THE ARTICULAR CARTILAGE REPAIR DILEMMA

Symptomatic Articular Cartilage Degeneration

The Impact in the New Millennium

Douglas W. Jackson, MD; Timothy M. Simon, PhD; and Harold M. Aberman, DVM

The symptomatic degeneration of articular cartilage and associated arthritis is among the most prevalent chronic conditions in the United States and the population most at risk is increasing. It is the leading cause of limitations in activities of daily living and is second to heart disease in causing work disability. The current and future socioeconomic impact of chronic articular cartilage disease on the healthcare system will be magnified by increasing numbers of patients who will seek relief of their symptoms and their disability to remain active. Because these individuals live longer and remain active, the proportion of their life living with symptoms and disability from articular cartilage degeneration increases. The economic, psychologic, and social impact of degenerative articular cartilage can be enormous for these individuals but it also impacts their family and society. The direct traditional medical costs and indirect economic and wage loss from arthritis in individuals the United States has reached in excess of $65 billion annually and is expected to increase as the population ages. In addition, the expenditures for complementary and alternative professional services and therapies for arthritis is increasing and is also in the billions of dollars annually. Because of these escalating costs, documenting the value of the patient and cost effectiveness to society of prevention and treatment programs for symptomatic articular cartilage degeneration will be required.

Articular cartilage is among the most incredible materials that nature has engineered. It provides a nearly friction-free load-bearing joint surface so humans can move about smoothly and without pain. It does this remarkable feat mainly with water that is bound and constrained by a special matrix produced and maintained by chondrocytes, the cells that reside in the cartilage. Although the composition of most of the matrix molecules are known, the materials scientist has not been...
able to duplicate the properties of native articular cartilage.

Unfortunately, articular cartilage is not immune to factors that can lead to its eventual breakdown and diseases. Joint trauma (direct and accumulative) and local chemical and mechanical factors can accelerate the degeneration process of the articular cartilage. Various forms of arthritis (two most common forms are osteoarthritis and rheumatoid arthritis) are the conditions most commonly associated with the degeneration of the involved joint’s articular surfaces and will have the largest increase in numbers of new patients of any disease in the United States.10,11 Osteoarthritis, also known as osteoarthrosis and degenerative joint disease, and to a lesser degree rheumatoid arthritis and the associated degeneration of articular cartilage currently is one of the most prevalent chronic conditions in the United States12 (Fig 1) and is second to heart disease in causing work disability.11 Its prevalence rate increases dramatically with age and remains higher in women in each age category.8,34 The associated limitations from the painful joint(s) often result in a reduced quality of life.

In 1994, the Centers for Disease Control and Prevention reported that by the year 2020, arthritis, the most prevalent of which is osteoarthritis, will have the largest increase in numbers of new patients of any disease in the United States.11 This is because approximately 20% of the population of the United States, approximately 60 million Americans referred to as baby boomers, are at risk. More than 80% of people older than 75 years are symptomatic with osteoarthritis with areas of denuded articular cartilage. Considering the cost of diagnosis, therapy (nonpharmacologic, pharmacologic, and surgical), side effects of therapy, alternative medicine and treatments, and lost productivity, it is one of the more expensive and debilitating diseases in the United States.40 Given the large numbers of patients and the expense of the disease, it is not surprising that the care of patients with symptoms from their articular cartilage degeneration will come under scrutiny.

**Economic Costs**

Patients with arthritis account for as many as 39 million physician visits and 500,000 hospitalizations per year.12 The use of the healthcare system by these patients has drawn the attention of payors. To estimate charges attributable to osteoarthritis in a managed care environment, a longitudinal study based on patient claims for osteoarthritis was sampled randomly to yield 20,000 subjects.12 Charges per person-year were determined and compared with charges for subjects without osteoarthritis who were matched for age, gender, and insurance claims. Patients with symptomatic osteoarthritis incur charges for medical care at approximately twice the rate of plan enrollees without claims for osteoarthritis and account for a substantial portion of total charges in a managed care plan. Although those individuals who have insurance coverage have most of the direct expenses for

the diagnosis and treatment covered, there often are considerable out-of-pocket expenses not covered by healthcare plans. Patients disabled with arthritis experience out-of-pocket expenses (medication, special aids, uninsured health services, modifications to the residence, transportation, and often need more personal services) because of their special needs.

Although the current disability and economic burden of arthritis is substantial, the future burden will increase considerably with the increasing age of the population. Looking at the data projections for 2000 and 2030, the population in the United States will increase by approximately 28% whereas the population of those individuals older than 65 years will double in that same time.42 As a percent of the United States population, individuals 55 years and older will increase from 21% in 2000 to 31% in 2030.42

Because many individuals with arthritis are working age, there also is significant lost productivity secondary to its impact. The indirect economic loss in productivity and wages is very high for arthritis. In 1997, the disabling and debilitating costs of arthritis was approximately $65 billion including direct medical costs of approximately $15 billion per year.12 The aggregate costs in 1999 were approximately 1.1% of the Gross National Product.12 According to the National Health Interview Survey done in 1995 as reported by Benson and Marano,5 the overall prevalence of osteoarthritis was estimated at more than 20 million individuals and the prevalence rate for osteoarthritis has been estimated to be 125 per 1000 persons.35 Resource use data showed that 6,542,000 physician visits, 265,000 emergency room visits, and 619,731 outpatient hospital visits were made in 1995 for osteoarthritis.35 Also, there were 454,140 discharges and 2,335,000 hospitalization days for patients with osteoarthritis.35

**Risk Factors**

The exact causes of osteoarthritis are unknown; however, genetic and environmental factors have been implicated (Table 1). Women older than 40 years seem to be particularly vulnerable and the ratio for women compared with men is 2:1. There is a strong correlation between the prevalence of arthritis and socioeconomic status. The highest incidence of osteoarthritis with its accelerated articular cartilage degeneration and disability is associated with a lack of formal education, low income, and poor personal support networks. Single, elderly women typically suffer the worst outcomes. Current statistics indicate that more than 50% of Canadians of working age with arthritis-related disabilities are forced to leave the labor force because of their condition.9 Half of all Canadians disabled with arthritis had a personal income below the poverty line, compared with 24% in the nondisabled population.9

Unlike patients with other chronic conditions, patients with conditions involving accelerated articular cartilage degeneration do not have any practical lifestyle changes that can prevent it. There are no existing therapies that alter the natural history of cartilage degeneration. Because the disease is the leading cause of disability and affects one in six Americans, the Centers for Disease Control and Prevention, the Arthritis Foundation, and state health departments now are working together to implement interventions that will improve patient identification and education, and reduce the socioeconomic burden. According to the Centers for Disease Control and Prevention’s National Center for Chronic Disease Prevention and Health Promotion in fiscal year 2000 Congress provided $12,000,000 funding to initiate a national arthritis prevention program. This was to

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**TABLE 1. Factors Implicated in Arthritis**

<table>
<thead>
<tr>
<th>Risk Factors for Osteoarthritis of the Knee Include</th>
</tr>
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<tbody>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Previous trauma to the involved joint</td>
</tr>
<tr>
<td>Genetics</td>
</tr>
<tr>
<td>Physical activity</td>
</tr>
<tr>
<td>Estrogen deficiency</td>
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<tr>
<td>Surgery to the involved joint</td>
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be split among 38 states. Establishment funding went to 30 state health departments to improve public awareness and establish surveillance and planning process. Funding also went to eight states with existing activities for training, establishing advisory panels, coordinating statewide arthritis activities, and pilot test interventions. It is appropriate, because of the aging population trends and the current and future socioeconomic burden of osteoarthritis, that society dedicates more resources to research and the evaluation of available treatments and future prevention programs.

Currently, there is a relatively low level of investment in arthritis research by society. Funding for fiscal year 2000 by the National Institutes of Health specifically for musculoskeletal diseases through the National Institute of Arthritis and Musculoskeletal and Skin Diseases was approximately $349 million dollars. Compared with other diseases, the government research dollars earmarked for the National Institute of Arthritis and Musculoskeletal and Skin Diseases is less than 2% of the total budget authorized for all other institutes, centers, and offices.

**Patient Therapies**

Patients with osteoarthritis have ups and downs in the severity of their symptoms. The natural history is unique to each joint and each individual. Patients may spontaneously experience short to long periods of remission of symptoms independent of being treated or a specific treatment. There is a strong placebo effect with any treatment of the symptoms associated with degenerative articular cartilage changes that make interpreting successful interventions difficult. The placebo effects can be experienced by as many as 30% to 40% of patients reporting improvement in drug and treatment protocols. They often will attribute a spontaneous remission to whatever modality, supplement, surgery, or medication they are taking or have taken at the time. The placebo effect in osteoarthritis is particularly high if the patient is convinced the medication, treatment, or surgery will help.

There is not a defined natural history for articular cartilage degeneration and wear. Use of the involved joint, differing individual pain tolerance, obesity, underlying genetic predilection, extremity alignment, and joint trauma are just a few of the variables that affect the natural history of each patient. The Bristol Osteoarthritis study looked at the natural history of peripheral joint osteoarthritis and its impact for 8 years in a prospective study of 500 patients. Joint sites involved, pain severity, change in index joints, global change in the condition, and use of medication, surgery, and walking aids all were recorded at each visit. After 8 years, disability was assessed by the Health Assessment questionnaire, and anxiety and depression were evaluated by the Hospital Anxiety and Depression scale. The outcome was heterogeneous. Of those completing the study, 60 patients (17.2%) reported worsening in all three subjective parameters (pain, index joint, and global change) compared with 22 (6.3%) who had improvement in all three parameters for 8 years. Osteoarthritis disease resulted in high levels of physical disability, anxiety, and depression, with a high level of use of healthcare resources, including joint replacement, drugs, and walking aids. Osteoarthritis in older people is characterized by the slow acquisition of new affected joint sites. Progression and outcome may depend on a complex set of psychosocial factors and biologic factors.

The link between obesity and osteoarthritis has been theorized to be from the repetitive application of greater loads to the joints; however, this does not explain why osteoarthritis occurs more often at the knee than at the hip and ankle. People who are obese are more than eight times as likely as their thinner counterparts to have osteoarthritis develop in both knees, according to a previous report. Obesity seems to be a mechanical rather than a systematic risk factor for osteoarthritis with varus malaligned knees being especially susceptible.

Results of a study cited by of the Centers for Disease Control and Prevention used data collected from patients seen at the Cooper Clinic between 1970 and 1995 who reported os-
The population sample included 16,961 patients between the ages of 20 and 87 years. The researchers found that the incidence of osteoarthritis among patients 50 years or older was higher among women, seven per 1000 person-years, than among men, 4.9 per 1000 person-years. For subjects younger than 50 years, the incidence of osteoarthritis was similar for men and women, at 2.6 and 2.7 per 1000 person-years, respectively. In men younger than 50 years, high levels of physical activity (running 20 or more miles per week) were associated with osteoarthritis. This relationship persisted after controlling for body mass index, smoking, alcohol, and caffeine use.

Patients seek the type of treatment they think will help, have heard will help, or as an alternative to what they have been doing. Currently, among patients seeking care from physicians for musculoskeletal conditions (without a referral), 42% see family medicine physicians, 21% see orthopaedic surgeons, 15% see internal medicine physicians, 8% see pediatricians, 4% see emergency medicine physicians, and 10% see all other physicians. In addition, many patients with musculoskeletal conditions are seen and treated by nonphysician providers.

Different physician providers often see a different patient profile. This is shown in studies comparing patients presenting with arthritis without a referral. Of the 2.23 million office visits by patients without a referral for arthritis, 56.1% were with a primary care physician, 26.6% were with an orthopaedic surgeon, and 7.2% were with rheumatologists. For the 807,000 referral office visits for patients with arthritis, 65.6% were to orthopaedic surgeons and 18.7% were to rheumatologists.

**Nonoperative and Nonpharmacologic Therapy**

Nonoperative and nonpharmacologic treatment of patients with osteoarthritis primarily involves patient education, answering questions, and addressing concerns. Most patients want to understand what factors are causing their joint symptoms and what these symptoms mean. In patients with early and milder involvement, answering their questions often is satisfying to the patient and he or she will make some simple lifestyle changes and will live with the condition. Often instituting a reduction in aggravating activity, a specific strengthening and fitness program, and weight reduction, if indicated, may be able to control the symptoms arising from the degenerative articular cartilage of weightbearing joints. Braces and physical modalities may be beneficial in selective situations.

**Pharmacologic Therapy**

A consideration in the treatment of patients with osteoarthritis is that it is not a fatal disease and to date no treatment has been shown to modify its long-term natural history. Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most widely prescribed medications in the world. They are the first choice for medication for osteoarthritis as determined by patient over-the-counter use and by physician prescription. There are no data to suggest that NSAIDs retard tissue destruction as measured by radiographic evidence. Comparable efficacy and toxicity have been shown for most NSAIDs; however, there is significant variability among patients with arthritis regarding therapeutic and adverse effects. Gastrointestinal upset and bleeding and a decline in renal function are the principal adverse effects. In 1997, for patients 65 years and older, an estimated 41,000 hospitalizations and 3300 deaths were associated with NSAID therapy. There were 107,000 hospitalizations and 16,500 deaths per year in the United States caused by NSAID-induced gastrointestinal bleeding in patients with arthritis as reported by the Arthritis, Rheumatism, and Aging Medical Information System Post Marketing Surveillance Program. Those at greatest risk are the elderly, those with comorbidities, those taking steroids, and those with a history of gastrointestinal bleeding or peptic ulcer disease. This is the same population with a high incidence of symptomatic degenerative changes in their joints.
The mechanism by which NSAIDs give analgesia and suppress the inflammation is the inhibition of the enzyme cyclooxygenase. This results in decreased prostaglandin synthesis, which also can produce gastric and renal toxicity and impair platelet function.\(^{36}\) The development and wide marketing of the selective COX-2 isoenzyme inhibitors spare the enzymatic activity of COX-1 inhibitors thereby reducing the risk of side effects.\(^{44}\) It is estimated the sales of antiarthritic drugs in the United States were $1.7 billion in 1998.\(^{28}\) The current patient cost for COX-2 inhibitors is approximately $100 per month. Although it seems the COX-2 inhibitors have less deleterious side effects, the cost-effective benefits and the documentation of long-term risk factors need additional evaluation.

The Food and Drug Administration approved the antiinflammatory drug infliximab (Remicade®) made by the Johnson and Johnson unit Centocor (Centocor, Malvern, PA); this drug prevents structural damage from rheumatoid arthritis by blocking the action of TNF.\(^{21}\) Lee Simon, MD, the panel’s acting chairman, said Centocor’s study showed “compelling” evidence that giving patients Remicade in addition to methotrexate, a standard treatment (for rheumatoid arthritis), reduced joint damage over 1 year when compared with patients who received methotrexate and a placebo.\(^{39}\) Panel members were divided, however, on whether Centocor should be able to advertise that Remicade prevents additional joint damage from the disease. Some worried that patients might think their disease never would progress, but studies only showed how the drug worked for 1 year. Remicade, on the market since August 1998, is approved for treating patients with rheumatoid arthritis who do not respond to methotrexate and for patients with the bowel disorder Crohn’s disease. Possible side effects of Remicade, which is given by infusion, include infections, headaches, and rashes. The drug costs approximately $1222 for each 8-week dose plus the cost of infusion.\(^{21}\)

In June 2000, the Food and Drug Administration gave Immunex Corporation (Seattle, WA) permission to market its rheumatoid arthritis drug entanercept (Enbrel®) as a treatment that could delay the progress of joint damage. Remicade and Enbrel inhibit TNF, a protein linked to inflammation.\(^{21}\) The drug costs approximately $1190 per month.\(^{21}\) Another drug, leflunomide (Arava®) by Aventis SA (Kansas City, MO), is approved for retarding the advance of rheumatoid arthritis. Arava affects T lymphocytes involved in the inflammation.\(^{21}\) The cost for Arava is approximately $244 per month’s supply.\(^{21}\) The expense of COX-2 inhibitors may be offset by the reduced costs associated with improved safety.

The aforementioned drugs are used for patients with rheumatoid arthritis. There are a small number of patients with rheumatoid arthritis in comparison with those with degenerative osteoarthritis. A major problem to date in the identification of effective therapeutic agents for osteoarthritis has been the absence of reliable molecular markers and diagnostic tools that can document early disease phases and subsequent progression accurately. In current orthopaedic practice, a diagnosis of osteoarthritis is confirmed by narrowing of joint spaces, signifying cartilage damage and loss, as seen by the naked eye on radiographs of the joint obtained with the patient weightbearing. The more advanced changes may be obvious without taking radiographs with the patient weightbearing. In addition to joint space narrowing, the degenerative articular cartilage changes often are associated with peripheral joint osteophytosis, subchondral bone sclerosis, and cystic bony changes. Although joint space narrowing is a common finding in elderly patients, not all narrowing is associated with symptoms.

There are numerous methods of grading the degenerative changes and injuries to articular cartilage at the time of surgery with direct observation of the involved surfaces.\(^{34}\) The gross observations made by direct visualization, and in some incidences probing, show that cartilage lesions vary by location, depth, size and shape. Combining multiple variables into one
grading scale is being proposed by the International Cartilage Research Society to standardize lesion grading. Essentially everyone will have some evidence of degenerative articular cartilage changes by age 40 and observable changes often are present at even younger ages. The majority of degenerative cartilage changes at age 40 are asymptomatic and are incidental findings during arthroscopic surgery of the knee.

The extent of the changes and degree of involvement in asymptomatic populations is conjecture, but a great deal can be gained from reviewing large numbers of arthroscopic surgeries. In a review of 31,516 knee arthroscopies obtained from a database provided by 136 surgeons, some idea may be gained of the incidence, location, and degree of articular cartilage lesions observed in patients undergoing arthroscopic surgery related to their joint symptoms. There were 53,569 hyaline cartilage lesions documented in 63% of these patients between the ages of 1 and 92 years with an average age of 43 years. Overall, lesions with underlying exposed bone were documented in 20% of these patients but only 5% of these patients were younger than 40 years. The study showed that articular cartilage lesions are a commonly found entity at arthroscopy, occurring in more than \( \frac{1}{2} \) of the arthroscopies, and they tend to be associated with more than one lesion.

Alternative Medicine

The goals of alleviating pain and improving function without having a joint replacement push patients to try any new treatment. One of these modalities being used more frequently is viscosupplementation. In osteoarthritis, the hyaluronan molecular weight and concentration is diminished. This has led to the concept of viscosupplementation in which hyaluronan-based products are injected into the articular space. A therapeutic benefit is reported to occur after these injections. The estimated market cost for these injections in the United States for 1999 exceeded $150 million with an estimated 70% of this use from orthopaedic surgeons doing the injections.

Many patients have been disenchanted with efforts to seek relief through traditional physicians. They think nonphysician providers can most effectively deal with their symptoms and disability and have chosen to pursue alternative treatments. These providers include podiatrists, chiropractors, acupuncturists, physical therapists, nurse practitioners, masseuses, personal trainers, herbalists, holistic practitioners, and others. Individuals are skeptical that high technology and prescription drugs are not the treatment they desire for their long-term arthritis care. As the American population ages, more individuals will require care for their arthritic impairments and the costs of caring for the aging population will escalate. Patients and society eventually will demand value-added care and evidenced-based appropriate treatments. The question has arisen as to how well physicians are prepared to meet the challenges of alternative and complementary treatment of musculoskeletal disease.

During a 7-year period from 1990 to 1997, the use of alternative therapies by Americans increased from 33% to 42%. Estimated out-of-pocket expenditures for alternative medicine professional services treatment in 1997 were $12.2 billion, which exceeded all out-of-pocket expenditures for all hospitalizations in the United States. Total out-of-pocket expenditures related to alternative therapies were conservatively estimated to be $27 billion in 1997. Former President Clinton established the White House Commission on Alternative Medicine in July 2000. The Commission on Alternative Medicine is charged with recommending legislation or administration action to help people make the most of alternative medicine while avoiding potential risks from unproven therapies. Moreover, the United States Government now has shown support of alternative medicine through the National Institutes of Health newly-created National Center for Complementary and Alternative Medicine and allocated nearly $70 million this year for research. Perhaps the large amount of money spent by the public on alternative medicine has caught the attention of policymakers and econ-
omists but the scientific community still is skeptical about clinically investigating every alternative therapy treatment with a double blinded, placebo-controlled study. However, because some patients get symptomatic relief with less general toxicity, additional studies may be warranted.

To the physician, scientific studies provide the necessary evidence that forms the basis of conventional medicine and their absence is responsible for the reluctance to accept alternative therapies. However, some of the population seems to have more faith in the alternative therapies. In 1998, the results of a national study stated that Americans seek alternatives to traditional Western medicine because they are dissatisfied with ineffective treatments, adverse side effects, a perceived impersonal nature to the doctor and patient communication, and therapies that are too technologically driven, too costly, or both. These patients' worldviews desired a more holistic approach to their health including prevention. Moreover, patients who may be using complimentary or alternative therapies are not inclined to discuss these with their physician. The physicians treating patients with osteoarthritis will need to be sensitive to this and also be familiar with the common alternative treatments to be able to discuss and counsel patients. In a survey of approximately 2200 primary care physicians and rheumatologists, and 800 patients with arthritis who were voluntarily part of Arthritis Today’s Reader Advisory Network, the most commonly accepted alternative therapies for each group, and those dismissed by the doctors were compiled. Patients' top choices for complementary alternative medications included prayer, meditation, visualization, glucosamine, journal writing, massage therapy, chondroitin, chiropractic medicine, magnets, metal jewelry, yoga, tai chi, qi gong, and melatonin. Interestingly, only 26% of the patients used chondroitin, whereas 45% of the doctors recommend glucosamine sulfate.

A study of glucosamine sulfate for the treatment of osteoarthritis has shown it to be as good as ibuprofen for osteoarthritis of the knee. Glucosamine sulfate and chondroitin sulfate are available as food supplements in the United States and Canada, but are approved drugs in Europe and South America. One large randomized controlled analysis that was placebo-controlled, double-blind, and prospective reported that glucosamine sulfate significantly reduced progression of osteoarthritis of the knee. Recently, the clinical outcome of long-term glucosamine therapy was compared with placebo in a double-blind trial. After 3 years of once daily oral dosing with either 1500 mg glucosamine sulphate or placebo, the group taking the glucosamine sulphate had no significant joint space loss, whereas the patients treated with the placebo had progressive joint space narrowing. According to this study, glucosamine sulphate could be a disease modifying agent in osteoarthritis. The exact amount of money spent in the United States on glucosamine and chondroitin sulfate is not known. An estimate of the out-of-pocket costs can be made by assuming that 26% of all patients with osteoarthritis take one of these supplements at an average cost of $500 per year. This gives a conservative figure of approximately $2.6 billion that could be spent in a given year in the United States on just this one form of supplement.

Surgical Therapy
The widespread prevalence of degenerative articular cartilage and full-thickness loss in specific areas presents another treatment dilemma. If often is difficult to determine which lesions are or will become symptomatic and which lesions could benefit from surgical intervention. During the past 2 decades, orthopaedic surgeons have evaluated and done numerous arthroscopic techniques for treating patients with articular cartilage defects. These techniques have had variable benefits to patient populations in controlling or modifying their symptoms. Current therapies may provide symptomatic relief, but they do not preserve or restore normal articular cartilage, and they have no significant effect on the pro-
gression of articular cartilage degeneration. Currently, surgeries that are done include joint lavage, debridement, microfracture, chondrocyte or osteochondral transplants, or replacement. Costs effectiveness of these procedures is difficult to estimate because of the lack of good long-term longitudinal studies. However, estimates of the cost per additional quality-adjusted life year after 2 years was $6791 for autologous chondrocyte transplantation compared with a cost of $6656 for total knee replacement. For total hip replacement, the cost effectiveness increases with age and is higher for men than for women.

In patients with advanced hip or knee arthritis, the effectiveness of total joint replacement compares favorably with nonsurgical treatments. Shortened hospitalization and limited surgical implant selection are unlikely to add to the cost effectiveness of replacement over nonsurgical treatments.

Disease Treatment

The United States spends the largest percentage of its gross national product on healthcare in the world. In the middle of the technological and scientific breakthroughs in disease diagnosis and treatment, the realities of costs out-of-control and variations in care delivery are being learned. Evidence-based medicine will be the underpinning of future disease treatment. A disease treatment program for osteoarthritis would be ideal because of large numbers of patients, the present and future significant socioeconomic burden, and the current widespread variation in treatments nationwide. There are no outcomes monitoring current treatments and no prospective effective prevention programs in the literature. The first step will be to decide which patients to treat and how to establish the priorities and funding. Treatment with medication management is a great challenge and it is related to the high cost of medications. One must weigh the high cost of lost productivity and rehabilitation and the costs of the side effects of treatments (as with NSAIDs). Currently, the healthcare industry and healthcare providers are lacking data benchmarks and mechanisms are not in place that are capable of delineating the effectiveness of arthritis treatments. Any future changes in existing therapy programs will need to be based on measurable outcomes. Future decisions will only be as good as the data infrastructure supporting them. Because of an abundance of information and direct marketing to educate patients, expectations from therapies rise and pressure is being placed on physicians to use the newest and latest therapies. Justifying the therapeutic costs and response will take carefully designed studies to differentiate the outcomes from placebo effects and from variations in the natural history of the disease process.

Using Medicare reimbursement schedules and average wholesale drug prices from July 1993 to July 1994, the costs of drugs and medical services were estimated. From followup of 10,101 patients with osteoarthritis, the average individual cost rate was $543 per year, and the total cost to the Health Maintenance Organization was $4.73 million. Of the total cost, 46% was for hospital care, 32% was for medications, and 22% was for ambulatory care. Although costs associated with rheumatoid arthritis care per patient are higher than the costs per patient with osteoarthritis, the managed care provider’s costs were relatively low, because of the lower incidence of rheumatoid arthritis. The largest component of the cost of care of patients with osteoarthritis was hospital care for a small proportion of patients (5%). Because osteoarthritis is more prevalent than rheumatoid arthritis, the cost to the managed care provider was approximately seven times more for patients with osteoarthritis than for the care of patients with rheumatoid arthritis.

Future Therapies and Treatments

New therapies designed to preserve the joint structure and function or alter the disease progression are being developed. For example, researchers have identified a gene in mice that may play a role in preventing mineral buildup in joints. Mice with a defective copy of the ankylosis (ank) gene have long been studied as
a model of arthritis, but this is the first time scientists have pinpointed the specific gene responsible for the condition and analyzed how it works. “This is the first identification of the progressive ankylosis (ank) trait in mice that’s responsible for the arthritis trait and the mechanism by which the gene might work.” The ank gene that the researchers found produces a protein thought to aid in the movement of pyrophosphate, which inhibits calcification and bone mineralization, in and out of cells. The ank gene may prevent arthritis by thwarting the buildup of bone mineral crystals. Using the mouse ank protein as a guide, the researchers also identified the human version of the gene and confirmed it is in a region of DNA previously implicated in joint disease in humans.

The cost of new drug development has become increasingly more costly. It has been estimated that $350 to $750 million is needed to bring a drug from concept to market. Parts of these expenses are attributable to the larger number of cohorts (in excess of 10,000 patients) in clinical trials and increased number of test procedures to ensure efficacy and reveal untoward reactions. However, not all drugs make it to market and these costs also must be absorbed. Who pays the cost? The pharmaceutical companies traditionally support the drug discovery pathway through a portion of their profits. Once the drug is on the market, the cost is passed on to the consumer and eventually the development costs are recouped and profit is realized. The patient pays for this either out-of-pocket, from medical insurance, or from government or state programs. However, if patients’ insurance drug formularies are not updated, patients must pay or do without the drugs.

New surgical procedures require large studies to validate their effectiveness and define indications. These new procedures often require new coding, because old codes may not be applicable and payment will be refused. Adding new coding is a slow process that requires significant documentation, diligence, and persistence to gain approval from the government, insurance providers, and the hospital. According to the American Academy of Orthopaedic Surgeons, approximately 1,000,000 patients per year undergo surgery for osteoarthritis of their knees, hips, shoulders, and spine. For just procedures involving cartilage surgery of the knee, the surgeon inpatient and outpatient services costs were conservatively estimated to be approximately $971 million (Table 2).

Currently, direct medical costs including surgery for osteoarthritis exceed $15 billion annually and are expected to increase significantly if new effective surgical and therapeutic treatments develop.

In the United States in 1995, arthritis and its associated cartilage degeneration was the most prevalent chronic condition among adults 65 years or older (48.9/100 adults), followed by hypertension (40.3/100) and heart disease

### TABLE 2. Prevalence and Outpatient Costs of Cartilage-Related Problems

<table>
<thead>
<tr>
<th>Procedure or Diagnosis</th>
<th>Total Patients*</th>
<th>Cost of Surgeon Services (Sm)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debridement and shaving (chondroplasty)</td>
<td>500,325</td>
<td>293.7</td>
</tr>
<tr>
<td>Removal of loose body</td>
<td>52,577</td>
<td>30.7</td>
</tr>
<tr>
<td>Abrasion arthroplasty or multiple drilling</td>
<td>76,166</td>
<td>67.0</td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>14,402</td>
<td>8.5</td>
</tr>
<tr>
<td>Osteochondral allograft transplantation system, mosaicplasty, chondrocyte transplant, periosteal graft (estimated)</td>
<td>1000</td>
<td>0.7</td>
</tr>
<tr>
<td>Synovectomy</td>
<td>158,405</td>
<td>92.6</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>244,000</td>
<td>478.4</td>
</tr>
<tr>
<td>Total (knee only)</td>
<td>1,046,875</td>
<td>971.6</td>
</tr>
</tbody>
</table>

*Procedures reported in United States 1999; **Average surgical reimbursement in Southern California, 1999.
As the percentage of the population of Americans are affected by arthritis, and this is expected to increase to an estimated 60 million people. As the percentage of the population with diseases of cartilage increases, the impact on the social and economic fabric of the healthcare system in the United States will stimulate novel treatments and therapies. Knowing what the future holds in terms of patient needs should convince the medical community to embark on programs to immediately establish disease treatment protocols for the degenerative articular cartilage symptoms that will impact the patients’ activity levels and their ability to afford the needed care. This will require that evidence be collected to establish new standards of cartilage disease therapy.

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