



Intervertebral Disc Prostheses

Number: 0591

POLICY

**Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Cervical Disc Arthroplasty

Aetna considers Food and Drug Administration (FDA)-approved prosthetic intervertebral discs medically necessary for the treatment of skeletally mature persons with symptomatic cervical degenerative disc disease or herniated disc at 1 level (Bryan Cervical Disc, M6-C Artificial Cervical Disc, MOBI-C, the Prestige Cervical Disc, Prestige LP Cervical Disc, PCM (Porous Coated Motion), ProDisc-C Total Disc Replacement, Secure-C Artificial Cervical Disc) or 2 contiguous levels (MOBI-C, Prestige LP Cervical Disc, and Simplify Cervical Artificial Disc) from C3 to C7, when *all* of the following criteria are met:

- I.* All other reasonable sources of pain have been ruled out; *and*
- II.* Presence of neck or cervico-brachial pain with findings of weakness, myelopathy, or sensory deficit; *and*
- III.* Imaging studies (e.g., CT or MRI) indicate:
 - A. nerve root or spinal cord compression at the level corresponding with the clinical findings; or

POLICY HISTORY

Last Review: 08/10/2021

Effective: 03/08/2002

Next Review: 06/09/2022

Review History

Definitions

Additional Information

Clinical Policy Bulletin
Notes

- B. central/lateral recess or foraminal stenosis graded as moderate, moderate to severe or severe (not mild or mild to moderate); *and*
- IV. Member has failed at least 6 weeks of conservative therapy (see note below) (unless there is evidence of cervical cord compression, which requires urgent intervention); *and*
- V. Member has physical and neurological abnormalities confirming the historical findings of nerve root or spinal cord compression (e.g., reflex change, sensory loss, weakness) at or below the level of the lesion and may have gait or sphincter disturbance (evidence of cervical radiculopathy or myelopathy) (This requirement may be waived where the radicular pattern of the symptoms corresponds to the dermatomal distribution of the level of surgery and other criteria (other sources of pain have been ruled out, failure of conservative therapy) are thoroughly documented); *and*
- VI. Member's activities of daily living are limited by persistent neck or cervico-brachial pain.

Aetna considers subsequent placement of a second artificial cervical disc medically necessary at a level contiguous to a previous placed artificial disc when criteria for artificial discs are met.

Aetna considers artificial cervical discs experimental and investigational for persons with prior disc replacement if the new request would result in more than 2 contiguous disc replacement levels from C3 to C7.

Aetna considers concurrent or planned sequential artificial cervical disc replacement with prior or planned cervical spinal fusion at adjacent levels medically necessary for the management of cervical spinal pathology when criteria for artificial discs and/or fusion surgery are met.

Note: Conservative measures must be recent (within the past year) and include the following non-surgical measures and medications unless neurologic signs are severe or rapidly progressive: patient education;

active physical therapy; medications (NSAIDS, acetaminophen, or tricyclic antidepressants), and (where appropriate) identification and management of associated anxiety and depression.

Lumbar Disc Arthroplasty

Aetna considers lumbar prosthetic intervertebral discs (e.g., the activL Artificial Disc, the Charite Artificial Disc, and the ProDisc-L Total Disc Replacement) experimental and investigational for lumbosacral degenerative disc disease and for all other indications.

Aetna considers lumbar partial disc prosthetics (e.g., Nubac, DASCOR Disc Arthroplasty System) experimental and investigational because of insufficient evidence of their effectiveness.

See also

[CPB 0016 - Back Pain - Invasive Procedures \(../1_99/0016.html\)](#) and
[CPB 0743 - Spinal Surgery: Laminectomy and Fusion \(../700_799/0743.html\)](#)

BACKGROUND

Artificial intervertebral disc replacement is an alternative to cervical and lumbar spinal fusion surgery for those individuals suffering from back or neck pain due to degenerative disc disease (DDD). The artificial disc was designed to restore normal disc height, to preserve the spinal flexibility and decrease degeneration of adjacent discs, which can occur as a result of DDD.

Examples of US Food and Drug Administration (FDA) approved for the cervical spine include, but may not be limited to: BRYAN cervical disc, MOBI-C cervical disc, PCM cervical disc, Prestige cervical disc, ProDisc-C total disc replacement and SECURE-C artificial cervical disc. Those FDA approved for the lumbar spine include, but may not be limited to, activL artificial disc, INMOTION lumbar disc system and ProDisc-L total disc replacement.

Since the 1970s, investigators have been working on developing an artificial prosthetic intervertebral disc (IVD) that can be used to replace degenerated intervertebral discs (Diwan et al, 1997). Most of the published clinical evidence for artificial prosthetic intervertebral discs has been of those that replace the entire disc.

The major potential advantage of a prosthetic intervertebral disc over current therapies for degenerated disks (such as spinal fusion or discectomy) is that the prosthetic intervertebral disk is intended to restore or preserve the natural biomechanics of the intervertebral segment and to reduce further degeneration of adjacent levels.

The Charite Artificial Disc

van Ooij et al (2003) reported a series of 27 patients who presented with unsatisfactory results or complications after Charite disc replacement. Most patients were operated on at the L4 - L5 and/or the L5 - S1 vertebral levels. The patients were evaluated with plain radiography, some with flexion-extension x-rays, and most of them with computed tomography scans. The group consisted of 15 women and 12 men. Their mean age was 40 years (range, 30 - 67 years) at the time of operation. The patients presented to the investigators a mean of 53 months (range 11 - 127 months) following disc replacement surgery. In two patients, an early removal of a prosthesis was required and in two patients a late removal. In 11 patients, a second spinal reconstructive salvage procedure was performed. Mean follow-up for 26 patients with mid- and long-term evaluation was 91 months (range 15 - 157 months). Early complications were the following: In one patient, an anterior luxation of the prosthesis after 1 week necessitated removal and cage insertion, which failed to unite. In another patient with prostheses at L4 - L5 and L5 - S1, the prosthesis at L5 - S1 dislocated anteriorly after 3 months and was removed after 12 months. Abdominal wall hematoma occurred in four cases. Retrograde ejaculation with loss of libido was seen in one case and erection weakness in another case. A temporary benefit was experienced by 12 patients, while 14 patients reported no benefit at all. Main causes of persistent complaints were degeneration at another level in 14, subsidence of the prosthesis in 16, and facet joint arthrosis in 11. A combination of pathologies was often present. Slow anterior migration was present in two cases, with compression on the iliac vessels in one

case. Polyethylene wear was obvious in one patient 12 years after operation. In eight cases, posterior fusion with pedicle screws was required. In two cases, the prosthesis was removed and the segment was circumferentially fused. These procedures resulted in suboptimal long-term results. In this relatively small group of patients operated on with a Charite disc prosthesis, most problems arose from degeneration of other lumbar discs, facet joint arthrosis at the same or other levels, and subsidence of the prosthesis.

Caspi et al (2003) reported results of lumbar disk prosthesis (Charite) after a follow-up period of 48 months. These investigators found that 80% of patients reported satisfactory to very good results. Poor results were reported by four patients, one of whom underwent postero-lateral fusion and another is waiting for the same operation. There were two dislocations of the prosthesis followed by immediate revision surgery. The authors concluded that contraindications for surgery appear to be the principal cause of failure rather than the prosthesis itself.

In a multi-center, prospective, randomized investigational device exemption study of the Charite intervertebral disc, Geisler et al (2004) compared the Charite artificial disc with lumbar fusion using the BAK cages in patients with lumbar degenerative disc disease (n = 304). The authors found that the neurological status was equivalent between the two groups at 6, 12, and 24 months, post-operatively. They concluded that the Charite intervertebral disc is safe and effective for the treatment of single-level degenerative disc disease, resulting in no higher incidence of neurological complications compared with BAK-assisted fusion, and leading to equivalent or better outcomes (as indicated by visual analog scale and Oswestry Disability Index scores) compared with fusion with those obtained in the control group and those reported in the lumbar fusion literature. The authors concluded that the findings of this study is promising, but that longer follow-up is needed to determine the durability of the Charite artificial disc and its long-term safety and effectiveness.

The United States Food and Drug Administration (FDA) has approved the Charite Artificial Disc for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. The indications for the Charite define DDD as discogenic back pain with degeneration of the disc that is confirmed by patient history and

radiographic studies. According to the FDA-approved labeling, these DDD patients should have no more than 3 mm of spondylolisthesis at the involved level. The FDA approved labeling states that patients receiving the Charite Artificial Disc should have failed at least six months of conservative treatment prior to implantation of the Charite Artificial Disc.

The Charite Artificial Disc was approved by the FDA based on a clinical trial comparing the device to anterior lumbar interbody fusion (ALIF) with BAK cages filled with iliac crest autograft in subjects with symptomatic single level degenerative disc disease from L4 to S1 who had failed at least 6 months of conservative management. The purpose of the study was to demonstrate the non-inferiority of the Charite Artificial Disc to an interbody fusion system. A total of 304 patients were enrolled in the study using a 2:1 (Charite to BAK) randomization scheme. One-hundred eighty four subjects receiving the Charite Artificial Disc and 81 subjects receiving interbody fusion (controls) completed 24 months follow up. Safety of the Charite Artificial Disc was assessed by monitoring the intraoperative and postoperative complications, including infection, thrombosis, disc migration, and disc subsidence, as well as reoperation and other adverse events. Efficacy of the Charite Artificial Disc was assessed primarily by a success criteria comprised of: level of disability (Oswestry Low Back Disability Index (ODI)), neurological assessment (functional status) and information from adverse event data. To be considered an overall success, a subject must have had: 1) an improvement of at least 25% in the ODI score at 24 months compared to baseline; 2) no device failures requiring revision, reoperation, or removal; 3) absence of major complications, defined as major blood vessel injury, neurological damage, or nerve root injury; and 4) maintenance or improvement in neurological status at 24 months, with no new permanent neurological deficits compared to baseline. Based on these criteria, the overall success rate was 64% for subjects receiving the Charite Artificial Disc and 57% for control subjects receiving interbody fusion. The FDA requested that the data be analyzed and reported using an improvement in the Oswestry Disability Index of greater than 15 points at 24 months compared to the score at baseline. Based on these alternate criteria, the overall success rate for subjects receiving the Charite Artificial Disc was 58%, and the success rate for control subjects was 54%.

The study sponsor considered the study a success if the overall success rates of the two treatment groups were non-inferior, i.e., the difference in overall success rates (i.e., non-inferiority margin) is no greater than 15 %. However, the FDA requested that the data also be analyzed and reported using a non-inferiority margin of 10 %.

The study demonstrated non-inferiority of the Charite Artificial Disc (within the 90 % 1-sided confidence interval) to interbody fusion for secondary endpoints, including pain (using a visual analog scale (VAS)), quality of life (Shoft Form-36 Questionnaire), disc height, and device migration.

At 24 months follow-up, subjects receiving the Charite Artificial Disc had 7.5 degrees vertebral range of motion (ROM) at the operative level, compared to 1.1 degrees vertebral ROM for subjects receiving interbody fusion. The FDA analyzed ROM data versus Overall Success Outcome for all Charite artificial disc subjects with available ROM data at 24 months. No statistically significant association was found between ROM and success/failure at 24 months.

Because the long-term safety and effectiveness of the Charite Artificial Disc are unknown, the FDA has required the manufacturer to conduct a post-approval study using a maximum of 366 subjects (201 randomized investigational subjects; 67 training investigational subjects; and 98 control subjects). The manufacturer will be required evaluate subjects on Overall Success and secondary endpoints, and submit annual reports for a total of 5 years post-implantation.

According to the FDA-approved labeling, the Charite Artificial Disc should not be implanted in patients with the following conditions: osteoporosis; osteopenia; pars defect; bony lumbar stenosis; active systemic infection or infection localized to the site of implantation; allergy or sensitivity to implant materials; and isolated radicular compression syndromes, especially due to disc herniation.

The FDA-approved labeling of the Charite Artificial Disc states that the safety and effectiveness of the device have not been established in patients with the following conditions: pregnancy; morbid obesity; two or more degenerative discs; spondylolisthesis greater than 3 mm; or two or more unstable segments.

Data on the long-term outcomes of the Charite Artificial Disc comes from France, where the artificial disc has been in use for more than a decade. David (2000) reported in abstract form on a retrospective review of the outcome of 92 patients with chronic low back pain who were implanted with the artificial disc. The investigators reported “excellent or good” results in 75% of patients after a minimum of 5 years follow up, with no disc space height loss and no loosening or expulsion of the core. Lemaire, et al., described their 5-year and 10-year results with the Charite Artificial Disc. In the paper reporting on 10-year results, Lemaire, et al. (2002) reported an excellent or good outcome in 90% of 100 patients with a return to work rate of 91.6%. In addition, the investigators reported no subluxations or core expulsions, a reoperation rate of 5% and a 2% rate of adjacent-level disc disease. The mean flexion/extension range of motion was 10.3 degrees, with a mean lateral bending motion of 5.4 degrees.

The National Institute for Clinical Excellence (2004) has concluded: “Current evidence on the safety and efficacy of prosthetic intervertebral disc replacement appears adequate to support the use of this procedure. However, there is little evidence on outcomes beyond 2-3 years and collection of long-term data is therefore particularly important”.

An assessment by the Ohio Bureau of Workers' Compensation (2005) concluded that the Charite artificial disc can be considered as an alternative to tradition lumbar fusion procedures.

The Ontario Health Technology Advisory Committee of the Ontario Ministry of Health and Long-Term Care (2006) recommended the adoption of lumbar artificial disc replacement according to well defined patient eligibility criteria. The Ontario Health Technology Advisory Committee recommended development of a patient registry to track long-term complications of lumbar artificial disc replacement. Because of the uncertainty in the estimates of benefits, risks and burdens associated with cervical artificial disc replacement, the Ontario Health Technology Advisory Committee did not recommend the use of cervical artificial disc replacement to treat degenerative disc disease of the cervical spine over the use of other alternatives such as spinal fusion.

The ProDisc-L Total Disc Replacement

Tropiano et al (2005) presented the clinical and radiographic results assessed 7 to 11 years following a Prodisc total lumbar disc replacement (n = 64 patients who had single or multiple-level implantation of a total lumbar disc replacement). The mean duration of follow-up was 8.7 years. Clinical results were evaluated by assessing pre-operative and post-operative lumbar pain, radiculopathy, disability, and modified Stauffer-Coventry scores. Pre-operative and post-operative radiographs were evaluated as well. These investigators concluded that the Prodisc lumbar total disc replacement appears to be effective and safe for the treatment of symptomatic degenerative disc disease. Gender and multi-level surgery did not affect the outcomes, whereas prior lumbar surgery or an age of less than 45 years was associated with slightly worse outcomes. The authors further stated that longer follow-up of this cohort of patients and randomized trials comparing disc replacement with arthrodesis are needed.

Leivseth et al (2006) presented their findings of a longitudinal prospective study on the use of the ProDisc II prosthesis in 41 consecutive disc prosthesis patients, covering a post-operative time period of at least 2 years. They stated that disc replacement in the lumbar spine by a ProDisc II implant failed to restore normal segmental rotational motion in the sagittal plane, specifically at levels L4 - L5 and L5 - S1. As segmental motion of the untreated segments was lower than normal as well, though not quite as conspicuous as that of instrumented segments, adaptation of soft tissue taken place during the pre-operative symptomatic time period is conjectured to cause the observed motion deficit.

On the other hand, findings from other studies indicated that the ProDisc is safe and effective in treating patients with low back pain (LBP).

In a prospective, longitudinal minimum 2-year follow-up study (n = 118), Bertagnoli et al (2005) evaluated the safety and effectiveness of the ProDisc implant in patients with disabling single-level discogenic LBP. Patients 18 to 60 years of age with disabling and recalcitrant discogenic LBP with or without radicular pain secondary to single-level discogenic LBP from L3 to S1 were included. Patients were assessed before surgery, and outcome measurements were assessed after surgery at 3, 6, 12, and 24 months. A total of 104 patients (88%) fulfilled all follow-up criteria. The median age of all patients was 47 years (range of 36 to 60 years).

Statistical improvements in VAS, Oswestry, and patient satisfaction scores occurred 3 months post-operatively. These improvements were maintained at the 24-month follow-up. Radicular pain also decreased significantly. Full-time and part-time work rates increased from 10 to 35% and 3 to 24%, respectively. No additional fusion surgeries were needed either at the affected or unaffected levels. Radiographical analysis revealed an affected disc height increase from 4 to 13 mm ($p < 0.001$) and an affected disc motion from 3 to 7 degrees ($p < 0.004$). The authors concluded that single-level ProDisc lumbar total disc arthroplasty is a safe and effective treatment for debilitating lumbar discogenic LBP. Significant improvements in patient satisfaction as well as disability scores occurred after surgery by 3 months and were maintained at the 2-year follow-up. No device-related complications occurred. Patients with severe to moderate disc height loss as well as those with symptomatic posterior annular defects with minimal disc height loss achieve functional gains and significant pain relief. Careful and appropriate patient selection is essential in ensuring optimal surgical outcomes.

Siepe et al (2006) presented their 3-year results with total lumbar disc replacement (TLDR) by means of the ProDisc II with a minimum follow-up of 24 months. They concluded that available data suggest beneficial clinical results of TLDR for the treatment of DDD in a highly selected group of patients. Better functional outcome was obtained in younger patients under 40 years of age and patients with DDD in association with disc herniation. Multi-level disc replacement had significantly higher complication rate and inferior outcome at mid-term follow-up compared with mono-segmental interventions. Thus, only longer follow-up evaluations will demonstrate the real benefit for patients. Results are significantly dependent on pre-operative diagnosis and patient selection, number of replaced segments, and age of patient at the time of operation. The authors stated that because of significantly varying outcomes, indications for disc replacement must be defined precisely.

Schroven and Dorofey (2006) conducted a prospective, non-randomised study on the ProDisc IVD ($n = 14$) versus anterior lumbar interbody fusion (ALIF, $n = 10$). In the ProDisc group, the Oswestry Disability Index improved from +/- 38.42 pre-operatively (60 being the worst possible condition) to +/- 15.21 after 6 months, and to +/- 12.5 after 12 months. This was markedly better than the ALIF group, where the corresponding

figures were +/- 38, +/- 25 and +/- 21.4. The ProDisc patients also scored better with respect to duration of hospitalization, blood loss and operation time. The complications were comparable in both groups.

Tropiano and colleagues (2006) presented the clinical and radiographical results assessed 7 to 11 years following a ProDisc TLDR. A total of 64 patients had single- or multiple-level implantation of a TLDR between 1990 and 1993. The mean duration of follow-up was 8.7 years. Clinical results were evaluated by assessing pre-operative and post-operative lumbar pain, radiculopathy, disability, and modified Stauffer-Coventry scores. Pre-operative and post-operative radiographs were evaluated as well. Subgroup analysis was performed to determine if gender, an age of less than 45 years, previous surgery, or multi-level surgery had an effect on outcome. At an average of 8.7 years post-operatively, there were significant improvements in the back pain, radiculopathy, disability, and modified Stauffer-Coventry scores. Thirty-three of the 55 patients with sufficient follow-up had an excellent result, 8 had a good result, and 14 had a poor result. Neither gender nor multi-level surgery affected outcome. An age of less than 45 years and prior lumbar surgery had small but significant negative effects on outcome. Radiographs did not demonstrate loosening, migration, or mechanical failure in any patient. Five patients had approach-related complications. These investigators concluded that the ProDisc TLDR appears to be effective and safe for the treatment of symptomatic DDD. Gender and multi-level surgery did not affect the outcomes, whereas prior lumbar surgery or an age of less than 45 years was associated with slightly worse outcomes. The authors noted that longer follow-up of this cohort of patients and randomized studies comparing disc replacement with arthrodesis are needed.

Bertagnoli and colleagues (2006a) conducted a prospective, longitudinal study (n = 20) to evaluate the effectiveness of ProDisc arthroplasty in patients in whom symptomatic adjacent-segment degeneration has developed after remote lumbar fusion. The follow-up period was a minimum of 2 years. Subjects in this study ranged in age from 18 to 67 years. They presented with disabling adjacent-level discogenic LBP with or without L1 - S1 radicular pain. Individuals with radiographic evidence of circumferential spinal stenosis or facet joint degeneration were excluded. Patients were assessed pre-operatively and post-operatively at 3, 6, 12, and 24 months. Eighteen patients (90%) fulfilled all follow-up criteria. The

median age of all patients was 50 years. Statistical improvements in VAS, Oswestry Disability Index, and patient satisfaction scores were documented 3 months after arthroplasty. These improvements remained at the 24-month follow-up examinations. Patient satisfaction rates were 86% at 24 months. Radicular pain was also significantly decreased. No additional surgeries were needed at affected or unaffected levels. The authors concluded that analysis of early results indicates that ProDisc lumbar total disc arthroplasty is an effective treatment for symptomatic adjacent-segment lumbar discogenic LBP following remote fusion. Significant improvements in patient satisfaction and disability scores were observed by 3 months post-operatively and were maintained at the 2-year follow-up examination. No device-related complications occurred. Patients should be screened carefully for evidence of facet joint impingement/degeneration, hardware-induced pain, and/or non-union at prior fusion levels before undergoing disc replacement surgery.

The same group of investigators (Bertagnoli et al, 2006b) also carried out a prospective, longitudinal study to obtain outcome (minimum follow-up period 2 years) regarding the safety and effectiveness of single-level lumbar disc replacement in patients 60 years of age or older. This analysis involved 22 patients in whom the ProDisc was used for total disc arthroplasty. All patients presented with disabling discogenic LBP with or without radicular pain. The involved segments ranged from L2 to S1. Patients in whom there was no evidence of radiographic circumferential spinal stenosis and with minimal or no facet joint degeneration were included. Patients were assessed pre-operatively and outcome was evaluated post-operatively at 3, 6, 12, and 24 months by administration of standardized tests (VAS, ODI, and patient satisfaction). Secondary parameters included analysis of pre- and post-operative radiographic results of disc height at the affected level, adjacent-level disc height and motion, and complications. Twenty-two subjects (100%) fulfilled all follow-up criteria. The median age of all patients was 63 years (range of 61 to 71 years). There were 17 single-level cases, 4 two-level cases, and 1 three-level case. Statistical improvements in VAS, ODI, and patient satisfaction scores were observed at 3 months post-operatively. These improvements were maintained at 24-month follow-up examination. Patient satisfaction rates were 94% at 24 months (compared with 95% reported in a previously reported ProDisc study). Radicular pain also decreased significantly. Patients in whom bone mineral density was decreased

underwent same-session vertebroplasty following implantation of the ProDisc device(s). There were 2 cases involving neurological deterioration: unilateral foot drop and loss of proprioception and vibration in 1 patient and unilateral foot drop in another patient. Both deficits occurred in patients in whom there was evidence pre-operatively of circumferential spinal stenosis. There were 2 cases of implant subsidence and no thrombo-embolic phenomena. These researchers concluded that significant improvements in patient satisfaction and ODI scores were observed by 3 months post-operatively and these improvements were maintained at the 2-year follow-up examination. Although the authors' early results indicate that the use of ProDisc lumbar total disc arthroplasty in patients older than 60 years of age reduces chronic LBP and improves clinical functional outcomes, they recommend the judicious use of artificial disc replacement in this age group. Until further findings are reported, the authors cautiously recommend the use of artificial disc replacement in the treatment of chronic discogenic LBP in patients older than age 60 years in whom bone quality is adequate in the absence of circumferential spinal stenosis.

Bertagnoli and associates (2006c) reported that lumbar total disc arthroplasty utilizing the ProDisc prosthesis is equally effective in smokers and non-smokers. These investigators performed a prospective analysis on 104 patients with disabling discogenic LBP treated with single-level lumbar ProDisc total disc arthroplasty. Smokers and non-smokers were evaluated before surgery and after surgery using patient satisfaction, Oswestry, and VAS. Additionally, pre-operative and post-operative neurological, radiographical, and pain medication assessments were performed at similar post-operative intervals. Oswestry, VAS, and patient satisfaction scores revealed statistical improvement beginning 3 months after surgery and were maintained at minimum 2-year follow-up. Patient satisfaction scores were higher in smokers (94%) than in non-smokers (87%) at 2-year follow-up ($p = 0.07$). Radiographical analysis revealed an affected disc height increase from 4 to 13 mm ($p < 0.05$) and an affected disc motion from 3 to 7 degrees ($p < 0.05$). No cases of loosening, dislodgment, mechanical failure, infection, or fusion of the affected segment occurred. The authors concluded that the findings of this study indicate that smokers do equally well as non-smokers when ProDisc

artificial disc replacement is used in the treatment of debilitating lumbar spondylosis. Patient outcome and radiographical scores showed significant improvement compared with pre-operative levels.

On August 14, 2006, the FDA approved the ProDisc-L Total Disc Replacement (Synthes Spine, Inc., West Chester, PA) for spinal arthroplasty in patients who meet all of the following criteria:

- Patients are skeletally mature; and
- Patients have DDD at 1 level in the lumbar spine (from L3 to S1); and
- Patients have no more than Grade 1 spondylolisthesis at the involved level; and
- Patients have had no relief from pain after at least 6 months of non-surgical treatment.

Hannibal et al (2007) examined if there is a clinical difference between the 1-level ProDisc patients versus the 2-level ProDisc patients at a minimum of 2-year follow-up. Patients were part of the FDA clinical trial for the Prodisc II versus circumferential fusion study at a single institution. These investigators identified 27 patients who received ProDisc at 1 level and 32 who received it at 2 levels with at least a 2-year follow-up, for a total of 59 patients. Unpaired t tests were performed on the mean results of VAS, ODI, 36-Item Short Form Health Survey (SF-36) Healthy Survey Physical Component Summary, and satisfaction using 10-cm line VAS to determine a clinical difference, if any, between the 2 populations. While patients receiving ProDisc at 2 levels scored marginally lower in all evaluation indexes, score differences in each category were also found to hold no statistical significance. The authors concluded that this study was unable to identify a statistically significant difference in outcome between 1- and 2-level ProDisc arthroplasty patients in a cohort from a single center. They stated that the equality of clinical effectiveness between 1- and 2-level ProDisc has yet to be determined.

In August 2007, the Centers for Medicare & Medicaid Services (CMS) concluded that lumbar artificial disc replacement (LADR) is not reasonable and necessary for the Medicare population over 60 years of age. CMS announced that Section 150.1 of the Medicare National Coverage Determination (NCD) Manual will be amended to reflect the

proposed change from non-coverage for a specific LADR implant to non-coverage for the LADR procedure for the Medicare population over 60 years of age. For Medicare beneficiaries 60 years of age and under, there is no national coverage determination, leaving such determinations to be made on a local basis.

An interventional procedure consultation document prepared for the National Institute for Health and Clinical Excellence (NICE, 2008) included the following provisional recommendations: "[c]urrent evidence on the safety and efficacy of prosthetic intervertebral disc replacement in the lumbar spine is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. A multi-disciplinary team with specialist expertise in the treatment of degenerative spine disease should be involved in patient selection for prosthetic intervertebral disc replacement in the lumbar spine. The procedure should only be carried out in patients for whom conservative treatment options have failed or are contraindicated. The current evidence is based on studies with maximum follow-up of 13 years. NICE encourages clinicians to continue to collect and publish data on longer-term outcomes, which should include information about patient selection and the need for further surgery."

Zigler and Delamarter (2012a) evaluated the long-term safety and effectiveness of the ProDisc-L total disc replacement (TDR) as part of an FDA-mandated post-market approval study. This report summarized the clinical findings after 5 years of follow-up. A total of 236 patients were treated and followed-up for 5 years; 161 TDRs and 75 fusions had been performed in these patients. The primary outcome was a 10-component success end-point. Secondary outcome measures included neurological status, secondary surgery, ODI, SF-36, VAS assessing pain and satisfaction, radiographic data, narcotic use, activity, and recreation status. Patients were monitored through their 5-year post-operative visits under the FDA post-market surveillance provisions in the original investigational device exemption approval. The overall follow-up rate at 5 years was 81.8 %. Study success demonstrated that TDR was non-inferior to fusion with a 12.5 % margin ($p = 0.0099$). Both TDR and fusion treatment groups maintained significant improvement on the ODI at 5 years compared with baseline ($p < 0.0001$). Secondary surgeries at the index level were performed in 12 % of fusion patients and 8 % of TDR

patients. Radiographically, none of the TDRs developed spontaneous fusion. The segmental ROM following TDR remained within normal range, although it decreased by approximately 0.5° in years 3 to 5. The VAS pain scores decreased from pre-operative values by 48 % in both treatment groups at 5 years. Patient satisfaction remained high in both groups (77 %), while the percentage of patients indicating that they would have the surgery again was higher in TDR patients (82.5 %) than in fusion patients (68.0 %). The authors concluded that patients in both groups maintained significant improvement during the 5-year follow-up. The TDR group had significantly better improvement on some scales. Although TDR patients avoid the stiffness of fusion and are more satisfied than fusion patients, both fusion and TDR are reasonable surgical options in this specific patient population.

Zigler and colleagues (2012b) reported the 5-year results for radiographically demonstrated adjacent-level degenerative changes from a prospective multi-center study in which patients were randomized to either TDR or circumferential fusion for single-level lumbar DDD. A total of 236 patients with single-level lumbar DDD were enrolled and randomly assigned to 2 treatment groups: (i) 161 patients in the TDR group were treated using the ProDisc-L, and (ii) 75 patients were treated with circumferential fusion. Radiographic follow-up data 5 years after treatment were available for 123 TDR patients and 43 fusion patients. To characterize adjacent-level degeneration (ALD), radiologists at an independent facility read the radiographic films. Adjacent-level degeneration was characterized by a composite score including disc height loss, endplate sclerosis, osteophytes, and spondylolisthesis. At 5 years, changes in ALD (Δ ALDs) compared with the pre-operative assessment were reported. Changes in ALD at 5 years were observed in 9.2 % of TDR patients and 28.6 % of fusion patients ($p = 0.004$). Among the patients without adjacent-level disease pre-operatively, new findings of ALD at 5 years post-treatment were apparent in only 6.7 % of TDR patients and 23.8 % of fusion patients ($p = 0.008$). Adjacent-level surgery leading to secondary surgery was reported for 1.9 % of TDR patients and 4.0 % of fusion patients ($p = 0.6819$). The TDR patients had a mean pre-operative index-level ROM of 7.3° that decreased slightly (to 6.0°) at 5 years after treatment ($p = 0.0198$). Neither treatment group had significant changes in either ROM or translation at the superior adjacent level at 5 years post-treatment compared with baseline. The authors

concluded that at 5 years after the index surgery, ProDisc-L maintained ROM and was associated with a significantly lower rate of Δ ALDs than in the patients treated with circumferential fusion. In fact, the fusion patients were greater than 3 times more likely to experience Δ ALDs than were the TDR patients. These researchers stated that the findings of this post-hoc analysis of data obtained from a randomized controlled trial (RCT) provided a baseline reference point in the evolving knowledge database for lumbar TDR and should serve as a benchmark for future study.

It is interesting to note that a Cochrane review on “Total disc replacement for chronic back pain” (Jacobs et al, 2012) concluded that “Although statistically significant, the differences between disc replacement and conventional fusion surgery for degenerative disc disease were not beyond the generally accepted clinically important differences with respect to short-term pain relief, disability and Quality of Life. Moreover, these analyses only represent a highly selected population. The primary goal of prevention of adjacent level disease and facet joint degeneration by using total disc replacement, as noted by the manufacturers and distributors, was not properly assessed and not a research question at all.

Unfortunately, evidence from observational studies could not be used because of the high risk of bias, while these could have improved external validity assessment of complications in less selected patient groups.

Non-randomized studies should however be very clear about patient selection and should incorporate independent, blinded outcome assessment, which was not the case in the excluded studies. Therefore, because we believe that harm and complications may occur after years, we believe that the spine surgery community should be prudent about adopting this technology on a large scale, despite the fact that total disc replacement seems to be effective in treating low-back pain in selected patients, and in the short term is at least equivalent to fusion surgery”.

In addition, a BlueCross BlueShield TEC assessment on “Artificial lumbar disc arthroplasty for treatment of degenerative disc disease of the lumbar spine” (2014) commented on the 5-year follow-up studies by Ziegler and colleagues (2012). The TEC assessment stated that “The manufacturer of ProDisc continued a 24-month investigational device exemption non-inferiority (NI) clinical trial ($d = 12.5\%$) to obtain 5-year follow-up data. The continuation trial used the same primary composite endpoint (referred to as 'success') as the original clinical trial. This endpoint

comprised the ODI, SF-36 Physical Component Score, neurological status, reoperations, and 6 radiographic criteria for fusion. To be deemed a 'success', a patient had to achieve all 10 endpoints of the composite measure. The proportion of patients reaching success in each group was compared using a 12.5 % NI margin. At 5 years follow-up, 53.7 % of ProDisc patients and 50.0 % of fusion patients achieved success, suggesting non-inferiority for ProDisc compared with fusion. However, this analysis was based on 75 % of the original ProDisc recipients and 85 % of fusion patients. An intent-to-treat analysis showed success was achieved in 53.3 % of ProDisc recipients and 47.3 % of fusion cases. An alternate analysis, using more conservative criteria requested by FDA (ODI minimum 15-point improvement for lower back pain and 10 % non-inferiority margin), showed 48.1 % of ProDisc recipients and 41.1 % of fusion patients achieved success at 5 years. The number of adverse events reported per patient did not differ between groups (5.4 for ProDisc versus 5.1 for fusion, $p = 0.507$), although unspecified severe or life-threatening adverse events were reported more commonly in fusion patients (0.58 per patient) than ProDisc recipients (0.38 per patient) ($p = 0.036$). This evidence is insufficient to demonstrate a relative clinical benefit of ProDisc versus fusion, particularly because the effectiveness of the comparator – fusion -- versus non-surgical treatments is not well defined. Thus, the randomized trial of ProDisc is suspect as a valid non-inferiority trial and does not prove superiority”.

Furthermore, an UpToDate review on “Subacute and chronic low back pain: Surgical treatment” (Chou, 2014) states that “Disc replacement is approved by the FDA for patients who are in good health, ≤ 60 years old, with disease limited to one disc between L3 and S1 and no associated deformity, spondylolisthesis, or neurologic deficit. Patients should be treated by surgeons experienced in performing disc replacement, to minimize complications and length of hospitalization. Guidelines from the American Pain Society found insufficient evidence regarding long-term benefits and harms of disc replacement to support recommendations Vertebral fusion is the most common surgery for chronic, nonspecific low back pain. Surgical instrumentation (use of pedicle screws or other hardware) increases fusion rates, but it is not known if instrumentation improves clinical outcomes. More research with longer follow-up is

needed to determine the appropriate role of artificial disc replacement versus fusion. We suggest that vertebral fusion be performed for patients who undergo surgical intervention for chronic low back pain”.

An assessment prepared for the Washington State Health Care Authority of artificial disc replacement (Hashimoto, et al., 2016) concluded that "[l]ow quality evidence suggests that 1-level L-ADR is comparable with single level anterior lumbar interbody fusion or circumferential fusion up to in terms of overall clinical success, ODI success and pain improvement and insufficient evidence with regard to neurological success [A]lthough results suggest that 24 month outcomes for L-ADR are similar to lumbar fusion, for non-inferiority trials the assumption is that reference treatment must have an established efficacy or that it is in widespread use. For the lumbar spine, the efficacy of the comparator treatment,, lumbar fusion, for degenerative disc disease remains uncertain, especially when it is compared with nonoperative care. Given what is known about lumbar fusion as a comparator and having evidence that only compares L-ADR with lumbar fusion limits the ability to fully answer the efficacy/effectiveness question."

The Washington State Health Care Authority Health Technology Clinical Committee (2017) concluded that "A majority of committee members found the evidence sufficient to determine that lumbar artificial discs replacements were unproven for safety and unproven for effectiveness compared to alternatives for some conditions, and unproven for cost-effectiveness. A majority of the committee voted to not cover lumbar artificial disc replacement."

Zigler et al (2018a) provided post-hoc analysis of 5-year follow-up data from a randomized, multi-center trial. These investigators examined the incidence of progression in radiographic adjacent-level degeneration (Δ ALD) from pre-operative assessment to 5 years after total disc replacement (TDR) and the relationship of these changes with range of motion (ROM) and clinical adjacent-level disease. They also compared adjacent-level degeneration (ALD) outcomes between TDR and fusion. In total, 175 patients with single-level, symptomatic, lumbar disc degeneration who had received activL or ProDisc-L and had a pre-operative and 5-year post-operative radiograph available were included. Over 5-year follow-up, Δ ALD was defined as an increase in ALD of

greater than or equal to 1 grade and clinical ALD was defined as surgical treatment at the level adjacent to an index TDR. Matching-adjusted indirect comparisons were conducted to compare ALD outcomes after TDR (current trial) with those after fusion (published trial). At 5-year follow-up, 9.7 % (17/175) of TDR patients had Δ ALD at the superior level. In patients with pre-operative ALD at the superior level, most (88 % [23/26]) showed no radiographic progression over 5 years. The rate of clinical ALD was 2.3 % (4/175) and none of these patients had ALD at baseline. For each degree of ROM gained at the TDR level, there was a consistent decrease in the percentage of patients with Δ ALD. After matching and adjustment of baseline characteristics, TDR had a significantly lower likelihood of Δ ALD than fusion (odds ratio [OR] 0.32; 95 % confidence interval [CI]: 0.13 to 0.76). The authors concluded that the rates of Δ ALD and clinical ALD in this TDR population were similar to those previously reported in the literature for TDR at 5-year follow-up; TDR had a statistically significant lower rate of Δ ALD than fusion. Level of evidence = III. It should also be noted that this study provided only mid-term (5 years) follow-up data.

The authors stated that this study had several drawbacks. First, this study was a post-hoc analysis of a subset of patients from the original randomized trial. Thus, it did not represent all patients originally evaluated because not all pre-operative and 5-year radiographs were available, primarily because of loss to follow-up. Nevertheless, the sample size of 175 patients was relatively comparable to a recent study that included 161 patients with ProDisc-L and evaluated ALD outcomes. Second, caution should be exercised when comparing results of various studies because of the potential for variations in scoring methods and follow-up duration. This study was aligned with the methods published in the 2012 study, which comprehensively considered several parameters, including disc height, endplate sclerosis, osteophytes, and spondylolisthesis, in the grading scheme. Furthermore, although the indications for TDR have generally been consistently applied in randomized controlled trials, fusion data may come from less homogeneous patient cohorts, particularly in studies not involving randomized comparison to TDR. Third, a matching-adjusted indirect comparison (MAIC) was conducted because of the absence of randomized data directly comparing currently marketed TDR devices (i.e., activL and ProDisc-L) with fusion for the ALD outcomes of interest.

Although MAICs involve consideration and adjustment for treatment-effect modifiers and/or prognostic factors, there was risk that treatment groups were not perfectly balanced. In the comparison of TDR with fusion, unanchored methods were used that involved more methodological assumptions. In the comparison of activL with fusion, anchored methods were used, wherein the ProDisc-L arm from each trial acted as an anchor treatment. Results for ALD outcomes were comparable using both anchored and unanchored methods, illustrating the robustness of the methods.

In a meta-analysis, Zigler et al (2018b) examined the long-term safety and efficacy of TDR compared with fusion in patients with functionally disabling chronic low back pain (LBP) due to single-level lumbar degenerative disc disease (DDD) at 5 years. PubMed and Cochrane Central Register of Controlled Trials databases were searched for RCTs reporting outcomes at 5 years for TDR compared with fusion in patients with single-level lumbar DDD. Outcomes included ODI success, back pain scores, re-operations, and patient satisfaction. All analyses were conducted using a random-effects model; analyses were reported as relative risk (RR) ratios and mean differences (MDs). Sensitivity analyses were conducted for different outcome definitions, high loss to follow-up, and high heterogeneity. The meta-analysis included 4 studies; TDR patients had a significantly greater likelihood of ODI success (RR 1.0912; 95 % CI: 1.0004 to 1.1903) and patient satisfaction (RR 1.13; 95 % CI: 1.03 to 1.24) and a significantly lower risk of re-operation (RR 0.52; 95 % CI: 0.35 to 0.77) than fusion patients. There was no association with improvement in back pain scores whether patients received TDR or fusion (MD -2.79; 95 % CI: -8.09 to 2.51). Most results were robust to sensitivity analyses. Results for ODI success and patient satisfaction were sensitive to different outcome definitions but remained in favor of TDR. The authors concluded that TDR was an effective alternative to fusion for lumbar DDD. It offered several clinical advantages over the longer term that could benefit the patient and reduce health care burden, without additional safety consequences. Again, this study provided only mid-term (5 years) follow-up data.

The authors stated that this meta-analysis had several drawbacks. A challenge of long-term lumbar TDR studies is loss of participants to follow-up. Included studies varied in the proportion of participants lost to

follow-up at 5 years, ranging from 1 % to 43 %. Despite the risk high participant loss poses to a study's validity, results of sensitivity analyses excluding studies with substantial loss to follow-up (i.e., greater than 30 %) were similar to those of the primary analysis. Because few RCTs comparing TDR with fusion have reported long-term data, these researchers opted for an inclusive approach to each outcome definition. Sensitivity analyses conducted to account for differences in the definitions and measures used for ODI success, back pain, and patient satisfaction consistently favored TDR over fusion despite the loss of statistical significance for some outcomes. Similarly, the analysis could not control for heterogeneity, a typical issue when addressing surgical outcomes. Nuances such as surgical technique and post-operative compliance could not be addressed by this study design. However, given the magnitude of centers involved in the 4 RCTs incorporated in this analysis, it appeared reasonable that many variations in technique were accounted for. The analysis incorporated the most recent literature available, but data from newer TDR devices such as the activL Artificial Disc was not included, since findings at 5 years have yet to be reported. Two-year follow-up results from the activL investigational device exemption (IDE) study aligned with the findings of the current analysis. Analyses including the long-term data for activL are expected to demonstrate similar or better findings favoring TDR than those shown in the current 5-year meta-analysis.

In a systematic review and meta-analysis, Mu et al (2018) compared the safety and efficacy of lumbar TDR with the safety and efficacy of anterior lumbar interbody fusion (ALIF) for the treatment of lumbar DDD (LDDD). The electronic databases PubMed, Web of Science and the Cochrane Library were searched for the period from the establishment of the databases to March 2018. The peer-reviewed articles that examined the safety and efficacy of TDR and ALIF were retrieved under the given search terms. Quality assessment must be done independently by 2 authors according to each item of criterion. The statistical analyses were performed using RevMan (version 5.3) and Stata (version 14.0). The random-effect model was carried out to pool the data. The I² statistic was used to evaluate heterogeneity. The sensitivity analysis was carried out to assess the robustness of the results of meta-analyses by omitting the articles one by one. A total of 6 studies (5 RCTs and 1 observational study) involving 1,093 patients were included in this meta-analysis. The

risk of bias of the studies could be considered as low-to-moderate. Operative time (MD = 4.95; 95 % CI: -18.91 to 28.81; p = 0.68), intra-operative blood loss (MD = 4.95; 95 % CI: -18.91 to 28.81; p = 0.68), hospital stay (MD = -0.33; 95 % CI: -0.67 to 0.01; p = 0.05), complications (RR = 0.96; 95 % CI: 0.91 to 1.02; p = 0.18) and re-operation rate (RR = 0.54; 95 % CI: 0.14 to 2.12; p = 0.38) were without significant clinical difference between groups. Patients in the TDR group had higher post-operative satisfaction (RR = 1.19; 95 % CI: 1.07 to 1.32; P = 0.001) and, better improvements in ODI (MD = -10.99; 95 % CI: -21.50 to -0.48; p = 0.04), VAS (MD = -10.56; 95 % CI: -19.99 to -1.13; p = 0.03) and post-operative lumbar mobility than did patients in the ALIF group. The follow-up time in the investigative and control groups ranged from 12 months to 60 months. The authors concluded that this meta-analysis based on the current available studies showed that the efficacy of TDR was superior to that of ALIF in the short-term; TDR may be an ideal alternative for selected patients with LDDD in the short term. However, the results of this study could not suggest the use of TDR above the use of ALIF for lumbar spinal treatments only on the basis of short term results. Furthermore, these researchers thought that this study still has a certain clinical significance, although the limitations of this meta-analysis led them to be cautious about the present conclusions. They stated that multi-center, well-designed, high-quality, large sample and long-term follow-up studies are needed to further evaluate the short- and long-term safety and efficacy of TDR comparison of ALIF or other fusion approaches in the treatment of LDDD.

The activL Artificial Disc

On June 11, 2015 the FDA approved the activL Artificial Disc, which is indicated for individuals who are skeletally mature, have LBP due to a problem with 1 lumbar disc, have been diagnosed as having DDD in only 1 lumbar disc at either level L4/L5 or L5/S1, and have gone through at least 6 months of non-surgical treatment without relief.

In a multi-center, randomized-controlled, IDE clinical trial, Garcia and colleagues (2015) evaluated the comparative safety and effectiveness of lumbar TDR in the treatment of patients with symptomatic DDD who were unresponsive to non-surgical therapy. Patients presenting with symptomatic single-level lumbar DDD who failed at least 6 months of

non-surgical management were randomly allocated (2:1) to treatment with an investigational TDR device (activL, n = 218) or FDA-approved control TDR devices (ProDisc-L or Charite, n = 106). These researchers hypothesized that a composite effectiveness outcome at 2 years in patients treated with activL would be non-inferior (15 % delta) to that in controls. The primary composite end-point of this study was met, which demonstrated that the activL TDR was non-inferior to control TDR ($p < 0.001$). A protocol-defined analysis of the primary composite end-point also confirmed that activL was superior to controls ($p = 0.02$).

Radiographical success was higher with activL versus controls (59 % versus 43 %; $p < 0.01$). Mean back pain severity improved by 74 % with activL and 68 % with controls; ODI scores decreased by 67 % and 61 % with activL and controls, respectively. Patient satisfaction with treatment was over 90 % in both groups at 2 years. Return-to-work was approximately 1 month shorter ($p = 0.08$) with activL versus controls. The rate of device-related serious adverse events (AEs) was lower in patients treated with activL versus controls (12 % versus 19 %; $p = 0.13$).

Surgical re-intervention rates at the index level were comparable (activL 2.3 %, control 1.9 %). The authors concluded that single-level activL TDR was safe and effective for the treatment of symptomatic lumbar DDD through 2 years.

The authors stated that this study had several limitations. First, the long-term durability of the activL TDR is unknown and requires further investigation (this study provided only short-term follow-up -- 2 years). Recent studies with the ProDisc-L and Charite TDR devices have reported excellent patient outcomes through 5 years. Second, a TDR should only be used in patients with confirmed lumbar DDD refractory to non-surgical treatment. Third, although patients, the Clinical Events Committee (CEC) and statisticians were blinded to treatment allocation and imaging was independently reviewed by a core laboratory, surgeons and clinical outcome assessors were not blinded, which may have influenced study results. Finally, this study was under-powered to evaluate activL in comparison to each control device separately. This limitation was partially mitigated by the fact that patient characteristics and main outcomes with the ProDisc-L and Charite' devices were comparable.

In a multi-center RCT, Furunes and colleagues (2017) evaluated the long-term relative efficacy of lumbar TDR compared with multi-disciplinary rehabilitation (MDR). The sample consisted of 173 patients aged 25 to 55 years with chronic LBP and localized degenerative changes in the lumbar intervertebral discs. The primary outcome was self-reported physical function (ODI) at 8-year follow-up in the intention-to-treat (ITT) population. Secondary outcomes included self-reported LBP (VAS), quality of life (EuroQol [EQ-5D]), emotional distress (Hopkins Symptom Checklist [HSCL-25]), occupational status, patient satisfaction, drug use, complications, and additional back surgery. Patients were randomly assigned to lumbar TDR or MDR. Self-reported outcome measures were collected 8 years after treatment. The study was powered to detect a difference of 10 ODI points between the groups. The study has not been funded by the industry. A total of 605 patients were screened for eligibility, of whom 173 were randomly assigned treatment; 77 patients randomized to surgery and 74 patients randomized to rehabilitation responded at 8-year follow-up. Mean improvement in the ODI was 20.0 points (95 % CI: 16.4 to 23.6, $p \leq 0.0001$) in the surgery group and 14.4 points (95 % CI: 10.7 to 18.1, $p \leq 0.0001$) in the rehabilitation group. Mean difference between the groups at 8-year follow-up was 6.1 points (95 % CI: 1.2 to 11.0, $p = 0.02$). Mean difference in favor of surgery on secondary outcomes were 9.9 points on VAS (95 % CI: 0.6 to 19.2, $p = 0.04$) and 0.16 points on HSCL-25 (95 % CI: 0.01 to 0.32, $p = 0.04$). There were 18 patients (24 %) in the surgery group and 4 patients (6 %) in the rehabilitation group who reported full recovery ($p = 0.002$). There were no significant differences between the groups in EQ-5D, occupational status, satisfaction with care, or drug use. In the per protocol analysis, the mean difference between groups was 8.1 ODI points (95 % CI: 2.3 to 13.9, $p = 0.01$) in favor of surgery; 43 of 61 patients (70 %) in the surgery group and 26 of 52 patients (50 %) in the rehabilitation group had a clinically important improvement (15 ODI points or more) from baseline ($p = 0.03$). The proportion of patients with a clinically important deterioration (6 ODI points or more) was not significantly different between the groups; 21 patients (24 %) randomized to rehabilitation had crossed-over and had undergone back surgery since inclusion, whereas 12 patients (14 %) randomized to surgery had undergone additional back surgery; 1 serious AE after disc replacement was registered (less than 1 %). The authors concluded that substantial long-term improvement could be expected after both disc replacement

and MDR. The difference between groups was statistically significant in favor of surgery, but smaller than the pre-specified clinically important difference of 10 ODI points that the study was designed to detect. These researchers stated that future research should aim to improve selection criteria for disc replacement and MDR.

The authors stated that this study had several drawbacks that should be acknowledged. First, the patients could not be blinded. This may have led to a difference in placebo effect between the groups. A considerable placebo effect has been reported for vertebroplasty compared with sham surgery. On the other hand, Freeman and colleagues (2005) did not find a significant change in outcome among patients with chronic LBP treated with intradiscal electrothermal therapy or sham surgery. No studies comparing TDR with sham surgery have been published. Also, these researchers did not know the natural course of LBP over 8 years, although Peng and colleagues (2012) observed a small, and not clinically important, improvement from 46.4 to 44.0 points in ODI over 4 years in an observational study. A 2nd drawback of the study was that only 179 (30 %) of the 605 patients screened for eligibility were included, which meant that this study was only valid for a strictly defined group among patients with chronic LBP. The most important exclusion criteria were nerve root involvement or presence of generalized disc degeneration. A 3rd drawback was the relatively high cross-over rate, especially from rehabilitation to surgery. Although all patients were informed that neither of the treatment methods were documented as being superior to the other, they were recruited as candidates for disc replacement, and some might have participated in the trial in hope of surgery. The number of patients who did not complete the treatment they were randomized to was similar in the 2 groups, but these researchers did not evaluate patients' treatment expectations before randomization. The cross-over rate was not higher than in other studies with long-term follow-up comparing spine surgery with non-operative treatment. The cross-overs probably had only a small impact on the result in the ITT analysis, because a similar change in ODI among patients randomized to rehabilitation was found in the per protocol analysis (14.1 points) and in the ITT analysis (14.4 points). A 4th drawback was the relatively high re-operation rate, similar to previous studies with long-term follow-up after TDR. A high re-operation rate made it difficult to untangle the results of TDR from the results of the re-

operation in the ITT analysis. In the per protocol analysis, patients re-operated on were excluded, thus probably removing the most inferior results of surgery from this analysis.

In a prospective, multi-center, randomized, controlled, IDE, non-inferiority trial, Yue et al (2019) compared the 5-year safety and effectiveness of the activL artificial disc with control TDR systems (ProDisc-L or Charite) in the treatment of patients with symptomatic single-level lumbar DDD. Eligible patients presented with symptomatic, single-level, lumbar DDD who failed greater than or equal to 6 months of non-surgical management. At entry, 324 patients were randomly allocated (2:1) to treatment with activL (n=218) or control (n=106, including n=65 ProDisc-L and n=41 Charite) TDR. At 5-year follow-up, a total of 261 patients (176 activL patients and 85 control patients) were available for analysis. The primary composite end-point at 5 years for activL patients was non-inferior to control TDR. Relative to baseline, reductions in back pain severity and improvements in ODI were maintained for both the activL and control TDR groups through 5 years. The activL group showed significantly better ROM for flexion-extension rotation, flexion-extension translation, and disc angle, compared with control TDR. Freedom from a serious AE through 5 years was 64 % in activL patients, 47 % in control patients (log-rank p=0.0068). Freedom from index-level and adjacent-level re-operation was high for TDR patients, ranging between 94 % and 99 %, respectively. The authors concluded that long-term evidence supported lumbar TDR as safe. The next-generation activL artificial disc was more effective at preserving ROM than 1st-generation lumbar TDRs (ProDisc-L and Charite) and offered a higher safety profile. Other primary and secondary outcomes were similar between disc designs. Level of Evidence =2.

The authors stated that this study had several drawbacks. First, although this study reported comparative outcomes among lumbar TDRs, direct inference to alternative treatments such as lumbar fusion or structured rehabilitation cannot be made. A 2-year network meta-analysis demonstrated favorable findings for the activL artificial disc relative to fusion and conservative care; however, these analyses will need to be updated to reflect 5-year outcomes. A 1-year retrospective study demonstrated that DDD patients receiving the activL artificial disc presented quicker return-to-work, less back pain, and lower disability scores compared with anterior lumbar fusion patients. Second, the

control group consisted of patients who received ProDisc-L or Charite at the discretion of the implanting physician. Third, while the use of rigorous inclusion criteria may be viewed as a strength in terms of mitigating potential confounding variables, the ability to generalize these findings to the population is unknown. Real-world, long-term data are increasingly available for lumbar TDR. For example, a Swiss nation-wide registry demonstrated that lumbar TDR (including the activL artificial disc) remained effective over 5 years for pain relief, reduction in pain medication, and improvement in quality of life (QOL). After the 1st year of a 10-year post-market surveillance study, surgeons were satisfied with the overall performance of the activL artificial disc and did not report any safety concerns. Additional long-term results from real-world activL usage would be a useful adjunct to these clinical trial findings to optimize generalizability. Last, as with any device trial, unblinding is always a potential concern. Aside from maintenance of single-blind status being an FDA requirement, several factors helped to mitigate this risk (e.g., high efforts to prevent knowledge of disc type, similar disc shapes).

Furthermore, an UpToDate review on “Subacute and chronic low back pain: Surgical treatment” (Chou, 2020) stated that “Artificial disc replacement is a newer alternative to fusion. A theoretic advantage of lumbar disc replacement compared with fusion is that a prosthetic disc could help preserve normal range of motion and spine mechanics. This could reduce the long-term degenerative changes in adjacent vertebral segments that have been observed following spinal fusion. However, the evidence suggests that the efficacy of this approach is similar to that of spinal fusion. A 2012 systematic review of seven randomized trials evaluated the use of disc replacement for chronic low back pain. Five trials (n = 1301) specifically compared disc replacement versus fusion for improvement of pain (VAS) and function (ODI) outcomes at 2 years. All studies had risk of bias due to lack of blinding and industry sponsorship; in addition, two of the trials evaluated an artificial disc that has not been approved by the FDA. Pooled results demonstrated no significant difference in pain scores between the two groups. There was a statistically, but not clinically, significant difference in improvement in function in the disc replacement group compared with the fusion group (4.3 points, 95 % CI 1.9-6.7). Only one trial has compared lumbar disc replacement versus a multidisciplinary rehabilitation program. This study included 173 patients with chronic pain, disability, and L4-5 and/or L5-S1

degenerative disc disease. Those randomly assigned to disc replacement had a statistically, but not clinically, significant improvement in disability score (difference of 8 points on a 100 point scale) at two-year follow-up and lower pain scores (difference 12 points on a 100 point scale) compared with the rehabilitation arm. Six patients in the surgery group had complications resulting in physical impairment, with one patient requiring a lower leg amputation following revision surgery. No major complications were reported for the rehabilitation arm ... A key limitation of existing evidence for the role of lumbar disc replacement is the lack of longer-term follow-up to assess efficacy and failure rates necessitating device removal and potential conversion to a fusion procedure. Regardless of treatment (disc replacement, fusion, or nonsurgical), few patients report complete symptom resolution. Disc replacement is approved by the FDA for patients who are in good health and ≤ 60 years old, with disease limited to one disc between L3 and S1 and no associated deformity, spondylolisthesis, or neurologic deficit. Patients should be treated by surgeons experienced in performing disc replacement to minimize complications and length of hospitalization. Guidelines from the American Pain Society found insufficient evidence regarding long-term benefits and harms of disc replacement to support recommendations ... More research with longer follow-up is needed to determine the appropriate role of artificial disc replacement versus fusion. We suggest that vertebral fusion be performed for patients who undergo surgical intervention for chronic low back pain (Grade 2B)".

In a review on lumbar arthroplasty, Sandhu et al (2020) noted that lumbar DDD is a pathologic process that affects a large portion of the aging population. In the recent past, surgical treatment has involved fusion procedures. However, lumbar disc arthroplasty and replacement provides an alternative for carefully selected patients. It provides the major advantage of motion preservation and thus keeps adjacent segments from significantly progressive degeneration. The history of lumbar disc replacement has roots that start in the 1960s with the implantation of stainless-steel balls. Decades later, multiple implants with different material design and biomechanical properties were introduced to the market. New 3rd-generation implants have made great strides in improved biomechanics and clinical outcomes. Although there is room for further advancement and studies are needed to evaluate the long-term durability and sustainability of lumbar disc arthroplasty, it has certainly

proven to be a very acceptable alternative within the surgical armamentarium that should be offered to patients who meet indications. Moreover, these researchers stated that intervertebral disc replacements for the lumbar spine have been under constant design improvements for over 4 decades and the latest design offers safe and effective motion preservation for carefully selected patients suffering from DDD. Maintaining motion clearly reduces the development of adjacent segment disease and need for additional surgical intervention on long-term follow-up. Questions regarding lifelong durability and consequences of the devices remain and will be only gleaned over time, but experience with current discs is promising.

Cervical Prosthetic Discs (e.g., the Bryan Cervical Disc, M6-C Artificial Cervical Disc, the MOBI-C, the Prestige Cervical Disc, the Secure-C Artificial Cervical Disc, and the Simplify Cervical Artificial Disc)

Acosta and Ames (2005) noted that cervical disc arthroplasty is a relatively new motion-preserving technique for the treatment of symptomatic DDD of the cervical spine. Unlike anterior discectomy and fusion, cervical disc replacement restores normal motion and a physiologic biomechanical environment to adjacent disc levels, thereby reducing the incidence of adjacent segment disease. To date, cervical disc arthroplasty has been at least as effective as cervical fusion in providing symptomatic relief while lowering peri-operative morbidity, eliminating the need for post-operative external immobilization, and allowing for earlier return to normal function. No significant complications have been associated with this procedure so far. The authors stated that further investigation in the form of large, randomized, prospective studies is needed to ascertain the long-term effectiveness of this procedure as well as to determine the patient populations that may benefit most from cervical disc arthroplasty. This is in agreement with the observations of Pracyk and Traynelis (2005) and Bertagnoli, et al. (2005). Pracyk and Traynelis stated that cervical arthroplasty (by means of devices such as Prestige, Bryan, and ProDisc) is a promising new technology that may improve patient outcome following anterior cervical decompression. Bertagnoli et al noted that long-term follow-up studies are needed before more definitive treatment recommendations can be made regarding cervical disc replacement by means of the ProDisc. Furthermore, in a

review on the state of the emerging field of cervical disc replacement, Phillips and Garfin (2005) stated that cervical disc replacement is an innovative technology that preserves motion at the instrumented level/s, and will potentially improve load transfer to the adjacent levels compared with fusion. Clinical reports of success of cervical total disc replacement are encouraging but are also quite preliminary. As the United States investigational device exemption studies are completed, a clearer role for the place of cervical disc replacement in the spine surgeon's armamentarium should emerge.

Traynelis and Treharne (2007) noted that the Prestige artificial cervical disc is a new motion-sparing device designed for use in the cervical spine to treat symptomatic degenerative disc disease in patients who have failed conservative care. It allows for the maintenance of normal cervical spinal motion. Furthermore, this new device does not require bone graft or as long a recovery time as needed for fusion of the joint.

In a prospective, randomized, controlled and double-blinded study, Sekhon and colleagues (2007) compared post-operative imaging characteristics of the four currently available cervical arthroplasty devices (Bryan, Prodisc-C, Prestige LP, and PCM) at the level of implantation and at adjacent levels. Pre-operative and post-operative magnetic resonance imaging scans of 20 patients who had undergone cervical arthroplasty were evaluated for imaging quality. Five cases each of the four devices were analyzed. Six blinded spinal surgeons scored twice sagittal and axial T2-weighted images using the Jarvik 4-point scale. Statistical analysis was performed comparing quality before surgery and after disc implantation at the operated and adjacent levels and between implant types. Moderate intra-observer and inter-observer reliability was noted. Pre-operative images of patients in all implant groups had high-quality images at operative and adjacent levels. The Bryan and Prestige LP devices allowed satisfactory visualization of the canal, exit foramina, cord, and adjacent levels after arthroplasty. Visualization was significantly impaired in all PCM and Prodisc-C cases at the operated level in both the spinal canal and neural foramina. At the adjacent levels, image quality was statistically poorer in the PCM and Prodisc-C than those of Prestige LP or Bryan. The authors concluded that post-operative visualization of neural structures and adjacent levels after cervical arthroplasty is variable among current available devices. Devices containing non-titanium metals

(cobalt-chrome-molybdenum alloys in the PCM and Prodisc-C) prevent accurate post-operative assessment with magnetic resonance imaging at the surgical and adjacent levels. On the other hand, titanium devices, with or without polyethylene (Bryan disc or Prestige LP), allow for satisfactory monitoring of the adjacent and operated levels. This information is crucial for any surgeon who wishes to assess adequacy of neural decompression and where monitoring of adjacent levels is desired.

Mummaneni and associates (2007) reported the results of a prospective randomized multi-center study in which the results of cervical disc arthroplasty with the Prestige ST Cervical Disc System (Medtronic Sofamor Danek) were compared with anterior cervical discectomy and fusion (ACDF). Patients with symptomatic (neck pain) single-level cervical DDD who failed at least 6 weeks of conservative treatment or had signs of progression or spinal cord/nerve root compression with continued non-operative care were included in the study. Degenerative disc disease was determined to be present if a herniated disc and/or osteophyte formation were confirmed by history and radiographic studies (e.g., CT, MRI, x-rays). A total of 541 patients were enrolled at 32 sites and randomly assigned to 1 of 2 treatment groups: (i) 276 patients in the investigational group underwent anterior cervical discectomy and decompression and arthroplasty with the Prestige ST Cervical Disc System; and (ii) 265 patients in the control group underwent decompressive ACDF. A total of 80% of the arthroplasty-treated patients (223 of 276) and 75% of the control patients (198 of 265) completed clinical and radiographical follow-up examinations at routine intervals for 2 years after surgery. Analysis of all currently available post-operative 12- and 24-month data indicated a 2-point greater improvement in the neck disability index score in the investigational group than the control group. The arthroplasty group also had a statistically significant higher rate of neurological success ($p = 0.005$) as well as a lower rate of secondary revision surgeries ($p = 0.0277$) and supplemental fixation ($p = 0.0031$). The mean improvement in the 36-Item Short Form Health Survey Physical Component Summary scores was greater in the investigational group at 12 and 24 months, as was relief of neck pain. The patients in the investigational group returned to work 16 days sooner than those in the control group, and the rate of adjacent-segment re-operation was significantly lower in the investigational group as well ($p = 0.0492$, log-rank test). The cervical disc implant maintained segmental sagittal

angular motion averaging more than 7 degrees. In the investigational group, there were no cases of implant failure or migration. The authors concluded that the Prestige Cervical Disc maintained physiological segmental motion at 24 months after implantation and was associated with improved neurological success, improved clinical outcomes, and a reduced rate of secondary surgeries compared with ACDF.

On July 17, 2007, the FDA approved the Prestige Cervical Disc (Medtronic Sofamor Danek, Memphis, TN) for the treatment of single level cervical degenerative disc disease (C3 to C7). The FDA approval was based on the findings of the study by Mummaneni, et al. (2007). In the approval letter, the FDA stated that Medtronic Sofamor Danek is required to perform a 7-year post-approval study to evaluate the long-term safety and effectiveness of the Prestige Cervical Disc.

Sasso et al (2007) evaluated the functional outcome and radiographical results of the Bryan artificial cervical disc replacement for patients with 1-level cervical disc disease. Twelve-month follow-up was available for 110 patients and 24-month follow-up was completed for 99 patients. There were 30 males and 26 females in the Bryan group and 32 males and 27 females in the fusion group. The average age was 43 years (Bryan) and 46 years (fusion). Disability and pain were assessed using the Neck Disability Index (NDI) and the VAS of the neck and of the arm pain. SF-36 outcome measures were obtained including the physical component as well as the mental component scores. Range of motion was determined by independent radiological assessment of flexion-extension radiographs. The average operative time for the control group was 1.1 hours and the Bryan Group 1.7 hours. Average blood loss was 49 ml (control) and 64 ml (Bryan). Average hospital stay was 0.6 days (control) and 0.9 days (Bryan). The mean NDI before surgery was not statistically different between groups: 47 (Bryan) and 49 (control). Twelve-month follow-up NDI is 10 (Bryan) and 18 (control) ($p = 0.013$). At 2-year follow-up, NDI for the Bryan group is 11 and the control group is 20 ($p = 0.005$). The mean arm pain VAS before surgery was 70 (Bryan) and 71 (control). At 1-year follow-up, Bryan arm pain VAS was 12 and control 23 ($p = 0.031$). At 2-year follow-up, the average arm pain VAS for the Bryan group was 14 and control 28 ($p = 0.014$). The mean neck pain VAS before surgery was 72 (Bryan) and 73 (control); 1-year follow-up scores were 17 (Bryan) and 28 (control) ($p = 0.05$); 2-year follow-up: 16 (Bryan) and 32 (control) ($p =$

0.005). SF-36 scores: Physical component -- before surgery Bryan 34 and control 32; at 24 months: Bryan 51 and control 46 ($p = 0.009$). More motion was retained after surgery in the disc replacement group than the plated group at the index level ($p < 0.006$ at 3, 6, 12, and 24 months). The disc replacement group retained an average of 7.9 degrees of flexion-extension at 24 months. In contrast, the average range of motion in the fusion group was 0.6 degrees at 24 months. There were 6 additional operations in this series: 4 in the control group and 2 in the investigational group. There were no intra-operative complications, no vascular or neurological complications, no spontaneous fusions, and no device failures or explantations in the Bryan cohort. The authors concluded that the Bryan artificial disc replacement compared favorably to anterior cervical discectomy and fusion for the treatment of patients with 1-level cervical disc disease. At the 2-year follow-up, there are statistically significant differences between the groups with improvements in the NDI, the neck pain and arm pain VAS scores, and the SF-36 physical component score in the Bryan disc population.

In December 2007, the FDA approved the ProDisc-C Total Disc Replacement (Synthes Spine, Inc., West Chester, PA) for use in skeletally mature patients for reconstruction of the disc from C3-C7 following removal of the disc at one level for intractable symptomatic cervical disc disease (SCDD). The FDA's approval of the ProDisc-C was based upon the results of a clinical trial (non-inferiority) involving 209 patients at 13 clinical sites comparing ProDisc-C to ACDF. Patients with SCDD who failed at least 6 weeks of non-operative treatment or had progressive symptoms or signs of nerve root/spinal cord compression in the face of conservative treatment qualified for the trial. Intractable SCDD was defined as neck or arm (radicular) pain, and/or a functional/neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, or x-rays): (i) herniated nucleus pulposus, (ii) spondylosis (defined by the presence of osteophytes), or (iii) loss of disc height. Patients were evaluated for pain and disability, neurologic status and range of motion at the index level. Patients were followed for 2 years post surgery. The study data indicated that the ProDisc-C is non-inferior to ACDF. According to the FDA-approved labeling, the ProDisc-C should not be implanted in patients with an active infection, allergy to any of the device materials, osteoporosis, marked cervical instability, severe

spondylosis, clinically compromised vertebral bodies at the level to be treated, and SCDD at more than one level. The device is implanted via an open anterior approach.

In December 2009, the FDA approved the Bryan Cervical Disc (Medtronic Sofamor Danek, Memphis, TN) for use in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The FDA's approval of the Bryan Cervical Disc was based upon the results of a clinical trial (non-inferiority) involving 463 patients at 30 clinical sites comparing the Bryan device to ACDF. Patients with intractable radiculopathy and/or myelopathy resulting in impaired function with at least one clinical neurological sign associated with the cervical level to be treated and who failed at least 6-weeks of conservative treatment qualified for the trial. Intractable radiculopathy and/or myelopathy was defined as any combination of the following conditions confirmed by imaging (computed tomography, myelography and computed tomography, and/or magnetic resonance imaging): (i) disc herniation with radiculopathy, (ii) spondylotic radiculopathy, (iii) disc herniation with myelopathy, or (iv) spondylotic myelopathy. Patients were evaluated for pain and disability, and neurological status. Patients were followed for 2 years post surgery. The study data indicated that the Bryan Cervical Disc is non-inferior to ACDF. According to the FDA-approved labeling, the Bryan Cervical Disc should not be implanted in patients with an active infection, allergy to any of the device materials, osteoporosis, moderate to advanced spondylosis, marked cervical instability, significant cervical anatomical deformity or compromised vertebral bodies at the index level, significant kyphotic deformity or significant reversal of lordosis, or symptoms necessitating surgical treatment at more than one cervical level. The Bryan device is implanted via an open anterior approach. Because the specific polyurethanes used in the device have not been exhaustively studied for use as sheaths or nuclei in a cervical disc prosthesis, the FDA recommended that the sponsor continue to evaluate explanted devices in a 10 year post-approval study.

An assessment by the BlueCross BlueShield Association Technology Evaluation Center (2009) found that artificial intervertebral disc arthroplasty for the treatment of patients with cervical DDD does not meet its criteria for improving net health outcomes or is as beneficial as ACDF.

A draft assessment by the California Technology Assessment Forum (2009) found insufficient evidence that cervical disc replacement for patients with cervical DDD improves health outcomes over the long term.

Quan et al (2011) evaluated the long-term outcome of cervical disc arthroplasty. A total of 21 patients underwent 27 total disc arthroplasties using the Bryan cervical disc after anterior cervical discectomy. Clinical and radiological data were obtained from the 8-year post-operative review. Nineteen of 21 patients were able to perform daily activities without limitation; 20 of 21 patients reported fair to excellent outcome according to Odom criteria and 21 of 27 (78 %) operated segments were mobile. Functional prostheses moved an average of 10.6°, which was similar to the range of movement of the adjacent non-operated segments of the cervical spine. Heterotopic ossification was evident in 13 of the 27 (48 %) operated segments and restricted movement of the prosthesis in 9 cases. Five of the 6 patients who received bilevel arthroplasties developed heterotopic ossification. There was 1 case of posterior migration of the prosthesis, which did not have any clinical repercussion. No other case showed evidence of migration, subsidence, loosening, or wear. Radiological evidence of adjacent segment degeneration was observed in 4 patients (19 %); however, each of these patients had pre-existing degenerative disc disease at these levels on pre-operative imaging. The authors concluded that at 8-year follow-up, the Bryan cervical disc arthroplasty maintains favorable clinical and radiological results, with preservation of movement and satisfactory clinical outcome in the majority of cases. However, the incidence of heterotopic ossification causing restricted range of movement of the prosthesis appears to increase with time, especially in bilevel procedures.

On September 28, 2012, the FDA approved the SECURE-C Artificial Cervical Disc, which is intended to be used in skeletally mature patients to replace a cervical disc (from C3 to C7) following removal of the disc for conditions that result from a diseased or bulging disc (intractable radiculopathy or myelopathy) at only 1 level.

Contraindications of the Secure-C Artificial Cervical Disc:

- Active systemic infection or an infection at the operating site

- Allergy to the metals in the device (cobalt, chromium, molybdenum, or titanium), or to the type of plastic used in the device (polyethylene)
- Facet joint arthropathy
- More than 1 cervical disc requiring treatment (since device has only been evaluated in patients with 1 cervical disc requiring treatment)
- Osteoporosis or osteopenia
- Severe spondylosis
- Unstable cervical spine
- Weakened bones at the affected level due to current or past trauma.

On August 23, 2013, the FDA approved the Mobi-C for 2-level cervical disease. However, pivotal clinical studies excluded patients with DJD at more than 1-level.

Beaurain and colleagues (2009) reported the intermediate results of an undergoing multi-center prospective study of TDR with Mobi-C prosthesis. These researchers evaluated (i) the safety and effectiveness of the device in the treatment of DDD and (ii) the radiological status of adjacent levels and the occurrence of ossifications, at 2-year follow-up (FU). A total of 76 patients had performed their 2-year FU visit and had been analyzed clinically and radiologically. Clinical outcomes (NDI, VAS, SF-36) and ROM measurements were analyzed pre-operatively and at the different post-operative time-points. Complications and re-operations were also assessed. Occurrences of heterotopic ossifications (HOs) and of adjacent disc degeneration radiographic changes have been analyzed from 2-year FU X-rays. The mean NDI and VAS scores for arm and neck were reduced significantly at each post-operative time-point compared to pre-operative condition. Motion was preserved over the time at index levels (mean ROM = 9 degrees at 2 years) and 85.5 % of the segments were mobile at 2 years. Heterotopic ossifications were responsible for the fusion of 6/76 levels at 2 years. However, presence of HO did not alter the clinical outcomes. The occurrence rate of radiological signs of ALD was very low at 2 years (9.1 %). There had been no subsidence, no expulsion and no sub-luxation of the implant. Finally, after 2 years, 91 % of the patients assumed that they would undergo the procedure again. The authors concluded that these intermediate results of TDR with Mobi-

C were very encouraging and appeared to confirm the safety and effectiveness of the device. However, they noted that long-term studies are needed to fully evaluate the future of operated spine and the ability of arthroplasty with Mobi-C to provide the good answers to numerous questions asked by treatment of cervical DDD (e.g., the preservation of the status of the adjacent levels).

Huppert et al (2011) compared the safety and effectiveness of disc replacement with an unconstrained prosthesis in multi- versus single-level patients. A total of 231 patients with cervical DDD who were treated with cervical disc replacement and completed their 24 months FU were analyzed prospectively: 175 were treated at 1-level, 56 at 2-level or more. Comparison between both groups was based on usual clinical and radiological outcomes (NDI, VAS, ROM, satisfaction). Safety assessments, including complication and subsequent surgeries, were also documented and compared. Mean NDI and VAS scores for neck and arm pain were improved in both groups similarly. Improvement of mobility at treated segments was also similar. Nevertheless, in the multi-level group, analgesic use was significantly higher; and occurrence of HOAs was significantly lower than in the single-level group. Subject satisfaction was nearly equal, as 94.2 % of single-level group patients would undergo the surgery again versus 94.5 % in the multi-level group. The overall success rate did not differ significantly. Multi-level DDD is a challenging indication in the cervical spine. This study showed no major significant clinical difference between the 2 groups. The authors concluded that there is a need for further studies to ascertain the impact of multi-level arthroplasty, especially on ALD, but these results demonstrated initial safety and effectiveness in this patient sample. The major drawbacks of this exploratory study were small sample size, lack of randomization, and the p values suggested a trend towards similar results in the outcomes of single-level versus multi-levels populations.

Davis et al (2013) compared the Mobi-C cervical artificial disc to ACDF for treatment of cervical DDD at 2 contiguous levels of the cervical spine. The primary clinical outcome was a composite measure of study success at 24 months. The comparative control treatment was ACDF using allograft bone and an anterior plate. A total of 330 patients were enrolled, randomized, and received study surgery. All patients were diagnosed with intractable symptomatic cervical DDD at 2 contiguous levels of the

cervical spine between C3 and C7. Patients were randomized in a 2:1 ratio (TDR patients to ACDF patients). A total of 225 patients received the Mobi-C TDR device and 105 patients received ACDF. At 24 months only 3.0 % of patients were lost to FU. On average, patients in both groups showed significant improvements in NDI score, VAS neck pain score, and VAS arm pain score from pre-operative baseline to each time-point. However, the TDR patients experienced significantly greater improvement than ACDF patients in NDI score at all time-points and significantly greater improvement in VAS neck pain score at 6 weeks, and at 3, 6, and 12 months post-operatively. On average, patients in the TDR group also maintained pre-operative segmental ROM at both treated segments immediately postoperatively and throughout the study period of 24 months. The re-operation rate was significantly higher in the ACDF group at 11.4 % compared with 3.1 % for the TDR group. Furthermore, at 24 months TDR demonstrated statistical superiority over ACDF based on overall study success rates. The authors concluded that the results of this study represented the first available Level I clinical evidence in support of cervical arthroplasty at 2 contiguous levels of the cervical spine using the Mobi-C cervical artificial disc. Moreover, they stated that additional rigorous research will further the understanding of the safety and effectiveness of multi-level cervical arthroplasty and arthrodesis procedures.

Coric et al (2013) evaluated the long-term results of cervical TDR and ACDF in the treatment of single-level cervical radiculopathy. The results of 2 separate prospective, randomized, FDA Investigational Device Exemption pivotal trials (Bryan Disc and Kineflex|C) from a single investigational site were combined to evaluate outcomes at long-term FU. The primary clinical outcome measures included the NDI, VAS, and neurological examination. Patients were randomized to receive cervical TDR in 2 separate prospective, randomized studies using the Bryan Disc or Kineflex|C cervical artificial disc compared with ACDF using structural allograft and an anterior plate. Patients were evaluated pre-operatively; at 6 weeks; at 3, 6, and 12 months; and then yearly for a minimum of 48 months. Plain radiographs were obtained at each study visit. A total of 74 patients were enrolled and randomly assigned to either the cervical TDR (n = 41) or ACDF (n = 33) group. A total of 63 patients (86 %) completed a minimum of 4 years FU. Average follow-up was 6 years (72 months) with a range from 48 to 108 months. In both the cervical TDR

and ACDF groups, mean NDI scores improved significantly by 6 weeks after surgery and remained significantly improved throughout the minimum 48-month follow-up ($p < 0.001$). Similarly, the median VAS pain scores improved significantly by 6 weeks and remained significantly improved throughout the minimum 48-month follow-up ($p < 0.001$). There were no significant differences between groups in mean NDI or median VAS scores. The ROM in the cervical TDR group remained significantly greater than the pre-operative mean, whereas the ROM in the ACDF group was significantly reduced from the pre-operative mean. There was significantly greater ROM in the cervical TDR group compared with the ACDF group. There were 3 re-operations (7.3 %) at index or adjacent levels in the cervical TDR group; all were cervical lamino-foraminotomies. There were 2 adjacent-level re-operations in the cervical TDR group (4.9 %). There was 1 re-operation (3.0 %) in the ACDF group at an index or adjacent level (a second ACDF at the adjacent level). There was no statistically significant difference in overall re-operation rate or adjacent-level re-operation rate between groups. The authors concluded that both cervical TDR and ACDF groups showed excellent clinical outcomes that were maintained over long-term FU. Both groups showed low index-level and adjacent-level re-operation rates. Both cervical TDR and ACDF appeared to be viable options for the treatment of single-level cervical radiculopathy.

Furthermore, in a systematic review on "Artificial cervical disc arthroplasty versus anterior cervical discectomy and fusion", Bakar et al (2014) concluded that "Given the long-term outcomes that have been studied for anterior cervical discectomy and fusion, it is difficult to assess the future potential of anterior cervical disc arthroplasty as an alternative to anterior cervical discectomy and fusion. It is important to note that current studies with follow-up to 4 years have shown promising outcomes. The ability of anterior cervical disc arthroplasty to decrease the potential for common and well-known late complications of anterior cervical discectomy and fusion (such as adjacent segment disease) is an important and interesting possibility. Future long-term randomized controlled trials and cost effectiveness studies are needed to properly assess the continued use of artificial cervical disc arthroplasty and to determine the relative cost effectiveness compared with anterior cervical discectomy and fusion".

Ren et al (2014) evaluated the mid- to long-term clinical outcomes after cervical disc arthroplasty (CDA) as compared with ACDF for the treatment of symptomatic cervical disc disease. A systematic review and a meta-analysis were performed for articles published up to March 2013. Randomized controlled trials (RCTs) that reported mid- to long-term outcomes (greater than or equal to 48 months) after CDA as compared with ACDF were included. Two authors independently extracted the articles and the predefined data. A total of 5 RCTs that reported 4 to 6 years of follow-up data were retrieved. Patients who underwent CDA had a lower mid- to long-term rate of re-operation and had greater mid- to long-term improvements in the Neck Disability Index, neck and arm pain scores, and Short Form 36 Health Survey physical component score than did those who underwent ACDF. Segmental motion was maintained in patients who underwent CDA. The mid- to long-term rates of adjacent segment disease and neurological success were not significantly different between the 2 groups. The authors concluded that CDA may result in better mid- to long-term functional recovery and a lower rate of subsequent surgical procedures than ACDF would. Moreover, they stated that a review of the literature showed that only an insufficient number of studies had investigated adjacent segment disease; therefore, it is mandatory that adequate future research should focus in this direction.

Alvin and Mroz (2014) evaluated the available literature on CDA with the Mobi-C prosthesis, with a focus on 2-level CDA. All clinical articles involving the Mobi-C disc prosthesis for CDA through September 1, 2014 were identified on Medline. Any paper that presented Mobi-C CDA clinical results was included. Study design, sample size, length of follow-up, use of statistical analysis, quality of life outcome scores, conflict of interest, and complications were recorded. A total of 15 studies were included that investigated Mobi-C CDA, only 1 of which was a level Ib RCT. All studies included showed non-inferiority of 1-level Mobi-C CDA to 1-level ACDF. Only 1 study analyzed outcomes of 1-level versus 2-level Mobi-C CDA, and only 1 study analyzed 2-level Mobi-C CDA versus 2-level ACDF. In comparison with other cervical disc prostheses, the Mobi-C prosthesis is associated with higher rates of heterotopic ossification (HO). Studies with conflicts of interest reported lower rates of HO. Adjacent segment disease or degeneration along with other complications, were not assessed in most studies. The authors

concluded that 1-level Mobi-C CDA is non-inferior, but not superior, to 1-level ACDF for patients with cervical degenerative disc disease. They stated that Mobi-C CDA procedure is associated with high rates of HO; 2-level Mobi-C CDA may be superior to 2-level ACDF. However, they noted that insufficient evidence exists, thereby mandating a need for unbiased, well-designed prospective studies with well-defined outcomes in the future.

Davis et al (2015) evaluated the safety and effectiveness of 2-level total disc replacement (TDR) using a Mobi-C cervical artificial disc at 48 months' follow-up. A prospective randomized, US FDA investigational device exemption pivotal trial of the Mobi-C cervical artificial disc was conducted at 24 centers in the U.S. A total of 330 patients with degenerative disc disease were randomized and treated with cervical total disc replacement (225 patients) or the control treatment, anterior cervical discectomy and fusion (ACDF) (105 patients). Patients were followed-up at regular intervals for 4 years after surgery. At 48 months, both groups demonstrated improvement in clinical outcome measures and a comparable safety profile. Data were available for 202 TDR patients and 89 ACDF patients in calculation of the primary end-point. TDR patients had statistically significantly greater improvement than ACDF patients for the following outcome measures compared with baseline: Neck Disability Index scores, 12-Item Short Form Health Survey Physical Component Summary scores, patient satisfaction, and overall success. ACDF patients experienced higher subsequent surgery rates and displayed a higher rate of adjacent-segment degeneration as seen on radiographs. Overall, TDR patients maintained segmental range of motion through 48 months with no device failure. The authors concluded that 4-year results from this study continue to support TDR as a safe, effective, and statistically superior alternative to ACDF for the treatment of degenerative disc disease at 2 contiguous cervical levels. This study provided mid-term follow-up results; long-term data are needed. Also, it is unclear whether the statistically significant improvements were clinically significant.

Furthermore, an UpToDate review on "Treatment of cervical radiculopathy" (Robinson and Kothari, 2015) states that "Artificial disc replacement -- Artificial cervical disc replacement surgery or arthroplasty is a developing technique for the treatment of single level cervical

radiculopathy that has been used in situations when an anterior cervical discectomy and fusion (ACDF) would otherwise be appropriate. The available evidence suggests that cervical disc replacement is equal to ACDF in terms of clinical outcomes. However, the long-term durability of the devices that have been developed is not known”.

In a meta-analysis, Zhao et al (2015) estimated the effectiveness of multi-level cervical arthroplasty over single-level CDA for the treatment of cervical spondylosis and disc diseases. To compare the studies of multi-level CDA versus single-level CDA in patients with cervical spondylosis that reported at least one of the following outcomes: functionality, neck pain, arm pain, quality of life, re-operation and incidence of heterotopic ossification, electronic databases (Medline, Embase, PubMed, Cochrane library, and Cochrane Central Register of Controlled Trials) were searched. No language restrictions were used; 2 authors independently assessed the methodological quality of included studies and extracted the relevant data. Out of 8 cohorts that were included in the study, 4 were prospective cohorts and the other 4 were retrospective. The results of the meta-analysis indicated that there was no significant difference in neck disability index scores, neck VAS, arm VAS, morbidity of re-operation, heterotopic ossification, and parameters of living quality when comparing multi-level CDA with single-level CDA at 1 and 2 years follow-up post-operatively ($p > 0.05$). The authors concluded that the findings of this meta-analysis revealed that the outcomes and functional recovery of patients performed with multi-level CDA were equivalent to those with single-level CDA, which suggested the multi-level CDA was as safe and effective as single-level invention for the treatment of cervical spondylosis. Moreover, they stated that more well-designed studies with large groups of patients are needed to provide further evidence for the benefit and reliability of multi-level CDA in the treatment of cervical disc diseases.

In a prospective, randomized, multi-center FDA-IIIDE study using TDR as surgical treatment of DDD at 1 or 2 contiguous levels of the cervical spine, Bae and colleagues (2015) evaluated the safety and effectiveness of TDR at single or 2 contiguous levels through 48 months of follow-up. Patients were randomized in a 2:1 ratio (TDR: ACDF) at 24 sites. Ultimately, 164 patients received TDR at 1 level and 225 patients received TDR at 2 contiguous levels. An additional 24 patients (15 1-

level, 9 2-level) were treated with TDR as training cases. Outcome measures included neck disability index, VAS neck and arm pain, Short Form 12-item Health Survey (SF-12) Mental Composite Score (MCS) and Physical Composite Score (PCS), ROM, major complication rates, and secondary surgery rates. Patients received follow-up examinations at regular intervals through 4 years after surgery. Pre-operative characteristics were statistically similar for the 1- and 2-level patient groups. Four-year follow-up rates were 83.1 % (1-level) and 89.0 % (2-level). There was no statistically significant difference between 1- and 2-level TDR groups for all clinical outcome measures. Both TDR groups experienced significant improvement at each follow-up when compared with pre-operative scores. One case of migration was reported in the 2-level TDR group. The authors concluded that a 4-year post hoc comparison of 1- and 2-level TDR patients concurrently enrolled in a 24-center, FDA-IDE clinical trial indicated no statistical differences between groups in clinical outcomes, overall complication rates, and subsequent surgery rates. They stated that longer-term studies may be needed to answer the question whether TDR, in comparison with ACDF, reduces clinical adjacent segment pathology.

In a prospective, multi-center, randomized, un-blinded clinical trial, Jackson et al (2016) evaluated subsequent surgery rates up to 5 years in patients treated with TDR or ACDF at 1 or 2 contiguous levels between C3 and C7. Patients with symptomatic DDD were enrolled to receive 1- or 2-level treatment with either TDR as the investigational device or ACDF as the control treatment. There were 260 patients in the 1-level study (179 TDR and 81 ACDF patients) and 339 patients in the 2-level study (234 TDR and 105 ACDF patients). At 5 years, the occurrence of subsequent surgical intervention was significantly higher among ACDF patients for 1-level (TDR, 4.5 % [8/179]; ACDF, 17.3 % [14/81]; $p = 0.0012$) and 2-level (TDR, 7.3 % [17/234]; ACDF, 21.0 % [22/105], $p = 0.0007$) treatment. The TDR group demonstrated significantly fewer index- and adjacent-level subsequent surgeries in both the 1- and 2-level cohorts. The authors concluded that 5-year results showed treatment with cervical TDR to result in a significantly lower rate of subsequent surgical intervention than treatment with ACDF for both 1 and 2 levels of treatment. The main drawbacks of this study included: (i) the inability to blind surgeons and patients to treatment, which opened the results to the potential of confirmation bias. Although the control group in this study

was limited to anterior plating with allograft, other fusion procedures and devices (e.g., standalone devices and the use of autograft) were viable treatment options, (ii) the comparative results between the control and investigational groups were limited to anterior plate and allograft and may not be consistent with those of other surgical alternatives for cervical fusion, and (iii) the control group consisted of patients receiving 3 different cervical plate systems, based on surgeon preference. This heterogeneity represented a study limitation because ACDF failures may not have been equally distributed across the 3 fusion systems implanted. The authors stated that the results from this clinical trial suggested that TDR may provide a substantial benefit over ACDF in providing a lower risk for subsequent surgical intervention.

Ament et al (2016) noted that the cost-effectiveness of cervical TDR was established by looking at 2-year follow-up, and this update re-evaluated the analysis over 5 years. Data were derived from a randomized trial of 330 patients. Data from the 12-Item Short Form Health Survey were transformed into utilities by using the SF-6D algorithm. Costs were calculated by extracting diagnosis-related group codes and then applying 2014 Medicare reimbursement rates. A Markov model evaluated quality-adjusted life years (QALYs) for both treatment groups. Univariate and multivariate sensitivity analyses were conducted to test the stability of the model. The model adopted both societal and health system perspectives and applied a 3 % annual discount rate. The cTDR costs \$1,687 more than ACDF over 5 years. In contrast, cTDR had \$34,377 less productivity loss compared with ACDF. There was a significant difference in the return-to-work rate (81.6 % compared with 65.4 % for cTDR and ACDF, respectively; $p = 0.029$). From a societal perspective, the incremental cost-effective ratio (ICER) for cTDR was -\$165,103 per QALY. From a health system perspective, the ICER for cTDR was \$8,518 per QALY. In the sensitivity analysis, the ICER for cTDR remained below the US willingness-to-pay threshold of \$50,000 per QALY in all scenarios (-\$225,816 per QALY to \$22,071 per QALY). The authors concluded that this study is the first to report the comparative cost-effectiveness of cTDR versus ACDF for 2-level DDD at 5 years; they stated that because of the negative ICER, cTDR is the dominant modality. The drawbacks of this study, which was conducted using decision analytical modeling included: (i) the Markov model is supposed to be conditional on the present

state alone; future and past events are assumed independent. With disease processes, it is rarely plausible to assume that a patient's transition to another health state was not in some way dependent on their previous health state, (ii) the model also assumed that surgical cohorts began in similar health states, (iii) despite the stringent criteria used in the RCT, it is rarely possible to blind patients or surgeons in a surgical trial. Thus, it is perceivable that patients receiving the novel cTDR intervention may have experienced more subjective improvement compared with the ACDF group. Similarly, surgeons may be biased toward one approach and made different intra-operative and post-operative decisions as a result, (iv) some cost data were not ascertainable, and (v) productivity loss also significantly contributed to cost. Although comprehensive, this analysis did not include aspects such as transportation costs, caregiver time/responsibilities, and educational days missed. Furthermore, in monetary terms, productivity loss was calculated by using the 2014 national average wage. It is unclear how these estimates may bias the conclusion.

Furthermore, the current version of UpToDate's review on "Treatment of cervical radiculopathy" (Robinson and Kothari, 2016) still maintains that "the long-term durability of the devices that have been developed is not known".

Zeng and co-workers (2018) stated that cervical disc arthroplasty (CDA) has been considered as an alternative to cervical arthrodesis in the treatment of cervical DDD (CDDD). These investigators evaluated the long-term clinical and radiographic outcomes of CDA with Prestige-LP Disc. A total of 61 patients who underwent single- or 2-level CDA with Prestige-LP Disc were retrospectively examined at a minimum of 6-year follow-up. Clinical assessments included VAS for neck and arm pain, NDI, and Japanese Orthopedic Association (JOA) score. Radiological evaluations included ROM of the index and adjacent levels, segmental angle, cervical sagittal alignment, HO and adjacent segment degeneration (ASD). Significant and maintained improvement in VAS for neck and arm, NDI and JOA were observed after a mean follow-up of 82.3 months ($p < 0.001$). The pre-operative ROM of the index level was 9.7° , which was maintained at 2- and 4-year follow-up (9.3° , $p = 0.597$;

9.0°, $p = 0.297$), but was decreased to 8.0° at final follow-up ($p = 0.019$). Mobility was maintained in 80.5 % (62/77) of the implanted prostheses at final follow-up; ROM of the superior and inferior adjacent segments, cervical sagittal alignment and cervical angle were all maintained. The incidence of HO was 42.9 % at final follow-up, but it did not influence the clinical outcome. Radiographic ASD were detected in 29.5 % of the patients. However, the incidence of symptomatic ASD was only 6.6 %. The authors concluded that cervical disc arthroplasty with Prestige-LP Disc demonstrated a maintained and satisfactory clinical outcome at a minimal of 6-year follow-up, with majority of the prostheses remained mobile. These researchers stated that cervical disc arthroplasty with Prestige-LP Dis can be considered as an effective surgical method in treating CDDD.

Pointillart and associates (2018) stated that the cervical TDR (CTDR) is a technique that treats CDDD. Initial shorter-term studies showed good clinical and radiological results. In a prospective study, these researchers evaluated the clinical and radiological results of Bryan cervical disc replacement (Medtronic Sofamor Danek Inc., Memphis, TN) at 15-year follow-up. This trial included 20 patients who underwent 22 CTDR, comprising a single-level procedure in 14 patients and 2-level procedures in 6 patients. The mean follow-up period was 15.5 years. The mean age at the intervention was 46.2 years (range of 26 to 65 years); 2 patients needed re-operation for recurrence of symptoms. According to Odom's criteria, 80.0 % (16 of 20 patients) had excellent outcomes, VAS for neck pain was 2.6 (0 to 10), for shoulder/arm pain it was 1.8 (0 to 7), and NDI at the final follow-up was 14.9. The SF-12 PCS was 46.1, and SF-12 MCS was 51.9. Mobility was maintained in 15 of the 22 (68.2 %) operated segments, ROM of prostheses were $9^\circ \pm 3.9^\circ$ (range of 4 to 15°). The prostheses were positioned in kyphosis in 14 of 22 levels (63.6 %). There was a positive correlation between the kyphosis of the prosthesis and the occurrence of HO, and their grade ($p = 0.36$, 95 % CI: -0.68 to 0.07); HO had developed at 12 of the 22 levels (54.5 %) and upper adjacent segment degeneration in 11 of 18 of patients (64.7 %). All these results were not significantly different to outcomes at 8 years follow-up. The authors concluded that in a cohort of 20 patients with 15-year clinical and radiological follow-up, the Bryan CTDR has demonstrated a

sustained clinical improvement and implant mobility over time, despite a moderate progression of degenerative processes at the prosthetic and adjacent levels.

Gao and co-workers (2019) presented a long-term clinical and radiographic comparison between the Prestige LP cervical disc replacement and the Zero-P spacer cervical disc fusion in the treatment of patients with symptomatic 2-level CDDD. A total of 36 patients in the ACDF group and 24 patients in the CDA group were analyzed before surgery and at 1 week and 3, 6, 12, 24, and 60 months after surgery. Clinical assessments included the JOA score, VAS, and NDI scores. Radiographic assessments included cervical lordosis, ROM of the total cervical spine, functional spinal unit (FSU), and superior and inferior adjacent segments. Complications including HO and ASD at 5-year follow-up were collected as well. Mean follow-up period was 65.6 months. Both the ACDF and CDA groups showed significant clinical improvements in terms of JOA score, VAS, and NDI ($p < 0.05$), but there was no significant difference between groups at the last follow-up period. A significant increase of cervical lordosis was observed in the CDA group after surgery whereas a significant difference was not observed between groups. ROM of the total cervical spine and FSU were maintained during the follow-up, and a significant decrease was observed in the ACDF group after surgery ($p < 0.05$). The ROM of the superior adjacent segment did not show any difference whereas the ROM of the inferior adjacent segment in the ACDF group presented a significant increase at 6 months and 1 year after surgery and a significant decrease at the last follow-up period. A total of 8 (33.3 %) patients in the CDA group had an occurrence of HO; ASD was observed in 2 (8.3 %) patients who underwent CDA surgery and 8 (22.2 %) patients who underwent ACDF surgery. The authors concluded that the use of the Prestige-LP and ZERO-P Spacer implantations was safe and effective. At 5 years after surgery, CDA with Prestige-LP was superior in terms of ROM of the total cervical spine, FSU, and inferior adjacent segment. It also had a relatively low occurrence rate of ASD. This procedure may be a suitable choice for the treatment of contiguous 2-level CDDD.

Xu and colleagues (2019) evaluated long-term radiographic and clinical effectiveness of cervical TDR with Prodisc-C prosthesis at a minimum of 10 years follow-up. The clinical data of 118 patients with CDDD treated

with TDR by using Prodisc-C prosthesis between December 2005 and April 2008 were retrospectively analyzed. There were 66 men and 52 women with the age of 25 to 62 years (mean of 46.8 years). There were 38 cases of cervical spondylotic radiculopathy, 28 cases of cervical spondylotic myelopathy, and 52 cases of mixed cervical spondylotic myelopathy. The operative segments were C3 to C7, including 90 cases of single segment, 20 cases of continuous double segments, and 8 cases of continuous 3 segments. A total of 154 Prodisc-C prostheses were used during the operation. The clinical effectiveness was evaluated by pain VAS score, NDI, JOA score, and Odom grade before and after operation. Imaging evaluation indicators included ROM, intervertebral disc height (IDH), sagittal lordosis angle, and prosthesis displacement, subsidence, loosening, locking, and HO, ASD, and other complications. Patients were grouped according to whether HO or ASD occurred or not, the ROM of surgical segment was compared. All patients were followed up for 121 to 150 months (mean of 135.8 months). No revision operation was performed during the follow-up period. The VAS, NDI, JOA scores and Odom grades were significantly improved at 1 week after operation and last follow-up when compared with pre-operative ones ($p < 0.05$); VAS and NDI scores were further improved at last follow-up than those at 1 week after operation ($p < 0.05$); there was no significant difference in JOA scores and improvement rates between at 1 week after operation and at last follow-up ($p > 0.05$). The ROM of the whole cervical spine and the operative segment decreased at 1 week and 10 years after operation when compared with pre-operative ones ($p < 0.05$), but there was no significant difference in the other time points ($p > 0.05$); there was no significant difference in the ROM between the upper adjacent segment (UAS) and the lower adjacent segment (LAS) at each time-point after operation ($p > 0.05$). There was no significant difference in sagittal lordosis angle of cervical spine before and after operation ($p > 0.05$); the sagittal lordosis angle of operative segment increased significantly at 1 week, 6 months, 1 year, and 2 years after operation ($p < 0.05$). The IDH of operative segment was significantly improved at each time-point after operation ($p < 0.05$), but there was no significant difference in IDH between UAS and LAS at each time-point after operation ($p > 0.05$). No prosthesis displacement, subsidence, or loosening occurred at each time-point after operation. There was no significant difference of the prosthetic displacement and subsidence distance between all time-points after 6 months after operation ($p > 0.05$). At last follow-up, the incidence of

prosthetic locking/fusion was 10.4 %, showing no significant difference when compared with 6 months (1.9 %) ($p < 0.05$). The incidence of upper ASD and lower ASD was 1.3 % and 2.6 % respectively at 1 week after operation. The incidence of upper ASD and lower ASD increased gradually with time prolonging, and there were significant differences between different time-points ($p < 0.05$). The ROM of operative segment in ASD group was lower than that in non-ASD group at each time-point after operation, but there was no significant difference ($p > 0.05$). HO appeared in 58.4 % of the segments at 6 months after operation, and the incidence of HO increased significantly with time, which was significantly different from that at 6 months after operation ($p < 0.05$). The ROM of operative segments in HO group was significantly lower than that in non-HO group at 6 months, 2 years, 5 years, and 10 years after operation ($p < 0.05$). The authors concluded that cervical TDR had little effect on adjacent segments, although there were some imaging complications, it had no significant effect on the improvement of overall clinical effectiveness. These investigators stated that Prodisc-C prosthesis could provide long-term, safe, and definite clinical effectiveness in the treatment of CDDD.

In a multi-center, FDA-regulated feasibility study, Laurysen and colleagues (2012) examined the safety and effectiveness of a next-generation CTDR device in patients with symptomatic cervical radiculopathy. This trial evaluated the safety and effectiveness of the M6-C Artificial Cervical Disc for the treatment of patients with symptomatic cervical radiculopathy at 1 or 2 levels from C3 to C7; NDI, VAS assessing neck and arm pain, SF-36, safety, and radiographic outcomes were assessed pre-operatively, at 6 weeks and 3, 6, 12, and 24 months post-operatively. A total of 30 patients were enrolled at 3 clinical sites.

Patients were implanted at either 1 or 2 levels. Mean NDI improved from 67.8 to 20.8 ($p < 0.0001$) at 24 months. Significant improvement was also observed through 24-month follow-up in neck and arm pain VAS ($p < 0.0001$) and in physical ($p < 0.005$) and mental component scores of the SF-36 at 3, 6, and 12 months ($p < 0.008$). There were no serious AEs related to the device or procedure as adjudicated by an independent clinical events committee. Radiographically, disc space height increased more than 50 % with a correlative increase in the post-operative disc angle; ROM decreased slightly from baseline during early follow-up but increased slightly and were maintained throughout the follow-up period.

The authors concluded that the M6-C cervical artificial disc represented a new generation of CTDR design; results of this study found the M6-C device to produce positive clinical and radiographic outcomes similar to other CTDRs, warranting further investigation.

Pham and associates (2018) compared the kinematics associated with the M6-C and Mobi-C against the normal range of motion in the non-degenerative population. Patients who underwent M6-C or Mobi-C disc replacements by the senior author from 2012 to 2015 were identified at a single tertiary institution. Routine 3-month post-operative lateral radiographs were analyzed for flexion and extension ROM angles at the involved vertebral level by 2 independent authors. Data were compared to previous published studies investigating cervical spine ROM of asymptomatic patients. There was no statistical significance in the difference of overall flexion range between M6-C and Mobi-C prostheses. However, overall range of extension of Mobi-C was greater compared to M6-C ($p = 0.028$). At C5 to C6, the range of flexion for both implants were similar but lesser compared to asymptomatic patients ($p < 0.001$). Range of extension was greater in the Mobi-C group ($14.2^\circ \pm 5.1^\circ$) compared to the M6-C ($7.3^\circ \pm 4.6^\circ$) ($p = 0.0009$). At C6 to C7, there were no statistical differences in both range of flexion and extension between the 2 prostheses and asymptomatic patients ($p > 0.05$). The authors concluded that early results regarding restoration of ROM following cervical arthroplasty using either M6-C or Mobi-C prosthesis are encouraging; long-term follow-up studies are needed to observe the change in ROM over time with physiological loading and wear patterns.

On February 6, 2019, the FDA approved the M6-C artificial cervical disc for reconstruction of the disc following single-level discectomy in skeletally mature patients with intractable degenerative cervical radiculopathy with or without spinal cord compression at 1 level from C3 to C7.

On September 18, 2020, the FDA approved the Simplify cervical artificial disc, which is indicated for use in skeletally mature patients for reconstruction of the disc at 1 or 2 contiguous levels from C3 to C7 following discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to abnormality localized to the disc space and manifested by at least 1 of the

following conditions confirmed by radiographic imaging (e.g., X-rays, CT, MRI): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. Patients receiving Simplify Cervical Artificial Disc should have failed at least 6 weeks of non-operative treatment or demonstrated progressive signs or symptoms despite non-operative treatment prior to implantation. The Simplify Cervical Artificial Disc is implanted via an open anterior approach.

https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200022B.pdf

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Lumbar Partial Disc Prosthetics (e.g., Nubac, and the DASCOR Disc Arthroplasty System)

Lumbar partial disc replacement is a minimally invasive procedure that replaces only the nucleus pulposus in an attempt to fill the therapy gap between discectomy and fusion. The procedure targets only the nucleus pulposus as the origin of pain while attempting to restore the biomechanical function of the whole segment. Careful patient selection is crucial since the prosthetic nucleus is not fixed into position. An intact annulus and properly functioning endplates must be present. Exclusion criteria include osteoporosis, endplate problems, posterior element disorder (e.g., stenosis, facet arthritis, isthmic pathologies), and infection tumors. There are several lumbar partial disc replacement devices currently under investigation. These devices use hydrogel, polymer/synthetic, or mechanical technologies, however, none are commercially available in the United States. All non-fusion spinal implants are considered Class III medical devices and require Pre-Market Approval (PMA) from the FDA prior to market release in the United States.

Nubac (Pioneer Surgical Technology, Inc., Marquette, MI) is an elastomeric nucleus replacement device composed of polyetheretherketone (PEEK) that is used in partial disc replacement. The Nubac procedure is intended to conserve most of the annular tissue and to be less invasive than total disc replacement and fusion allowing further treatment options if revision is required. Alpizar-Aguirre, et al. (2008) reported the results of 10 patients with DDD who underwent

discectomy with the Nubac device. Surgical approach was anterolateral (n = 4), posterior (n = 3) and anterior (n = 3). After 3-months post-operatively, ODI improved from 58.2% to 24.2% ($p < 0.05$), VAS improved from 8.1 to 2.5 ($p < 0.05$), and disc height improved from 9.4 mm to 12.5 mm, but lumbar motion did not improve. The authors concluded that the Nubac prosthesis improved lumbar discogenic pain in a short time, however, a minimum follow-up of 4 years is needed to make a definite conclusion. According to a review of nucleus replacement technologies (Coric & Mummaneni, 2008), a challenge of using preformed elastomeric devices is implant extrusion due to their inherently deformable nature. Other issues include their durability and their effectiveness compared to established alternatives (e.g., laminectomy, percutaneous discectomy) for lumbar disc herniation. Available published peer reviewed evidence of the Nubac disc prosthesis is of a preliminary nature. Well controlled clinical studies are necessary to evaluate the effectiveness, safety and durability of results of this device.

The DASCOR (Disc Dynamics Inc., Eden Prairie, MN) is a balloon device that is inserted into the disc space after total nucleus removal. The balloon is then filled with an injectable polyurethane polymer that conforms to the individual's anatomy. The remaining implant is designed to restore the original disc function and replaces the nucleus. Ahrens, et al. (2009) reported the results from 2 prospective, non-randomized multi-center European studies on lumbar disc nucleus replacement using the DASCOR disc arthroplasty device for DDD (n = 85). Data were collected before surgery and after surgery at 6 weeks and at 3, 6, 12, and 24 months. The clinical outcome measures were obtained from VAS for back pain, ODI, radiographic assessments, and records of analgesic medication use. Mean VAS and ODI scores improved significantly after 6 weeks and throughout the 2 years. Radiographic results demonstrated, at a minimum, maintenance of disc height with no device expulsion and, despite Modic-Type 1 changes, no subsidence. Fourteen patients had serious adverse events including device explants in 7 patients (7 of 85), in which the main complication was resumed back pain after time. Patients' rate of analgesic medication decreased dramatically over time, with all patients experiencing significant improvements after 3 months and nearly no analgesic medication or narcotic drug use at 2 years. The authors concluded that these interim outcomes showed significant improvements

in mean ODI and VAS scores and suggest that the DASCOR device may be a safe and effective less-invasive surgical option for patients with DDD.

Further clinical investigation with well-designed prospective, randomized trials is needed to determine the efficacy of nucleus replacement in the treatment of lumbar DDD, as well as its ideal indications.

One versus Two Cages in Lumbar Interbody Fusion

Liu and colleagues (2014) compared the fusion rate and safety of lumbar interbody fusion using 1 cage versus 2 cages for the treatment of degenerative lumbar spinal diseases. All randomized controlled trials (RCTs) and comparative observational studies written in English comparing the outcome of lumbar interbody fusion using 1 or 2 cages in patients with degenerative lumbar spinal diseases were identified by a comprehensive search of PubMed Central, MEDLINE, EMBASE, BIOSIS and the Cochrane Central Registry of Controlled Trials. An exhaustive electronic search up to July 2013 was carried out. The quality of the methodology was assessed and relevant data retrieved independently by 2 reviewers, after which the resultant data were subjected to meta-analysis. All meta-analyses were performed using Review Manager 5.0, which was recommended and provided by the Cochrane Collaboration. The systematic search yielded 745 studies from the selected databases. After duplicate studies had been identified and the titles and abstracts screened, 736 studies were excluded because they were irrelevant to the topic. The full texts of the remaining 9 potentially relevant references were comprehensively evaluated and 4 excluded for the following reasons: 2 studies involved co-interventions and the other 2 lacked control groups. Two relevant RCTs and 3 comparative observational studies involving 384 patients and 501 spinal segments with at least 1 year follow-up were identified. Analysis of the pooled data demonstrated no significant difference in fusion rate between the 1-cage and 2-cage groups. However, intra-operative blood loss and operating time were less and the complications rate lower in the 1-cage group. The authors concluded that in patients with degenerative lumbar spinal diseases, lumbar interbody fusion using 1 cage has an equal fusion rate and is

safer compared with using 2 cages. However, because this meta-analysis had some limitations, more high quality RCTs are needed to strengthen the evidence.

Artificial Cervical Disc Arthroplasty versus Anterior Cervical Discectomy and Fusion

In a systematic review on “Artificial cervical disc arthroplasty versus anterior cervical discectomy and fusion”, Bakar et al (2014) concluded that “Given the long-term outcomes that have been studied for anterior cervical discectomy and fusion, it is difficult to assess the future potential of anterior cervical disc arthroplasty as an alternative to anterior cervical discectomy and fusion. It is important to note that current studies with follow-up to 4 years have shown promising outcomes. The ability of anterior cervical disc arthroplasty to decrease the potential for common and well-known late complications of anterior cervical discectomy and fusion (such as adjacent segment disease) is an important and interesting possibility. Future long-term randomized controlled trials and cost effectiveness studies are needed to properly assess the continued use of artificial cervical disc arthroplasty and to determine the relative cost effectiveness compared with anterior cervical discectomy and fusion”.

Jang et al (2017) evaluated the safety and efficacy of 3-level hybrid surgery (HS), which combines fusion and cervical disc replacement (CDR), compared to 3-level fusion in patient with cervical spondylosis involving 3 levels. Patients in the anterior cervical discectomy and fusion (ACDF) group (n = 30) underwent 3-level fusion and the HS group (n = 19) underwent combined surgery with fusion and CDR. Clinical outcomes were evaluated using the visual analog scale (VAS) for the arm, the neck disability index (NDI), Odom criteria and post-operative complications. The cervical range of motion (ROM), fusion rate and adjacent segments degeneration were assessed with radiographs. Significant improvements in arm pain relief and functional outcome were observed in ACDF and HS group. The NDI in the HS group showed better improvement 6 months after surgery than that of the ACDF group. The ACDF group had a lower fusion rate, higher incidence of device related complications and radiological changes in adjacent segments compared with the HS group. The better recovery of cervical ROM was observed in HS group. However, that of the ACDF group was significantly decreased and did not

recover. The authors concluded that the HS group was better than the ACDF group in terms of NDI, cervical ROM, fusion rate, incidence of post-operative complications and adjacent segment degeneration.

The authors stated that this study had several drawbacks. First, this study was a retrospective cases series. Second, in HS group, the surgical method and types of artificial discs were not homogeneous. Thirds, the number of patients was small (n = 19 in the HS group) and the follow-up period was too short (6 months) to draw a firm conclusion. These researchers stated that a randomized controlled trial will be needed to evaluate these procedures in the future.

Lee and Cho (2017) compared the safety and efficacy of ACDF and cervical total disc replacement (CTDR) as revision surgeries for symptomatic adjacent segment degeneration (ASD) in cases with previous ACDF. Between 2010 and 2014, a total of 41 patients with previous cervical fusion surgery underwent ACDF or CTDR for symptomatic ASD; 22 patients in the ACDF group underwent 26 ACDFs, and 19 patients in the CTDR group underwent 25 arthroplasties for symptomatic ASD. Clinical outcomes were assessed by a VAS for arm pain, the NDI and Odom's criteria. Radiological evaluations were performed pre-operatively and post-operatively to measure changes in the ROM of the cervical spine and adjacent segments and arthroplasty level. The radiological change of ASD was assessed in radiographs. Clinical outcomes as assessed with VAS for arm pain and Odom's criteria were significantly improved in both groups. The CTDR group showed better NDI improvement after surgery ($p < 0.05$). The mean C2-7 ROM of the CTDR group revealed faster recovery than did that of the ACDF group and the pre-operative values were recovered at the last follow-up visit. There was a significant difference in the ROM of the inferior adjacent segment between the ACDF and CTDR groups ($p < 0.05$). The ACDF group had a higher incidence of radiological changes in the adjacent segment compared with the CTDR group ($p < 0.05$). The authors concluded that the 2-year clinical results of CTDR for symptomatic ASD were safe and were comparable to the outcomes of ACDF in terms of arm pain relief and functional recovery. The CTDR group showed better NDI improvement, faster C2-7 ROM recovery, less of an increase in ROM in the inferior adjacent segment, and a lower incidence of adjacent segment degeneration than did the ACDF group.

This study had similar drawbacks as the afore-mentioned study by Jang et al (2017) -- retrospective design, small number of patients (n = 19) and relatively short-term (2 years) follow-up. Also, it is unclear whether these "advantages" of ACDF plus CTDR would hold up beyond 2 years.

Rajakumar et al (2017) noted that adjacent-level disc degeneration following cervical fusion has been well reported. This condition poses a major treatment dilemma when it becomes symptomatic. The potential application of cervical arthroplasty to preserve motion in the affected segment is not well documented, with few studies in the literature. These investigators presented their initial experience of analyzing clinical and radiological results in such patients who were treated with arthroplasty for new or persistent arm and/or neck symptoms related to neural compression due to adjacent-segment disease after ACDF. During a 5-year period, 11 patients who had undergone ACDF and subsequently developed recurrent neck or arm pain related to adjacent-level cervical disc disease were treated with cervical arthroplasty at the authors' institution. A total of 15 devices were implanted (range of treated levels per patient: 1 to 3). Clinical evaluation was performed both before and after surgery, using a VAS for pain and the NDI. Radiological outcomes were analyzed using pre- and post-operative flexion/extension lateral radiographs measuring Cobb angle (overall C2 to C7 sagittal alignment), functional spinal unit (FSU) angle, and ROM. There were no major peri-operative complications or device-related failures. Statistically significant results, obtained in all cases, were reflected by an improvement in VAS scores for neck/arm pain and NDI scores for neck pain. Radiologically, statistically significant increases in the overall lordosis (as measured by Cobb angle) and ROM at the treated disc level were observed; 3 patients were lost to follow-up within the 1st year after arthroplasty. In the remaining 8 cases, the duration of follow-up ranged from 1 to 3 years. None of these 8 patients required surgery for the same vertebral level during the follow-up period. The authors concluded that artificial cervical disc replacement in patients who have previously undergone cervical fusion surgery appeared to be safe, with encouraging early results based on this small case series, but more data from larger numbers of patients with long-term follow-up are needed.

Wu et al (2017) stated that the safety and efficacy of CDA performed adjacent to previous fusion for the treatment of ASD remains unknown. In a systematic review, these researches examined clinical evidence on the outcomes of CDA performed adjacent to previous cervical fusion. They carried out a systematic search of PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Medline and Embase for literature published through March 2017. All the studies on CDA for the treatment of ASD after cervical fusion surgery were included. Two independent reviewers searched and assessed the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). A total of 5 studies were identified. The overall quality of evidence was low. All included studies demonstrated that clinical outcomes reflected by several assessment scales improved following arthroplasty. Cervical lordosis ROM after arthroplasty remained and was even enhanced post-operatively. The rate of complications and subsequent surgeries was low. The authors concluded that there is a dearth of information regarding the outcomes of CDA for the treatment of ASD in the literature. In general, CDA may be a safe and effective surgical procedure to treat ASD, but this conclusion needs to be confirmed by future long-term, prospective clinical trials.

Luo et al (2018) noted that the concern of ASD has led to the development of motion-preserving technologies, such as CDA. However, there is still controversy whether CDA is superior to ACDF as to the incidence of ASD. These investigators evaluated the rate of ASD between CDA and ACDF. They performed a systematic searches of all relevant studies through November 2017 from the Cochrane Library, PubMed, Embase, and CNKI; RCTs comparing the clinical effectiveness of CDA and ACDF for cervical DDD were included. Two independent reviewers searched and assessed all literature according to the standard of Cochrane systematic review. Data extraction and quality assessment were conducted, and RevMan 5.2 was used for data analysis. The random effects model was used if there was heterogeneity between studies; otherwise, the fixed effects model was used. A total of 21 studies were included in this meta-analysis. The pooled data revealed that the CDA group had significantly lower ASD than the ACDF group did. Furthermore, there were fewer adjacent segment re-operations in the CDA group compared with the ACDF group. The authors concluded that CDA was better than the ACDF in terms of ASD and adjacent segment

re-operations. These researchers stated that this conclusion suggested that CDA is a superior alternative invention for the treatment of cervical DDD to preserve cervical ROM and reduce the risk of ASD; however, this requires further validation and investigation in prospective, randomized, larger sample-size trials with long-term follow-up.

Pron and associates (2019) stated that cervical DDD is a multi-factorial condition that begins with deterioration of the intervertebral disc and results in further degeneration within the spine involving the facet joints and ligaments. On behalf of Health Quality Ontario, these investigators conducted a health technology assessment to examine the safety, effectiveness, durability, and cost-effectiveness of cervical ADR (C-ADR) versus fusion for treating cervical degenerative disc disease. These researchers carried out a systematic literature search of the clinical evidence comparing C-ADR with fusion. They examined the risk of bias in each study and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. They carried out a systematic review of the economic literature and evaluated the cost-effectiveness of C-ADR compared with fusion. Furthermore, these investigators estimated the budget impact of publicly funding C-ADR in Ontario over the next 5 years. A total of 8 studies of C-ADR for 1-level cervical DDD and 2 studies of C-ADR for 2-level disease satisfied the criterion of statistical non-inferiority compared with fusion on the primary outcome of 2-year overall treatment success (GRADE: Moderate). In 2 studies of C-ADR for 2-level disease, C-ADR was statistically superior to fusion surgery for the same primary outcome (GRADE: Moderate). C-ADR was also non-inferior to fusion for peri-operative outcomes (e.g., operative time, blood loss), patient satisfaction, and health-related QOL (GRADE: Moderate). C-ADR was superior to fusion for recovery and return-to-work, had higher technical success, and had lower rates of re-operation at the index site (GRADE: Moderate). C-ADR also maintained motion at the index-treated cervical level (GRADE: Moderate), but evidence was insufficient to determine if adjacent-level surgery rates differed between C-ADR and fusion. Current evidence is also insufficient to determine the long-term durability of C-ADR. The primary economic analysis showed that C-ADR was likely to be cost-effective compared with fusion for both 1-level (\$11,607/QALY) and 2-level (\$16,782/QALY) degeneration. Various sensitivity and scenario analyses confirmed the robustness of the results.

The current uptake for 1-level and 2-level C-ADR in Ontario is about 8 % of the total eligible. For 1-level involvement, the estimated net budget impact increased from \$7,243 (18 procedures) in the 1st year to \$395,623 (196 procedures) in the 5th year following public funding, for a total budget impact over 5 years of \$916,326. For 2-level involvement, the corresponding values were \$5,460 (7 procedures) in the 1st year and \$283,689 (76 procedures) in the 5th year, for an estimated total budget impact of \$705,628 over 5 years. Individuals with cervical DDD reported that symptoms of pain and numbness can have a negative impact on their QOL. Individuals with whom these investigators spoke had tried a variety of treatments with minor success; surgery was perceived as the most effective and permanent solution. The authors concluded that for carefully selected patients with cervical DDD, C-ADR provided patient-important and statistically significant reductions in pain and disability. Furthermore, unlike fusion, C-ADR allowed patients to maintain relatively normal cervical spine motion. Compared with fusion, C-ADR appeared to represent good value for money for adults with 1-level cervical DDD (\$11,607/QALY) and for adults with 2-level disease (\$16,782/QALY). In Ontario, publicly funding C-ADR could result in total additional costs of \$916,326 for 1-level procedures and \$705,628 for 2-level procedures over the next 5 years. Individuals with whom these researchers spoke who had undergone C-ADR surgery spoke positively of its impact on their QOL and ability to move their neck after surgery. The limited availability of C-ADR in Ontario was viewed as a barrier to receiving this treatment.

Wang and colleagues (2020) examined the long-term safety and efficiency of CDA and ACDF for cervical disc disease. These researchers carried out this trial according to the Cochrane methodology. An extensive search was performed in PubMed, Embase, and Cochrane databases up to June 1, 2019 using the following key words: "anterior cervical fusion", "arthroplasty", "replacement" and "artificial disc".

RevMan 5.3 (Cochrane, London, U.K.) was used to analyze data. Safety and efficiency outcome measures included the success rate, functional outcome measures, AEs, ASD, secondary surgery, and patients' satisfaction and recommendation rates. The OR and MD with 95 % CI were used to examine discontinuous and continuous variables, respectively. The statistically significant level was set at $p < 0.05$. A total of 11 RCTs with 3,505 patients (CDA/ACDF: 1,913/1,592) were included in this meta-analysis. Compared with ACDF, CDA achieved significantly

higher overall success (2.10, 95 % CI: 1.70 to 2.59), NDI success (1.73, 95 % CI: 1.37 to 2.18), neurological success (1.65, 95 % CI: 1.24 to 2.20), patients' satisfaction (2.14, 95 % CI: 1.50 to 3.05), and patients' recommendation rates (3.23, 95 % CI: 1.79 to 5.80). Functional outcome measures such as VAS neck pain (-5.50, 95 % CI: -8.49 to -2.52) and arm pain (-3.78, 95 % CI: -7.04 to -0.53), the SF-36 physical component score (SF-36 PCS) (1.93, 95 % CI: 0.53 to 3.32), and the SF-36 mental component score (SF-36 MCS) (2.62, 95 % CI: 0.95 to 4.29), revealed superiority in the CDA group. CDA also achieved a significantly lower rate of symptomatic ASD (0.46, 95 % CI: 0.34 to 0.63), total secondary surgery (0.50, 95 % CI: 0.29 to 0.87), secondary surgery at the index level (0.46, 95 % CI: 0.29 to 0.74), and secondary surgery at the adjacent level (0.37, 95 % CI: 0.28 to 0.49). However, no significant difference was found in radiological success (1.35, 95 % CI: 0.88 to 2.08), NDI score (-2.88, 95 % CI: -5.93 to 0.17), total reported AE (1.14, 95 % CI: 0.92 to 1.42), serious AE (0.89, 95 % CI: 0.71 to 1.11), device/surgery-related AE (0.90, 95 % CI: 0.68 to 1.18), radiological superior ASD (0.63, 95 % CI: 0.28 to 1.43), inferior ASD (0.45, 95 % CI: 0.19 to 1.11), and work status (1.33, 95 % CI: 0.78 to 2.25). Furthermore, subgroup analysis showed different results between US and non-US groups. The authors concluded that the findings of this study provided further evidence that compared to ACDF, CDA had a higher long-term clinical success rate and better functional outcome measurements; and resulted in less symptomatic ASD and fewer secondary surgeries.

Hybrid Surgery for Multi-Level Cervical Degenerative Disc Disease

Jia et al (2014) noted that the optimal surgical technique for multi-level cervical DDD remains controversial. Hybrid surgery (HS) incorporating ACDF and CDR is increasingly performed for cervical DDD. These researchers examined the biomechanical and clinical evidence available for HS and provided a systematic review of current understanding of HS. This systematic review was undertaken by following the PRISMA Statement. Multiple data-bases and online registers of clinical trials were searched up to February 2014. The biomechanical and clinical studies on HS for cervical DDD written in English were included; 2 authors independently assessed methodological quality and extracted data. A total of 15 studies including 8 biomechanical studies and 7 clinical studies were identified. The biomechanical studies showed that HS was

beneficial to motion preservation of the operative levels and revealed less adverse effect on adjacent segments. All clinical studies demonstrated improvement in validated functional scores after HS. Segment motion and immobilization were achieved at the arthroplasty level and arthrodesis level, respectively. Post-operative assessments and complication rate were similar or in favor of HS when comparing with ACDF or CDR. The authors concluded that there is a paucity of high quality evidence for HS. These researchers stated that HS may be a safe and effective technique to benefit a select group of multi-level cervical DDD.

Grasso (2015) stated that although several studies have established the safety and efficacy of CDA as compared to ACDF, few studies have examined the role of HS that incorporates ACDF and CDA techniques in multi-level cervical DDD (MLCDDD). This prospective study enrolled patients with MLCDDD who underwent HS. A total of 20 consecutive patients who underwent HS were compared with patients who underwent ACDF and CDA at the same level of surgery. Patients were followed-up for more than 2 years. Intra-operative parameters, clinical features and outcome scores were recorded. Radiological assessments included overall ROM, disc height (DHI), and changes in adjacent disc spaces. Duration of surgery was significantly shorter for ACDF compared with HS and CDA ($p < 0.05$). The VAS, SF-36, JOA, and NDI scores improved significantly after surgery in all the patients without significant differences among the groups. Cervical ROM increased significantly in CDA and HS groups as compared with ACDF-treated patients ($p < 0.05$). The mean DHI at the treated level was significantly restored after surgery in all the groups. The HS group returned to work faster (30 days) when compared with both ACDF (62 days) and CDA (65 days) ($p < 0.05$). The authors concluded that HS was an effective, reliable, and safe procedure for the treatment MLCDDD. Such a surgical construct was comparable to ACDF and CDA in terms of safety and feasibility.

In a meta-analysis, Tian et al (2015) compared HS and ACDF for MLCDDD. Systematic searches of all published studies through March 2015 were identified from Cochrane Library, Medline, PubMed, Embase, ScienceDirect, CNKI, WanFang DATA and CQVIP; RCTs and non-RCTs involving HS and ACDF for MLCDDD were included. All literature was searched and evaluated by 2 independent reviewers according to the

standard of Cochrane systematic review. Data of functional and radiological outcomes in the 2 groups were pooled, which was then analyzed by RevMan 5.2 software; 1 RCT and 4 non-RCTs entailing 160 patients met the inclusion criteria. Meta-analysis revealed significant differences in blood loss ($p = 0.005$), post-operative C2 to C7 ROM ($p = 0.002$), ROM of superior adjacent segment ($p < 0.00001$) and ROM of inferior adjacent segment ($p = 0.0007$) between the HS group and the ACDF group. No significant differences were found regarding operation time ($p = 0.75$), post-operative VAS ($p = 0.18$) and complications ($p = 0.73$) between the 2 groups. The authors concluded that HS demonstrated excellent clinical efficacy and radiological results; post-operative C2 to C7 ROM was closer to the physiological status. No decrease in the ROM of the adjacent segment was noted in the HS group.

Lu et al (2017) stated that the traditional surgical approach to treat MLCDDD has been ACDF. There has been recent development of other surgical approaches to further improve clinical outcomes. Collectively, when elements of these different approaches are combined in surgery, it is known as HS that remains a novel therapeutic option. These investigators carried out a systematic review and meta-analysis to compare the outcomes of HS versus ACDF for the treatment of MLCDDD. Relevant articles were identified from 6 electronic data-bases from their inception to January 2016. From 8 relevant studies identified, 169 patients undergoing HS were compared with 193 ACDF procedures. Operative time was greater after HS by 42 mins ($p < 0.00001$), with less intra-operative blood loss by 26 ml ($p < 0.00001$) and shorter return-to-work by 32 days ($p < 0.00001$). In terms of clinical outcomes, HS was associated with greater C2 to C7 ROM preservation ($p < 0.00001$) and less functional impairment ($p = 0.008$) after surgery compared to ACDF. There was no significant difference between HS and ACDF with respect to post-operative pain ($p = 0.12$). The post-operative course following HS was not significantly different to ACDF in terms of length of stay ($p = 0.24$) and post-operative complication rates ($p = 0.18$). The authors concluded that HS is a novel surgical approach to treat MLCDDD, associated with a greater operative time, less intra-operative blood loss and comparable if not superior clinical outcomes compared to ACDF.

Laratta and colleagues (2018) stated that DDD and spondylosis resulting in radiculopathy and retrodiscal myelopathy are among the most frequently encountered cervical spinal disorders. Traditionally, ACDF has successfully achieved neural decompression and restored intradiscal height in these conditions. Unfortunately, non-union and iatrogenic adjacent segment pathology associated with fusion procedures in the cervical spine has led to an interest in motion-preserving procedures; CDA was developed in hopes of preserving cervical biomechanics while mitigating the complications associated with ACDF. Through a systematic review of both published and ongoing studies on single- and multi-level CDA, and HS, these investigators provided evidence on their safety and efficacy in the treatment of various cervical pathologies. A systematic search of several large data-bases, including Cochrane Central, PubMed, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry was conducted to identify published studies and ongoing clinical trials on CDA and HS. Among the relevant studies reviewed, 3 were RCTs, 2 systematic reviews, as well as multiple prospective case series, biomechanical studies, and meta-analyses. The authors concluded that over the past 10 years, multiple high-quality studies had shown that single-level CDA can offer equivalent clinical outcomes with a reduction in secondary procedures and total cost when compared to ACDF. However, more recently there has been an increasing prevalence of 2-level CDA and HS. Although the data regarding these multi-level procedures is less robust, it appeared that they may be as effective as their single-level counterparts.

Xiong et al (2018) compared the mid-term outcomes of HS and ACDF for the treatment of contiguous 2-segment CDDD. From 2009 to 2012, a total of 42 patients who underwent HS (n = 20) or ACDF (n = 22) surgery for symptomatic contiguous 2-level CDDD were included. Clinical and radiological records, including JOA, NDI, VAS, local cervical lordosis, and ROM, were reviewed retrospectively. Complications were recorded and evaluated. Mean follow-up was 77.25 and 79.68 months in HS group and ACDF group, respectively (p > 0.05). Both in HS group and ACDF group, significant improvement for the mean JOA, NDI, and VAS scores was found at 2-week post-operation and at the last follow-up (p < 0.05).

However, there were no significant differences between the 2 groups (p > 0.05). At the last follow-up, the ROM of superior adjacent segments in ACDF group was significantly larger than HS group (p < 0.05), while the

ROM of C2 to C7 was significantly smaller ($p < 0.05$). In the HS group, 2 (10 %) sagittal wedge deformities, 1 (5 %) heterotopic ossification, and 1 (5 %) anterior migration of the Bryan disc prosthesis were found. No symptomatic ASD occurred in the 2 groups. The authors concluded that HS appeared to be an acceptable option in the management of contiguous 2-segment CDDD. It yielded similar mid-term clinical improvement to ACDF, and demonstrated better preservation of cervical ROM. The incidence of post-operative sagittal wedge deformity was low; however, it could significantly reduce the cervicallordosis.

Xu et al (2019) compared the cervical sagittal balance and surgical outcomes between ACDF and hybrid decompression and fusion (HDF; 1-level corpectomy combined with 1-level discectomy) for consecutive 3-level cervical spondylotic myelopathy (CSM). From January 2013 to June 2016, a total of 82 patients with 3-level CSM who underwent ACDF ($n = 40$) and HDF ($n = 42$) were retrospectively reviewed. Peri-operative parameters, clinical outcomes, and radiologic sagittal alignment were analyzed and compared. Patients were followed-up for 35.5 ± 6.5 months (range of 25 to 53 months). All patients had achieved significant improvement in NDI and JOA scores following operation, with similar clinical outcomes between both groups ($p > 0.05$). In the ACDF group, 2 patients were found with axial symptoms, and 1 with hoarseness. In the HDF group, 5 patients were found with axial symptoms, 1 with hoarseness, 1 with dysphagia, and 1 with pseudarthrosis. The ACDF group had less operation time and bleeding compared with the HDF group ($p < 0.05$). The restoration of segmental and C2 to C7 lordosis were significantly greater in the ACDF group than the HDF group ($p < 0.05$). The C2 to C7 sagittal vertical axis and T1 slope minus C2 to C7 lordosis decreased in the ACDF group at final follow-up ($p < 0.05$); however, there was no obvious change in those of the HDF group ($p > 0.05$). The authors concluded that both ACDF and HDF were safe and effective for the treatment of 3-level CSM; ACDF showed superiority to HDF in terms of less blood loss, shorter operation time, and better post-operative sagittal balance.

Zhang et al (2020) examined the outcomes and reliability of HS versus ACDF for the treatment of multi-level cervical spondylosis and disc diseases. Hybrid surgery, combining CDA with fusion, is a novel treatment to MLCDDD in recent years. However, the effect and reliability

of HS are still unclear compared with ACDF. These investigators examined the studies of HS versus ACDF in patients with multi-level cervical disease -- electronic databases (Medline, Embase, PubMed, Cochrane library, and Cochrane Central Register of Controlled Trials) were searched. Studies were included when they compared HS with ACDF and reported at least one of the following outcomes: functionality, neck pain, arm pain, cervical ROM, QOL, and incidence of complications. No language restrictions were used. Two authors independently assessed the methodological quality of included studies and extracted the relevant data. A total of 7 clinical controlled trials were included in this study; 2 were prospective and the remaining 5 were retrospective. The results of the meta-analysis indicated that HS achieved better recovery of NDI score ($p = 0.038$) and similar recovery of VAS score ($p = 0.058$) compared with ACDF at 2 years follow-up. Moreover, the total cervical ROM (C2 to C7) following HS was preserved significantly more than the cervical ROM after ACDF ($p = 0.000$) at 2 years follow-up. Notably, the compensatory increase of the ROM of superior and inferior adjacent segments was significant in ACDF groups at 2-year follow-up ($p < 0.01$), compared with HS. The results demonstrated that HS provided equivalent outcomes and functional recovery for cervical disc diseases, and significantly better preservation of cervical ROM compared with ACDF in 2-year follow-up, suggesting that the HS is an effective alternative invention for the treatment of multi-level cervical spondylosis to preserve cervical ROM and reduce the risk of adjacent disc degeneration.

Two-Level Lumbar Total Disc Replacement versus Fusion

Radcliff et al (2018) noted that lumbar TDR has been found to have equivalent or superior clinical outcomes compared with fusion and decreased radiographic incidence of adjacent level degeneration in single-level cases. In a long-term (5 years) analysis of a prospective, randomized clinical trial, these researchers determine the incidence and risk factors for secondary surgery in patients treated with TDR or circumferential fusion at 2 contiguous levels of the lumbar spine. A total of 229 patients were treated and randomized to receive either TDR or circumferential fusion to treat DDD at 2 contiguous levels between L3 and S1 (TDR, $n = 161$; fusion, $n = 68$). Overall, at final 5-year follow-up, 9.6 % of subjects underwent a secondary surgery in this study. The overall rate of adjacent segment disease was 3.5 % (8/229). At 5 years, the

percentage of subjects undergoing secondary surgeries was significantly lower in the TDR group versus fusion (5.6 % versus 19.1 %, $p = 0.0027$).

Most secondary surgeries (65 %, 17/26) occurred at the index levels.

Index level secondary surgeries were most common in the fusion cohort (16.2 %, 11/68 subjects) versus TDR (3.1 %, 5/161 subjects, $p = 0.0009$).

There no statistically significant difference in the adjacent level re-operation rate between TDR (2.5 %, 4/161) and fusion (5.9 %, 4/68). The most common reason for index levels re-operation was instrumentation removal ($n = 9$). Excluding the instrumentation removals, there was not a significant difference between the treatments in index level re-operations or in re-operations overall. The authors concluded that there were significantly fewer re-operations in TDR patients compared with fusion patients. However, most of the secondary surgeries were instrumentation removal in the fusion cohort. Discounting the instrumentation removals, there was no significant difference in re-operations between TDR and fusion. These findings were indicative that lumbar TDR was non-inferior to fusion.

CPT Codes/ HCPCS Codes/ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”

Code	Code Description
CPT codes covered if selection criteria are met	
+0098T	Revision including replacement of total disc arthroplasty (artificial disc), anterior approach, each additional interspace, cervical (List separately in addition to code for primary procedure)
22856	Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophylectomy for nerve root or spinal cord decompression and microdissection); single interspace, cervical

Code	Code Description
22858	Total disc arthroplasty (artificial disc), anterior approach, including discectomy with end plate preparation (includes osteophylectomy for nerve root or spinal cord decompression and microdissection); second level, cervical (List separately in addition to code for primary procedure)
22861	Revision including replacement of total disc arthroplasty (artificial disc), anterior approach, single interspace; cervical
CPT codes not covered for indications listed in the CPB	
+0163T	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression), each additional interspace, lumbar (List separately in addition to code for primary procedure)
+0165T	Revision including replacement of total disc arthroplasty (artificial disc), anterior approach, each additional interspace, lumbar (List separately in addition to code for primary procedure)
22857	Total disc arthroplasty (artificial disc), anterior approach, including discectomy to prepare interspace (other than for decompression), single interspace, lumbar
22862	Revision including replacement of total disc arthroplasty (artificial disc), anterior approach, single interspace; lumbar
Other CPT codes related to the CPB	
+ 0095T	Removal of total disc arthroplasty (artificial disc), anterior approach, each additional interspace, cervical (List separately in addition to code for primary procedure)
+ 0164T	Removal of total disc arthroplasty (artificial disc), anterior approach, each additional interspace, lumbar (List separately in addition to code for primary procedure)
22864	Removal of total disc arthroplasty (artificial disc), anterior approach, single interspace; cervical
22865	lumbar
97010 - 97039	Modalities
97110 - 97546	Therapeutic procedures
HCPCS codes covered if selection criteria are met	

Code	Code Description
<i>Artificial cervical discs, Prosthetic intervertebral disc, M6-C Artificial Cervical Disc, Bryan Cervical Disc, MOBI-C, the Prestige Cervical Disc, Prestige LP Cervical Disc, PCM (Porous Coated Motion), ProDisc-C Total Disc Replacement, Secure-C Artificial Cervical Disc, Prestige LP Cervical Disc- no specific code</i>	
HCPCS codes not covered for indications listed in the CPB	
<i>activL Artificial Disc, Charite Artificial Disc, ProDisc-L Total Disc Replacement no specific code</i>	
ICD-10 codes covered if selection criteria are met	
G54.2	Cervical root disorders, not elsewhere classified [nerve root/spinal cord compression]
G54.9	Nerve root and plexus disorder, unspecified [nerve root/spinal cord compression]
M48.02	Spinal stenosis, cervical region
M50.00 - M50.03	Cervical disc disorder with myelopathy [nerve root/spinal cord compression]
M50.10 - M50.13	Cervical disc disorder with radiculopathy [nerve root/spinal cord compression]
M50.20 - M50.23	Other cervical disc displacement
M50.30 - M50.33	Other cervical disc degeneration
M53.1	Cervicobrachial syndrome [with findings of weakness, myelopathy, or sensory deficit]
ICD-10 codes not covered for indications listed in the CPB	
M51.36 - M51.37	Other intervertebral disc degeneration, lumbar and lumbosacral region
Z98.1	Arthrodesis status [prior fusion at an adjacent cervical spine level]

The above policy is based on the following references:

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