Using Evidence-Based Medicine to Evaluate Interbody Spinal Fusion Device Materials

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Many spinal interbody fusion technologies are being brought to market today. Unsurprisingly, their introduction also brings an array of research data and clinical studies detailing bone ongrowth, fusion rates, and complications such as subsidence and delamination.

With such a rapid introduction of new technologies, how can today's surgeons determine the most effective technologies and products for enhancing their patient's standard of care? The answer is Evidence-Based Medicine (EBM).

What is Evidence-Based Medicine?

The most common definition of evidence-based medicine is 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient'.[1]

This means the integration of clinical expertise, patient values and the best research evidence into the decision making process for patient care. Clinical expertise refers to the clinician's cumulative experience, education and clinical skills. The patient brings to the encounter his or her own personal preferences and unique concerns, expectations and values. The best research evidence is usually found in clinically relevant research that has been conducted using sound methodology.[2]

Ultimately, the goal of evidence-based medicine is to improve patient outcomes, quality of care and provide standardization of treatment.

When reviewing clinical evidence in a particular therapeutic area it is important to understand there are different levels of evidence; that is, not all forms of evidence can be considered equal in value. Evidence-based medicine essentially classifies available clinical evidence and assigns a quality level, based on its freedom from various biases and most importantly determines its correlation with positive clinical outcomes.

Levels of Evidence

The key to evidence-based medicine and effective clinical decision-making is the level of evidence supporting the performance of medical devices and therapeutics. Several organizations have developed level of evidence grading systems for assessing the quality of evidence. For this article, we will utilize the Oxford (UK) CEBM (Centre for Evidence-Based Medicine) Levels of Evidence, which were last updated in March 2009.[3]

In simple terms, the levels of evidence can be summarized below:

Levels of Evidence

Level 1a	Evidence from systematic review of randomized controlled trials
Level 1b	Evidence from an individual randomized controlled trial
Level 2a	Evidence from systematic review of cohort studies (with homogeneity)
Level 2b	Evidence from individual cohort study or low-quality randomized controlled trial
Level 2c	Evidence from outcomes research and ecological studies
Level 3a	Evidence from systematic review of case-control studies (with homogeneity)
Level 3b	Evidence from an individual case-control study
Level 4	Evidence from case-series or low-quality cohort and case-control studies
Level 5	Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'

Level 1 data is the most rigorous and is generally accepted as the most reliable evidence of whether a treatment is effective. In contrast, Level 5 data offers the least amount of evidence in this regard. For example, while basic animal and *in vitro* data are helpful, they do not necessarily correlate to patient clinical outcomes and should be viewed only as a supplement to higher level clinical evidence.

To understand what these levels of clinical evidence offer, further explanation is provided:[3]

Level 1 Clinical Evidence

- **Systematic Reviews** are literature reviews of peer-reviewed publications about a specific health problem. They use rigorous, standardized methods for selecting and assessing articles, and may or may not include a meta-analysis, which is a quantitative summary of the results.
- **Homogeneity** is a systematic review that is free of worrisome variations (heterogeneity) between individual studies. Studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
- **Randomized Control Trials** randomly allocate subjects into study and control groups, either receiving or not receiving an experimental preventive, therapeutic

or diagnostic procedure. They are then followed to determine the interventional effects. The results are assessed by rigorous comparison of outcomes in both groups.

Level 2 Clinical Evidence

- **Cohort Studies** involve subsets of a defined population that have been or may be exposed to factors, which may influence the probability of a disease occurrence or other outcome. Large numbers are typically observed over a period of years with incidence rates compared in groups with different exposure levels.
- **"Outcomes" Research; Ecological Studies** seek to understand the end results of particular health care practices and interventions that people experience and care about. Measures can include quality of life and preferences, effectiveness of health-care delivery, cost-effectiveness, health status and disease burden.[4]

Level 3 Clinical Evidence

- **Case Control Studies** include subjects with a specific disease or outcome and a control group without the disease or outcome. A specific disease attribute is studied by comparing it against the non-diseased with regard to frequency of presence or the quantitative levels in each group.

Level 4 Clinical Evidence

- **Case Series** consist of a group of case reports including patients who were provided similar treatment. They typically contain detailed information about the individual patients including: demographic information, diagnosis, treatment, treatment response, and post-treatment follow-up.

Level 5 Clinical Evidence

- **Non-Human Clinical Studies** include animal and biomechanical studies, *in-vitro* studies and expert opinions.

When considering new interbody spinal fusion materials, surgeons must consider not only key clinical data such as fusion and subsidence rates, but also how robust the data is in terms of level of evidence.

The following review and evaluation considers key clinical data, results and the associated level of evidence for some of today's interbody spinal fusion device materials including:

- PEEK-OPTIMA™ Natural
- PEEK-OPTIMA HA Enhanced
- Titanium-Coated PEEK
- Titan Spine Endoskeleton®
- Porous Trabecular Metal™
- 3D Printed Titanium

Existing Standard of Care

PEEK-OPTIMA Natural

PEEK-OPTIMA Natural polymer with over 15 years of clinical history, has been used in approximately nine million implanted medical devices worldwide, including interbody fusion devices. Among the product's benefits are its high mechanical strength and biocompatibility. However, of greatest clinical significance are its radiolucency and bone-like modulus of elasticity, which promotes higher stress distribution and consequently, bone remodeling and fusion. In contrast, titanium can stress shield the bone graft, creating concentrations between implants and endplates resulting in subsidence.

PEEK-OPTIMA Natural spinal cages are backed by years of quality, high-level clinical evidence reporting high fusion rates and correspondingly good clinical outcomes. Systematic reviews and meta-analyses (Level 1a Clinical Evidence) have reported at least equivalent fusion rates and lower subsidence rates with PEEK-OPTIMA Natural compared to titanium interbody spinal cages.[5-7] Dozens of peer-reviewed clinical papers and a majority of the clinical studies have yielded similar results, as indicated in the charts below.

PEEK Clinical Literature Review

Systematic Review: PEEK and PEEK CF-Reinforced vs. Titanium in ACDF[5]

Cage Material	Good-to-excellent Clinical Outcome (%)	Fusion Rate at 12 months (%)	Subsidence (%)
CF-Reinforced PEEK	76.8	62-98	29.2-49
Titanium	46-95	86.5-99	9-45
PEEK	80-96	93-100	0-14.2

Chart 1: "a majority of studies have reported improved fusion rates, lower subsidence rates and radiolucency with PEEK versus Ti cages"

Meta-Analysis: PEEK vs. Titanium[6]

Cage Material	Clinical Functional Status by Odom	Fusion Rate at 12 months	Subsidence
Titanium	70/101	93/124 (75%)	33/211 (15.6%)
PEEK	70/98	86/91 (94.5%)	11/84 (6%)

Chart 2: "Although more subsidence occured in the titanium group, the effects of loss of local segmental angle or the whole cervical Cobb angle on cervical function in the long-term are still not clear"

Although the literature reports overwhelmingly positive clinical outcomes, PEEK-OPTIMA is not a perfect material. The surface of PEEK-OPTIMA is relatively inert and not osteoconductive, therefore bone does not consistently attach to PEEK-OPTIMA. Consequently, surgeons who choose not to use PEEK-OPTIMA frequently cite its lack of bone ongrowth as the primary reason they select other materials.

PEEK-OPTIMA HA Enhanced

To address this market need for earlier bone ongrowth, Invibio developed PEEK-OPTIMA HA Enhanced, a unique compound material that incorporates the well-known oseteoconductive material hydroxyapatite (HA) into the bulk PEEK-OPTIMA matrix.

HA has a chemical and crystalline structure similar to the mineral component of bone. In fact, apatite crystals comprise around 70% of bone's dry mass.[8] HA's proven medical success spans four decades in applications including dental and orthopedic implant coatings, bone void fillers and coated screw systems for improved fixation. Its make up and benefits are also ideal for interbody spinal fusion.

Unlike surface coatings and roughened metal technology for interbody spinal fusion, PEEK-OPTIMA HA Enhanced addresses the entire environment. HA particles are fully integrated into the PEEK-OPTIMA matrix, making it available on all surfaces of a finished device. Consequently, both inner- and outer-cage graft materials are exposed to HA, resulting in enhanced osteoconductivity and eliminating delamination. Like PEEK-OPTIMA Natural, it offers a bone-like modulus of elasticity, reduced stress-shielding of bone graft and artifact-free imaging.

Pre-Clinical Studies

Pre-clinical animal studies (Level 5 Clinical Evidence) with PEEK-OPTIMA HA Enhanced are encouraging. They demonstrate greater osteointegrative benefits when compared to PEEK-OPTIMA Natural (ref. figure 1, 2).

- Enhanced bone apposition with greater than 75% direct bone contact as early as 4 weeks[9]
- Greater new bone formation at 6 weeks in a cervical fusion study[10-11]
- Higher quality new bone bridging at 6 and 12 weeks in a cervical fusion study[10-11]

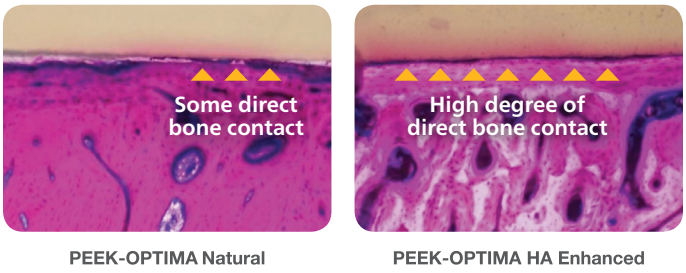


Figure 1: Cortical bone histology: Enhanced bone apposition at 12 weeks, greater direct bone contact with PEEK-OPTIMA HA Enhanced compared with PEEK-OPTIMA Natural.[9]

Bone Contact Comparison[9,11]

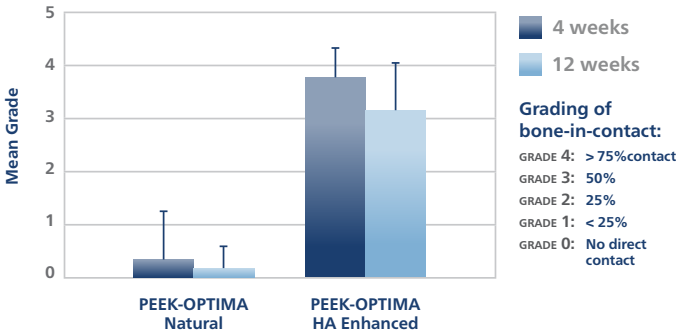


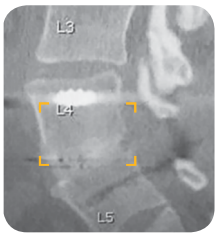
Figure 2: Earlier Bone Ongrowth: PEEK-OPTIMA HA Enhanced promotes greater than 75% direct bone contact after 4 weeks compared with PEEK-OPTIMA Natural.

Early Clinical Results

Early human clinical evidence for PEEK-OPTIMA HA Enhanced, including findings by Dr Timothy Bassett, concur with the pre-clinical studies.

Dr Timothy Bassett (SouthEastern Spine Specialists, Tuscaloosa, AL, USA) has been in private practice for 23 years and specializes in cervical and lumbar spine problems with primary focus on adult degenerative lumbar spine problems and failed lumbar fusions. He also has over 23 years experience using interbody implants and grafts.[12*]

Between October 2015 and October 2016, Dr Bassett conducted Transforaminal Lumbar Interbody Fusion (TLIF) procedures on 59 patients (78 levels). In all cases, he used the Cutting Edge Spine EVOS-HA cage made from PEEK-OPTIMA HA Enhanced. Dr Bassett later presented findings from nine cases at the 2016 North American Spine Society (NASS) Annual Meeting. In this 9-patient case series (Level 4 Clinical Evidence), 9 of 10 levels were definitively fused as shown on the 6-month, post-op CT scan, while the final case was progressing toward complete fusion. Notably, areas of dense bone apposition were observed around the implant in several patients (ref. figure 3). Correspondingly, good clinical results were achieved in this case series despite some challenging patients.



"CASE SERIES: PEEK-OPTIMA™ HA Enhanced Polymer Shows Early Clinical Success in Interbody Spinal Fusions." For further results see page 3-7.

Figure 3: Solid lumbar fusion at 6 months on CT scan.
Image courtesy of Timothy Bassett, MD

Although more quality, high evidentiary level studies are warranted, PEEK-OPTIMA HA Enhanced early successes, as an interbody spinal fusion material are promising.

Titanium (Ti) Coated PEEK

Capitalizing on PEEK-OPTIMA Natural's clinical benefits and titanium's natural propensity for bone ongrowth, Ti-Coated PEEK Cages were developed and first gained FDA 510(k) clearance in 2011. Since then, this technology has been adopted by several medical device manufacturers in their interbody spinal fusion devices. Various Levels of Clinical Evidence have been developed for this technology since its introduction into the marketplace.

A 2016 biomechanical study (Level 5 Clinical Evidence) investigated whether wear debris or delamination occurred following simulated impaction of Ti-coated PEEK cages into the disc space. It also tested whether similar sheer loading resulted in failure in surface-etched titanium cages.[13]

The same study showed mechanical testing negatively impacted Ti-coated PEEK, but not surface-etched titanium.[13] Ti-coated PEEK cages showed partial delamination, wear debris and surface damage, with more than half of the detached particles being in the size range capable of being phagocytosed.[13]

One 2017 clinical study (Level 1b Clinical Evidence) has pointed to the potential of Ti-coated PEEK devices in facilitating rapid and stable fixation with a high fusion rate.[14] However, other studies directly comparing Ti-coated PEEK and PEEK only devices have been less than definitive. A 2015 randomized clinical and radiological trial aimed to compare fusion rates and clinical results of titanium-coated PEEK cages vs. PEEK-OPTIMA Natural cages for Posterior Lumbar Interbody Fusion (PLIF) surgery.[15]

Radiographic results between the two groups were indistinguishable. At 12-month follow up, there was no migration or dislocation observed in either the Ti-coated PEEK or PEEK-OPTIMA Natural cages groups. Clinically, the two cages also performed equally well with 100% fusion rates at 12 months (ref. chart 3).

Randomized Clinical and Radiological Trial: PEEK vs. Ti-Coated PEEK Cages in PLIF[15]

	PEEK-OPTIMA	Ti-Coated PEEK
Oswestry score reduction	45 to 20	43 to 20
VAS low back pain reduction	5.2 to 2.6	6.1 to 2.6
Fusion by CT scan:		
Bone growth through cage pores	100%	100%
Bone growth outside cages	61%	48%
Fusion Rate	**100%**	**100%**

Chart 3: "Pure PEEK and Ti-coated PEEK cages for PLIF produce equally favorable clinical and radiological results 12-months post-surgery."[15]

A final prospective single-arm clinical study (Level 2b Clinical Evidence) recently published in *Patient Safety in Surgery* merits consideration.[16] This study reported outcomes for Ti-coated PEEK cages and PEEK-OPTIMA Natural cages in Anterior Cervical Discectomy and Fusion (ACDF).

As seen in Chart 4, PEEK & Ti patients had somewhat better fusion scores at 6 months. However, these differences did not persist at 12 and 18 months. The authors thereby concluded that partial Ti coating of PEEK cages does not improve the fusion rate sufficiently or confer other lasting clinical benefits.[16]

Despite the popularity of Ti-coated PEEK devices, clinical evidence, fusion and biomechanical studies to date have shown mixed results.

Multi-Center Comparative Analysis: Ti-Coated PEEK vs. PEEK-OPTIMA Natural Cages in ACDF[16]

49 patient pairs	Both PEEK & Ti PEEK Fused	Both PEEK & Ti PEEK **not** Fused	Only PEEK Fused	Only Ti PEEK Fused
6 month	14	17	5	13
12 month	28	6	6	9
18 months	33	4	6	6

Chart 4

Titan Spine Endoskeleton®

Titan Spine received 510(k) clearance for their Endoskeleton interbody fusion implants, made from Titanium, with proprietary nanoLOCK™ surface technology in 2014. The technology is promoted as having a unique combination of roughened topography at the macro, micro and nano levels. Such topography is claimed to create optimal host bone response, up-regulate osteogenic and angiogenic growth factors that promote bone growth, and encourage natural production of bone morphogenetic proteins (BMPs).

These claims are supported only by *in vitro* cell studies (Level 5 Clinical Evidence) and strictly measure material-cell response. While *in vitro* cell data is reasonable basic science for assessment of cell response to materials, these results do not take into account biomechanical factors such as stress, micro-motion, and potential patient co-morbidities including diabetes, smoking and poor bone quality, which contribute to a more complex clinical environment. These studies represent the lowest level of clinical and scientific evidence available in the literature. Therefore, conclusions on clinical benefits cannot be reached based on *in vitro* cell studies alone.

Market adoption of Endoskeleton spinal implants with the nanoLOCK surface technology will require studies with higher quality and Level of Evidence.

Porous Trabecular Metal

Introduced in 2006, porous Trabecular Metal technology is not new to the spinal industry and has demonstrated clinical use in a variety of orthopedic applications.[17-19] It is a highly porous biomaterial made from tantalum with structural, functional and physiological properties similar to that of bone.[20] Early animal studies (Level 5 Clinical Evidence) comparing porous Trabecular Metal to PEEK-OPTIMA Natural appeared promising.

In one study, porous Trabecular Metal supported bone growth into and around the implant margins better than PEEK-OPTIMA Natural.[21] Its open-cell porous nature facilitated the host-bone ingrowth and bone bridging through the device. However, subsequent clinical human data did not correlate with the animal results.

In a higher level, prospective randomized, controlled clinical study (Level 1b Clinical Evidence), porous Trabecular Metal fusion rates were just 69%.[22] Another 2013 study indicated even lower fusion rates of 38% and showed significant device fragmentation (ref. figure 4).[23]

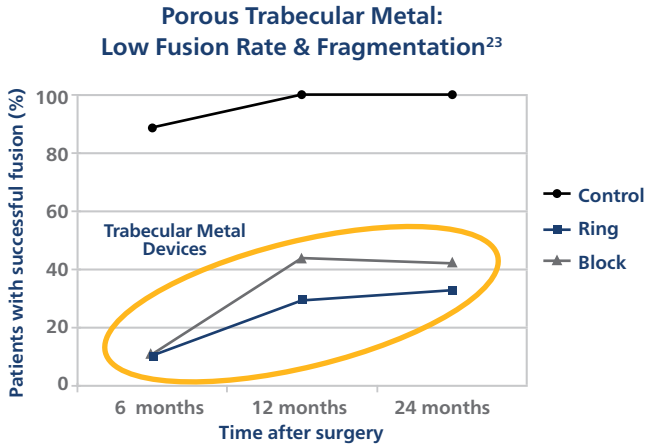


Figure 4: Only 38% of patients fused at 24 months; 27.8% exhibited device fragmentation.[23]

Animal and clinical data ambiguity again shines a spotlight on the importance of Level of Evidence in determining clinical efficacy. Moreover, such ambiguities clearly indicate a need for further non-animal, high Level of Evidence studies for effective evaluation of and confidence in new technologies.

3D Printed Titanium

3D Printed Titanium devices are offered by several companies including Stryker, K2M and 4Web. This technology is new to the interbody spinal fusion market and these devices have been developed to promote bone ongrowth. In addition to promoting bone ongrowth, K2M claims bone in-growth with 70% porosity and rough surfaces for enhanced cellular activity.[24]

Due to the technology's short history, little clinical data is available in the public domain. Proving clinical efficacy for 3D Printed Titanium lies with each device manufacturer.

Summary

As new spinal fusion technologies are introduced and before device selection, surgeons must continue to carefully weigh the Level of Clinical Evidence behind the claims to determine if it correlates to actual human clinical benefit (ref. chart 5 for a summary of the Level of Clinical Evidence for studies reviewed in this article). For their part, device and material manufacturers must continue to conduct high Level of Evidence studies that provide the proof required to demonstrate patient benefit, drive market adoption and continue to advance medical, and particularly, spinal interbody fusion materials and technology. ▲

Technology	Highest Level of Clinical Evidence	Type of Study
PEEK-OPTIMA	Level 1a	Systematic Reviews and Meta-Analyses
PEEK-OPTIMA HA Enhanced	Level 4	Case Series
Titanium (Ti) Coated PEEK	Level 5	Mechanical Testing
	Level 1b	A Randomized Clinical and Radiological Trial
	Level 2b	Prospective Single Arm Clinical Study
Titan Spine Endoskeleton	Level 5	*in vitro* cell studies
Porous Trabecular Metal	Level 5	Animal Studies
	Level 1b	Prospective Randomized Controlled Clinical Study
3D Printed Titanium	Level 5	Animal Studies

Chart 5: Table is based on the studies reviewed in this article.

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Dr Sheryl O'Farrell holds the position of Clinical Study Manager at Invibio Biomaterial Solutions. Previously, Dr O'Farrell worked at Medvance Ltd. for 10 years as the Head of Clinical Operations & Quality Assurance, Johnson & Johnson as Project Manager for Spine, Bio-medical Research, Ltd. as Head of Clinical Research, among other medical technology companies. In 2003, she received her PhD from the University of Liverpool, United Kingdom.

Mark Brady, PhD

Dr Mark Brady is the Senior Spine Technology Manager for Invibio Biomaterial Solutions where he was responsible for leading the development of PEEK-OPTIMA HA Enhanced. Prior to his position at Invibio, Dr Brady was a Principal Scientist at Renovo working on the mechanism of action of lead drug candidates and, prior to that, a Senior Research Associate at the University of Liverpool. In 2001, he received his PhD from the University of Liverpool, United Kingdom.

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* The case studies and testimonial presented have been provided by a practicing orthopedic surgeon. His view and experiences are his own and do not necessarily reflect those of others. "Invibio" disclaims any liabilities or loss in connection with the information herein.

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