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Effect of titanium coating  
on PEEK osteoconductivity in an ovine model

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TI-COATED INTERBODY FUSION DEVICE



## Titanium Coated PEEK Enhanced Bone Contact

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# Effect of titanium coating on PEEK osteoconductivity in an ovine model

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## ABSTRACT

Polyetheretherketone (PEEK) is used primarily in spinal fusions, in virtue of biocompatibility, radiolucency, and also its stiffness, which is close to that of bone. However, PEEK inertness may result in limited fixation to bone. This comparative study evaluated in an ovine model whether PEEK fixation can be improved by plasma-sprayed titanium coating. PEEK and titanium-coated PEEK (TiPEEK) cylindrical implants were placed in press-fit in the cancellous bone, and in cortical bone in a line-to-line bicortical manner. Push out testing was conducted in the cortical samples at 4 and 12 weeks, while histologies were performed in cortical and cancellous samples at the same time points. Compared to PEEK, TiPEEK implants showed significantly higher shear strength and stiffness at the bone-implant interfaces and intimate contact with the bone whilst PEEK showed a non-reactive fibrous tissue at the bone-implant interface. No adverse reactions were observed.

In conclusion, the preclinical evaluation on ovine model showed that TiPEEK elicited extensive bony ongrowth earlier than PEEK, followed by further bone apposition and differentiation, thus generating a bone-implant interface much stronger than PEEK at any time points. TiPEEK appears to effectively promote bony fusion in vivo showing bioactive and osteoconductive properties. These findings substantiate its use in spinal fusion.

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## BACKGROUND AND INTRODUCTION

Polyetheretherketone (PEEK) has been increasingly employed as biomaterial for trauma, orthopaedic and spinal implants. Today, as a relatively new implant material, PEEK has gained widespread acceptance as a high-strength polymer used primarily in spinal fusions due to its inherent properties. Unlike metal implants, PEEK elastic modulus closely matches native bone<sup>[1,2]</sup>. Therefore, PEEK spinal implants can provide a physiological-like support allowing for proper load transmission at the implant-tissue interface, thus minimizing stress shielding. This should prevent bone resorption and eventually facilitate bony fusion. PEEK favorable imaging compatibility has been another major driver for its widespread adoption for spinal applications, since PEEK X-Ray and CT translucency, as well as MRI compatibility, greatly facilitates the assessment of fusion in vivo. Finally, the chemical structure confers to PEEK stability and inertness, which explains its biocompatibility. Previous studies in vitro<sup>[3,4,5]</sup> and in vivo<sup>[6,7]</sup> have confirmed that PEEK is relatively inert in a biological context.

Unfortunately, whilst chemical structure and semi-crystalline nature provide high strength and biocompatibility, the hydrophobic inert surface of PEEK may limit local bone attachment<sup>[8]</sup>. In fact, despite its widespread clinical use in load-bearing orthopaedic implants, PEEK has also been associated with poor bone

fusion and consequent osseointegration often resulting in pseudoarthrosis. Osseointegration is a physiological phenomenon that leads to the direct anchorage of an implant by the formation of bony tissue around and through the implant without the growth of fibrous tissue at the bone-implant interface. In spinal fusion, a lack of fusion and osseointegration at the bone-implant interface of the interbody device may end up with failure of the fusion.

To overcome this limitation, increasing research effort has been directed to improve PEEK bone-implant interface and stimulate bone apposition, such as coating PEEK implant surfaces with plasma sprayed Titanium. Without compromising PEEK native properties, this process combines the advantages of PEEK with the biocompatibility and bioactivity of Titanium. Moreover, the thin titanium layer obtained through plasma spray deposition features a complex rough surface which is more favourable to bone apposition. Surface micro-roughness is known to influence the attachment of proteins to implants during initial contact with bodily fluids<sup>[9]</sup> as well as gene expression for Type I collagen, alkaline phosphatase and osteocalcin<sup>[10]</sup>. It is also known that enhancing roughness through surface modifications results in increased bone cell adhesion, growth, differentiation and long-term osseointegration<sup>[11,12]</sup>. Moreover, bioactive materials, such as titanium metals, allow the surrounding bone to spontaneously bond to the metal through a bone-like apatite layer<sup>[13]</sup>. Therefore, in addition to the increased

roughness, titanium plasma spray deposition on PEEK can result in bioactivation of the PEEK surface, which elicits bone ongrowth<sup>[14]</sup>. Bioactivation of titanium coatings on PEEK was recently demonstrated in vitro in a study comparing PEEK and titanium-coated PEEK (TiPEEK) cages soaked in Simulated Body Fluid. After just 1 day of incubation TiPEEK cage surface showed small globular masses, indicating calcium phosphate formation, which became more extensive structures after 7 days. In contrast, no deposition of calcium phosphate was seen on PEEK samples<sup>[15]</sup>.

In order to assess whether the titanium coating bioactivity found in vitro could be observed also in vivo, thus substantiating the use of TiPEEK cages for spinal fusion, a comparative study was set up and conducted in an established ovine bone ongrowth model<sup>[16-24]</sup>. The purpose of the study was to evaluate the response in vivo of two implant surfaces - PEEK and TiPEEK - mainly in terms of new bone formation assessed through histology and mechanical properties of implants in bone evaluated through standard push out tests at 4 and 12 weeks following surgery.

## MATERIALS AND METHODS

The study was conducted according to a protocol developed and validated at Surgical & Orthopaedic Research Laboratories of New South Wales University in Randwick, Sydney, Australia. Both protocol and qualifications of personnel involved in the study were reviewed and approved by the Institutional Animal Care and Ethics Committee.

Adult male sheep were used for comparative testing of implants, which consisted of two types of PEEK cylindrical dowels, 25 mm in length with a diameter of  $6 \pm 0.3$  mm (with or without the titanium coating). Coating of PEEK cylinders was performed with CP titanium using plasma spray technology. A schematic drawing of implants is shown in Figure 1.

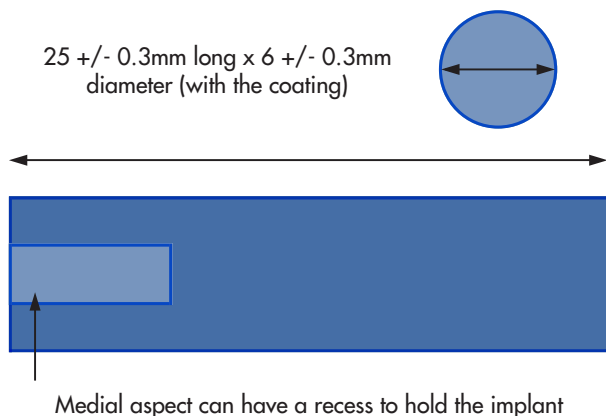


Figure 1. Schematic drawing of implants

Before implantation, surface morphology of test materials was observed using Environmental Scanning Electron Microscopy (eSEM) and surface roughness was analyzed (Federal Products, RI) along implant long axis in 4 different positions. Four sheep were selected for the study, examined for general health and randomly allocated to either the 4 week or 12 week survival group. After anaesthesia each animal underwent bilateral surgery in supine position. Five cylindrical dowels were implanted in each hind limb, two in cancellous bone and three in a bi-cortical method. Cancellous implantation was performed in a press-fit manner by impacting the cylinder in a 5.5 mm hole drilled in the medial distal femur and medial proximal tibia exposed through a 1 cm incision made on the medial aspect of the femoral condyles, followed by blunt dissection of the quadriceps muscle. After impaction of both cancellous implants (femur and tibia side), tissues were reflected and skin closed. In contrast, cortical implantation was performed in a line-to-line way in the diaphyseal portion of the tibia, which was accessed through a 3 cm incision made 50 mm from the articular surface along the anterior-medial aspect of the tibia followed by sharp dissection of the exposed periosteum. After three bi-cortical 6 mm holes approximately 20 mm apart had been prepared using sequentially larger drills, implants were fully inserted. Thereafter, soft tissues were reflected and sutured in layers. Overall, two cancellous (1 in distal femur, 1 in proximal tibia) and three bi-cortical (in diaphyseal tibia) dowels were implanted in each hind limb, as shown in Figure 2.

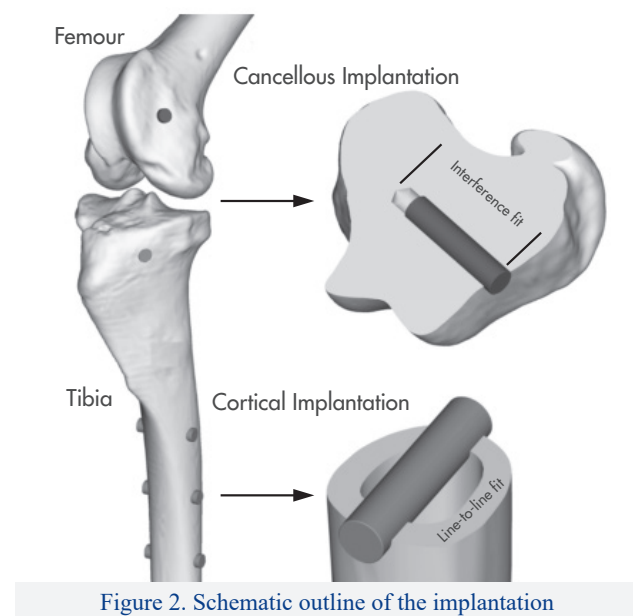


Figure 2. Schematic outline of the implantation

At 4 and 12 weeks following surgery animals were euthanized, then the femurs and tibia of left and right hind limbs were harvested for macroscopic observation followed by X-Ray analysis (Faxitron, IL) in anterior-posterior and lateral views. Distant organs (heart, liver, lung, kidney and spleen) were also harvested for routine histopathology. After isolation of all implantation sites, implant-bone interface shear stress was measured at the cortical sites using a standard push-out test to calculate the force required to dislodge the respective PEEK and TiPEEK implants. Specimens were tested at 0.5 mm/min on a calibrated servo-hydraulic testing machine (MTS Mini Bionix®, MTS Systems Inc., Minneapolis, MN, USA). All specimens (cancellous and cortical) were eventually fixed in buffered formalin, dehydrated, embedded in polymethylmethacrylate (PMMA) and sectioned.

The resulting sections were prepared for eSEM observation (Hitachi, Japan) and stained for examination with light microscope (Olimpus, Japan) to assess response at the implant-bone interface and local effects according to ISO 10993-6. Sample size per implant and allocation group in cortical bone was  $n=6$  for mechanical testing (medial side) and  $n=12$  for histological analysis (medial and lateral sides), whilst in cancellous bone was  $n=4$  for histology. These sample sizes were deemed appropriate based on previous experiments and relevant power calculation<sup>[23]</sup>.

Mechanical data was analyzed using a two-way analysis of variance (ANOVA) with post hoc tests for pairwise comparisons to assess the influence of time and surface coating on each parameter.

## RESULTS

### Pre-operative testing

Surface analysis of PEEK and TiPEEK implants revealed a mean surface roughness (Ra) of 0.98 microns and 7.98 microns, respectively. Implant surface macroscopic appearance is shown in Figure 3, whereas Figure 4 shows surface microscopic appearance, as revealed by eSEM.

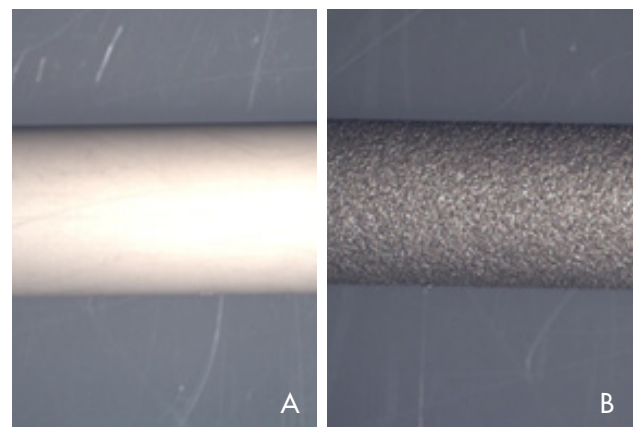


Figure 3. Stereo-zoom images of PEEK (a) and TiPEEK (b) implant surfaces

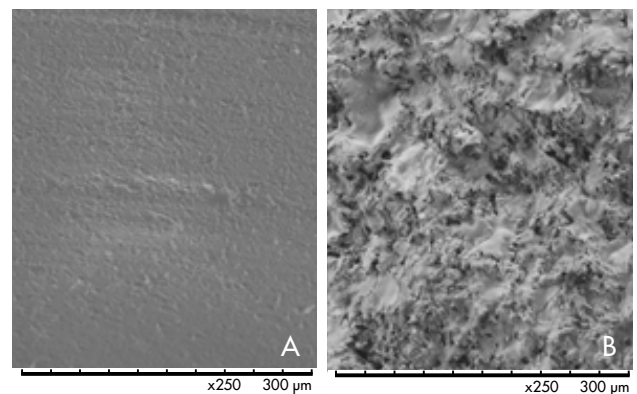


Figure 4. eSEM images of PEEK (a) and TiPEEK (b) implant surfaces

### Mechanical Testing

Push out tests on implants isolated from the medial cortex revealed significant differences between PEEK and TiPEEK samples ( $p<0.05$ ) at 4 and 12 weeks for all mechanical parameters.

A significant effect was detected for both factors, titanium coating and time. Whilst no significant difference was detected for the uncoated implants between 4 and 12 weeks, mean shear strength and stiffness at the

bone-implant interface for the TiPEEK implants were significantly greater than the uncoated implants at both 4 and 12 weeks ( $p < 0.05$ ). Moreover, a significant further increase for both mechanical parameters was observed in the TiPEEK implants between 4 and at 12 weeks ( $p < 0.05$ ), as shown in Figures 5 and 6.

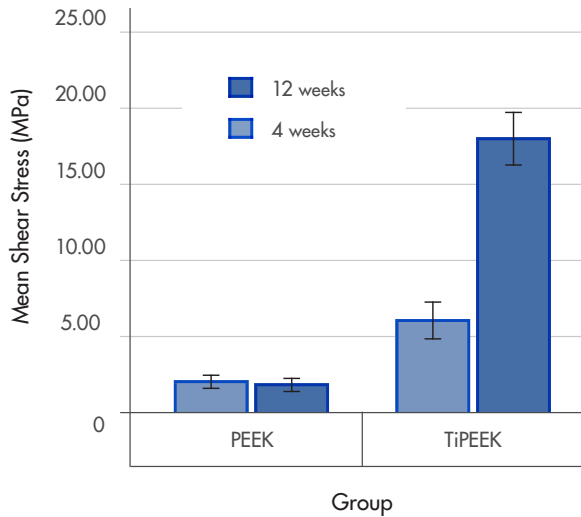


Figure 5. Shear stress at bone-implant interface (Error bars:  $\pm 1$  SE)

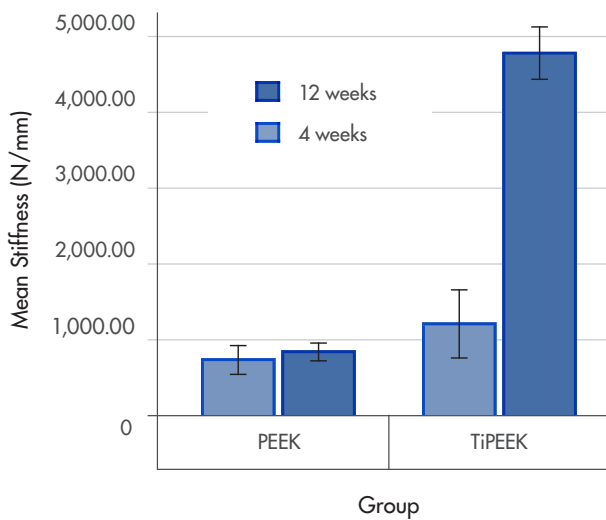


Figure 6. Stiffness at bone-implant interface (Error bars:  $\pm 1$  SE)

### Histology

Under light microscope examination, a non-reactive fibrous tissue interface was present between cancellous or cortical bone and PEEK implants at any time point. In contrast, the bone implant interface for the TiPEEK implants demonstrated an intimate contact between implant and cancellous or cortical bone, with direct apposition of new forming bone on implant surface and no intervening fibrous tissue at 4 weeks (Figures 7 and 8). This scenario further improved at the 12-week time point. Direct bone ongrowth on the titanium coating was also clearly confirmed by eSEM at 12 weeks (Figure 9). Neither around the uncoated implants nor around the coated ones was there evidence of adverse reactions at any time points.

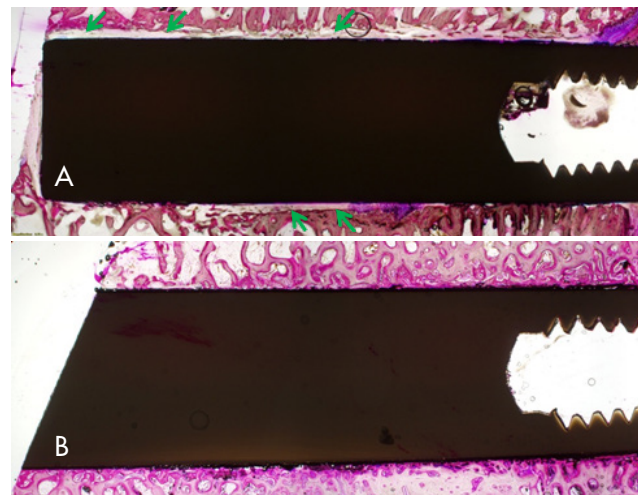


Figure 7. Cancellous interface in PEEK (a) and TiPEEK (b) implants at 4 weeks. A non-reactive fibrous tissue can be seen on PEEK implant interface (see arrows), while TiPEEK shows an intimate contact with the surrounding bone.

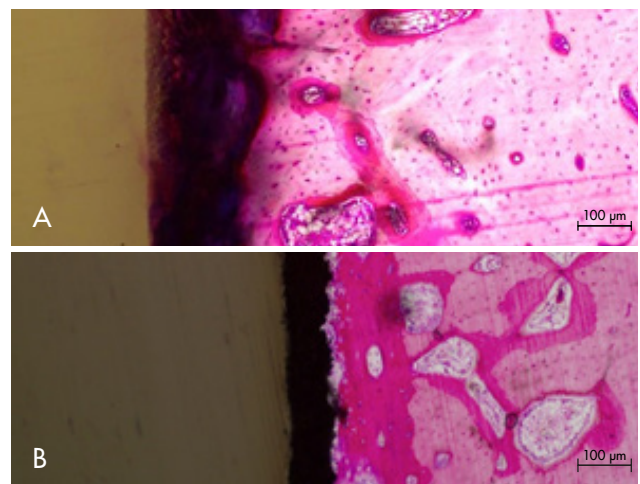


Figure 8. Cortical interface in PEEK (a) and TiPEEK (b) implants at 4 weeks. Non-reactive fibrous tissue is clearly visible on PEEK implant interface, while direct bone ongrowth can be seen on TiPEEK implant.

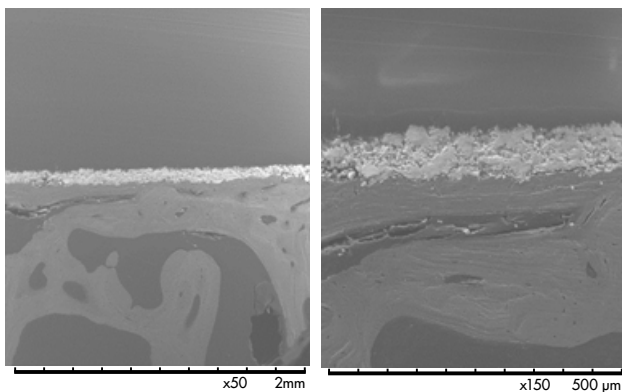


Figure 9. eSEM at 12 weeks demonstrating the direct bone ongrowth on the titanium coating

### Adverse events

Surgery was successfully completed in all animals without intraoperative adverse events. All animals reached the time of euthanasia without any post-operative adverse events. Neither evidence of infection nor adverse reactions to any implants were noted by macroscopic examination of harvested samples based on radiographic review and histology at any sites and time points. No adverse reactions were observed in the distal organs.

## DISCUSSION

The ultimate goal of most medical implants is to restore impaired biological function and achieve functional integration with the body. The bone-implant interface is known to be extremely important in joint arthroplasty, where proper function and longevity for joint replacement implants relies on secure fixation to the surrounding bone. The bone-implant interface is likewise crucial in spinal fusion, since the way bone integrates with an interbody device will dictate the transfer of load of the device to the neighbouring vertebral cancellous bone and, ultimately, the success of fusion. Osseointegration is key for obtaining maximal stability of spinal fusion implants, and it is desirable to achieve it as quickly as possible. Many factors can affect what happens at the bone-implant interface of vertebral cages, either inherent in patient conditions, such as age and comorbidities, or related to surgical preparation or to the features of the implanted device. Among the device-related factors, materials and coatings play an important role.

Despite initial biomedical applications of PEEK in trauma and joint arthroplasty, current widespread use is in the spine field since PEEK is now the material of choice for fusion cages. In fact, for long term load bearing applications, PEEK offers the unique combination of biocompatibility, radiolucency, and

mechanical properties similar to those of human bone<sup>[1,2]</sup>. Nevertheless, PEEK's relative inertness has also been the biggest hindrance to an even wider diffusion. One of the key factors that leads to successful implantation is the biological response to the implant, which very much depends on implant bioactivity. A material can be considered bioactive if it obtains a particular biological answer to the interface of the element, which ends in the formation of a bond between the tissue and the material<sup>[14]</sup>. Bioactive materials, such as Titanium metals, elicit the formation of an apatite layer on their surfaces which thereafter allows spontaneous bonding of the surrounding bone<sup>[13]</sup>. PEEK inertness results in a lack of bioactivity, which in a bony environment potentially means the formation of a non-reactive fibrous tissue at the bone-implant interface, i.e. limited fixation of the implant with the surrounding bone.

Plasma spray deposition of titanium on PEEK has the premises to address this issue, by enriching PEEK advantages with a higher surface roughness and the bioactive behaviour of Titanium. These two properties are known to positively affect protein early adhesion<sup>[9]</sup>, gene expression<sup>[10]</sup>, osteoblast adhesion, growth and differentiation<sup>[11,12]</sup>, and bone growth<sup>[13,14]</sup>. In fact, bioactivation of titanium plasma sprayed coatings on PEEK cages was recently demonstrated *in vitro*<sup>[15]</sup>.

The results obtained *in vivo* in the present comparative study corroborate the findings observed in all previous studies. Biocompatibility appears confirmed for both PEEK and TiPEEK implants by the total absence of adverse reactions at all implant sites at any time points. Mechanical data combined with histological findings show that Titanium coating of PEEK can eventually enhance implant osseointegration by promoting not only bioactivity but also osteoconductivity. Shear stress, which represents the amount of force required to disrupt the bone-implant interface, was significantly superior with TiPEEK implants at any time points. This superiority was shown to be more than 5 times that of PEEK at 4 weeks and more than 16 times at 12 weeks. In contrast, shear stress with PEEK implants remained unchanged throughout the same time interval. The histological images can explain the different mechanical behaviours. At 4 and 12 weeks PEEK implants did not show, or at least showed partial direct bone-implant contact, and presented a non-reactive fibrous tissue interface. Direct and intimate contact between the implant and the host bone was found in the TiPEEK implants, with new forming bone on the surface at 4 weeks, which further increased by 12 weeks. Therefore, shear stress significantly increased over time in TiPEEK as the new formed bone matured and remodeled. Accordingly, stiffness, which is a reflection of bone quality at the bone-implant interface, was always significantly higher in TiPEEK implants compared to

PEEK. Moreover, it increased over time at the TiPEEK interface as bone mineralized and became stronger.

In TiPEEK cages, Titanium coating on PEEK is capable to elicit surface bioactivity at a very early stage<sup>[15]</sup> thus determining bone growth observed at 4 weeks in cortical and cancellous sites. For TiPEEK and PEEK implants, the quality of bone at their interfaces was very different, as reflected by the respective mechanical properties: bone was more differentiated and mineralized, therefore stronger on TiPEEK, versus minimal and less mature on PEEK. Bone ongrowth at an early stage, promoted by titanium coating because of its bioactive properties, is followed by further bone growth immediately after. When the initial bony layer bonds to the rough TiPEEK, titanium acts as an osteoconductive scaffold for further bone apposition and ingrowth.



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