Department of Labor and Industries
Office of the Medical Director
Technology Assessment
Autologous Chondrocyte Implantation (ACI)
2002 Update

I. Background

Genzyme Tissue Repair developed a process termed Carticel to culture autologous chondrocytes. Physicians use Carticel and autologous chondrocyte implantation (ACI) for the repair of cartilaginous defects of the femoral condyle caused by trauma.

The ACI process involves:

- Obtaining chondrocytes - The surgeon arthroscopically obtains 300 to 500 mg of healthy cartilage from the upper-medial or upper-lateral femoral condyle of the damaged knee.

- Culturing chondrocytes - The cartilage samples are shipped to Genzyme Tissue Repair where cells are cultured until 12 million cells have been isolated.

- Transplanting chondrocytes - The patient receives a medial or lateral parapatellar arthrotomy under general anesthesia. The surgeon covers the defect with a healthy periosteal flap transplanted from the proximal medial tibia. The cultured chondrocytes are then injected through the flap, which keeps the cells in place.

Following implantation, the patient restricts activity for up to a year as activity may "compromise the durability of clinical benefit from Carticel." (Genzyme 2000) Patients also enroll in an intensive rehabilitation program with 2 to 3 months of post-operative nonweightbearing and continuous passive motion.

Evidence suggests that the implanted chondrocytes generate hyaline-like matrices to replace the damaged tissue. As a result, Carticel's durability compared to other treatments may more effectively prevent tissue degeneration characteristic of secondary osteoarthritis. (Cole 2001)

Genzyme indicates that only physicians who have completed their Surgery Training Program should conduct the implantation procedure. Of the 3,500 surgeons who have received training, 694 are located in the Western United States. Genzyme also keeps data on the number of procedures that each surgeon has conducted. To date, surgeons have treated over 4,500 knees. (Kaska 2002)

II. Reason for Review

The Office of the Medical Director (OMD) reviewed ACI in October 1997 and April 1998. (State 1997)(State 1998) OMD decided to approve coverage for specific patients who enrolled in the Study for the Treatment of Articular Repair. Enrollment for the study has ended, but physicians continue to request the procedure.

III. Food and Drug Administration History and Status

In 1995, the Food and Drug Administration (FDA) granted Genzyme Tissue Repair approval to culture autologous chondrocytes, a process termed Carticel. Because Carticel did not fall within existing medical technology regulations, the FDA concurrently developed guidelines for Manipulated Autologous Structural (MAS) cell technology. In August 1997, the FDA issued a Biologics License under MAS guidelines to Genzyme indicating Carticel for the repair of cartilaginous defects of the femoral condyle caused by trauma. (FDA 1997) The FDA based its approval on case reports from Swedish and American patient registries.

As required for the FDA's accelerated approval, Genzyme planned two randomized controlled studies. However, due to inadequate enrollment, Genzyme requested to change ACI from first line to second line therapy. In March 2000, the FDA issued a supplement to the original Biologics License granting Genzyme's request. (FDA 2000)

In an April 2002 letter, Genzyme's Vice-President of Research described two current studies required by the FDA.

- The registry-based study examines the durability of Carticel implantation to non-Carticel surgical treatment in Cartilage Repair Registry patients.

- The Study for the Treatment of Articular Repair (STAR) assesses long-term outcomes in patients who previously failed other surgical repair procedures within the previous 3 years. The prospective, longitudinal study is currently evaluating 100 patients from 20 centers in the US and Canada. Investigators will monitor subjects for 4 years.

The FDA has approved Carticel "for the repair of symptomatic, cartilaginous defects of the femoral condyle (medial, lateral, or trochlear), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure. Carticel is not indicated for the treatment of cartilage damage associated with osteoarthritis. Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation." (Genzyme 2000)

IV. Review of Published and Unpublished Literature

A literature search of ACI clinical data included English articles published in or after 1998, but excluded review articles.

A. Two published articles reported patient case studies.

1. Cole detailed the experiences of a 37-year-old male with recurrent knee pain. (Cole 2000) The man had a full-thickness lesion measuring 6 cm^2 after debridement on the medial femoral condyle. Six weeks after undergoing ACI, the patient resumed full weight bearing activity. After 8 months, he resumed normal athletic activity. At 1 year, the patient reported nearly normal knee function.

2. Richardson studied 2 patients, ages 28 and 32 years, who presented with defects (sizes 4 cm^2 and 2 cm^2, respectively) of the medial femoral condyle. (Richardson 1999) The investigators conducted immunohistochemical analyses of repair tissue. Both subjects experienced symptomatic improvement according to Lysholm scores. Biopsies showed tissue integration with underlying bone and some hyaline cartilage formation. After 1 year, the repair tissue matrix and organization were heterogeneous. Lower zones resembled hyaline-like cartilage, but upper zones were more fibrocartilaginous.

B. Five published articles reported data from prospective, case series studies that did not include comparison or control groups. Patient samples tended to be small and to have varied medical histories. Investigators may not have been blinded.

1. Cole's report described Cincinnati Knee scores after a minimum of 12 months. (Cole 2001)

   Study Population: The average follow-up for the 11 patients was 21 months. The lesions were located on the medial (7) and lateral (3) femoral condyle and the trochlea (3). Lesion size averaged 3.55 cm^2. Five of the 11 patients had work-related injuries.

   Results: Patients experienced improved scores and decreased pain. All workers' compensation cases returned to work. Adverse events included 3 repeat arthroscopies for intra-articular adhesions associated with motion loss and 1 arthroscopy for tissue hypertrophy.

   Conclusion: Lesions of the femoral condyle and trochlea respond well to ACI.

2. Gillogly used Knee Society, modified Cincinnati, and self-report data to assess subjects for up to 36 months after ACI.[i] (Gillogly 1998)

   Study Population: The study included 41 patients with 53 defects in the medial (27) and lateral (12) femoral condyle, trochlea (7), patella (6), and lateral tibial plateau (1). The defect size averaged 5.74 cm^2. Of the 41 patients, 6 patients had osteochondritis dissecans of a femoral condyle. Previous surgeries had failed in 29 patients.

   Results: Of the 25 patients with over 1-year follow-up, 22 subjects (88%) had Good, Very Good, or Excellent scores. The subjects also experienced improvement in pain and swelling. Three treatment failures occurred.

   Conclusion: ACI appears to provide hyaline-like repair tissue, with corresponding improvement in histological, biomechanical, and durability characteristics as reflected by better clinical outcomes in up to 90% of patients with femoral condyle defects.

   Additional Data Limitations: Investigators did not report sample sizes, losses to follow-up, or attrition rates at follow-up dates. The use of intention to treat in data analysis is unclear.

3. Micheli used multi-center data to report case series results at 3-year follow-up.[i] (Micheli 2001) Clinicians and patients tracked progress with case report forms and modified Cincinnati knee scores. By analyzing median scores for 50 subjects, investigators achieved adequate power to detect statistical significance.

   Study Population: The series included 50 patients from 19 centers in the US treated for Grade III or IV defects in the medial (33) or lateral (7) condyle, patella (5), and intercondylar notch (5). The mean defect size was 4.2 cm^2. Failure of cartilage repair surgery occurred in 78% of the patients, including 36% who failed marrow stimulation techniques. Workers' compensation covered 36% of the subjects.

   Results: Clinician and patient evaluations indicated statistically significant score improvements of 4 and 5 points, respectively, at 3 years compared to baseline. In addition, 84% of patients improved according to the clinician, and 85% of patients self-reported improvement. Patients on workers' compensation self-reported significantly less improvement at 3 years compared to non-workers' compensation patients. Of the 11 patients who required reoperation, 3 experienced graft failures. Investigators included reoperations and treatment failures in data analysis.

   Conclusion: Improvement in overall knee condition and symptomology lasts up to 3 years.

4. Minas reported the effect of ACI on patients with simple and complex lesions.[i] (Minas 2001) Investigators followed subjects for a minimum of 12 months by evaluating clinical outcomes and quality of life with several questionnaires.

   Study Population: The study included 169 patients with 295 lesions. Twelve subjects presented with simple, isolated lesions to the condyle (mean size 4.3 cm^2). The 12 simple subjects did not have other surfaces with greater than Grade II chondromalacia. Investigators classified 86 subjects as complex because the subjects presented with unipolar single or multifocal lesions (mean total size 6.75 cm^2) of the distal femur, including trochlea, patella, or tibia. Osteoarthritis was present in 71 salvage patients whose mean total defect size was 11.66 cm^2. Complex and salvage patients may have required concomitant osteotomy, ligament reconstruction, or bone graft.

   More than 50% of subjects with complex or salvage lesions and 43% of subjects with simple defects failed previous surgical repair techniques. The defects affected the medial (127) and lateral (37) femoral condyle, trochlea (76), patella (43), and lateral (8) and medial (4) tibial plateaus.

   Of the 169 patients, 107 patients were at least 12-months post-implantation, and 56 patients had more than 24-months follow-up.

   Results: Overall physical health and physical function showed statistically significant improvement at 12-month follow-up for complex and salvage patients who did not undergo osteotomies. The complex and salvage patients who reached 24-month follow-up showed statistically significant improvement in pain. Knee Society scores improved significantly in all patient categories at 2 years.

   Of the 169 patients, 22 patients (13%) failed treatment due to complete delamination (13), noncompliance to rehabilitation (2), traumatic event after ACI (4), or progressive degenerative disease (4). Treatment failure occurred in the simple patient category (2 of 12, 16.7%), complex category (8 of 86, 9.3%), and salvage category (12 of 71, 16.9%). Failures were included in data analysis.

   Conclusion: ACI is a good treatment option for young individuals with large chondral injuries.

5. Peterson examined the biomechanics and long-term durability of ACI after 2 to 11 years.[ii] (Peterson 2002) The durability outcome rating compared long-term (5 to 11-year) with 2-year follow-up data. Other outcomes included the histological and biomechanical assessment of repair tissue.

Study Population: The series included 61 patients from the Swedish patient registry treated for isolated femoral condyle lesion (19), osteochondritis dissecans lesion (14), patellar lesion (17), and femoral condyle lesion with anterior cruciate ligament reconstruction (11). The Grade III or IV lesions ranged in size from 1.3 to 12 cm^2. Investigators included 4 cases that had failed prior to 2-year follow-up and 1 case lost to follow-up. Of the remaining 56 patients, 27 had undergone previous orthopedic knee procedures.

Results: The investigators reported the percentage of patients with excellent or good clinical scores.

Percentage of Patients with Excellent or Good Clinical Scores

Lesion	At 2-year Follow-up	At Latest Follow-up
Isolated femoral condyle	89%	94% (mean 7.4 yrs)
Osteochondritis dissecans	86%	86% (mean 6.5 yrs)
Patella	65%	76% (mean 7.4 yrs)
Femoral condyle and ACL repair	81%	81% (mean 7.8 yrs)

Of the 12 patients who agreed to biopsy, 8 showed hyaline matrices. Stiffness measurements in the hyaline cartilage were twice that for fibrous cartilage samples.

Ten treatment failures (16%) occurred among the 61 study subjects. Investigators included treatment failures in data analysis.

Conclusion: The evidence suggests that ACI endures for up to 11 years with hyaline cartilage formation and good stiffness of repair tissue.

C. Two published articles described histological examinations of tissue from failed treatments.

1. Muellner studied a 42-year old male whose ACI failed due to graft delamination. (Muellner 2001) The man had a full-thickness defect measuring 25mm by 25mm on the lateral portion of the femoral groove. Six months following ACI, an MRI scan showed normal cartilage repair. Fourteen months after ACI, the patient resumed former levels of activity. At 22 months, the subject returned to the physician because of a locked knee. The physician confirmed cartilage delamination, and the subject underwent an osteochondral graft.

   A biopsy of the delaminated cartilage showed irregular orientation of the collagen fibers. Furthermore, the inner zone was calcified and contained chondrocytes without normal nuclear structures.

2. Nehrer retrieved tissue during revision surgeries for patients who failed abrasion arthroplasty (12), perichondrial flap grafting (4), and ACI (6). (Nehrer 1999)

   Results: An average of 17.8 months passed between index and revision surgeries. The material from arthroplasty patients appeared as fibrous, spongiform tissue with Type I collagen in an average of 22% of cross-sectional areas. Degenerating hyaline tissue (30%) and fibrocartilage, Type II collagen (28%) also filled the area. Specimens from perichondrial flap graft subjects showed bone formation in 19% of cross-sectional area. Degenerative hyaline cartilage comprised 50% of the area for graft subjects. ACI subjects experienced early suture failures on graft edges. For these failures, fibrous tissue accounted for 55% of the section area. However, graft tissue that had attached to bone displayed hyaline tissue (up to 6%) and fibrocartilage (up to 12%).

   Conclusions: Tissue evaluations from repair procedures revealed histological features that may have reflected failure mechanisms.

D. One published article reported the inappropriate applications of ACI.

1. Investigators examined patient characteristics to assess whether the patients met ACI criteria. (Mont 1999) Evaluation factors were based on clinical notes, radiographs, and operative notes.

   Study Population: Investigators examined 24 cases rejected for reimbursement by insurers and later appealed by orthopedic surgeons.

   Results: In 23 cases (96%), patients did not meet the indications for the procedure or presented with specific contraindications. Reasons for not meeting indications included:

   - Large lesions greater than 10 cm^2 (11 patients)
   - Multiple, small lesions (9 patients)
   - Tricompartmental arthritis (9 patients)
   - Reflex sympathetic dystrophy (2 patients)
   - Patellar lesion indicated for transplantation (5 patients)
   - Patient age greater than 60 (3 patients)

   Fifteen cases (63%) had multiple contraindications.

   Conclusions: Controlled, application-limited experience must precede the release of new procedures for widespread clinical applications. The uncontrolled use of ACI may negatively skew results of a procedure that may work for correct indications.

E. Genzyme provided unpublished, February 2002 outcomes data from a voluntary, American patient registry.[iii] (Genzyme 2002)

1. The report described case series data at 72-month follow-up based on Cincinnati knee scores.

   The report included:
   - 33 patients treated for isolated or multiple medial, lateral, or trochlear lesions of the femoral condyle
   - 6 off-label patella or tibial plane patients

   Of the 39 patients, 28 patients had single defects (mean 3.9 cm^2), and 11 patients had multiple defects (mean total surface area 11.3 cm^2). Previous articular cartilage procedures failed in 92% of the subjects, including 28% who had prior marrow stimulation procedures. Workers' compensation recipients comprised 39% of the study subjects.

   The mean Cincinnati score increased from 3.15 at baseline to 6.93 at 72-month follow-up for the 33 patients with femoral defects. According to self-report, improvement occurred in 81.8% of the patients.

2. Of the registry's 6,286 patients, 5.8% reported adverse events or complications to the Registry. The Registry Advisory Board considered 2.9% to have experienced complications possibly related to autologous chondrocytes. The most frequent complications included adhesions or fibroarthrosis (1.6%), treatment failures (1.3%), and hypertrophic changes to the defect site (1.1%).

   Cumulative incidence rates of treatment failures were calculated as:
   - 0.7% at 12 months
   - 1.8% at 36 months
   - 3.3% at 72 months

   Of all patients, 4.8% reported reoperations following ACI. The most frequent procedures were arthroscopic debridement, shaving, or trimming (3.3%). Manipulation and lysis of adhesions (1.2%) were also frequently performed.

V. Review of Presentation Abstracts

Abstracts are from the American Academy of Orthopaedic Surgeons annual meetings.[iii, iv]

A. One presentation reported the results from a mid-term follow-up. The study does not include a control or comparison group. Investigator blinding is uncertain, and patients had varying medical histories.

1. Browne examined 5-year outcomes from multi-center, prospective, case-series that used the Cincinnati knee score.[i] (Browne 2002)

   Study Population: Investigators tracked 86 patients from 38 medical centers. Seventy-two patients had single lesions (mean area 4.2 cm^2), and 14 patients had multiple lesions (mean total area 9.1 cm^2). Prior surgery failed in 90% of the patients, including 35% who failed a marrow stimulation technique.

   Results: Improvement at 5 years occurred in 78% of subjects. The mean overall score improved from 3.2 to 6.1. Improvement occurred in 63% of patients with large lesions ($\geq$6 cm^2) compared to 85% of patients with small lesions. Eighteen patients required reoperation, including 8 treatment failures. Investigators included treatment failures in data analysis.

   Conclusion: ACI can return patients to a high level of physical function, including sports.

B. Two presentations examined the effects of ACI on lesion location and type. Researchers generated the data from case series studies without control or comparison groups. Neither study indicated whether investigators were blinded or whether intention to treat was practiced. The small number of patients often had varying medical histories.

1. Mandelbaum used Cincinnati knee scores to examine the effect of ACI after 4 years on trochlear defects. (Mandelbaum 2002)

   Study Population: The study included 31 patients with full-thickness defects of the trochlea. Twelve patients presented with single lesions (mean 5.1 cm^2), and 19 patients presented with multiple lesions (mean 4.8 cm^2). Previous cartilage repair procedures failed in 94% of the patients, including 42% who failed marrow stimulation techniques.

   Results: Improvement from baseline to follow-up resulted in 77% of patients. Mean knee scores significantly increased from a 2.8 at baseline to 5.9 at 4-year follow-up. Multiple lesions or obesity adversely affected results. Three treatment failures occurred.

   Conclusion: Outcomes of ACI for the treatment of trochlear defects resemble previously reported ACI outcomes for the medial and lateral condyles.

2. Peterson examined the effect of ACI among patients with osteochondritis dissecans.[ii] (Peterson 2001)

   Study Population: The study included 32 patients with radiographically confirmed osteochondritis dissecans on the medial (22) and lateral (10) femoral condyle (mean lesion size 5.5 cm^2). Eleven subjects agreed to a second arthroscopic evaluation. Eighty-eight percent had failed a mean of 3.2 prior surgeries.

   Results: At average 5.3-year follow-up, 84% of patients received a Good or Excellent rating from the clinician. Of the 11 patients that agreed to second arthroscopies, 1 patient rated below 9 on macroscopic graft integrity evaluations. Two subjects failed treatment.

   Conclusion: ACI for osteochondritis dissecans produces integrated repair tissue resulting in successful outcomes for over 80% of patients.

C. Three researchers compared ACI to other surgical techniques. Investigators did not describe their methods for generating comparison groups. The small samples had varying medical histories and were followed for different amounts of time. Investigator blinding and intention to treat are uncertain.

1. Anderson compared ACI with marrow stimulation techniques for full-thickness femoral lesions. (Anderson 2002) Investigators followed subjects prospectively for at least 36 months and evaluated Cincinnati knee scores.

   Study Population: The study included 23 patients who underwent marrow stimulation techniques (abrasion, drilling, or microfracture) and 31 ACI patients. Subjects had at least 1 femoral defect of 2 cm^2 and no treated defects of the patella or tibia. Previous articular cartilage surgery failed in 35% of marrow stimulation patients and 87% of ACI patients. Marrow stimulation previously failed in 22% of marrow stimulation patients and 32% of ACI patients.

   Results: At 3-year follow-up, 52% of marrow stimulation and 86% of ACI patients improved. The overall Cincinnati Knee Score increased from 4.3 to 5.7 for marrow stimulation patients and from 3.1 to 7.1 for ACI patients. ACI patients showed statistically significant improvement compared to marrow stimulation patients. Five marrow stimulation patients and 2 ACI patients required reoperation.

   Conclusion: ACI produces a higher level of function and greater probability of return to sport than marrow stimulation.

2. Coleman used clinical and magnetic resonance (MR) data to compare ACI to microfracture for isolated medial femoral condylar lesions. (Coleman 2002)

   Study Population: The study included 17 patients who received ACI and 18 patients who received microfracture. Condyle lesions measured 472 mm^2 for ACI patients and 326 mm^2 for microfracture subjects. Follow-up for ACI averaged 2.6 years while follow-up for microfracture averaged 2.8 years.

   Results: Cincinnati knee scores representing clinical improvement increased an average of 22% for ACI patients and 42% for microfracture patients. On the 100% MR scale rating normal cartilage appearance, ACI subjects averaged 66% while microfracture subjects scored 44%. ACI patients (59%) required additional procedures.

   Conclusion: Clinical improvement was 2 times greater for microfracture patients compared to ACI patients. MR scores rating appearance did not correlate with clinical outcomes.

3. Fu evaluated patients with full-thickness femoral lesions for a minimum of 36 months following either ACI or debridement. (Fu 2001) The study used clinician and patient evaluations based on the Cincinnati knee score.

   Study Population: Investigators examined 36 ACI and 86 debridement patients from multiple centers treated for single or multiple Grade III or IV lesions on the medial or lateral femoral condyle or trochlea. Nineteen percent of debridement and 28% of ACI patients had multiple lesions. Marrow stimulation failed in 23% of debridement subjects and 39% of ACI patients.

   Results: At 5-year follow-up, 55% of debridement subjects and 83% of ACI patients improved at least 1 point on the Cincinnati score. ACI Cincinnati scores (7.6) differed significantly from debridement scores (5.8) at 5 years. The overall score decreased with increasing lesion size in the debridement group, but not in the ACI group. Debridement patients (23%) and ACI patients (14%) required reoperation. One ACI and 4 debridement patients failed treatment.

   Conclusion: ACI may be more efficacious than debridement for chondral lesions, especially large lesions.

VI. Cost and Cost Effectiveness

The total cost for the ACI procedure falls between $17,600 and $38,400. (Minas 1998)

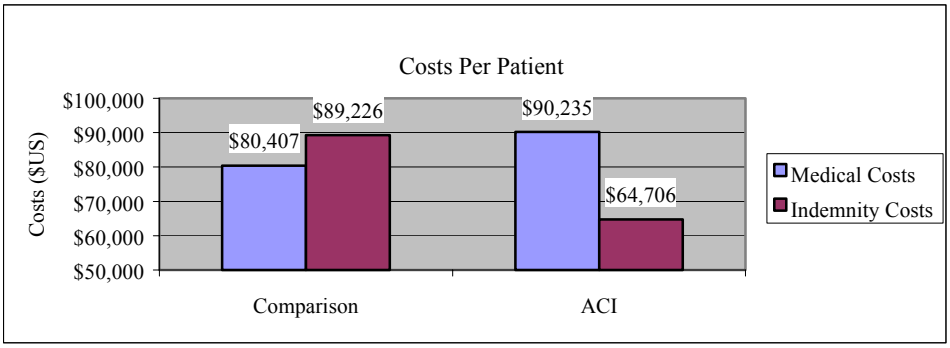
The Average Wholesale Price for Carticel alone is $15,000 under HCPCS Code J7330. However, as indicated in a letter, the direct price is $13,300 effective July 8, 2002. Genzyme charges this amount to either the hospital or payer, but not the physician. (Kaska 2002)

A. Three investigators examined ACI's cost-effectiveness.

1. Seidner presented a study abstract that compared injured workers who underwent ACI to injured workers who received other treatments for knee injuries. (Seidner 2001) Investigators used workers' compensation data to assess return to work status and total medical and time loss costs. ACI subjects were followed until claim closure.

   Study Population: Investigators tracked 24 workers' compensation recipients who underwent ACI. They identified from workers' compensation data 76 closed claims that had received alternative treatments.

   Results: Seventy-one percent of the ACI group and 83% of the comparison group returned to work. ACI subjects had higher total medical costs, but lower lost work costs.



   The average total costs equaled $167,734 for an ACI patient in contrast to $183,608 for a comparison subject.

   Conclusion: ACI resulted in a slightly lower return to work rate with an average net cost savings of $15,874 compared to patients not treated with ACI.

   Data Limitations: Statistically significant differences existed between the comparison and treatment groups. Investigators did not track the comparison group prospectively. Subjects had varying medical and work histories.

2. Lindahl's published article examined the health economic benefit of ACI for Swedish patients with focal chondral lesions of the knee. (Lindahl 2001) Investigators reviewed records from Swedish social affairs offices and treating facilities. They monitored changes in disability and costs at 3 time points: disability determination, ACI procedure, and 2 years following ACI.

   Study Population: The 57 subjects were either Swedish ACI patients whom investigators followed for a minimum of 5 years or ACI patients from Gothenburg whom investigators followed for a minimum of 2 years. No patients were lost to follow-up. Femoral condyle lesions afflicted 58% of the patients. Investigators also included patients who presented with condylar defects with ligamentous instability (9%), osteochondritis dissecans (14%), and defects of the patella (19%).

   Results: The mean follow-up for assessing patient disability and absenteeism was 7.3 years, ranging from 2 to 10 years. ACI reduced the number of disabled individuals and the number of missed days of work. The probability of an individual reporting disability decreased from 100% before ACI to 13% after ACI. Patients were significantly less likely to require sick leave after ACI (18%) compared to before ACI (78%). Average patient absenteeism decreased from 155 days to 1.5 days per year.

   Number of Patients Reporting Disability, Mean Follow-up 7.3 Years

Disability Status	Pre-ACI	Post-ACI
No sickness	0	44 (77%)
Disabled	57 (100%)	1 (2%)
Re-injured	0	2 (4%)

   In the 10-year period prior to ACI, patient projections indicated that 2 necessary surgeries with rehabilitation required $5,875. In addition, patient absenteeism resulted in costs equaling $122,807. In the 10 years following ACI, patients required an additional .3 surgeries at a cost of $881. Absenteeism after ACI resulted in costs of $1,189.

   Investigators also conducted sensitivity analyses to determine the thresholds required for equalizing pre and post-ACI costs. Thresholds occurred when either the total number of pre-ACI surgeries fell below .5 or post-ACI surgeries exceeded 1.8. Thresholds also occurred when pre-ACI absenteeism fell below 28 days or when post-ACI loss exceeded 128 days. Lost days varied independently from surgery number.

   Conclusions: ACI reduces the number of patients on disability as well as absenteeism. The procedure produces a cost-savings of $88,146.

3. Minas' published article calculated the cost of ACI per quality-adjusted life years (QALY) gained. (Minas 1998) Investigators followed patients for 24 months after implantation. An independent third party collected data using standard quality of life and functionality scales.

   Study Population: Forty-four patients underwent ACI for full-thickness cartilage lesions. The number of lesions for the group totaled 87 with an average of 2 lesions per patient. The defect size averaged 5.5 cm^2 (range 1.5 to 21 cm^2). The defects were located on the medial (38) and lateral (11) femoral condyle, patella (15), trochlea (18), and lateral (4) and medial (1) tibial plateau.

   Results: Quality of life and social functioning scores improved significantly from before surgery to 12-month follow-up. The base-case analysis assumed ACI costs equaled $29,000. The resulting cost per QALY gained was $4701 for a life expectancy of 60 or more years, $6791 for 40 or more years, and $9403 for 30 or more years.

   Conclusion: ACI is a cost-effective treatment that provides improved quality of life for patients with full-thickness cartilage defects of the knee.

VII. Alternative Surgical Treatments

Physicians and patients consider the etiology of the defect and the desired level of activity in choosing a treatment option. Small lesions under 2 cm^2 may respond more well to surgical treatment than larger lesions. Treatments for articular defects of the knee may be categorized as palliative, reparative, restorative, or reconstructive. (Cole 2000) (Gill 2000)

A. Palliative treatments often provide short-term symptomatic relief, but may inadequately treat active patients since the underlying pathology remains uncorrected.

   1. Lavage rids the knee of loose debris and inflammatory mediators through irrigation.

   2. Debridement exposes healthy tissue by removing foreign matter and devitalized tissue. Investigators found satisfactory results in 50%-85% of patients with follow-up of at least 3 years.[v, vi, vii] A retrospective comparison of debridement to abrasion arthroplasty found better results in debridement subjects.[viii]

B. Reparative treatments include marrow stimulation techniques that treat lesions by creating repair tissue. The arthroscopic techniques penetrate subchondral bone in order to form a fibrin clot, which contains stem cells. Differentiation of the stem cells results in fibrocartilaginous tissue repair.

1. Abrasion arthroplasty employs a motorized burr to erode the surface of the subchondral bone. Researchers found satisfactory results among 60% to 80% of abrasion arthroplasty patients after at least 1 year.[ix, x, xi]

2. Subchondral drilling involves drilling the defect area in pinpoint fashion to penetrate the subchondral bone. Comparisons between drilling and perichondrial grafting showed that drilling had a higher success rate after 10 years.[xii]

3. Microfracture uses small picks to broach the subchondral bone surface. In a recent review, Grana suggested that microfracture heals as well as tissue grafts or ACI. However, researchers have not conducted controlled, prospective studies to compare techniques. (Grana 2000) At 5 years, researchers showed that 75% of patients improved. Histological analysis showed that microfracture generated a hybrid of hyaline and fibrocartilage repair tissue.[xiii] Evidence suggests that continuous passive motion for 8-weeks increases healing in microfracture patients.[xiv]

C. Restorative procedures treat lesions through the formation of hyaline-like cartilage.

1. ACI requires surgical implantation of cultured cells into the lesion site.

2. Osteochondral grafts may involve autografts, also called mosaicplasty, or cadaveric allografts. The procedures may require either arthroscopic or open knee surgery. After removing damaged cartilage, the surgeon transfers dowels of hyaline cartilage with attached subchondral bone into the lesion. Osteochondritis dissecans may respond well to grafting because of the bone loss that occurs. (Sledge 2001)

   Researchers report good and excellent graft results for up to 7.5 years in 63% to 86% of patients.[xv, xvi, xvii] Evidence suggests that grafting may be as good or better than marrow stimulation for small lesions.[xviii]

D. Reconstructive treatments are often considered final, salvage procedures for failed alternative treatments.

1. Realignment procedures using unloading osteotomy involve removing a wedge of tibial or femoral bone to transfer weight-bearing stress away from the damaged cartilage. This treatment shows good and excellent results for two-thirds of patients at 5 years, but has a high joint replacement conversion rate.

2. Joint replacement may act as a final treatment option for failed allograft transplantations or for end-stage osteoarthritis. The procedure provides symptomatic relief for up to 10 years in older adults, but has a high failure and complication rate.

VIII. Professional Organizations

Neither the American Academy of Orthopaedic Surgeons nor The Knee Society endorse or have policies regarding ACI for knee injuries. (Sung 2002)(Majewski 2002)

IX. Other Health Insurers

Over 100 payers have medical policies that cover Carticel, including Cigna, Prudential, and United Healthcare. An example of coverage language may be found in Aetna's January 2002 policy, which allows ACI if both surgeons and patients meet specific selection criteria. (Aetna 2002)

Over 50% of the 43 independent Blue Cross and Blue Shield Association members representing 25 States allow coverage for ACI. (Kaska 2002) For example, Alabama, California, Iowa, Massachusetts, Minnesota, North Carolina, and South Dakota decided in 2001 to cover ACI for specific patients with prior authorization. However, the Regence Group decided not to cover ACI because they consider ACI investigational. (Regence 2001)

The Centers for Medicare and Medicaid Services have not issued a national opinion about ACI.

Humana has made Carticel available to self-funded Federal Employee Health Benefit Plan members only. The 2000 policy states, "further studies are necessary to determine the long-term efficacy of this treatment as compared to standard means of treatment..." (Humana 2000)

The National Institute for Clinical Excellence of the National Health Service in the United Kingdom recommended in December 2000 that ACI should only be performed as part of a clinical trial. The institute has scheduled a second review for ACI in 2003. (NICE 2000)

X. The Department's Experience

Between January 1999 and December 2001, the Office of the Medical Director allowed ACI for 6 claims. Lesions affected the medial femoral condyle (2), lateral femoral condyle (2), and trochlea (2). One case presented with osteochondritis dissecans.

Current information for the six claims includes:

- 1 closed claim that later reopened due to a reinjury. An accident during surgery complicates evaluation of ACI's clinical effect on the original injury.
- 1 closed claim. The injured worker returned to work, but not to her original occupation as a ski instructor. The claim closed after 462 days.
- 4 open claims. By last physician visit, all 4 claims had attained excellent range of motion. Physicians released 2 for light duty, and 3 are currently in vocational retraining.

The department paid an average of $4320 per claim for the ACI. However, this amount does not include Genzyme's $13,000 culturing fee. The six cases received an average of $25,740 time loss for an average of 260 days.

XI. Conclusion

ACI may benefit some patients with full-thickness chondral defects involving the surface of the femoral condyle.

Published midterm and long-term case series data suggest that ACI improves patient outcomes and restores knee function. Published histological case studies also indicate that ACI may show increased durability due to the hyaline-like matrices of the repair tissue. Conference abstracts present some evidence that ACI is as effective as alternative treatments. However, researchers have not published in peer-reviewed journals any controlled studies documenting ACI's effectiveness.

The literature shows that physicians have performed ACI outside of FDA indications and company recommendations. Due to the possible misuse of ACI, narrow patient and surgeon criteria for the procedure would help to ensure that the surgery occurs for appropriate indications.

[i] Micheli (IV.B.3.) included some Gillogly (IV.B.2.) and Minas (IV.B.4.) subjects in the 3-year follow-up. In addition, Browne (V.A.1.) included 45 of the 50 Micheli subjects and some Mandelbaum (V.B.1.) subjects in the 5-year follow-up that he presented at the American Academy of Orthopaedic Surgeons 2002 meeting.

[ii] Peterson included some of his durability subjects (IV.B.5.) in the American Academy of Orthopaedic Surgeons presentation about osteochondritis dissecans (V.B.2.).

[iii] The subjects in the Genzyme patient registry may be described in other published articles or presentations. This assessment includes Genzyme's data because the report shows the longest follow-up with American registry

[iv] The ACI studies presented at the American Academy of Orthopaedic Surgeons meeting may have included subjects described in other published articles. This assessment includes the conference abstracts because the investigators studied different hypotheses or outcomes.

[v] Aglietti studied subjects with osteochondritis dissecans who underwent curettement and debridement. After an average of 9 years, 17 patients (85%) maintained satisfactory results, but with significant decreases in activity. The author concluded that removal of an osteochondral fragment and debridement of the crater show better results with lesions smaller than 2 cm^2. (Aglietti, P., et al. "Results of Arthroscopic Excision of the Fragment in the Treatment of Osteochondritis Dissecans of the Knee." *Arthroscopy*. 2001 Sept; 17(7): 741-746.)

[vi] Angermann used chondrectomy in patients with femoral condyle lesions. The prospective, case series included 53 patients who received only chondrectomy. A majority of patients (69%) reported improvement after an average follow-up of 6.5 years, and 34 subjects (77%) considered their improvement permanent. (Angermann, P., et al. "Arthroscopic Chondrectomy as a Treatment of Cartilage Lesions." *Knee Surgery, Sports Traumatology, Arthroscopy*. 2002 Jan; 10(1): 6-9.)

[vii] Of 137 patients who underwent lavage and debridement, 68 subjects (50%) maintained improvement for up to 3 years. (Jackson RW., et al. "Arthroscopic Treatment of Degenerative Arthritis of the Knee." *Journal of Bone and Joint Surgery (Br)*. 1988; 70:332. Cited by: Gill, T. "The Treatment of Articular Cartilage Defects Using Microfracture and Debridement." *American Journal of Knee Surgery*. 2000 Winter; 13(1): 33-40.)

[viii] Shahriaree reported 72% success at 5 to 7-year follow-up for gonarthrosis patients who underwent debridement. Jackson reported 68% of patients improved at mean 3.3-year follow-up. (Shariaree, H., et al. "Seven Years Follow-up Arthroscopic Debridement of the Degenerative Knee." *Field of View.* 1982; 1:1. Cited by: Bert, JM., et al. "The Arthroscopic Treatment of Unicompartmental Gonarthrosis: A Five Year Follow-up Study of Abrasion Arthroplasty Plus Arthroscopic Debridement and Arthroscopic Debridement Alone." *Arthroscopy*. 1989; 5(1): 25-32.) A study of gonarthrosis patients compared the results of arthroplasty to debridement. Of the 59 subjects that received arthroplasty, 51% had good to excellent scores while 33% had poor results. Of the patients with poor results, 10 subjects became worse. Of the 67 debridement subjects, 66% received good to excellent scores, and 21% had poor results. Twelve debridement subjects became worse. (Bert 1989)

[ix] One year following abrasion arthroplasty for gonarthrosis, 60% of patients showed fair and good results, and 6% became worse. (Friedman, M., et al. "Preliminary Results with Abrasion Arthroplasty in the Osteoarthritic Knee." *Clinical Orthopaedics*. 1984; 182:200. Cited in: Bert 1989, Note viii) Chandler reported satisfactory results among 80% of the 55 knees that underwent abrasion arthroplasty after 1.8 years. Sixteen percent of the subjects became worse. (Chandler, EJ. "Abrasion Arthroplasty of the Knee." *Contemporary Orthopaedics*. 1985; 11(2): 21. Cited in: Bert 1989, Note viii)

[x] Of 100 degenerative arthritis patients with an average age of 60 years, 74 reported improvement at minimum 2-year follow-up. Seven subjects required reoperation. (Johnson, LL. "Arthroscopic Abrasion Arthroplasty Historical and Pathologic Perspective: Present Status." *Arthroscopy*. 1986; 2(1): 54-69.)

[xi] Johnson found that subjects could maintain their results up to 9 years after the procedure. (Johnson, LL. "Arthroscopic Abrasion Arthroplasty: A Review." *Clinical Orthopaedics*. 2001 Oct; 391S: S306-S317.)

[xii] A retrospective comparison of drilling (n=11) to perichondrial grafting (n=14) showed a 100% success rate in the drilling group and a 78% success rate in the grafting group after 10 years. (Bouwmeester, PS., et al. "A Retrospective Analysis of Two Independent Prospective Cartilage Repair Studies: Autogenous Perichondrial

Grafting Versus Subchondral Drilling 10 Years Post-surgery." *Journal of Orthopaedic Research*. 2002 Mar; 20(2): 267-273.)

[xiii] Patients followed for at least 7 years showed that pain was the criteria with the most improvement. At 3 and 5 years, 75% of patient improved, 20% of patients remained unchanged, and 5% became worse. Improvement in conducting activities of daily living and strenuous work occurred in 67% of patients. Researchers also compared subjects with isolated lesions to subjects with associated injuries such as ACL repair. Combined injury subjects had higher knee function scores for the first 5 years. The scores for the two groups became similar from 6 years on. (Steadman, JR., et al. "Microfracture Technique for Full Thickness Chondral Defects: Technique and Clinical Results." *Operative Techniques in Orthopaedics*. 1997 Oct; 7(4): 300-304.)

[xiv] Researchers compared 46 microfracture patients who received continuous passive motion (CPM) for 7.8 weeks to 31 microfracture patients who did not receive CPM. No improvement occurred in 15% of the CPM group versus 45% of the non-CPM group. However, the two groups differed significantly in lesion size and age. (Rodrigo, J., et al. "Improvement of Full-Thickness Chondral Defect Healing in the Human Knee after Debridement and Microfracture Using Continuous Passive Motion." *The American Journal of Knee Surgery*. 1994; 7(3): 109-116.)

[xv] Mosaicplasty allowed 63% of competitive athletes to return to full-level sporting. (Kish, G., et al. "Osteochondral Mosaicplasty for the Treatment of Focal Chondral and Osteochondral Lesions of the Knee and Talus in the Athlete." *Clinical Sports Medicine*. 1999; 18: 45. Cited in: Cain, EL., "Treatment Algorithm for Osteochondral Injuries of the Knee." *Clinics in Sports Medicine*. 2001 Apr; 20(2): 321-342.)

[xvi] One study of cadaveric allografting of the medial compartment showed that after an average follow-up of 48 months, 13 of 16 grafts had Good or Excellent results. For lateral compartment subjects with 57-month follow-up, 7 of 11 rated Good or Excellent. (Convery, F., et al. "Chondral Defects of the Knee." *Contemporary Orthopaedics*. 1994 Feb; 28(2): 100-107.)

[xvii] One clinical study of fresh allograft found success in 85% of 126 knees after an average of 7.5 years. (Ghazavi, MT., et al. "Fresh Osteochondral Allografts for Post-traumatic Osteochondral Defects of the Knee." *Journal of Bone and Joint Surgery*. 1997; 79-b(6): 1008-10013. Cited in: O'Driscoll, SW. "The Healing and Regeneration of Articular Cartilage." *The Journal of Bone and Joint Surgery*. 1998 Dec; 80-A(12): 1795-1812.)

[xviii] The review reported that 5-year data for autograft of small lesions show results that are as good if not better than marrow stimulation. (Hangody, L. et al. "Arthroscopic Autogenous Osteochondral Mosaicplasty for the Treatment of Femoral Condylar Articular Defects: A Preliminary Report." *Knee Surgery, Sports Traumatology, Arthroscopy.* 1997; 5(4): 262-267.)