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Medical Technology and Research Update

Track: Health

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Summary: Medical research, technology, and treatment advances continue to affect patient options. Panelists discuss recent developments that may impact health care costs over the next few years, such as:

- *Trends in research and treatment for various diseases*
- *Advances in diagnoses, therapies, and medications that will be available in the near future*
- *Various clinical trials*

MR. GRADY C. CATTERALL: I'm an independent consulting actuary in Bethesda, Maryland. My work focuses on pricing, contract negotiations, and cost projections for managed health care and pharmacy benefit plans. The other panelist is Marjorie Rosenberg, who is a professor at the University of Wisconsin. Dr. Rosenberg holds a joint appointment in the Actuarial Science/Risk Management and Insurance Department of the school of business and in the Biostatistics and Medical Infomatics Department of the medical school. Her research interests are in the application of statistical methods to health care and applying actuarial expertise to cost and policy issues in health care. She's currently working on developing statistical tools for monitoring health care outcomes. She is also involved in the development of models for cost effectiveness analysis, which she'll be talking about in more detail. She holds bachelors and masters degrees in mathematics and statistics, and a Ph.D. in business, all from the University of Michigan.

DR. MARJORIE A. ROSENBERG: I will provide an introduction to the economic evaluation of health programs—including technology—and then Grady is going to follow up with some examples of things that are going on in order to give you an idea of the kinds of economic tools that are used in the evaluation of health care programs. The outline of this talk will be to provide some basic definitions and terminology. We'll talk about costs, but we won't get into much detail because there is a real controversy as to what is a cost and what is not a cost. We will

Note: The chart(s) referred to in the text can be found at the end of the manuscript.

focus on different viewpoints that we can take in terms of doing any economic analysis. We'll talk a little bit about actuarial modeling and how that will fit into this process, and then we'll talk about some of these methods such as cost effectiveness analysis. Some of the definitions that we'll deal with include what a health care program is, what health care services are, and the equipment or resources that are used.

An economic evaluation is a systematic method of determining whether health care resources are spent efficiently. Examples in technology would include equipment, drugs, procedures, and different techniques (e.g., in the operating room). The assumptions are that dollars spent on health care resources are scarce. Choices must be made to determine how to spend these resources. Alternatives have been identified and shown to work, and can be accessible to those who need it. Some examples are screening for cancer or some genetic diseases, smoking cessation benefits, the alternatives of one plan versus the other, physician-assisted suicide, and the whole ranking system used in the Oregon Medicaid program.

We need to identify choices, costs, and consequences between alternatives. We need to identify the choice when comparing one program with an alternative. We need to measure the costs, and actually identify those costs. We need to value the consequences such as additional life years saved or additional quality life years saved, which means whether the next years of life are better than they would have been had we not intervened. Then we need to compare the results.

The theoretical issues are to determine the appropriate health resource costs. In this day and age, it's very difficult to identify costs. If you had some kind of cost system, you might be able to identify hospital costs. But what is a physician cost? How do you measure what a physician cost is? This "cost" item actually differs from one study to the next, and should be viewed with caution. We need to develop consistent methods of measurement of health outcomes, and we need to develop the methods to actually bring everything together. That's where the actuaries, I believe, can actually bring value to the process today, because of our background.

Net direct costs are fundamental to any cost study. We need both the direct and indirect costs of a procedure. For example, what are the direct costs of implementing a new surgical technique? What are the costs of other procedures and tests induced by that procedure? What is the cost of diagnosing and treating side effects and complications? But also, what are the cost savings for diagnosis and treatment of the morbidity averted by the procedure? We might have additional costs up front, but maybe a year or two down the road we'd actually save costs, because the procedure actually improved the long-term mortality of that person.

We'd also want to add the net change in health care resources resulting in the change in life expectancy. So, if I had a surgical treatment performed that improved my life, then I would have additional costs after five years when I would have died, had I not had the procedure. Another good example of this would be smoking

cessation benefits. If you stopped people from smoking, they would improve their cardiovascular system and lower their risk of cardiovascular disease. They would lower their risk of lung cancer, so they would actually have more health costs in the future, because we've saved their lives.

So how do we value health programs? The old way of thinking is just using the net direct costs and tallying up the cost of the intervention. The new way of thinking is to take all those net costs, but then maintain the efficiency in terms of costs per unit of health produced. Measure it against something that's important. What are those things? One way is cost per case. Take the costs and divide them by the number of cases, such as dollars per cancer found. You also could look at dollars per cost of per life-year saved. Instead of looking at number of lives, you're looking at number of years of life saved. A newer concept is to look at quality adjusted life year (QALY) saved. By using the measure of QALYs saved, you would be able to calculate a quantity to address prolonging one's life by a year, but maybe not in the best of health. Maybe that additional year of life should only be measured at 50% or 80%. Or perhaps the measure could be negative—as something that is worse than death.

There are different viewpoints of looking at an economic analysis. One point of view belongs to the patient. Another would be from the insurance provider, which would be different from that of the government, which would be different from that of society. For example, when you do a public policy cost-effectiveness analysis, the motive is that you take the viewpoint of the society. It's important to mention the viewpoint of a study at the beginning of any article.

From the societal point of view, you would take those net direct costs and actually factor in patient time any time that the patient sat in the doctor's office, or any resources that were donated in terms of any caretaker time or family time. The costs would be measured against some effectiveness or consequences of the benefits accrued to the patient or to the family and caregivers. You improve the benefits if you improve their lives.

From the federal point of view, the costs of providing care are usually measured by some form of production costs or proxies for Medicare costs. The costs usually exclude out-of-pocket costs to the patient, any patient time costs, and non-medical expenditures. The benefits would be the benefits to the patients and sometimes to the caregivers.

From the managed care point of view, we'd look at net direct costs, and also at indirect benefits to the organization providing good care, such as increased enrollments.

From the patient's point of view, we would look at costs incurred by the patient. Health care deductibles, non-covered health care costs, and time costs directly consumed by the intervention would be included. Health outcomes would also be included, which would be the consequences experienced by the patient or by others that the patient values, such as the caregiver and other family members.

Those are the definitions. Now I want to conceptually tie some of these things into what we already know as actuaries. This is a quote that I took from the Society Web site at one time: "An actuarial risk is a phenomenon that has economic consequences and is subject to the uncertainty with respect to one or more of the actuarial risk variables: occurrence, timing, and severity." That's exactly what we're doing here. If you think about a timeline, you can set up costs at different time points. What you would need are assumptions for the incidence, the duration, and the present value discounting. You can do the same thing for the effect timeline, which would involve those QALYs saved or life expectancy.

The modeling part comes in when we consider another quote that I found on the SOA Web site: "An actuarial model is a stochastic model together with a present value model, if applicable, of actuarial risks, based on the assumptions about the probabilities that will apply to the actuarial risk variables in the future, including assumptions about the future environment." Somehow we need to combine all these things in a stochastic model so that we can make some inference or forecast.

If you think about that cost and effect time line, there's uncertainty and variability in all the costs and the consequences. If you do a study, you'd have a sample of patients that you would actually observe for a certain period of time, but that's just one sample. What you want to do is generalize from that sample to the entire population to make some kind of statement as to whether this procedure is effective or not.

I am alluding to the survival models that we've studied which are very important in completing any analysis. For those who are unfamiliar with survival models, complete data would mean that you would follow people to their death. You would then be able to measure costs and effects from the beginning of the study until their time of death. That's the ideal, but of course it's not feasible and will never be done, except in a laboratory setting. Usually you have censored data, which means you would have a study, say for five years, and at the end of the study period you have to make some conclusions. People might get tired of participating in the study and leave. Censored data, especially with costs, is a very sticky issue, even if you knew what the costs were to the time the person was censored. Even if you could identify all these costs, it's still difficult to model when you have censored data. You can't just make simple averages on the sample because you need to make projections beyond the end of the study period.

You also need to define discounting. What is the rate of interest? Gold, Siegel, Russell, and Weinstein's *Cost-Effectiveness in Health and Medicine* recommends 3% or 5% for the rate of discounting, in which case the effect of discounting would not be too much, but still impact the analysis.

This portion of the presentation is for those that have studied from the actuarial mathematics book, and thought they'd never use this stuff again. I just wanted to let people know that you can actually use it. $T(x)$ is a random variable for time until

death for a person aged x. That's our standard notation. This is the cumulative distribution function (CDF):

$$F_{T(x)}(t) = \text{CDF of } T(x)$$

This is the probability density function (PDF):

$$f_{T(x)}(t) = \text{PDF of } T(x)$$

$$\begin{aligned} E[T(x)] &= \text{Expected time until Death} \\ &= \int t\, f_{T(x)}(t)\, dt \\ &= \int (1 - F_{T(x)}(t))\, dt \\ &= \int s_{T(x)}(t)\, dt \end{aligned}$$

where $s_{T(x)}(t)$ is the survivorship function. That is, the expected time until death is the integral of a survivorship curve.

For the old actuaries, we would call this $\overset{o}{e}_x$. The important thing is that you're integrating over or under the survival curve, and this notion of integrating under the survivorship curve is what's used in the health services research all the time.

Usually a survivorship curve starts at 1.0 and decreases uniformly until death. It's usually a smooth curve if you use what we call a parametric model, but if you use empirical data and develop an empirical distribution, it would look choppy. However, with quality-adjusted life survivorship curves, the curve does not necessarily decrease monotonically. As actuaries, we could create this curve somehow. So the quality adjusted life years (QALYs) is the area under the curve, and then the quality adjusted life expectancy is based on the average number of qualities experienced by cohorts of the same starting age and quality of life.

How do we use this? With this same curve we had before, let's suppose that we had an intervention before that downturn. So an intervention occurs and changes the life path. What ends up happening is that you gain life years because you're above the original curve and you've extended it further. So you live longer, and you've improved the quality of life. Another possibility is that we improve life, but then the patient dies early so we gain and lose QALYs with the net effect that we have a shorter life but a higher quality of life.

Another possibility is an intervention where we've reduced quality of life, but we've extended the length of life. In this case, we've lost QALYs because we've reduced

the quality, but we've extended it, because we're living longer. The bottom line depends on your survival model.

Now we have the definitions and some actuarial techniques that perhaps we can build on, as well as conceptual ideas, in terms of dealing with QALYs and costs. The methods that you may have heard about are cost minimization, cost effectiveness, cost benefit, and cost utility. Cost minimization is when the outcome data indicates no difference in the effectiveness in alternatives. You want to compare costs to figure out the smaller cost. Cost effectiveness is when you use net direct costs measured in dollars, and when health outcomes are measured in objective units, such as the number of cases found or the number of life years gained. Cost utility would be the same costs as the cost effectiveness analyses, but the outcomes would be measured in terms of QALYs, where the quality of life is measured on a utility scale of preference.

We have these models and I've shown you some curves, so now the question is, how do you create these models? You can create them through non-parametric models and, as actuaries, the life table method (which is one of the prevalent ones). For parametric models you can assume a Gompertz or Makeham distribution; you can do decision trees where you map out a process with probabilities; or you can use a state transition model, such as people are using now in Course 3 with Markov models.

Let's focus on the incremental cost effectiveness analysis:

$$CER = \frac{\sum_{k=0}^{\infty} v^{k+\frac{1}{2}} \overbrace{\{c_s(k) - C_c(k)\}}^{\text{DCosts}}}{\sum_{k-0}^{\infty} \underbrace{v^{k+\frac{1}{2}}}_{\substack{Discount \\ Rate}} \underbrace{\{E_s(k) - E_c(k)\}}_{\text{DEffectiveness}}}$$

s = screened; c = control

Here we take the difference in costs over the difference in the effects for the screened group and the control group. You would include some discount rate; here I arbitrarily assumed that all of the costs and the effects would be incurred halfway through the year.

Now there are new variations of the cost effectiveness ratio. People didn't like the fact that this denominator, if the effects are really close to one another, could go to zero, then cause the ratio to blow up. So they introduced new variations to accommodate this. One way is called the net benefit approach, where you just take the change in costs and some factor times the change in effectiveness:

$$NB = \Delta C + \Delta E \cdot k$$

The other is net health benefits where you just take the change in costs multiplied by 1 over k, plus the change in effectiveness:

$$NHB = \Delta C \cdot (1/k) + \Delta E$$

where k is some given parameter.

In the literature for cost effectiveness analysis, you'll see that people rank procedures, and if it's less than $50,000 per QALY, then it's deemed to be cost effective. The $50,000 is just a number that felt good to people, and it's become the industry norm in terms of whether a procedure, a drug, any of these technology issues, would be considered cost effective.

The question is, when you're doing cost effectiveness studies, and you have a ratio, what are you comparing things to? In Chart 1, we're looking at the change in costs relative from the current level of care to the intervention, based on the effectiveness. What ends up happening is, as in economics, you'd have some frontier where if this was one of your new interventions, relative to the current level of care, you'd have a change in cost. But a change in effectiveness wouldn't be considered adequate and this alternative is dominated by all these other alternatives. All the economic theory in terms of dominance applies to this as well.

Chart 2 shows the huge change in cost for just a tiny change in effectiveness, and that's what's called the flat curve of medicine. The change in the QALY is good for the lower values because it's a steep curve, yet at that higher end, at that flat curve of the medicine, it's not worthwhile to increase the cost relative to the quality obtained or saved.

In summary, I wanted to provide an introduction to the vocabulary, and to introduce the fact that, as actuaries, we provide a lot of knowledge in terms of doing healthcare studies like this. These studies need to be done. It's not just whether the procedure is clinically effective; we need to make it cost effective given the scarce resources. There are thousands of papers on this subject if you want to search. The literature, as well as some textbooks, are actually very strong references in terms of introducing you to this concept.

Grady will now give you real life examples as to what's happening today.

MR. CATTERALL: I'm going to be touching on the qualitative aspects of setting research priorities to complement what Marjorie was saying about the quantitative aspects. What I want to go over first is how the National Institute of Health (NIH) sets its research priorities, and I'll then talk about some of NIH's current investments and future plans. Then I'll talk about pharmaceutical company research and some of the drugs in the pipeline that are expected to come out within the next year or two. Finally, I'll have a few words to say about the overall cost impact of new drugs.

Setting research priorities at the NIH is based on both an assessment of population health needs and an assessment of scientific opportunities. Looking at the population health needs is the main focus for applied research, which is usually disease-specific. It may be clinical or epidemiological research. If it's clinical, then you're looking at the specific effect of a certain intervention or new drug on a defined group of patients. If it's epidemiological, you're looking at the general characteristics of a large population and trying to determine, for example, risk factors for certain diseases.

Assessing scientific opportunities is mainly for the basic research carried on at the NIH, or sponsored by the NIH but carried on in other places. It may or may not have currently discernible applications. The NIH is interested in advancing basic science, which is expected to pay off eventually. It doesn't have to have an immediate practical application.

The first question is, which diseases do we focus on when we're using the health-based priorities? One option is to look at the number of cases and the number of deaths caused by a given disease or condition. Two measures of the number of cases are: (1) the incidence, which is the number of people who develop a disease within a given time period–usually one year, and (2) the prevalence, sometimes called the disease burden, which is the number of people who have the disease at any given time.

Sometimes you will hear epidemiologists talk about "lifetime incidence," which is the likelihood of an individual developing a disease during his or her lifetime. For example, you may have heard that one in nine women will develop breast cancer at some point in her life.

Another thing to look at is the number of deaths caused by the disease. Such measures are used for the really severe conditions. You can either look at the population mortality rate, which is based on the number of people out of the whole population who die from a given disease, or the case fatality rate, i.e., how fatal the condition is if you develop that condition. An example for which the latter measure is used is AIDS. When it first became known, AIDS was essentially a death sentence; anybody who developed full-blown AIDS was expected to live only another year, or a few years at the most. Now with improved treatment, a lot of AIDS patients are living much longer. Population mortality rates are often used in describing the diseases that cause the most deaths in the U.S. Note that the leading causes of death usually are the conditions that a lot of people have. That is, they have high prevalence and high incidence, but the case fatality rates may be relatively low. The reason they cause a lot of deaths is that so many people develop these conditions in the first place.

Another criterion that is used is the urgency of action needed to control the spread of the disease. Urgency was certainly a feature of the early years of the AIDS epidemic when it was spreading very rapidly. Research was needed to figure out how it was spread and, mainly, how to change behaviors to reduce the spread of

the disease. Another disease that might fall into the "urgent" category now is Hepatitis C.

The NIH is also looking at the economic and social costs of disease. That's what Marjorie was talking about—looking at the cost of treatment and the lost wages and productivity either caused by time spent in treatment, the disease itself, or the resulting premature deaths. Also, one has to look at the cost of care giving, transportation, and other support and ancillary costs.

Finally, there's the catchall category of the extent to which the disease diminishes either the length or the quality of life. This criterion focuses on the reduction in life expectancy or the increase in number of deaths as a result of the disease, the number of additional disabilities caused, or the severity of disability. The phrase used in the 1997 NIH report, *Setting Research Priorities at the National Institutes of Health* is "the degree to which the disease cuts short a normal, productive and comfortable lifetime." So anything that makes you less productive or less comfortable, or reduces your overall life expectancy, is potentially worthy of attention.

The other main way to judge and set priorities, is to assess the scientific opportunities. What they're looking for is the payoff; that is, which investments are likely to yield a payoff. The definition of payoff, in this case, is an important discovery that significantly advances knowledge in a given scientific field. What constitutes a significant advance is a relative value judgement, but the people at the NIH who are deciding what projects to fund are looking for projects that are likely to lead to other important discoveries, and, as I mentioned earlier, it doesn't have to have an immediate practical application. If it's something that is fundamental to understanding a disease process or general physiological systems, it's likely to lead to practical applications later on.

The criteria that are applied to research proposals—and this is listed in that 1997 NIH report—are:

(1) *The importance or centrality of the problem to be addressed.* Is it something that's likely to lead to other important discoveries? Is this the key that unlocks a whole roomful of important discoveries, advances, and applications?

(2) *How innovative is the proposed approach?* Is it something that has not been tried before? It's worth taking a gamble every now and then that a completely different approach will pay off, especially when previous approaches haven't.

(3) *The adequacy of the methodology.* That includes whether or not you have enough test subjects to ensure sufficient statistical sensitivity to detect a difference in effect for a given treatment.

(4) *The qualifications and experience of the investigator.* If the investigator has a good track record, then he or she is more likely to get funding. That favors people

with more experience, whereas the "innovation of approach" criterion may favor those who are newer to the field, for example, more recent doctorates.

(5) *How rapidly is the field progressing?* Some fields of science are seen to be progressing more rapidly than others. The fields that are progressing more rapidly will change over time. But if a lot is happening in a given field, then the assumption is that helping that field along can lead to some big breakthroughs, or lots of small but still significant breakthroughs in a short period of time.

Now I want to talk about the current investments and future plans of five of the institutes at the NIH.

The National Cancer Institute (NCI)

The National Cancer Institute is focusing on a couple of areas such as biomarkers of cancer and the molecular classification of tumors.

Biomarkers can be either molecular or genetic. They make it possible to detect tumors that can't be detected otherwise, and they provide non-invasive diagnostic techniques. For example, you can detect certain cancers through blood tests.

Developing a molecular classification of tumors can allow scientists and physicians to diagnose more accurately so that they can base their diagnoses not just on the appearance or texture of a tumor, but on its molecular or genetic characteristics. A more precise diagnosis can lead to more targeted interventions and, just as importantly, to fewer side effects. If you can target your interventions better, rather than taking a sledge hammer to the problem, then you're going to do less damage to the patient. You want to focus the damage on the tumor instead.

A couple of other things that the NCI is focusing on are (1) molecular target agents and (2) in vivo cellular and molecular imaging.

With molecular target agents, the idea is to reverse or block molecular defects that can lead to the development of cancer. This can also be used to inhibit tumor growth if you can figure out a way to keep a defect from replicating itself and spreading.

Cellular and molecular imaging can be used as another non-invasive means of detecting cancer and studying its progression. If you can produce better images of a tumor through an MRI or other techniques, then you can track its progression. This is important for clinical purposes for individual patients, and also for research purposes; that is, just to better understand how the disease progresses.

The National Heart, Lung and Blood Institute

At the National Heart, Lung and Blood Institute, scientists are focusing on the diseases that constitute the leading causes of death in this country. Cancer, I think,

is #2, but heart disease is #1, and various lung diseases are at #4 and #5 on the list. So there are a lot of important issues here.

The first area of research is genomic applications and gene therapy—identifying genes linked to heart and lung function for diagnosis, prevention and possibly for treatment purposes.

Another area is developing vectors for therapeutic genes. There has been a lot of work on developing ways to combat diseases with recombinant gene technology and other gene-based technologies. One of the things you have to do is figure out some way to get the recombined genes to the target (i.e., the diseased area within the patient).

Another goal is to develop ways to produce biological re-agents in large quantities; this is helpful from an economic perspective. Sometimes a discovery will be made of a way to treat a disease, but the cost is so high to develop and produce the therapeutic agent that the number of persons treated exceeds the number of persons needing treatment.

Some other areas that are being looked at are (1) developing functional substitutes for tissues and organs, (2) biomarkers for chronic obstructive pulmonary disease (COPD), which is, I believe, the 4th or 5th leading cause of death in this country, and (3) the role of infectious agents in vascular disease.

The development of functional substitutes for tissues aims at repairing and replacing diseased tissues, and, possibly, at creating substitute organs for end-stage organ diseases, such as renal failure.

The work on COPD focuses on early diagnoses and more accurate prognoses that can help develop treatments that are tailored to individual patients.

Some very interesting work is being done on the role of infectious agents in vascular disease. More and more conditions, both of the circulatory system and other systems, that were previously thought to be purely chemical or physiological in nature have turned out to have infectious origins. The best known example in recent years is peptic ulcers. Scientists eventually found the cause of this condition. Now, instead of treating the symptoms, doctors can just kill the cause, and in many cases, they can treat ulcers very effectively in that way. Thus, scientists at the NIH are working on applying the same kind of technology to heart and lung diseases.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD)

The National Institute of Diabetes and Digestive and Kidney Diseases is focusing on a couple of areas related to diabetes: (1) cell replacement therapy, and (2) finding genes for susceptibility to Type II or adult onset diabetes.

With cell replacement therapy, the idea is to try to find ways to either replace or regenerate defective pancreatic beta cells that no longer produce insulin, or to prevent beta cell failure in the first place in order to prevent the progression of diabetes. Finding genes for susceptibility to Type II diabetes can help in the prevention and treatment of beta cell failure and insulin resistance.

The NIDDKD is focusing on explaining poor response to antiviral drugs. This is particularly important in the treatment of Hepatitis C. A lot of people do respond to the antiviral medications that are currently available for Hepatitis C, but many people show no response at all. The scientists at the NIDDKD are trying to understand this better, and this might lead to the development of effective treatments for those cases. Also, the NIDDKD is looking into halting the progression of precursor kidney diseases that can lead to end-stage renal failure and the need for dialysis.

Another area they're looking at is the genetics of inflammatory bowel disease. Just as researchers eventually found the bacterium that causes peptic ulcers, it is hoped that they will be able to find the bacteria or viruses that cause Crohn's disease and ulcerative colitis. NIDDKD scientists also want to be able to understand how genes interact with the environment. This refers both to the environment external to the person and also to the internal environment within the intestines. There are a lot of bacteria which are helpful to us that live in the intestines, and it might be an interaction between some of those bacteria and the immune system that leads to certain digestive diseases.

Finally, NIDDKD scientists want to study the etiology and complications of precursor liver diseases that can lead to liver failure and the need for transplants.

The National Institute of Neurological Disorders and Stroke (NINDS)

The National Institute of Neurological Disorders and Stroke is focusing on the causes and progression of Parkinson's disease. The idea is to develop drugs that more effectively treat the underlying disease and halt its progression. Right now, the main focus of available drug therapies is to treat the symptoms of Parkinson's disease. But if you can actually halt the progression of the disease, since Parkinson's often has very mild symptoms at the beginning, that can prevent a lot of severe disabilities down the road.

Another research area is emergency treatment of stroke. The idea here is that if you can treat strokes more effectively in the first few hours after they occur, then, first of all, you can save a lot of lives, and secondly, you can prevent a lot of future disabilities, or reduce the severity of future disabilities.

NINDS scientists are also looking at bioengineering research, such as: (1) neuroprosthesis development to replace damaged or non-functioning nerve tissue, (2) prediction and prevention of epileptic seizures, and (3) magnetic resonance imaging (MRI) for multiple sclerosis patients to produce better (i.e., more accurate) diagnoses and prognoses.

The National Institute of Allergy and Infectious Diseases (NIAID)

The National Institute of Allergy and Infectious Diseases is looking at immune tolerance. This means looking at a variety of diseases, specifically autoimmune conditions, to try to understand how they occur and whether these immune responses can be selectively suppressed. If you have an autoimmune condition, and you're treating it by general suppression of the immune system, then you're increasing the risk of contracting an infection. But if you can target the intervention to affect just the immune response that is causing that autoimmune disease, then you can reduce the corollary risks.

The NIAID has worked on HIV vaccine trials in order to prevent the spread of AIDS, which is particularly an issue in Africa where it affects such a large percentage of the population. Mentioning that brings up the point that while the first focus at the NIH is on treating health conditions that prevail in the U.S., certainly it wants to develop treatments that can help people in other parts of the world. For example, you might see a lot of AIDS cases in the U.S., but the severity of the epidemic is not nearly as great here as in Africa. Malaria is another example; you have very few cases in this country, but it kills a million people a year worldwide. So that is another important area of research.

Another area that the NIAID is looking at is pathogen genomics. If you can figure out the gene codes for various germs that cause disease, then you can target drugs to effectively disable those pathogens.

The NIAID wants to learn more about the infectious etiology of chronic diseases, as well. There are, as I mentioned, many diseases that may have unrecognized infectious causes. NIAID scientists are hoping to find these infectious causes in order to be able to prevent or treat the diseases better.

Now I want to switch gears and address pharmaceutical company research. It has a different emphasis because pharmaceutical companies are generally investor-owned organizations, so they're looking for a financial payoff to their investment. Because of that, they are focusing on diseases with the largest patient populations and they are looking at drugs with the greatest sales potential. That changes the focus a bit. The NIH is also concerned about large groups of people, but they are willing to spend some of their research dollars on conditions that affect a small number of people very severely.

Key areas that the pharmaceutical companies are looking at are cardiovascular, central nervous system, gastrointestinal, and endocrine diseases (such as diabetes). Other areas of great importance in terms of the research priorities of pharmaceutical companies are anti-infectives, either antibiotics or antiviral medications, and medications for osteoporosis.

There are currently over 1,000 new drugs in development worldwide, so it's a difficult area to follow. The Food and Drug Administration (FDA) approves between 40-80 new drugs per year. About half of these new drugs are "breakthrough drugs." These are often defined as new molecular or biologic entities that are expected to offer a significant gain over existing therapies. These drugs are classified by the FDA as 1P drugs, which means they're given the highest priority status for the review process. They are the ones that the FDA thinks are the most important to get to the market quickly.

Information on clinical trials is often not publicly available, so I was a little worried when I saw in the program that one of the things we were supposed to talk about is clinical trials. One can get some information on that, but you can't really do a comprehensive review. You can get information when the FDA is in the final stages of review for a drug that is likely to come out in the next year or two, as opposed to something that won't be ready for sale for five or ten years.

Some of the drugs that are in the pipeline, according to mmrxconsultant.com (the Merck-Medco Web site for consultants) are:

- Symlin, a synthetic hormone for diabetes. To give you an idea of the cost implications, the cost of this treatment is $2 to $4 a day, and there are 4.4 million people in the United States with insulin-dependent diabetes.

- Forteo is a recombinant parathyroid hormone for severe post-menopausal osteoporosis. That treatment would cost $10 a day and there are 10 million Americans who are affected by this. These medications are expected to win final approval and become available at the end of this year or the beginning of next year.

- Lotestrol has been shown to be effective in treating prostate cancer by inhibiting the production of testosterone. This can cost $350 to $450 a month. There are almost 200,000 new cases of prostate cancer each year.

- Elidel, being developed by Novartis, is a non-steroidal cream for the treatment of atopic dermatitis. It's $50 to $60 for one tube of this medication. I think that typically would be a month's worth of treatment. There are 15 million Americans who have atopic dermatitis.

- Nicostatin is a combination of niacin and Lovastatin. There's been a lot in the news recently about how the statin drugs for lowering cholesterol turn out to be effective for a lot of other conditions as well. New guidelines have come out recommending expanded treatment for high cholesterol. At the time this information was posted, there were 25 million Americans who were considered candidates for this therapy. It might be higher now with the newly released guidelines.

- The BuSpar patch. BuSpar is currently available as a pill for the treatment of anxiety disorders. This new treatment is a weekly transdermal patch, and is

expected to be released near the end of the year. It costs $14 to $20 per week. Anxiety disorders affect about 20 million Americans.

By the way, when I mention the number of people that a disease affects, it doesn't mean that's the number of people who will be taking the drug once it's approved. Rather, that number is the potential market for the drug.

I want to finish up with a few comments about the cost impact of new drugs. This is a quote from J. D. Kleinke, in an article that appeared in the March/April 2000 issue of *Health Affairs*. He was saying that, to some extent, increasing pharmacy costs represent the fulfillment of managed care's original promise to manage costs by managing disease. So it's not just a problem (although it certainly is one from the cost side), but it's also a tremendous benefit, because by treating all these diseases and conditions with new drugs a lot of times you're preventing future surgeries and future hospitalizations, as well as increasing lifespans.

Cost effectiveness and cost utility evaluations, however, usually do not show a net savings from these new treatments, but rather gains in QALYs. And the question is, how much do we pay for each additional QALY? Different studies show the cost per QALY gained as being anywhere from $4,000 to $400,000 for an individual drug. As Marjorie was mentioning, some analysts look at anything under $50,000 as something that's probably worthwhile. The average cost (over all drugs evaluated) ranges from $5,000 to $56,000 per QALY, depending on who sponsors the study. Pharmaceutical company studies tend to show slightly lower costs per QALY, thereby providing a stronger testament to a drug's value, but it's not a huge difference.

Here's some data from the 1999 Express Scripts Drug Trend Report. New drugs first available in 1999 accounted for 1.6% of total pharmacy costs in 1999. That's a surprisingly high number, given that it includes drugs that weren't available until near the end of the year. If you look at new drugs introduced in a given year and follow them for three or four years after that, almost 6% of total pharmacy costs are attributable to those drugs three years after introduction. They do have a significant cost impact.

A Merck-Medco report (*Managing Pharmacy Benefit Costs*, 2000 edition) offers some other statistics and predictions. They believe that recently introduced drugs and pipeline drugs (drugs that are nearing the end of the approval process and are expected to be available within the next year or two) will account for 40%, perhaps 50% or more, of the increase in drug spending over the next few years.

There's a headline that you may have seen in various newspapers earlier this month: "New Guidelines Call for Intensive LDL Cholesterol-Lowering in Certain Groups." Updated practice guidelines for the treatment of high cholesterol were released, and the new guidelines suggest that almost twice as many Americans would benefit from taking cholesterol-reducing medications as was previously believed. This was based on a cost effective analysis, and, yes, it will lead to greater costs in terms of pharmacy benefits. But the payoff is expected to be huge in terms

of avoiding future heart attacks. So there will be savings, perhaps even net savings. But the savings on the heart attack treatment and surgical side will be years down the road, and there will have to be a large initial investment to achieve those savings.

In closing, the take-home points are:

1) Research priorities are based on assessments of both health needs and scientific opportunities, so you're looking for a problem that's urgent and has some likelihood of being solved in the foreseeable future.

2) There are dozens of new drugs approved each year, and half of these are breakthrough drugs.

3) Economic evaluations may show that a new treatment is *cost effective* in terms of providing significant advances or significant gains in terms of QALYs for not too high a price, but it might not generate *cost savings* per se. Generally, the new treatments do replace old treatments, thereby eliminating the cost of the superseded treatments, and do prevent future treatments, but it's usually a net additional cost for better health care.

4) Much of the increase, perhaps half, in new drug costs over the next few years will be attributable to these new drugs.

5) Cost increases can come from old technologies being more widely applied, as well as from the development of new technologies.

MR. TONY WITTMANN: I'm with Blue Cross/Blue Shield of Louisiana. I thought the analysis for QALY was a very interesting approach, but I don't often run into places these studies are being done or how they're being implemented in managed care protocols, etc. Can you comment on that?

DR. ROSENBERG: I would say that most of these studies are in the health services literature. Go to Journals like *Health Services Research*, *Medical Care & Technology*, or *Medical Care and Review*. I believe there are many journals that actually deal with this. I would assume that any employee of a managed care organization that deals with health outcomes and costs would know that this literature exists and would go to that literature.

A lot of the pharmaceutical companies have their own staff who does these analyses themselves, as Grady mentioned. Then people on the outside, particularly university researchers, complement those studies with their own inquiries or take different data to see if they come up with the same conclusions. I don't know, from a practical standpoint, how managed care organizations make decisions, but the literature exists and studies are in process, so it's just a matter of surveying the literature to see what decisions you should make.

MR. TONY WITTMANN: Grady, in terms of prescription drugs, one of the biggest endeavors that we continually embark on is trying to forecast healthcare cost trends, which is the biggest variable in setting premium rates. We've seen a great increase in the last couple of years in healthcare costs due to increased reimbursement and improvements in technology.

I've tried in the past to do some modeling, considering the impact of new drugs and off-patent drugs, etc., and getting together with the pharmacists and trying to figure out at least the direction of trends over our current trend level, whether they're going up or down, with mixed results. I've never really seen anything that forecasts the effect of technology on increasing cost trends. Is there any work being done on that?

MR. CATTERALL: My impression is that no one has really been able to develop precise numbers on that. Generally, all you can do is get an idea of the order of magnitude. We know the general direction of costs, but the overall cost trends are based on, essentially, extrapolations of the recent data on utilization increases and price increases, as well as the cost increases due to new drugs. So I don't think there's an effective way to really put some hard numbers on what's expected, say, five years out. You can get a pretty good idea of what's to be expected in the next year or two, and, generally, the current trends of 15-20% are expected to continue for at least the next year. But I haven't found anything that makes a precise prediction going further out than that.

MR. TONY WITTMANN: Then what about on the non-drug side? It seems as if this NIH data ought to make us able to forecast the impact of the new technology coming out.

MR. CATTERALL: I haven't seen studies that deal with the impact on overall health care costs of these technologies. There are studies of individual treatments, and lots of cost effective analyses are performed. But I haven't seen the same kind of general analysis of how the new non-drug technologies will impact future costs the same way that this has been done on the drug side. This might be because, for new drug technologies it's possible to spread the use of that technology rapidly, whereas there's often a large capital investment for non-drug technologies and there's often a large investment in the training of physicians. Those technologies tend to spread more slowly, and I think that's why there have been more studies done on the dollar impact of the new drug technology as opposed to new non-drug technologies.

Chart 1

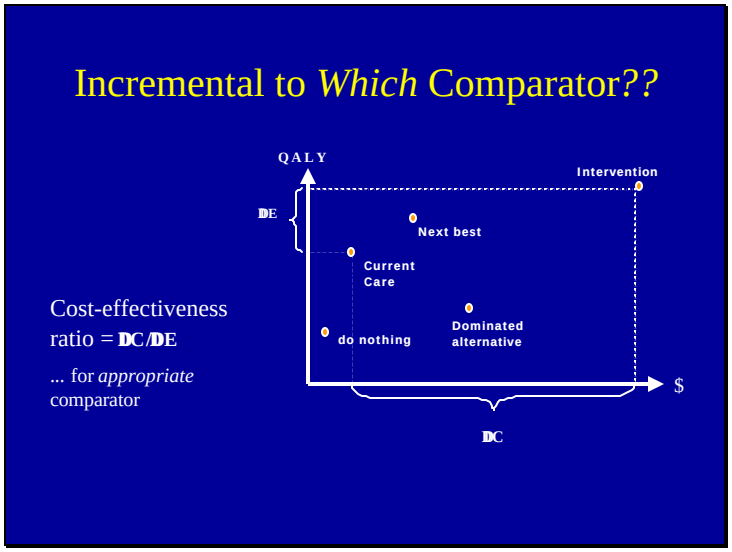

Chart 2