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Personalized Approaches to Spine Surgery

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ABSTRACT

Patient-centric decision-making has imbued all aspects of health care, including spine surgery. This review describes how spine surgeons can use evolving technologies and knowledge of disease and pain states to tailor their surgical approach to the individual patient. This includes preoperative screening for and optimization of low bone mineral density, intraoperative selection of implant material and customization of interbody cages and screws, and postoperative personalization of pain regimens and rehabilitation courses. By working in a multidisciplinary fashion, spine surgeons can avail themselves of these advances to provide individualized care.

Special Issue (Invited)

Keywords: personalized medicine, spine surgery, biologics, bone mineral density, robotics, surgical planning, spine implants, outcomes, pain, artificial intelligence

INTRODUCTION

While personalized medicine has its roots in preventative care, favoring a proactive rather than a reactive approach to disease, its principles have now permeated all aspects of health care. In an era of performance-based reimbursements, there is growing emphasis on providing patient-centric decision-making during all aspects of their care. This includes all facets of spine care, from preoperative optimization to customization of intraoperative implants and postoperative pain management. While it has long been understood that a “1 size fits all” approach is inadequate for instrumentation selection, we now know there are other patient customizations of intraoperative implants and postoperative pain management. This article aims to provide an overview of evolving technologies and management algorithms and their implementation in a personalized approach to spine surgery.

PREOPERATIVE

Bone Mineral Density Assessment

The number of spine surgeries performed annually in the United States has increased alongside the aging population; however, the incidence of osteoporosis has also risen. Spine surgeons can work with endocrinologists to better understand how to mitigate the effects

of osteoporosis preoperatively, thereby achieving better fusion and avoiding hardware failure in this population.

Low bone mineral density (BMD) is strongly associated with postoperative complications^{1,2} such as pseudoarthrosis,³ cage subsidence,^{4,5} screw lucency,⁶ and proximal junction failure.^{7,8} Identifying potentially osteoporotic patients and implementing a personalized BMD optimization regimen in the preoperative setting improves the odds of successful fusion and favorable postoperative outcomes (Figure 1).

Dual-energy x-ray absorptiometry (DEXA) is the gold standard for assessing BMD (Figure 1a).^{9–12} The DEXA scan measures areal BMD through the degree of x-ray attenuation in patients exposed to low-level x-ray radiation.^{11,13} The areal BMD is then *T*-scored using the National Health and Nutrition Examination Survey III.¹⁴ A *T*-score of -2.5 or lower indicates osteoporosis and an elevated fracture risk. Central DEXA, measured at the hip and distal radius, is most commonly used to define osteoporosis and treatment thresholds for preventing osteoporotic fractures.^{15,16} It is not recommended to measure the spine itself, as osteophytes can confound *T*-scores.¹⁷ With a grade B rating, the U.S. Preventive Services Task Force recommends routine DEXA screening of women aged 65 years or older and postmenopausal women younger than 65 years who are at increased risk of fracture.⁹

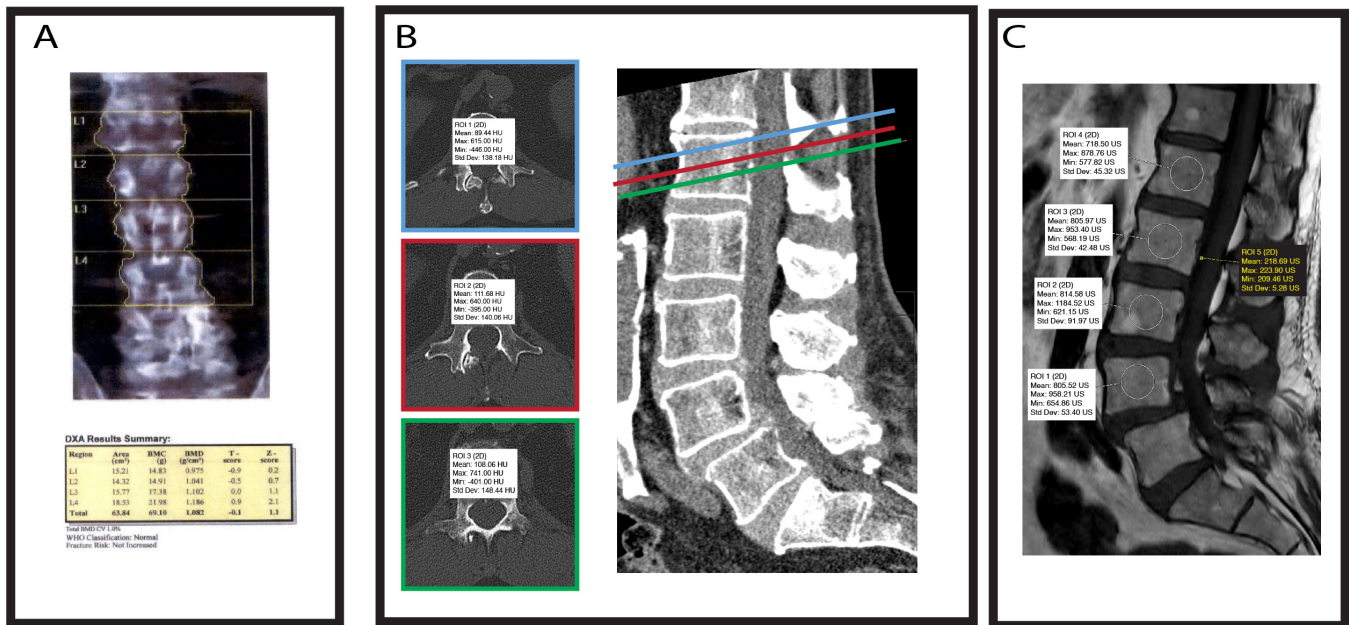


Figure 1. An 80-year-old man undergoing preoperative spinal imaging. (A) Lumbar dual-energy x-ray absorptiometry scan. (B) Hounsfield unit (HU) bone mineral density at a given level is calculated as the average HU of the superior endplate, middle of the vertebral body, and the inferior endplate. (C) Vertebral bone quality is calculated by dividing the median signal intensity of the medullary portions of L1–L4 vertebral bodies by the average signal intensity of the cerebrospinal fluid at L3.

There are some limitations to DEXA. Spinal osteophytes associated with spondylosis have been shown to overestimate DEXA-measured BMD.¹⁷ This may partially explain the elevated rates (over 50%) of osteoporotic compression fractures in patients with “normal” spine DEXA scores.^{18,19} The DEXA scan has been shown to have limited accuracy in patients with obesity²⁰ and prior instrumentation.^{10,21} Many spine surgery experts, including the AOSpine Knowledge Forum Deformity working group, advise DEXA screening of the femur or distal radius in all patients being considered for elective screening.^{12,22}

Ancillary software, like the trabecular score (TBS), can be applied alongside a DEXA scan to obtain complementary measures of BMD. The TBS is a textural index that evaluates pixel gray-level variations in the lumbar spine DEXA permitting accurate clinical evaluations of skeletal microarchitecture and bone quality.^{23,24} TBS is independent of degenerative bone abnormalities and can avoid underestimating fracture risk in patients with nonpathological DEXA *T*-scores.^{25,26} TBS indicative of degraded bone is less than 1.23.²⁶ Another example of BMD assessment software includes the fracture risk assessment tool (FRAX), a computer-based algorithm that uses clinical features (eg, age, sex, race, and evidence of secondary osteoporosis) to estimate the 10-year probability of major

osteoporotic and hip fractures.²⁷ Unlike TBS, treatment decisions can be made on FRAX alone in patients who are treatment naïve.^{28,29} FRAX-based indications for treatment are at least 3% for hip or at least 20% for hip or major osteoporotic fractures, respectively.^{28,30} TBS is most useful for individuals who lie close to a FRAX or BMD *T*-score intervention threshold.²⁶ We recommend primary BMD screening with DEXA at this time, along with the use of TBS and FRAX as adjuncts.

Computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used to assess surgical spine pathology preoperatively. Currently, neither CT nor MRI is clinically validated to evaluate BMD. Still, growing evidence explores their utility as a viable alternative to DEXA scans, especially in practice settings where DEXA scans are not readily available and for patients in whom the DEXA scan may have limited interpretability. To reiterate, we endorse DEXA scans as the gold standard for BMD assessment.

Widely available across standard medical imaging viewing software, the Hounsfield unit (HU) is a helpful tool for assessing BMD from CT scans. The HU is a unitless measure of density derived from a normalization of the CT image such that –1000 HU corresponds to air, while HU corresponds to pure distilled water. Schreiber et al describe estimating the BMD of a given vertebra by taking the average of HU measured at 3 distinct locations: immediately

inferior to the superior end plate, middle of the vertebral body, and superior to the inferior end plate (Figure 1b).³¹ Investigators comparing HU measurements in the spine to DEXA-derived *T*-scores have established thresholds indicative of poor BMD to range from 73 to 202 HU. Irrespective of HU findings, a DEXA scan must still be used to assess BMD as it is a clinically validated tool. Concordance between DEXA *T*-scores and HU ranges anywhere from 40% to 54%.³² The use of DEXA in assessing BMD in patients with pre-existing spinal hardware has proven challenging due to interference from the metallic artifact.²¹ Compelling work suggests that HU measurements may best suit this use case. Wanderman et al collected pre- and post-operative HU measurements from lumbar CT scans of 50 patients who underwent L2 and distal instrumented lumbar fusions, finding that the postoperative HU at the upper instrumented vertebra was strongly correlated with and not significantly different from the preoperative HU.³³

It is crucial to bear in mind that the CT acquisition technique influences HU measurements. CT kilovoltage settings have been shown to alter the HU unit thresholds for predicting osteoporotic *T*-scores.³⁴ Furthermore, intravenous contrast has been shown to slightly overestimate HU. A study comparing HU at L1 between CT with and without contrast found differences of up to 8%.³⁵ These confounders must be accounted for when using HU to determine BMD.

Recent work has established MRI-based equivalents of the HU as well.³⁶ Ehresmen et al described the vertebral bone quality (VBQ) score collected from T1-weighted MRI. VBQ is calculated by dividing the median signal intensity of the medullary portions of L1 to L4 vertebral bodies by the average signal intensity of the cerebrospinal fluid at L3 (Figure 1c). VBQ scores had a predictive accuracy of 81% in detecting osteopenic/osteoporotic bone³⁶ and have been shown to correlate moderately with DEXA *T*-scores.^{37,38} VBQ thresholds indicative of poor BMD range from 2.18 to 3.06.^{30,31} Irrespective of VBQ findings, a DEXA scan must still be used to assess BMD as it is a clinically validated tool.

VBQ analysis is not without its shortcomings. Hyperlipemia has been shown to overestimate the presence of osteoporosis compared with DEXA.³⁹ Although future research is needed to validate this new methodology, it remains a viable screening tool for osteoporosis.

Pharmacological BMD Optimization for Instrumented Spinal Surgery

It is well understood that low BMD is tied to poor fusion outcomes.⁴⁰ Adequate preoperative BMD optimization of patients meeting diagnostic criteria for osteoporosis is paramount to increasing the odds of adequate fusion and maximizing post-operative outcomes. Our approach to preoperative BMD treatment employs apt, interdisciplinary collaboration with endocrinologists, who play a pivotal role in optimizing osteoporotic patients before and after spinal surgery.⁴¹⁻⁴⁵ First, we employ nonpharmacological methods, such as physical therapy and weight bearing as tolerated. All secondary osteoporosis, such as hypogonadism, hypothyroidism, and renal calcium leak, must be explored and treated. We then consider pharmacological treatment. The standard pharmacological armamentarium comprises vitamin D3, bisphosphonates, denosumab, and anabolics (Figure 2).

Vitamin D3 is routinely used as a preventive and therapeutic pharmacologic for osteoporosis. Vitamin D3 is essential for calcium absorption and bone mineralization, and it is generally well tolerated when used to improve BMD.⁴⁶ In a retrospective study evaluating the effect of perioperative vitamin D3 supplementation on fusion rates in patients with osteoporosis, Xu et al found that supplementation significantly improved 6-month fusion rates (76.19% vs 43.48%, $P = 0.03$).⁴⁷ In our practice, we aim for a serum-level goal of 35 to 60 ng/mL.^{48,49}

Bisphosphonates are the first-line treatment for osteoporosis. This drug class improves BMD through osteoclast inhibition and subsequent reduction of bone resorption. Common side effects include reflux and esophagitis.⁵⁰ Rarely, patients may experience osteonecrosis of the jaw and atypical fracture.⁵¹ Evidence supporting bisphosphonate therapy as a single-agent regimen in the treatment of osteopenic patients undergoing spinal surgery is largely inconclusive.⁵² While Nagahama et al found higher fusion rates in patients given alendronate after posterior lumbar interbody fusion, Kim et al failed to find any differences when using the drug for single-level posterior fusions.^{53,54} Similarly, zoledronic acid, an intravenously delivered bisphosphonate, has shown ambiguous results.⁵⁵ At this time, the use of bisphosphonates is not recommended 6 months pre- or post-operatively in patients undergoing spinal fusion, as the data supporting their use are inconclusive.⁵²

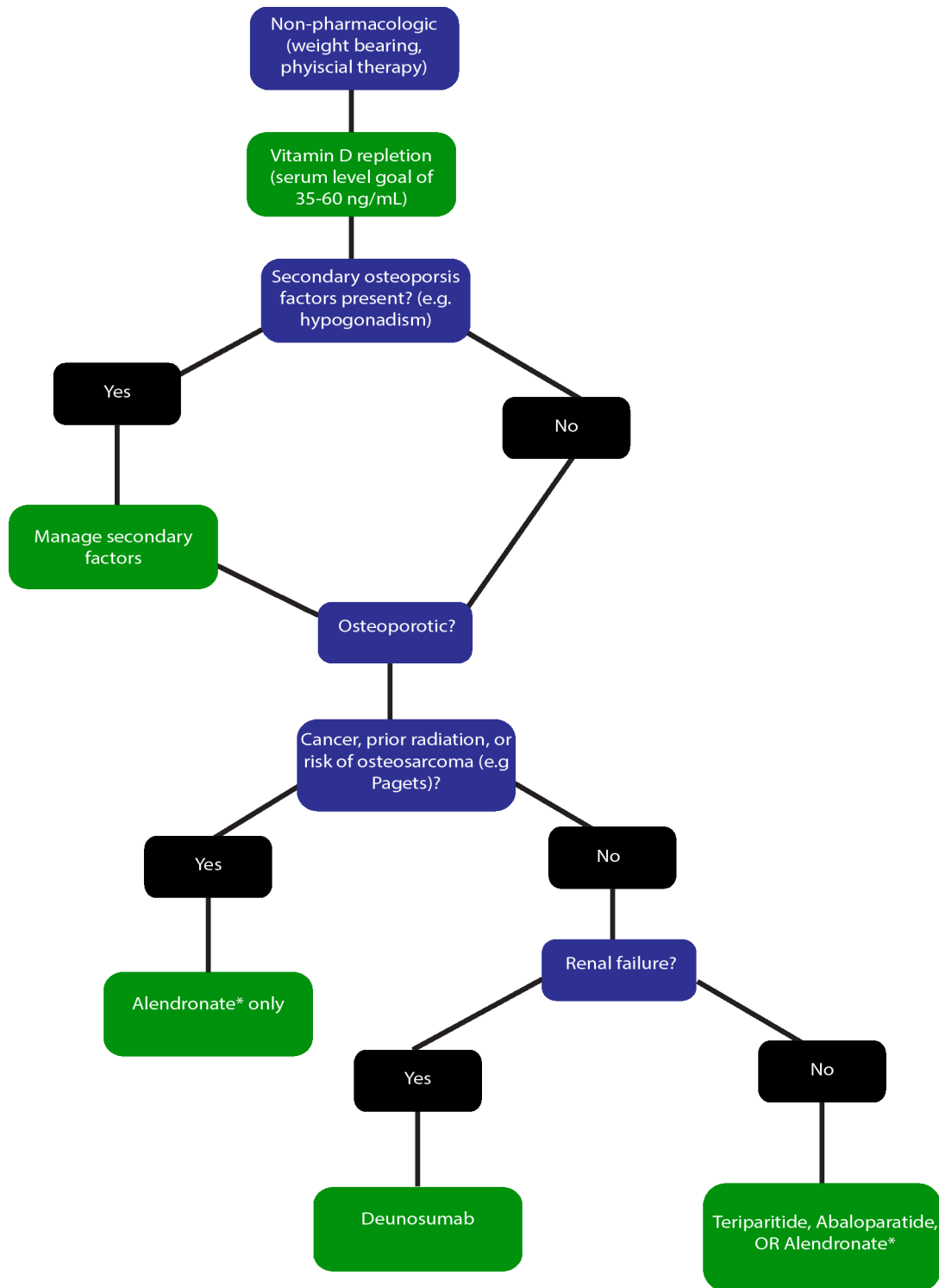


Figure 2. Algorithm for optimization of preoperative bone mineral density. *Evidence for bisphosphonates (eg, alendronate) is inconclusive and, at this time, not recommended for use 6 mo pre- or postoperatively.

Anabolics such as teriparatide, a recombinant human parathyroid hormone analog, are second-line medications for osteoporosis. It increases osteoblast activity and promotes bone growth.⁵⁶ Due to a rare risk of bone malignancy, we generally

avoid anabolics in patients with active cancer, prior radiation, or patients at risk of osteosarcoma (eg, Paget's).^{57,58} In a prospective, nonrandomized study, Ohtori et al found that teriparatide treatment not only resulted in higher fusion rates

compared with bisphosphonates (82% vs 68%) but also conferred faster time to fusion (8 months vs 10 months).⁵⁹ Ohtori et al also found a reduced incidence of pedicle screw loosening in patients treated with teriparatide compared with those treated with bisphosphonate (7% vs 13%).⁵⁹ Cho et al compared cyclic combination treatment of teriparatide and bisphosphonates to bisphosphonate monotherapy and found that the combination group achieved fusion faster.⁶⁰

Denosumab is another second-line medication for osteoporosis. Denosumab is a monoclonal antibody against the receptor activator of nuclear factor- κ B ligand, and its interactions with receptor activator of nuclear factor- κ B ligand lead to decreased osteoclast activity.⁶¹ In our practice, we employ denosumab for patients who cannot tolerate bisphosphonates due to renal failure.⁶² Ide et al followed 16 patients treated with denosumab and teriparatide, enabling higher fusion rates at 6 months compared with those treated with teriparatide alone.⁶³

Other popular second-line treatments include selective estrogen receptor modulators and romosozumab; however, there is limited clinical evidence investigating the use of these agents in the context of spinal surgery outcomes, and this is beyond the scope of this review. Ultimately, our practice is in line with the Congress of Neurological Surgeons' recommendations, which endorse the use of anabolics, such as teriparatide, for preoperative osteoporosis treatment with a grade B rating.⁵² Future randomized controlled trials are needed to further substantiate this position.

Utility of EOS and Robotics in Perioperative Surgical Planning

In addition to improvements in preoperative BMD detection and optimization, several new technologies have been introduced to facilitate the interpretation of patient-specific spinopelvic parameters and surgical planning.

Historically, spinopelvic parameters have been assessed on standing sagittal and coronal whole-spinal radiographs.⁶⁴ While this method is effective in assessing spinal malalignment, it is hindered by image distortion at the edge of the radiograph and poor interobserver reliability.^{64,65} EOS, a low-dose biplanar imaging system, offers a novel method for assessing spinopelvic parameters in the preoperative setting (Figure 3). In general, EOS has several advantages over conventional spinal radiographs. Conventional x-ray radiography requires multiple



Figure 3. A 78-year-old man with a history of prior lumbar laminectomy underwent a 2-stage lumbosacral fusion: L3–L5 anterior lumbar interbody fusion and L2–pelvic minimally invasive fixation for severe back pain, right leg pain, and chronic right foot weakness. (A) Preoperative anteroposterior and (B) lateral full spinal imaging generated from an EOS scan, revealing severe degenerative changes, spinal stenosis worst at L2–L3 and L3–L4, and scoliosis with a significant mismatch between lumbar lordosis and pelvic incidence. (C) Postoperative coronal and (D) sagittal full spinal imaging generated from EOS showing instrumentation.

exposures followed by stitching of images to generate a full-body image (Figure 4c and d; Figure 5d and e). However, EOS imaging avoids the need for multiple exposures, thereby reducing the examination time, decreasing the overall radiation exposure per examination, and eliminating the distortion and stitching artifacts seen in conventional radiography.⁶⁶ Not only does the EOS produce distortion-free, high-quality images, but it also generates 3D renderings that cannot be produced from conventional radiography.⁶⁷ Recent work from Shakeri et al shows that spinopelvic parameters measured from EOS films are reliable and comparable to those generated by traditional radiographs.⁶⁷

Recent developments in robot-assisted spinal surgery have allowed for safer, faster, and more personalized care.⁶⁸ The Mazor X and Globus Excelsius systems are examples of this technology. They incorporate 3-dimensional (3D) analytical software as an adjunct to preoperative planning. With this software, surgeons can simultaneously inspect implant size and trajectory in all 3 planes.⁶⁹ In an updated iteration of this software, the Mazor X and ExcelsiusGPS now provide real-time 3D visualization in the operative setting as surgeons use instruments and/or place screws along preoperatively planned trajectories.⁶⁸

After surgeons surmount the learning curve, robotic planning has been shown to augment operative efficiency and reduce operative times.^{62–64}

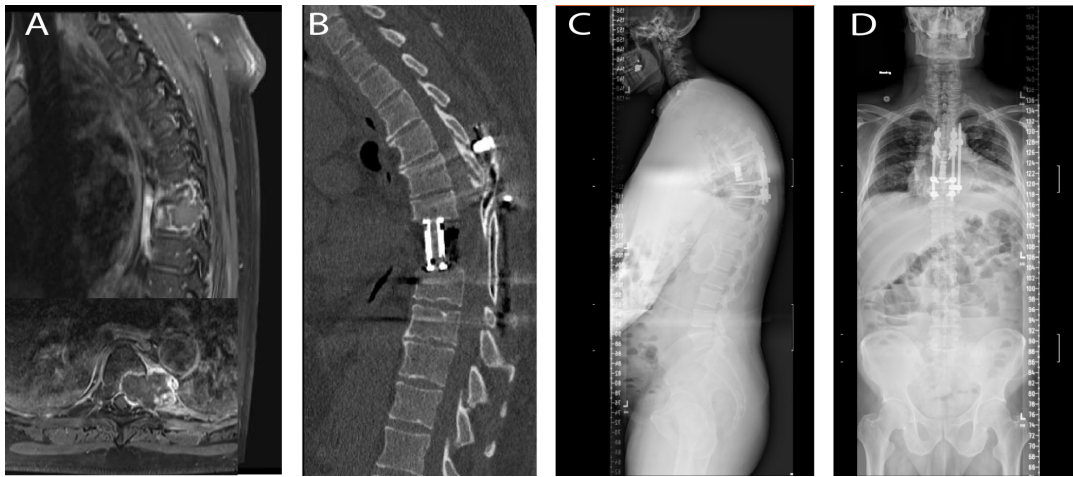


Figure 4. Fifty-two-year old man who underwent a T7 corpectomy with en bloc resection of a grade 2 chondrosarcoma and T5–T9 posterior fusion. This is an example of a case in which a custom implant would have been advantageous given the irregular margins of the tumor resection cavity. (A) Preoperative T1-post gadolinium magnetic resonance imaging revealed a 1.4 cm bony destructive mass within the T7 vertebral body and left pedicle with expansile component to the left paravertebral space and also left epidural component abutting the thoracic cord without cord compression (inset). (B) Postoperative computed tomography scan demonstrating an expandable titanium cage flush to the endplates of T6 and T8. (C) and (D) Postoperative stitched standing scoliosis films demonstrating anterior and posterior instrumentation.

INTRAOPERATIVE SETTING

Technological advances have also changed the landscape of the operating room with regard to the customization of spinal implants. While neuronavigation systems allow for intraoperative planning of screw size and trajectories in addition to implant size based on an intraoperative CT, 3D printing, and the ability to choose implant materials based on patient-related factors take this personalization 1 step further.

Implant Choice

Information derived from preoperative imaging can be used to fashion digitally modeled 3D implants.

Printed implants can cater to the patient’s anatomy and biomechanical requirements; their specificity allows for minimal removal of surrounding structures and preservation of normal anatomy during implantation.^{70,71} Moreover, custom implants allow for a more even distribution of stress and shearing forces and optimize osteointegration. Additionally, custom implants that optimize fit with superior and inferior endplates mitigate the need for adding bone grafts, reducing the overall surgical time that would have been spent harvesting said graft. D’Urso et al were the first to describe 3D printing for preoperative planning in 1999; the first 3D printed implant was used in 2014. 3D modeling is

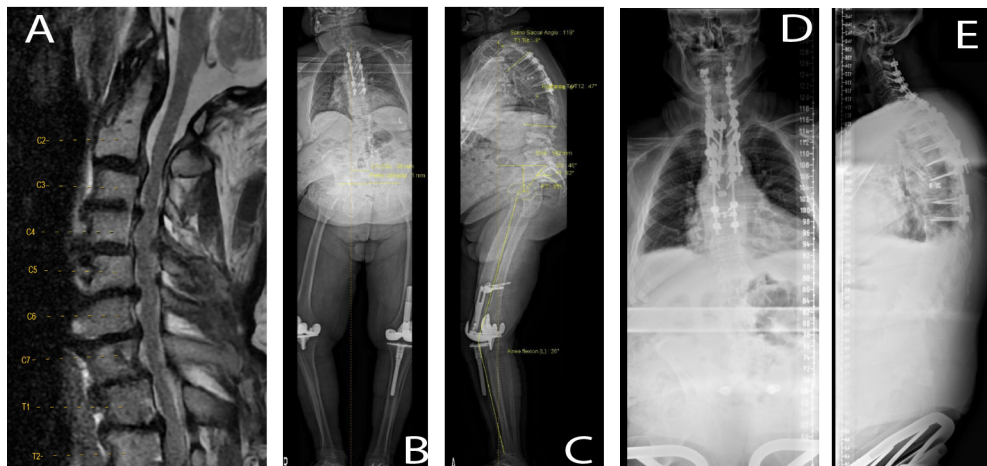


Figure 5. Sixty-eight-year-old man who underwent posterior C2–T6 fusions extension into prior fusion construct and C2–T2 laminectomy for progressive cervical myelopathy status post prior T7 corpectomy and T4–T9 fusion following T6–T7 pathologic fracture secondary to osteomyelitis. (A) Preoperative magnetic resonance imaging demonstrating severe stenosis from C2 to T2. (B) Preoperative anteroposterior (AP) and (C) lateral EOS scans demonstrating prior posterior hardware. (D) Postoperative AP and (E) lateral stitched scoliosis films highlighting a titanium rod construct spanning C2–T9.

particularly helpful in spine oncology; tumors irregularly erode and invade adjacent structures, and modeling the tumor configuration can help with preoperative planning and lead to an overall decrease in operative time and blood loss associated with tumor resection (Figure 4).⁷² Moreover, as a result of the invasive nature of tumors, tumor resection cavities are often irregularly shaped and an ill fit for standard vertebral prosthetics, necessitating custom implants for restoration of load-bearing segments.^{73,74} The use of custom implants has been associated with better long-term stability and decreased periods of activity restriction after spine tumor surgery. Custom implants offer a new solution in the operative management of axis tumors since current cervical implants are optimized for the subaxial spine and have difficulty recapitulating the biomechanics of the axis.^{75,76}

Beyond surgical oncology, 3D-printed implants can also be useful for congenital deformities. In the case of adolescent idiopathic scoliosis, where curvature makes it difficult to visualize the optimal screw trajectory, a drill guide can be 3D printed based on preoperative imaging to lay down on the entry point and guide screw placement. In a retrospective study of 126 adolescent idiopathic scoliosis patients, using a 3D-printed biomodel was associated with decreased operative time, blood loss, and transfusion volume without an increase in postoperative complications or length of stay.⁷⁷ Another opportunity would be in the case of congenitally abnormally sized pedicles and vertebral bodies, such as in achondroplasia. With 3D printing, we are no longer forced to repurpose our existing implants to accommodate these patients, often resulting in a less-than-ideal construct; instead, we can offer a customized and well-planned construct.

Materials

The properties of constructs are an essential consideration when deciding which material to use, and another important realm is where an individualized approach can be taken (Table 1). Most commonly, stainless steel (SS), titanium (Ti), cobalt chromium (Co-Cr), and polyethylethylketone (PEEK) are used in spinal constructs (Figure 5).⁷⁸ Each material has its own set of advantages and indications for use. The appropriateness of each material is typically assessed based on its Young's modulus, tensile strength, fatigue strength, and radiopacity.⁷⁸ In cases of adult spinal deformity correction, where it is important to maintain the initial correction made, rod material is especially important. While Co-Cr and ultrahigh strength SS rods generate the greatest corrective forces compared with SS and Ti, they come at the cost of greater plastic deformation.⁷⁹ Co-Cr multiple-rod constructs also have a higher occurrence of proximal junctional kyphosis when compared with Ti alloy 2-rod constructs.⁸⁰ While there are variable reports on breakage between Co-Cr and Ti rods, there is no difference in other outcomes, including Cobb angle, sagittal vertical axis, pelvic tilt angle, and pseudoarthrosis.⁸¹

Radiopacity becomes a decision-making factor for patients requiring frequent screening or oncological treatment. For patients with primary and metastatic spinal tumors, carbon-fiber-reinforced (CFR) PEEK constructs can be useful for reducing imaging artifacts.⁸² CFR PEEK hardware may also reduce radiotherapy perturbations while having an 89% fusion rate, which is comparable to Ti implants.⁸³ In a comparative study with more than 7 years of follow-up for multilevel cervical spondylotic myelopathy, PEEK cages were found to have lower subsidence rates and improved maintenance of intervertebral height and cervical lordosis

Table 1. Summary of implant materials and their applications and characteristics.

Material	Young's Modulus ⁶⁶	Applications	Pros	Cons
Ti6Al4V	110	• Rods	• Lightweight	• Relatively expensive
Ti	50.2	• Cages • Plates • Screws • Rods	• Flexible • Alloys available	• Imaging artifacts
Co-Cr	53.15	• Rods	• High corrective force for scoliosis	• Risk of plastic deformation • Risk of PJK • High imaging artifacts • High imaging artifacts • Corrosion
Stainless steel	51.07	• Rods	• Inexpensive	• Low Young's modulus
CFR PEEK	17.94	• Rods • Cages	• Reduced imaging artifacts	
Cancellous bone	3.87			

Abbreviations: CFR, carbon fiber reinforced; Co-Cr, cobalt chromium; PEEK, polyethylethylketone; PJK, proximal junctional kyphosis; Ti, titanium.

when compared with Ti.⁸⁴ A survey conducted by the North American Spine Society section of spinal oncology found varied opinions on CFR PEEK. Respondents were largely concerned with the high cost and low availability, which was reflected in their low utilization for anterior and posterior constructs following tumor resection.⁸⁵

Material considerations for osteoporotic patients warrant special attention due to the increased risk of hardware failure. Screw loosening in osteoporotic patients is not entirely understood, but it appears that craniocaudal toggling can significantly reduce screw pullout strength in osteoporotic vertebrae. It is thought to occur through tissue failure around the screw.⁷⁷ Some approaches to improve pullout strength in osteoporotic vertebrae include using fenestrated pedicle screws. Compared with conventional pedicle screws, fenestrated pedicle screws allow for the injection of polymethylmethacrylate, calcium phosphate, or hydroxyapatite cement into cannulation and out of the fenestrations, thereby reducing the risk of screw loosening and improving screw fixation and overall fusion rates. Additionally, other less commonly used methods of screw fixation in osteoporotic vertebrae include using allograft bone particles, calcium phosphate cement, or demineralized bone matrix. These can be used for pedicle augmentation and are found to improve the screw-bone interface and increase screw pullout force and fatigue load cycle.

Other methods that increase maximum pullout force in osteoporotic bone are expandable pedicle screws and cortical trajectory screws. Each of these individually can increase the maximum pullout force by approximately 130% compared with unreinforced screws.^{65,78}

Technique

In addition to material choice, there are numerous techniques for contouring rods to patients' unique anatomy. Manual bending can introduce stress and strain into rods, which has implications for breakage, plastic deformation, and maintenance of correction. For adolescent patients with idiopathic scoliosis, notch-free prebent rods were found to have higher thoracic kyphosis postoperatively compared with those with manually bent rods. This was achieved because the notch-free prebent rods maintained their curvature better than the manually bent rods.⁸⁶ Several groups have recapitulated these findings in adolescent idiopathic scoliosis.⁸⁷ Beyond demonstrated efficacy in adolescent pathology, patient-specific rods have demonstrated significant improvement in patient-reported outcomes and spinopelvic parameters in adult deformity as well.⁸⁸⁻⁹⁰

Proper rod choice and alignment are also important for avoidance of screw pullout. Forcing a rod to fit into a tulip head when there is a gap discrepancy significantly reduces the pullout strength of the screws.⁹¹ The stress in a construct can also be determined by the method of shaping rods. Finite element studies have shown that using a French bender induces more stress than an in-situ bender. There are currently efforts to use machinery to bend rods to patient-specific anatomy. They are designed to reduce forces on the screw-bone interface compared with freehand bending.⁹²

CT-Guided Navigation

Imaging and navigation enhance the surgeon's ability to understand, verify, and plan surgeries based on their patient's anatomy. Intraoperative CT-guided navigation has proven to be an essential tool in the spinal surgeon's armamentarium for adult deformity and degenerative pathologies. Placing pedicle screws using the freehand technique is challenging due to obscured anatomical landmarks, a common issue in deformity correction surgeries. CT-guided navigation systems enhance placement accuracy by providing real-time, 3-dimensional imaging, which allows for precise localization of anatomical structures. Studies have shown that navigation use can improve placement accuracy⁹³⁻⁹⁵ and reduce pedicle screw placement time and breach rates.⁹⁶

Whether in the form of C-arm fluoroscopy or CT, intraoperative x-rays are vital tools during spine surgery. When comparing cone-beam CT and fluoroscopy, cone-beam CT has a reduced mean screw placement time, operative time, and length of stay. However, it also yields a higher total radiation dose. This is an important consideration when planning imaging for adolescent idiopathic scoliosis: patients younger than 18 being treated for a spinal deformity may have an increased estimated risk of developing cancer due to the radiation they are exposed to during surgical intervention.

POSTOPERATIVE SETTING

Ultimately, patient-reported outcomes and patient satisfaction after surgery are contingent upon a host of factors independent of the adequacy of their surgical construct; as such, surgeons' planning does not stop as soon as the patient leaves the operating room. With an improved knowledge of the importance of postoperative nutrition and rehabilitation, spine surgeons can work with nutritionists and physical therapists to optimize these 2 aspects of postoperative recovery and improve the chances of maximizing functional outcomes.

Personalized Postoperative Pain Regimens

Pharmacogenomics and Inter-Individual Differences in Drug Clearance

For patients undergoing spine surgery, personalized pain regimens can serve as an important component in reducing the duration of postoperative pain and decreasing opioid dependency. Approximately half of the patients indicate continued postoperative pain following back surgery, with nearly 40% of the patients at the 6-month postoperative period still reporting the use of pain medications.⁹⁷ These findings suggest the need for pain regimens that are tailored to a patient's specific characteristics. Over the past 2 decades, pharmacogenomics has increasingly offered new insights into creating patient-specific pain regimens using genetic screening for polymorphisms present in pain-associated genes. White and Kehlet discuss how differences at the individual level in pain sensitivity can lead to different responses to similar painful stimuli such that some individuals, through genetic differences, can be categorized as either low- or high-pain responders.⁹⁸ Categorizing patients into these groups in the preoperative period can dictate the quantity and type of pain medications in the postoperative period. Indeed, several genes have been identified over the years that can serve as possible screening targets, with many being investigated in the context of spine surgery (Table 2).

Catechol-O-methyltransferase (COMT) is an important enzyme involved in metabolizing various catecholamine neurotransmitters, such as dopamine, epinephrine, and norepinephrine. Polymorphisms in this gene have an important role in the context of modulating pain. Similar to the idea discussed by White and Kehlet, COMT is a screening target that can play a role in categorizing patients who are more or less susceptible to painful stimuli.⁹⁸ In a study by Diatchenko et al, 3 COMT haplotypes, with primary differences in the rate of COMT protein translation, were found to be associated with low-, average-, or high-pain sensitivity.¹⁰¹ Those who were homozygous for the low-pain sensitivity haplotype had the greatest tolerance for different forms of noxious stimuli, while those with

the high-sensitivity haplotype had the least tolerance. In addition to pain sensitivity, polymorphisms in the COMT gene have been associated with variations in the quantity of opioid dosages required to treat pain. Rakvåg et al, in a study involving patients with cancer-related pain, performed genotyping of 11 single nucleotide polymorphisms of the COMT gene to construct COMT haplotypes.¹⁰⁰ Patients with the most frequent haplotype required less morphine compared with those patients who did not possess these haplotypes to treat cancer-related pain. The results of this study not only carry implications for patients with malignancies in general but can be a topic of further investigation in the pre- and postoperative context for patients with spinal malignancies.

Focused studies on pharmacogenomics in patients with spinal pathologies have been explored in the context of both the COMT gene and additional pain-related genes. In a recent study by Ernst et al in 2024, the genes COMT and Neuropeptide Y (NPY) were investigated to determine if polymorphisms in these genes are related to symptom severity and treatment outcomes in patients with lumbar spinal stenosis.¹⁰⁰ Patients with a specific COMT genotype displayed greater severity of symptoms at baseline, while patients with a specific NPY genotype displayed not only greater baseline symptom severity but also better treatment outcomes. Although this study specifically focused on patients with lumbar spinal stenosis receiving nonoperative treatment modalities, the results can possibly be translated toward using variations in NPY and COMT in predicting postoperative symptom levels in patients with degenerative spinal conditions. Other foundational studies have specifically laid the groundwork for the role of assessing genetic polymorphisms in operative spine cohorts. Tegeder et al found that in patients who had undergone discectomy for radicular back pain, a specific haplotype in the gene Guanosine triphosphate cyclohydrolase 1 was associated with decreased pain levels after surgery.¹⁰⁴ Similarly, a subsequent study focusing

Table 2. Overview of pain-associated genes that can be used as screening targets in the context of spine surgery.

Gene	Function	Example Polymorphism(s) Associated With Pain
Catechol-O-methyltransferase	Metabolism of catecholamines (dopamine, epinephrine, and norepinephrine)	rs4680 GG (Ernst et al, 2024) ⁹⁹ Val158Met (Rakvåg et al, 2008 ¹⁰⁰ ; Diatchenko et al, 2006 ¹⁰¹)
Neuropeptide Y Guanosine triphosphate cyclohydrolase 1	Neuropeptide implicated in pain modulation Rate-limiting enzyme in the synthesis of tetrahydrobiopterin (BH4)	rs16147 TT (Ernst et al, 2024) ⁹⁹ rs998259 (minor allele T) (Kim et al, 2010) ¹⁰²
Opioid Receptor Mu 1	Encodes for the mu opioid receptor	Asn118Asp (Lötsch et al, 2004) ¹⁰³

on patients undergoing instrumented fusion or disc arthroplasty in patients with lumbar degenerative disease demonstrated that a single nucleotide polymorphism in the Guanosine triphosphate cyclohydrolase 1 gene was significantly associated with improvement in the Oswestry Disability Index score and Numerical Rating Scale back pain scores following surgery.¹⁰² Through screening patients with this particular polymorphism in the preoperative setting, patients with lumbar degenerative disc disease or other degenerative pathologies of the spine can possibly have tailored pain dosages and regimens in association with their expected postoperative outcome.

The mu opioid receptor, encoded by the OPRM1 gene, is also implicated as an important preoperative screening target. The mu opioid receptor is the binding site for several opiates, including morphine, methadone, and fentanyl. Polymorphisms in the OPRM1 gene are associated with different analgesic effects and dosage requirements to treat pain. For example, the single nucleotide polymorphism A118G for the OPRM1 gene is associated with not only decreased analgesic effects of both morphine and morphine metabolites in the laboratory setting but also with postoperative pain scores, morphine use, and morphine-related side effects. In patients with spine pathologies, inter-individual differences in the OPRM1 regulatory site have been shown to have associations with postoperative pain.¹⁰³ In a study by Chidambaran et al in 2016 of 133 adolescents undergoing spinal fusion for idiopathic scoliosis, differences in DNA methylation at methylation sites of the OPRM1 gene promoter were found to be associated with preoperative pain measures along with the development of acute and chronic postsurgical pain.¹⁰⁵

Other important factors for optimal personalized pain regimens for patients undergoing spine surgery include individual differences in drug clearance. For example, polymorphisms in drug efflux pumps are associated with differences in the development of morphine-related side effects and, therefore, serve as additional screening targets for determining optimal dosage requirements in the postoperative setting.¹⁰⁶ Finally, outside of genetic screening, concomitant medications being taken alongside pain medications should be carefully reviewed for possible drug-drug interactions.¹⁰⁷ Morphine, when used alongside other drugs that interfere with morphine metabolism, can result in

either potentiated side effects or a reduced therapeutic effect.

AI Tools for Predicting Postoperative Pain

Artificial intelligence (AI) prediction tools, including machine-learning models, are important for assessing which patients are more likely to develop postoperative pain and opioid dependency following surgery based on preoperative clinical, radiographic, and genetic variables. In a Quality Outcomes Database study by Park et al, machine-learning models were implemented to determine the likelihood a patient with cervical spondylotic myelopathy will achieve a clinically meaningful improvement in neck pain following surgery.¹⁰⁸ Similarly, in a study performed using the Norwegian Registry for Spine Surgery, machine-learning models were trained on over 20,000 patients with surgery for lumbar disc herniation to determine treatment success with respect to a range of postoperative pain measures.¹⁰⁹ Through using machine-learning models and AI-powered calculators, patients with spinal pathologies who are at greater risk of not developing significant improvement in pain can be screened for in the preoperative setting for more aggressive follow-up in the postoperative setting for optimized pain control and additional therapeutic interventions.

Machine learning in the preoperative setting has also shown promise in determining patients who are at high risk of needing an extended duration of postoperative opioid medications after lumbar disc herniation surgery.¹¹⁰ Patients who are predicted to have greater postoperative opioid needs following surgery can undergo greater surveillance to ensure that pain needs are being met adequately without the need for an extended duration. AI prediction tools are, therefore, valuable for screening patients with a greater need for postoperative pain control. Through future incorporation of a patient's specific genetic polymorphisms and preoperative radiographic features, AI models can potentially offer high prediction accuracy for patients who are at the highest risk of postoperative pain.

Personalized Physical and Nutritional Therapy in the Postoperative Period

Postoperative rehabilitation approaches optimized to a patient's particular characteristics have the opportunity to improve functional outcomes in patients following spine surgery. Several prior studies have demonstrated

the importance of a personalized rehabilitation approach as opposed to standardized rehabilitation methods. Millisdotter et al performed a study comparing the performance of a neuromuscular customized training program with a traditional rehabilitation approach following lumbar disc herniation.¹¹¹ At 12 months surgery, patients who underwent the customized approach had improved disability levels compared with those patients who underwent the traditional approach. A personalized physical rehabilitation approach should additionally be supplemented with approaches emphasizing biopsychosocial domains. Prior studies have demonstrated the importance of addressing these domains in patients undergoing spine surgery. For example, in a study of patients undergoing lumbar fusion, the postoperative recovery trajectory was found to be also determined by biopsychosocial factors such as depression, anxiety, and fatigue.¹¹² Similarly, for patients undergoing spinal cord stimulation surgery, a personalized biopsychosocial rehabilitation program can potentially offer improved postoperative outcomes in areas such as functional disability, quality of life, and return to work.¹¹³ Adequately screening for these factors prior to surgery and ensuring that a patient's biopsychosocial needs are being met postoperatively are important, given the complex interplay of these factors with surgical outcomes.

Health-related technologies are additionally important during the postoperative period for monitoring patients who need earlier postoperative care. Such technologies offer the capability of customized follow-up times following spine surgery as opposed to standardized postoperative follow-ups. Prior to surgery, AI tools offer the potential capability to predict patients at greater risk of functional deterioration postoperatively. In a study by DeVries et al, machine learning was used to predict ambulatory activity in patients following spinal cord injury surgery with relatively good accuracy.¹¹⁴ Those patients who were predicted to develop poor ambulatory status could, therefore, undergo more aggressive postoperative monitoring and physical therapy. Similar models can be developed to predict functional outcomes in patients with other pathologies of the spine.

In addition to preoperative tools, mobile digital platforms and wearable devices are possible avenues for close postoperative monitoring. Patient-reported outcome measures can be supplemented with objective data points from these digital health technologies to gain insight into the postoperative recovery trajectory. Ambulatory activity, tracked by measuring step counts using smartphones, serves as an objective metric

to track changes in functional activity following spine surgery.¹¹⁵ Furthermore, wearable devices, such as the tri-axis accelerometer, provide information into additional parameters beyond step count, such as cadence and posture. Patients with a slower than anticipated improvement in ambulatory activity can have shortened follow-up times to analyze for new deficits or a need for a more aggressive physical rehabilitation. Mobile health applications allow not only activity monitoring but also monitoring of wound healing, pain management, and new deficits reported by a patient.¹¹⁶ Other technologies include wearable cameras that allow for the measurement of functional limb usage, thereby allowing for monitoring of neurorehabilitation progress.¹¹⁷

Outside of customized physical therapy and patient-specific activity monitoring, optimizing a patient's nutritional status relative to their baseline frailty plays an important role in the postoperative surgical course. Screening for patients with poor nutritional status includes tools such as the Nutritional Risk Score and measurements of body mass index, sarcopenia, and other metabolic markers of frailty, such as albumin, which has been shown to be an independent predictor of postoperative complications after certain types of spine surgery.^{118,119} In a study by Rigney et al, patients who underwent surgery for metastatic spinal tumors and who received a nutrition consultation preoperatively were less likely to develop complications related to wound healing during the postoperative course.¹²⁰ Additionally, those patients who were determined to have a normal nutritional status at baseline were more likely to have improved survival following surgery. Similarly, in a study by Elsamadicy et al, patients with poor nutritional status and who underwent lumbar fusion for spondylolisthesis had greater rates of readmissions, length of stay, and adverse events such as pneumonia and skin/soft tissue infections.¹²¹ Optimizing a patient's nutritional status based on their specific nutritional needs is therefore important prior to surgery with continued optimization postoperatively.¹¹⁹

CONCLUSION

Evolving technologies and a deeper understanding of patient-specific factors have changed the landscape of spine surgery. By working in a multidisciplinary fashion with other health care providers, including but not limited to endocrinologists, nutritionists, and physical therapists, spine surgeons can avail themselves of personalized, precision care and tailor each stage of the surgical pathway to the individual patient.

In this review, we described some ways to do so, from the initial clinic visit to the ultimate rehabilitation. BMD should first be assessed with DEXA scans, with complementary information gleaned from TBS or FRAX scores. In collaboration with endocrinology, preoperative optimization of BMD is essential to mitigate the risks of osteoporosis-related complications, thereby improving surgical outcomes. Additionally, the intraoperative setting has seen significant advancements with the customization of implants. The use of 3D printing technology enables the creation of implants tailored to the patient's unique anatomical and biomechanical needs, enhancing the fit and functionality of the surgical constructs. Furthermore, the integration of cutting-edge technologies such as EOS imaging and robot-assisted surgery has improved the precision and efficiency of surgical interventions. These technologies facilitate accurate assessment of spinopelvic parameters and allow for meticulous preoperative planning and intraoperative execution. Equally important is the emphasis on postoperative care, where personalized pain management regimens, increasingly informed by pharmacogenomic and AI insights, as well as individualized physical and nutritional therapy plans, created with nutritionists and physical therapists, are crucial for optimizing recovery and functional outcomes.

By focusing on these critical factors, spine surgeons can significantly enhance patient care and outcomes through a personalized, patient-centric approach to spine surgery. This comprehensive, tailored care ensures that each patient receives optimal treatment throughout their surgical journey, ultimately leading to improved overall health and well-being.

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