Process

The attached figure presents a stylized timeline of the drug development process. There are several key decision-points that might be altered by the various cost control strategies.

Basic Research

At the start is basic research which that identifies the fundamental biological pathways, and constituent molecules--the proteins, lipids, and other molecules—involved in the pathway, the factors regulating the pathway, etc. This type of research is unlikely to be affected at all by what occurs in the financing or delivery systems.

Basic research is an attempt to understand the fundamental elements of biological systems. The forces driving basic research are scientific opportunities created by other scientific discoveries, advances in assays, and other breakthroughs. This research is predominantly funded by the NIH and to a lesser degree by charities and predominantly occurs at universities, medical schools, and other institutes. A small proportion of basic research is conducted by private companies, usually as a complement to the more applied research.

It is virtually impossible to imagine how changes in the delivery system, especially cost control mechanisms, would affect this basic science research. It is driven by scientific opportunity and curiosity not commercial interests. It is much more likely to be affected by changes in the NIH budget and philanthropy than by changes in the health care delivery system.

Translational Research

The products of basic research are insights into biological pathways. These insights identify potential targets for drugs and other agents that might affect normal and disease processes. With the identified potential targets, translational research is aimed at trying to identify what changes will modify a defective pathway in a disease. This translational research attempts to identify ways to modify the disease whether *in vitro* or in trusted animal models of human disease. The aim here is simply to identify “big effects” –interventions that can substantially modify a critical biological pathway.

Translational research occurs in universities, medical schools, private institutes, as well as drug and biotechnology companies. Its funding is both public and private.

How might cost-control affect Translational Research? It is unlikely that any cost control mechanism will affect which agents receive attention. It is very difficult to actually produce a big effect on any biological pathway. Thus, once a drug or other compound is identified that produces a big effect, it is hard to imagine cost control mechanisms influencing the selection of what effects are studied. Once a target that has a big effect on the disease model is identified, it is likely to be pursued.

Conversely, an emphasis on cost control might influence what diseases are studied. There is likely to be a shift in focus to 1) more common diseases, 2) diseases with big unmet health needs, and 3) diseases in which costs are high even if few interventions exist. Even in a cost controlled environment, discovering interventions for common diseases is likely to be more lucrative; affecting a larger number of patients will permit greater sales because of the bigger demand for the agent. But just because there are many potential beneficiaries of a new intervention does not mean that a new

intervention will be highly reimbursed in a new health system. It is unlikely, for example, that another hypertension medication will be of sufficiently high value in comparison to other treatments to command a high price. Thus, it is a disease that is unlikely to see much new research.

More importantly, curing or ameliorating conditions in which there are few existing interventions but serious unmet health needs is likely to be reimbursed more highly in a cost conscious environment. Developing interventions that cure cancers or make a substantial improvement in the care of Parkinson's or multiple sclerosis is likely to be reimbursed. Therefore, companies are likely to focus their research on pathways relevant to these diseases.

Finally, diseases in which there are few interventions which are only partially effective but for which health care is costly and a new treatment might displace costly care might become a focus of research. Thus research might focus on Alzheimer's because a new intervention that kept patients functional could substitute for expensive nursing care.

To summarize, once a target is found in Basic Research that significantly affects the disease process, that target will be followed up. The cost conscious environment is likely to affect the selection of pathways that are pursued, not how.

Lead Identification and Lead Optimization

In the Lead Identification stage, compounds are identified that modify the activity of the target. These compounds may be small molecules, antibodies, or other agents,

identified through library screening or through rational design. These compounds can be used as tool compounds to test the effect of modifying the target in *in vitro* assays and potentially in animal models. If leads with drug-like properties and evidence of disease modification are obtained, the project may move into Lead Optimization. In this stage, the family of drugs, antibodies, or other agents that affect a pathway linked to a disease process is narrowed, based on desirable characteristics such as efficacy, specificity, half life, solubility, mode of administration, mode of excretion, and preliminary toxicology studies in rodents. This stage of research is largely conducted by drug and biotechnology companies and likewise funded by these companies.

It is difficult to see how a cost conscious delivery system would really affect Lead Identification and Lead Optimization stages. This research is about creating a drug with desirable characteristics given the underlying disease.

Clinical Candidate Selection

After completion of the research stage, a decision is made about which candidate drug or agent will be developed for clinical trials in humans. This is identification of the most promising clinical candidate and possibly one or more back-up candidates (which may continue to be optimized). The evaluation of the candidates and whether to pursue development depends upon an evaluation of the promise of the potential agents: 1) do they have the right characteristics for a drug or agent in humans? And 2) are they likely to have acceptable or at least manageable toxicity, given the underlying condition being targeted?

This evaluation is focused on whether a potential drug or agent affects a biological pathway in the correct manner, has the right chemical and biological characteristics, and appears on preliminary evaluation to have minimal toxicities. These determinations are independent of cost considerations and unlikely to be affected by a cost conscious health care system.

IND preparation (“Phase 0”)

This stage focuses on toxicology in multiple animal species using extended exposures, that is exposure to high doses of the drug or agent and over long periods of time. It also focuses on developing efficient and reliable manufacturing processes that meet Good Manufacturing Process (GMP) standards. These developmental stages are all conducted by drug and biotechnology companies. They are unlikely to be affected by a cost conscious health system.

Commercial Determination

Around the time of clinical candidate selection, and through the IND enabling phase, a company has to decide whether to go forward with an IND –Investigational New Drug— application to the FDA and enter clinical trials. Since clinical trials are the most expensive part of the research and development process, costing about \$500 million, this is a major decision point.

At this stage, a “GO-No go” determination is based on data regarding the biological effect size in animal models, toxicology, and ease of manufacturing. A company must make a commercial determination (such as a Net Present Value

determination) for the potential drug based on 1) the likelihood of having an effect in humans, 2) the likely size of that effect, 3) the size of the affected population, 4) the price that can be charged for the product in the health care marketplace, and 5) the competitive landscape. Since clinical trials for successful drugs and other agents require 8 or so years, this determination of whether to go forward depends upon estimates of the marketplace many years into the future.

This is the second major stage in the research and development of new medical technologies where a cost conscious delivery environment will affect decision making. A cost conscious delivery system is likely to raise the thresholds needed to initiate clinical trials for potential drugs and other agents. Thus 1) the estimated likelihood of having an effect in humans will have to be larger, and 2) the estimated effect size will have to be larger. Drugs or agents that are anticipated to have a large effect or are very likely to have an effect in humans will still be pursued. However, agents that are estimated to be “middling” —those drugs or agents estimated to have smaller effects or whose likelihood of effect are estimated to be lower—are more likely to be stopped in development.

This more conservative strategy will probably result in fewer INDs, and those agents that are taken to clinical trials will be the ones more likely to succeed currently. In this way, the success rate of commercially sponsored clinical trials is likely to be higher.

Those who worry that a cost conscious environment will hinder innovation will argue that this strategy may generate more false negatives and missed opportunities—drugs or other agents where the effect size is predicted to be low but would have turned out to be substantial. Conversely, those who argue for a more cost conscious health care environment will emphasize that this determination is likely to

generate more high-value drugs and technologies—those that make a substantial difference in disease—while curtailing the development of low value drugs and technologies. “Me too” drugs are unlikely to command high prices. While they may receive FDA approval because they would be safe and effective, they might not be adopted by physicians or reimbursed because their benefits do not outweigh increased costs. These marginal technologies would be likely to be terminated more frequently.

Potential Ways to Enhance Innovation in a Cost Conscious Environment

One way that might be used to encourage introduction of more drugs and other technologies into clinical trials is to reduce the risks of a negative trial. This might lower the threshold for taking a potential drug or agent into clinical trials. How can this risk be reduced?

There are several ways. One is to develop a diverse portfolio of agents. If any one fails, there are still a few that will succeed. This can be undertaken only by big pharmaceutical companies because of the large demands for capital. Another possibility is to spread the risk of clinical trials. This is done by having multiple partners funding the clinical trials. This is analogous to multiple studios producing one film or multiple investment banks underwriting a corporate buy out.

In a cost conscious health care delivery system, the government itself might invest at the clinical trials stage to reduce risk and encourage the entry of more drugs or agents into clinical trials. By having the cost of the clinical trials supplemented by the government, the risk for pharmaceutical companies could be lowered. This is already done in many cases where the government has established a trials network—such as the

cancer cooperative groups or the AIDS trial networks— to conduct clinical trials of new drugs or agents. (Given recent FDA actions these NIH sponsored trials networks may no longer be as useful for FDA new drug applications.) Having these clinical trials networks conduct the research reduces drug company costs for trials. Another is having clinical trials co-funded by an NIH institute or other governmental agency (military).

At the moment, there is no explicit quid pro quo for using these government clinical trials supplements. In a new health care system, however, the government could require either lower prices or a share of profits in exchange for more direct financial supplementation of clinical trials phase of research. Since it is hard to determine a fair price, an alternative might be for the government to secure a share of the profits and use that money to offset drug costs.

For drug companies, this co-development with the government is desirable because it would spread the risk and allow companies to lower the threshold for likelihood of effect and effect size in deciding whether to proceed with clinical trials. There would be more drugs in clinical trials, thus reducing the false-negative rate. For the government, this would encourage more drugs in clinical trials but would not sacrifice market discipline. The government would not have to pick winners but could rely on the expertise of the technology companies. Furthermore, profits would be put back into the health care system.

This approach is not novel. As mentioned already it is done implicitly by NIH sponsored clinical trials networks or through NIH co-sponsorship of clinical trials. Also there are the recent efforts by the government to guarantee purchase of drugs, vaccines, and other agents for bioterrorism in which the market is currently non-existent. The

experience with these efforts is that they do lower the threshold for proceeding with clinical trials—a good example is the Merck HIV vaccine trial. However, they also are likely to have their biggest effect on small biotechnology and device companies rather than large pharmaceutical companies. Large pharmaceutical companies already have reduced the risk of any single drug by diversifying through large pipelines. Small companies with fewer potential products are more willing to partner. To the extent that innovation by small firms is desirable this incentive mechanism for overcoming the hurdle of entering clinical trials might be considered.

Other Technologies

The model for this paper has been drug development. How might this analysis apply to other technologies—devices, imaging equipment, diagnostic tests, surgical innovations, etc. For most of these new technologies there will be a time at which the equivalent of the commercial determination. In a cost conscious delivery system the bar for going forward will be raised. The chances that devices will be sufficiently safer or superior in efficacy to command a good return will have to be higher to go forward. Similarly, imaging technologies will have to show a marked improvement in some measure to justify their cost. The only exception to this might be surgical innovations which often do not go through the same type of commercial review before be evaluated. Therefore the factors influence drug development decisions are likely to influence development decisions for other technologies.

Conclusion

Comprehensive health care reform is likely to include serious efforts at cost control. These efforts will have to include efforts at controlling the development, adoption and diffusion of new medical technologies. The efforts are likely to include some form of technology assessment and some mechanism to incorporate the information from these technology assessments into coverage, provider reimbursement, and/or care protocols.

The primary impact of such cost control on new technology development will be at two stages of research and development. Early in research, when a decision is being made about what diseases and pathways to focus research on, cost conscious health delivery system will shift the focus to conditions that have larger numbers of patients, greater unmet health needs, and high costs with few interventions. Thus the impact of cost control will be to shift resources to higher value research where a new drug is likely to have a bigger health impact that will command a higher price.

The second place that a more cost conscious delivery system will impact biomedical innovation is at the stage of commercial determination when it has to be decided whether to pursue clinical trials for FDA approval. A cost conscious environment is likely to increase the threshold for pursuing a drug or other agent—expecting a higher likelihood of an effect and a bigger effect size than currently. Drugs where the anticipated results are more uncertain or the effect size is more in the middle may not be pursued.

There may be some approaches to reduce the risk of clinical trials, lowering the threshold to enter trials.