In 1965, Dr Marshall R. Urist first identified a substance that was capable of inducing new bone formation in a non-bony, or soft-tissue, environment. He observed bone formation in a rat muscle pouch following the implantation of demineralized bone matrix. Urist proposed the concept that a “bone-induction principle” was present within the demineralized bone matrix. Proteins were later identified as bone promoting agents and were termed bone morphogenetic proteins (BMPs). Urist’s long-term vision was to have BMPs available for use in the operating room by orthopedic surgeons.

Bone morphogenetic proteins are capable of inducing the entire bone formation cascade. It is this unique property that allows these proteins along with a suitable carrier to be used as a bone graft replacement. Allograft demineralized bone matrix, if it is properly demineralized and sterilized, contains small amounts of natural BMPs. In fact, the amount of BMP present in demineralized bone matrix materials is more than one million times less than that provided in an equivalent volume of recombinant BMP-2 technologies such as INFUSE Bone Graft (Medtronic Sofamor Danek, Memphis, Tenn), the first commercially available BMP in the United States. It is the relatively high concentration of BMP that is required for autograft replacement applications.

The clinical effectiveness of recombinant, or genetically engineered, human bone morphogenetic protein (rhBMP-2) from three similar human studies was investigated. The efficacy of INFUSE Bone Graft, which is a combination of rhBMP-2 and a bovine collagen carrier, was compared with iliac crest autograft when used inside the LT-CAGE Lumbar Tapered Fusion Device.
(Medtronic Sofamor Danek), a threaded metallic fusion cage that is inserted into the disk space in single-level anterior lumbar spinal procedures. The cage restores the disk space, providing short-term stability while rhBMP-2 or the bone chips fuse the vertebrae to provide for long-term stability. Details regarding spinal fusion procedures and the use of cages have been reported elsewhere.9–11 Results were integrated from three similar large-scale clinical trials using either autograft or rhBMP-2 for the same indication and measured in the same way to check for statistical superiority. These data came from published and unpublished studies.9–11 Additional details about the studies, surgical approaches used, and methods of statistical analysis have been reported elsewhere.12 Wyeth BioPharma (Andover, Mass) genetically engineered the rhBMP-2 component. The absorbable collagen sponge component is manufactured by Integra LifeSciences (Plainboro, NJ). Together, the components are distributed commercially under the trade name INFUSE Bone Graft.

**MATERIALS AND METHODS**

**Patient Population**

Data sets from a published randomized trial10 were combined with those from two additional sequential clinical trials11 to increase the sample size and statistical power for analysis. All studies used the same major inclusion-exclusion criteria and procedures.12 All patients were considered candidates for a single-level, stand-alone anterior lumbar interbody fusion.

Because no single surgeon performed >10% of the procedures, the outcomes represent typical results from a wide variety of surgeons with different degrees of experience. Approximately all patients had two LT-CAGE devices implanted anteriorly at one lumbar level, and all were included in prospective, multicenter studies using the same outcome measurement tools and methodology of analysis. The investigational group comprised 277 patients who received INFUSE Bone Graft and the control group comprised 402 patients who were treated with autogenous iliac crest bone grafts.

**Surgery**

All patients underwent an anterior lumbar diskectomy and interbody fusion. An open mini-laparotomy approach or a laparoscopic approach to the lumbosacral spine was undertaken. In each procedure, a diskectomy was performed. The nucleus pulposus and cartilaginous endplates were removed; however, the bony endplates were preserved prior to reaming and tapping of the endplate for receipt of the interbody construct. Two LT-Cage devices were inserted into each disk space.

The rhBMP-2 was reconstituted using sterile water and applied to the absorbable collagen sponge. The BMP-soaked sponge was placed into the central portion of the LT-CAGE implant prior to its insertion into the prepared disk space. The cages were filled with an appropriate volume of graft and no additional rhBMP-2 prepared sponges were placed outside of the cages. No autogenous grafts were used in the investigational group. The control group received morsellized autogenous iliac crest graft in the cages.

**Intraoperative blood loss,**

<table>
<thead>
<tr>
<th>Variable</th>
<th>INFUSE</th>
<th>Autograft</th>
<th>P Value</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (y)</td>
<td>42.9</td>
<td>40.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average weight (lbs)</td>
<td>174.6</td>
<td>178.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>135/142</td>
<td>210/192</td>
<td></td>
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</tr>
<tr>
<td>Workers’ compensation (%)</td>
<td>32.1</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal litigation (%)</td>
<td>10.5</td>
<td>12.8</td>
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</tr>
<tr>
<td>Tobacco use (%)</td>
<td>31.4</td>
<td>32.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous surgeries (%)</td>
<td>31.4</td>
<td>41</td>
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</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>INFUSE</th>
<th>Autograft</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (hr)</td>
<td>1.8</td>
<td>2.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>127.4</td>
<td>192.9</td>
<td>&lt;.024</td>
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<tr>
<td>Hospital stay (days)</td>
<td>2.2</td>
<td>3.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Bone morphogenetic proteins are capable of inducing the entire bone formation cascade.**
Operative time, hospital stay, and perioperative complications were assessed.

Clinical Outcome Measurements
Clinical outcomes were measured at postoperative intervals of 3, 6, 12, and 24 months using two well-established instruments: the Oswestry Low Back Pain Disability Questionnaire and the Short Form SF-36 Questionnaire. In addition, patients completed return-to-work questionnaires.

Radiographic Outcome Measurements
Anteroposterior, lateral, and flexion-extension lateral radiographs, and 1-mm slice computed tomography (CT) were used to assess fusion. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, <5° of angular motion, ≤3 mm of translation, and an absence of radiolucent lines around >50% of either implant surface. Thin-slice (1-mm) CT with sagittal and coronal reconstructions were evaluated at 6, 12, and 24 months. On CT, fusion was defined by continuous trabecular bone formation between the vertebral bodies. Two independent, blinded radiologists interpreted all radiographs with differences arbitrated by a third.

RESULTS
Surgery
Operative time, blood loss, and length of hospital stay for the INFUSE and autograft groups are shown in Table 2. Because a second surgical site was not necessary for bone graft harvesting to complete anterior lumbar interbody fusion, operative time and blood loss were less in the INFUSE group. The surgical time in the INFUSE group averaged 54 minutes less than in the autograft group ($P=.001$). Blood loss in the INFUSE group also averaged 66 mL less than in the autograft group ($P=.024$).

Avoiding the bone graft harvesting reduced with statistical superiority surgical time and blood loss. During anterior lumbar interbody fusion, bone graft harvesting necessitates making a second surgical incision. This secondary surgical procedure has its own specific complications and lengthens the overall surgical time and blood loss. Complications associated specifically with graft harvesting include infection, hematoma, sensory nerve injury (lateral femoral cutaneous nerve), and fracture of the ilium. These two factors, blood loss and surgical time, also impacted the length of hospital stay. The INFUSE group had, on average, a reduction of the length of their hospitalization of approximately 1 day compared with the autograft group ($P=.001$). Overall, this analysis reveals...
superior benefits of the combined INFUSE group compared with the autograft group for all three variables.

**Oswestry Disability Index**

The Oswestry Disability Index identifies functional improvements in patients with low back pain. Preoperatively, the autograft group had lower average Oswestry Disability scores (ie, less disability) than the INFUSE-treated group. In the adjusted P values were statistically significant at all postoperative intervals.

**SF-36 Health Survey**

The physical component scores on the SF-36 Health Survey measure a patient’s physical well being after surgery. Preoperatively, the autograft group had higher physical component scores than the INFUSE group. As with the Oswestry Disability Index low back pain scores, the results of the SF-36 were statistically superior in the INFUSE group compared with those in the autograft group at 3, 6, 12, and 24 months postoperatively (Figure 2).

**Additional Surgery**

Additional surgical events in both study groups were assessed. Simple Fisher exact tests show that statistically fewer reoperations occurred in the INFUSE group than in patients who were implanted with autograft (P=.0036). At 2 years, the revision rate in INFUSE patients approached statistical superiority (P=.0631).

**Return to Work**

Perhaps the most important milestone in assessing patient improvement after low back surgery is the ability to return to work. The return-to-work status of both patient groups was assessed. A higher percentage (75%) of the INFUSE patients who were working before surgery returned to work after surgery compared with 65% of patients in the autograft group. Again, 35% of the INFUSE patients who were not working before surgery returned to work after surgery compared with 31% of the autograft patients. These differences in return-to-work status showed a trend toward greater return to work in the INFUSE treated group of patients; however, by themselves, the numbers of patients who returned to work were not statistically significant.

The statistically significant difference between the two groups was the length of time it took for the patients to return to work (Figure 3). The median number of days to return to work was 54.5 days less for the patients implanted with INFUSE Bone Graft. This difference was statistically significant in favor of the INFUSE patients (adjusted P value=.0156). The decrease in the INFUSE patients’ low back pain must be at least part of the explanation for their returning to work approximately 2 months earlier than the autograft patients.

Patients were able to return to work more rapidly when...
treated with INFUSE Bone Graft because they did not have to recover from two surgical procedures. The pain, disability, and recovery time from the bone-graft harvest procedure was eliminated in these patients. Radiographic studies have also shown that fusion occurs more rapidly in patients treated with INFUSE Bone Graft.  

**Discussion**  
Spine fusion is a complex process. Unlike fracture repair, a spine fusion, even under the best of circumstances, does not heal successfully in all patients. Spine fusion represents, in part, a race between resorption of the graft material and the formation of new bone growing through the graft and connecting the two adjacent vertebral bodies. 

The gold standard, or benchmark, for all graft materials used today is fresh, autogenous iliac crest cancellous bone graft. Because the amount of autogenous iliac crest cancellous bone is limited, an adequate supply of autograft for multilevel fusions, for example, is not always possible. Further, patients who have had previous fusions necessitating graft harvests may not have enough graft available to support a spinal fusion. With all graft harvesting procedures, substantial donor site morbidity is always possible. Reports of pain at the iliac crest graft site persist in as many as one-third of patients with some patients having iliac crest pain for the rest of their lives. In addition to these graft site issues, the healing of spinal fusion with autogenous bone graft is not perfect. For these reasons, the need is great for an unlimited, safe supply of an effective bone graft substitute material. The use of INFUSE Bone Graft resulted in statistically significant differences between the two study groups in many of the surgical, clinical, and radiographic endpoints measured. More specifically, statistically significant differences in the INFUSE group were noted in shorter operating room times, less blood loss, and reduced hospital stays. It is likely that the elimination of second-site surgery contributed to the improvements seen in these surgical endpoints. 

The use of INFUSE also resulted in statistically significant improvement in Oswestry Disability scores, physical SF-36 survey scores, and an earlier return to work. None of the patients in the INFUSE group suffered from the complications of second-site surgery required for bone graft harvesting. Also, fewer reoperations occurred in the INFUSE group. 

The use of INFUSE with the LT-CAGE device also resulted in a statistically significant improvement in the rate of interbody fusion. INFUSE Bone Graft reliably and predictively induced bone in the disk space after insertion of the LT-CAGE devices. Fusion rates in patients treated with INFUSE Bone Graft were statistically higher than those in patients treated with autogenous iliac crest bone grafts. 

The additional costs of this bone graft replacement are offset by reductions in the use of other medical resources. The initial cost of using INFUSE Bone Graft is partially recovered by the reduction in anesthesia costs, operating room time, length of hospitalization, and avoidance of other bone graft extenders or stimulators. Once the patient leaves the hospital, additional costs are reduced by avoiding the potential complications of bone graft harvesting, reduced reoperation for symptomatic nonunions, and pain medication requirements. Earlier return to work lessens the burden on workers’ compensation insurance outlays. 

Having statistically superior fusion rates and statistically lower pain scores in the same patient supports the fundamental tenant of spinal fusion surgery: motion causes pain, fusion stops motion, and, therefore, fusion stops pain.
These results with rhBMP-2 represent a dramatic improvement in the health care of our patients, as Dr Urist’s 1965 vision becomes a reality.

REFERENCES