AMERICAN RE HEALTHCARE
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A New Era of Emerging Cancer Therapies

The Center for Medicare and Medicaid Services estimates that health cost trends will exceed growth rates for the general economy. They further estimate that two-thirds of this growth is directly due to the development and adoption of new technologies. To pay thousands of dollars per month for pharmaceutical therapy was once limited to rare situations, but as biologic compounds are developed and found to be more effective than traditional therapy for an ever-increasing number of conditions, more patients are consuming these expensive drugs. We explore the contribution to this trend from newly emerging cancer therapies. See page 2.

Recent Advances in Perinatal and Neonatal Care

As a result of several advances in providing medical care to pregnant women and premature infants, medical science has achieved a 50% decrease in both neonatal mortality and morbidity rates over the past 25-30 years. We illustrate some of these advances and offer suggestions on how healthcare providers might use these interventions to reduce high-risk deliveries and catastrophic outcomes, as well as contain costs. See page 4.

Comparison of PPO Discounts among Rating Manuals

Rating manuals are constructed with data from various sources. We explore some of the differences in rating manual methodologies that one must account for in assuring a valid comparison of discounts. For example, depending upon whether the manual has been constructed from paid charges, billed charges, or some discount upon billed charges, a different "average" assumed discount is implicitly assumed. See page 6.

- American Re HealthCare is proud to have sponsored AHIP's 2005 Institute in Las Vegas.
- Patrick Collins, Vice President and reinsurance underwriter, presented at the Society of Actuaries Spring Meeting in New Orleans. He discussed current issues and trends in the health reinsurance marketplace.

- Advances in High Intensity Focused Ultrasound (HIFU) are gaining promise in research circles as a non-invasive scalpel that focuses heat without damaging surrounding tissues. It is likely that the FDA could approve some indications for treatment this year. Applications range from uterine fibroids to cancer.

Hope is Emerging for Nanotechnology in Cancer

Chemotherapy-loaded nanoparticles (upper left) form the core of the nanocell (upper right). *Images courtesy of the Sasisekharan Lab.*

A team at MIT has conducted successful studies in mice, showing that nanotechnology may provide the ability to fight cancer. They created a nanocell, filled its interior with chemotherapy, and loaded a drug to prevent the growth of tumor blood supply along its outer membrane. "Stealth" surface chemistry allowed these nanocells to evade the immune system. The nanocells were small enough to pass through tumor blood vessel walls into the tumor tissue, but large enough not to fit through the pores of normal vessels and pass into normal tissues. Once inside the tumor, the nanocell's outer membrane disintegrated and deployed the drug that prevents growth of additional tumor blood supply. The blood vessels feeding the tumor then collapsed, trapping the loaded nanocell in the tumor, where it slowly released chemotherapy. Essentially, the drug effectively sought its target, sealed the exits, and detonated a lethal dose of anti-cancer toxins, all while leaving healthy tissues unscathed. Yet, not all the outstanding questions have been answered. For example, attacking the blood supply may stimulate growth of new blood vessels, instigate metastasis or favor other self-survival behaviors of the tumor.

A New Era of Emerging Cancer Therapies

Several factors impact the cost associated with the adoption of new technologies and medical therapies. For example, some new injectable cancer drugs command a retail price of as much as $100,000 for a course of treatment that lasts only a few months. The high price helps to recover costs of research, development, and sophisticated biotechnical manufacturing (e.g. the production of monoclonal antibodies from engineered genes). In addition, physicians may accelerate overall spending by extending application of these drugs to "off-label" and unproven situations, for related diseases that are distinct from the condition in which the treatment was initially studied and approved.

In earlier stages of the adoption process, the cost and therapeutic impact of these new cancer therapies may not yet be seen. The expected profile of repeated treatments, complications, additional treatment failures, and cost from traditional chemotherapy and its related practice patterns continue until the new and more effective therapies are more routinely utilized.

Although adoption rates vary by drug, most of the newer cancer drugs help patients only marginally, prolonging life by a few weeks or months, thereby further contributing toward their delayed adoption. An exception is Gleevec®, a leukemia drug from Novartis that has been reported to produce spectacular results.

The Role of Clinical Trials in Pediatrics vs. Adults

Many promising treatments have been, and still remain to be, discovered and proven. Clinical trials provide an important contribution toward the further development of cancer care while safeguarding patients. In pediatrics, there has been a long-standing tradition to direct children with cancer to clinical trials. Nearly 85% of all childhood cancer is being treated within the parameters of a clinical trial. The structured protocols of clinical trials have effectively treated and cured many of the common childhood cancers.

In contrast, fewer than 3% of adult cancer cases are treated within clinical trials. The resulting lack of structure in adult cancer care produces highly varied outcomes of therapy from center to center, even for like cancers.

Bioinjectables: The Newest Pharmaceuticals

In the last couple of years, several new bioinjectable drugs for cancer have been introduced and have been proven by clinical trials to impact the outlook for patients. We now live in a time where pharmaceutical companies are capable of developing larger molecules, which require more complex research and are more expensive to produce. Examples include pharmaceutical inhibitors, synthetic antibodies, and other engineered proteins. These bioinjectable strike at cellular characteristics specific to cancer cells and uncommon in normal tissues. Because these drugs are similar to actual body proteins, they can target diseased tissues with a greater 'biologic' precision, meaning greater effectiveness of control (or even cure) of the tumor with less injury to other tissues.

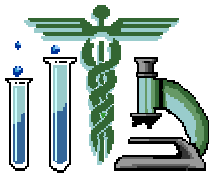
The Success Story of Gleevec

The most stunning example of the beneficial new technologies is Gleevec® (imatinib mesylate), first approved for the treatment of chronic myelogenous leukemia (CML) in December, 2002. Gleevec® is a biological agent that targets a genetic mutation called *the Philadelphia Chromosome*. The mutation is responsible for producing an enzyme that promotes the abnormal cell growth and division characteristics of the disease. 95% of CML patients have this genetic mutation, and Gleevec works in these cases because it prevents production of the responsible enzyme.

In clinical practice, Gleevec® has resulted in prolonged remissions, and offers a potential for cure. It has essentially eliminated the need for bone marrow transplants (BMTs), which were previously the standard of care for CML. BMT is now reserved only for those resistant to Gleevec®. To date no other agent, traditional or emerging, has demonstrated Gleevec's effectiveness in treating a previously unresponsive disease.

Researchers from Duke University recently conducted a clinical study to evaluate the cost-effectiveness of Gleevec® in the treatment of CML. The researchers concluded that Gleevec® is superior to the previous standard chemotherapy (interferon/cytarabine) for CML in terms of survival. Despite the fact that Gleevec® costs approximately $3,000 per month or $36,000 annually, treatment with Gleevec® saved patients over $43,000 per life-year in medical costs.

Herceptin® – Another Success



Another clinical breakthrough may be Herceptin® (Trastuzumab), a drug for breast cancer. Herceptin® was the second monoclonal antibody approved for cancer treatment in the US (November, 1998). Herceptin® is a protein that has been shown to destroy breast cancer cells through an immune process, but only if a specific cell surface protein, called HER-2/neu, is present upon biopsy. Herceptin® adds significant cost to breast cancer care, yet reportedly provides additional tumor destruction, delays disease recurrence and progression, and increases survival for women with metastatic disease. The drug's expense results not only from the sophisticated manufacturing process required, but also from costs related to administration of this injectable agent.

Avastin™ – A Breakthrough Approach

Avastin™ (Bevacizumab), another monoclonal antibody, was approved in February, 2004 as an effective treatment for colon cancer. Avastin™ extends life by about 5 months, according to the FDA. Previous treatments for metastatic colon cancer had been largely ineffective. Avastin™ provided an important validation to the strategy of treating tumors by inhibiting their blood supply. Avastin™ is a monoclonal antibody that is directed against Vascular Endothelial Growth Factor (VEGF), which is required by the tumor to promote a tumor nourishing blood supply. Without functional VEGF, tumors are unable to grow as they lack the necessary stimulants to produce an adequate blood supply.

The cost issues for Avastin™ production and administration are similar to other monoclonal antibodies, resulting in an average cost per dose of $5,000 (meaning around $50,000 for a typical eleven-month treatment cycle). Though all tumors theoretically require VEGF, clinical trials to date have specifically demonstrated increased patient survival with Avastin only for colon cancer. Regardless, there are reportedly a growing number of requests to use Avastin for the treatment of advanced kidney, bladder, lung, and breast cancer. Though "off-label" use may theoretically occur outside of a formal clinical trial, utilization should probably still be confined to National Cancer Institute approved clinical trials, unless state mandates insist on its availability as a covered benefit.

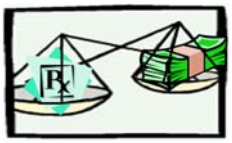
Cost Implications and Management Techniques

The following data appeared in the New York Times on July 12, 2005 regarding the estimated cost of several agents of this class:

Drug	Approved	Cancer	Cost/Year
Erbitux	2004	Colorectal	$111,000
Avastin	2004	Colorectal	$54,000
Herceptin	1998	Breast	$38,000
Tarceva	2004	Lung	$35,000

Source: Sanford & Bernstein & Co

The cost implications for these potentially life-saving agents are extraordinary. They are manageable, provided that the payor has appropriate benefit language and ready access to pertinent clinical data. Some basic insurance coverage strategies include:



1. Ensure that those individuals who would clearly benefit from the therapy are given access to it. For instance, people suffering with CML involving the Philadelphia chromosome should be directed to care utilizing Gleevec when referred for BMT. In fact, reluctance to consider Gleevec with its brighter promise of success may be enough of a reason to refer the patient to a more accomplished center.

2. Make sure that the tumor type and diagnostic characteristics are suitable for these highly targeted therapies. For example, coverage for Herceptin® should be dependent on the documentation of HER-2/neu positive expression on biopsy material.

3. Limit "off-label" usage. "Off-label" use should be restricted to centers participating in applicable clinical trials that are approved by the National Cancer Institute. Most bioinjectables used in cancer treatment are of limited proven benefit outside of their existing indications. Ethical practice should prohibit exposing patients to unproven treatments without the safety controls and oversight of an established research program. In addition, such interventions may prematurely exhaust the patient's benefits (lifetime maximum benefit) and personal resources. However, be sure to first check for relevant state mandates and requirements for coverage regarding "off-label" use.

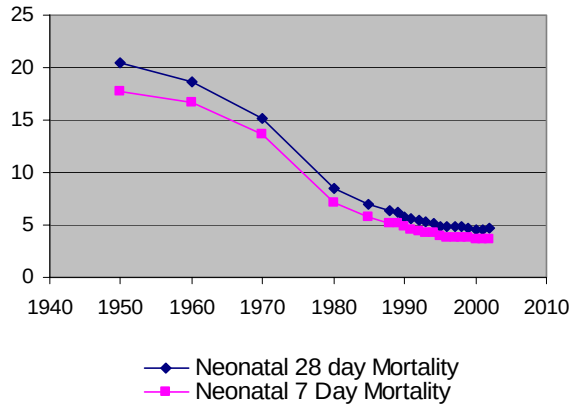
The pipeline of cancer treatment bioinjectables is just begining to impact clinical care. As more effective and even marginally effective drugs are released in the coming years, expect that these drugs will continue to improve cancer survival and increase treatment costs.

Recent Advances in Perinatal and Neonatal Care

Background

The advances made in the past few decades in obstetrical and neonatal care have impacted birth statistics around the world, yet the rate of low birth weight in the United States remains high relative to other developed countries. In addition, despite important technological advances, neonatal mortality rates and infant mortality rates have fallen only modestly over the past 10 to 15 years.

Neonatal Mortality (per thousand) by Year



Sources: Centers for Disease Control and Prevention, National Center for Health Statistics. From Health, United States, 2004.

Prenatal Strategies

The outcome of a given delivery is determined by a multitude of factors, both genetic and environmental.

Prenatal care monitors factors of concern and allows for mitigation of scores of potentially devastating outcomes. Interventional strategies that are successful in prolonging a pre-term pregnancy by even a few weeks, for example from 26 weeks to 28 weeks, can dramatically improve mortality and morbidity rates as well as the short-term and long-term cost of healthcare.

Maternal behavior during gestation is largely determined long before a mother contemplates pregnancy. Education, the development of self-esteem, the ability to delay gratification, and good health habits impact the mother's health, social support structure, and knowledge of the need for comprehensive prenatal care.

When the above challenges are present, extra assistance should be available to mitigate, or even to avoid, an otherwise catastrophic result. For example, regularly scheduled visits to the obstetrician provide patient education to modify the impact of high-risk habits or medical conditions. In addition, a variety of prenatal screening tests such as the triple screen, Rh testing, amniocentesis, and prenatal ultrasound can detect problems in the mother and/or the fetus that may be treated prior to the expected date of delivery.

A recent study reviewed a low-tech, low-cost intervention to improve the outcome of pregnancy. It involved high-risk pregnant women, who were frequently from lower socioeconomic status or other high-risk demographic groups. These at-risk mothers were paired with a *Resource Mother*, trained to be a role model, to counsel pregnant women, and to provide transportation to prenatal, postnatal and well child

appointments. The study found that the addition of a *Resource Mother* increased access to prenatal care, decreased the incidence of low birth weight, lowered neonatal morality and improved other indicators of pediatric health. In addition, hospital charges for infants born to Resource Mother Program participants were $50,000 less than a comparable group of infants not in the program.

Even with the best prenatal care and education, a premature delivery may still occur. These expectant mothers should be transferred to a level III perinatal center to receive the highest level of medical care available for both mother and newborn. Benefits of early intervention in a level III facility include the potential to stop labor with drugs, provide IV hydration with bed rest, and administer steroids to a mother to improve the likelihood that prematurely delivered infants will have sufficiently mature lung function.

Postnatal Strategies

The administration of artificial surfactant in the delivery room may represent the most significant improvement in neonatal survival in the past 15 years. This therapy has become one of the standards of care in the prevention and treatment of respiratory distress syndrome (RDS), a form of respiratory failure in premature infants who have not yet developed the ability to produce surfactant.

In addition, relatively inexpensive technologies, such as the pulse oximeter, have made it much easier to non-invasively monitor a critically ill baby's oxygen levels. The pulse oximeter allows the clinician to assess appropriate oxygen delivery without the need for more invasive and painful blood sampling, decreasing the need for frequent and costly blood gas determinations.

Nitric oxide therapy, although expensive, provides an alternative for infants with persistent pulmonary hypertension, a frequent complication associated with perinatal oxygen deprivation and inhaled meconium (stool) at delivery. Nitric oxide has improved survival and decreased hospital stays. It has also decreased the likelihood of requiring more invasive therapies, such as such as Extracorporeal Membrane Oxygenation (ECMO), and their associated catastrophic costs.

A proliferation of infant ventilators including: pressure-limited, time-cycled, volume-controlled, patient triggered, and a variety of high-frequency ventilators have enabled the neonatologist to better manage an infant with respiratory failure. Finally, a host of other technological improvements in IV pumps, incubators, and cardiac, respiratory and blood pressure monitors have contributed to the improved outcome of premature infants.

Future and Developing Strategies

Research continues to provide additional techniques and technologies to improve care. Recent reports have suggested improved outcomes with ventilation strategies that employ the technique of "gentle ventilation." However, more studies are needed to evaluate the wisdom of accepting the associated higher carbon dioxide and lower oxygen levels. Similarly, preliminary reports indicate that outcomes are improved for infants resuscitated with room air rather than 100% oxygen. These results also need further study to determine whether current resuscitation protocols should be altered.

Conclusions

Healthcare providers should do everything possible to enable women to carry their pregnancies to at least 32 weeks gestation, since that appears to be the point at which infants who survive have virtually the same outcome as those that deliver at term. Programs that stress prevention, early identification, and counseling for social and medical problems achieve this goal. Moreover, to continue to see a cost-effective reduction in the prematurity rate and further decreases in neonatal mortality and morbidity, practitioners must responsibly use the technologies that are already available.

Finally, medical practice today is driven largely by the incentives of fee-for-service medicine, which promotes utilization. Hospitals and physicians have little financial incentive to employ the additional resources necessary for peer review, or to implement processes that ensure adherence to best practice standards. The use of a company such as CareAssist to provide clinical peer reviews may help to utilize the efficiencies of technology when its expense is most justified to produce better outcomes and to achieve significant savings in healthcare costs.

Comparison of PPO Discounts among Rating Manuals

Imagine that you are quoting on a potential customer and that you are using the same PPO as the incumbent carrier. The carrier's analytics are well-respected, and you know that the incumbent PPO pricing discount was 30%. Would the same 30% PPO discount be valid for a quote generated from *Your Rating Manual*?

The Basis for Manual Rates may Differ

The starting point for every rating manual is the base rate, which is derived from claims data. Various factors are applied to the base rate to modify price to accurately reflect the risk for different circumstances, for example by specific deductible. The data used to build base rates for any manual implicitly determines the "average" discount that is assumed for a quote derived from it.

For example, base rates may be derived from undiscounted billed charge data. In other circumstances, base rates are constructed with various degrees of network discounts that impact the base rate. Base rates built using paid amounts implicitly assume a PPO discount equal to the average discount found within the data source. Base rates built using paid amounts "grossed up" by a fixed discount also assume a PPO discount, based on the difference between the average discount found within the data source and the "gross-up" factor.

Basis upon Billed Charges versus Paid Charges

Although manuals are typically derived from large quantities of data, consider a simplified example of a manual derived from the following annual costs, where the network contracts always pay 80% of charges.

Member #	Billed Charge	Paid Amount
1	$100	$80
2	$400	$320
3	$1000	$800
AVERAGE	$500	$400

A manual based upon billed charges would result in a base rate of $500. Alternatively, a manual based upon paid charges would result in a base rate of $400. Finally, a manual based upon paid charges that attempts to estimate billed charges by assuming that claims were paid at a 15% discount results in a base rate of $471 ($400 /0.85)

Recall our fictitious case, and assume that the customer utilizes a PPO network that always pays exactly 30% off billed charges. The PPO discount off base rates will be different for each of the following manuals:

- For a manual based upon billed charges, the appropriate discount remains 30%
- The discount for a manual based upon paid charges would be 12.5%, as 30% off $500 is $350, and the manual states $400 for the rate. 1-($350 / 400) = 0.125
- The discount for a manual based upon "grossed up" paid charges would be approximately 26%, as 30% off $500 is $350, and the manual states 15% over $400, or $471 (400/(1-.15)), for the rate. 1-($350 / 471) = 0.256

The Basis for Area Factors may Differ

Like base rates, area factors can include an implicitly assumed PPO discount. For example, at least one commercial entity calculates area factors based on billed charges. Another calculates area factors based on average premium rates (similar to use of paid amounts).

To illustrate the potential differences, first-dollar costs based on billed charges in the Philadelphia area appear to run 35%-60% higher than the national average. Discounts at Philadelphia-area hospitals also tend to be significantly larger than average. These effects tend to equalize for Philadelphia area factors built from paid amounts (or average premium rates). As a result, discounted prices in Philadelphia are much closer to the national average than might be expected from either a review of their billed charges or their discounts against billed charges alone. Yet PPO discounts for the Philadelphia area will appear to be much higher when using a manual with area factors that are based upon billed charges.

Summary

When comparing PPO factors from different quoting entities using the same PPO, it is prudent to keep in mind the following questions. What is

the basis used to calculate the base rates in your manual versus that of the manuals used by your competitors, and are the area factors comparable and calculated on the same basis?

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