

TECHNICAL MONOGRAPH



PRESERVE[™] | Bone Graft System

Paragon

SUMMARY

The PRESERVE[™] Bone Graft System

Safe and Efficacious

- ► 25,000+ grafts distributed¹
- ▶ 10-year history of use
- <0.15% complaint rate²
- Eliminates the risks associated with iliac crest graft harvesting
- Chronic pain, fracture and infection⁶

Unique, Patented Allografts

- Customized Aseptic Process
 - No gamma irradiation, No hydrogen peroxide, No bleach
- Patented procedure-specific shapes

Compare to:

- Up to 20% non-union for autograft³
- ▶ Up to **30%** complication rate for autograft⁴
- ▶ Up to 24% non-union for structural allograft⁵



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RATIONALE AND SAFETY

Design Rationale

Paragon 28° launched the PRESERVE Bone Graft System to meet an unmet need of foot and ankle surgeons: to provide pre-shaped, anatomically specific, aseptically processed bone grafts. Since then, over 25,000 PRESERVE allografts have been implanted by hundreds of surgeons across the United States and in Europe. This innovative bone graft system was the first of its kind in foot and ankle and has gone on to reshape how surgeons think about allografts.

"The challenge is to prepare allografts that are well cleaned, sterile, and free of virus, while still preserving the natural biologic and biomechanical properties of the tissue." Boyce, et al.⁸

Safety and Usage

The PRESERVE Bone Graft System has a complaint rate of less than 0.15% with a more than 10-year history of safe use.²

PRESERVE Complaint Rate ² approx. 1 in 685
Iliac Crest Autograft Complication Rate ³ up to 3 in 10
Iliac Crest Autograft Non-Union Rate $^4.\ldots\ldots\ldots\ldots$.up to 1 in 5
Structural Allograft Non-Union Rate $^{\scriptscriptstyle 5}$

PROVEN TRACK RECORD¹

Implanted by 900+ surgeons





Available in **850+ facilities**



Sold across all 50 States and Internationally



CLINICAL CASE STUDIES

Neglected Calcaneal Fracture

Dr. Thomas Chang, DPM — Clinical Professor, Department of Podiatric Surgery, California College of Podiatric Medicine

Presentation

65 year-old female with daily hindfoot and ankle pain from neglected calcaneal fracture.

Corrective Procedure

Bone block distraction arthrodesis with Subtalar PRESERVE Graft

Outcome



At final follow-up (one year), radiograph shows improvement in talar declination angle and improved ankle joint alignment. Patient is able to perform daily activities with minimal pain and limitations.



PEDIATRIC FLATFOOT

Dr. Thomas Chang, DPM — Clinical Professor, Department of Podiatric Surgery, California College of Podiatric Medicine

Presentation

12 year-old male with arch pain and flatfoot collapse.

Corrective Procedure

- Evans osteotomy with Evans PRESERVE Graft
- Cotton osteotomy with Cotton PRESERVE Graft
- Gastrocnemius lengthening

Outcome

At one year post-operative, the radiograph shows excellent consolidation of the Evans and Cotton PRESERVE Grafts.

LAPIDUS ARTHRODESIS

Dr. Thomas San Giovanni, MD

- Clinical Professor, Florida International University, Herbert Wertheim College of Medicine
- ▶ Team Physician: Miami Dolphins, Florida Panthers, Miami FC

Presentation

23 year-old female with hallux valgus and 1st TMT instability.

Corrective Procedure

- ▶ Lapidus arthrodesis with Lapidus PRESERVE Graft
- Derotation of 1st metatarsal
- Distal soft tissue realignment (modified McBride)

Outcome

- ▶ At 10 weeks, CT scan shows patient bone incorporation into the PRESERVE allograft.
- > At one year post-operative, correction is maintained and the patient is back to normal activity.



Lapidus Graft

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BIOMECHANICAL TESTING

Comparison of the Biomechanical Properties of Non-Gamma Irradiated and Gamma Irradiated Dense Cancellous Bone⁹

Study Goal: To compare failure rates of dense cancellous bone under dynamic testing that have been processed with and without gamma irradiation. The hypothesis is that samples that have not been subjected to gamma irradiation will outperform samples that have been gamma irradiated in dynamic testing.

Methods: 72 cylindrical, freeze dried cancellous bone samples were tested under cyclic dynamic loading using a load cell. All samples were processed and tested at Community Tissue Services (Kettering, OH). Samples were processed using one of two methodologies:

Non-Gamma Processing

 Processed according to the protocol set for PRESERVE Bone Grafts

Gamma Processing

- Series of static soaks
- ▶ Gamma irradiation at 13 kGy

Dynamic Testing

- Ramp displacement at 1 N/s up to 7N compression
- Sinusoidal load waveform
- > 27N amplitude (7N to 61N) at 2Hz
- ▶ 10,000 cycle runout



Dynamic Testing Success Rate



Results: Two samples (one aseptic and one gamma irradiated) were lost to testing equipment error, leaving 35 samples in each group. **Six gamma irradiated samples failed (17.1%)** compared to just **two from the radiation-free group (5.7%)**. Three of the gamma irradiated samples failed prior to reaching 4,000 cycles with one sample failing at 690 cycles.

Conclusion: Gamma irradiated bone samples failed at a higher rate than non-irradiated bone samples.



DENSE CANCELLOUS ALLOGRAFT

Why dense cancellous bone?

Faster Incorporation

- Cancellous bone is 8x more metabolically active than cortical bone.⁷
- Trabecular nature of cancellous bone has more surface area than cortical bone.⁷
 - More space for host osteoblasts and mesenchymal stem cells to incorporate.
- The osteointegration of cancellous graft is faster than cortical graft.⁷
 - Cortical bone walls must first be resorbed by osteoclasts.⁷
- More rapid revascularization for cancellous bone compared to cortical bone.
 - 2 days vs. 2 months⁷

Higher Union Rate

▶ 93.6% for cancellous allograft versus 86.9% for cortical allograft.⁵



Are dense cancellous allografts strong enough?

Paragon 28° works with experienced AATB accredited tissue banks to establish strict donor parameters, locations and guidelines to follow in order to get the highest quality cancellous bone available.

- Select Donors
 - Strict density requirements
- High Density Donor Sites
 - Femoral head, femoral calcar, distal femur, talus, patella, calcaneus and proximal tibia
 - Each graft must pass density requirements

Balanced Needs

Structural demands are balanced with revascularization needs for every • type of PRESERVE graft.

Customized Aseptic Processing

Helps preserve the biomechanical properties of the bone.¹⁰

Although dense cancellous bone is not as inherently strong as cortical bone, allograft bone must be resorbed for osteointegration to occur. During this process, cortical grafts may temporarily lose up to 75% of its mechanical strength.^{7,11}

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CLINICAL OUTCOMES OF ALLOGRAFT & AUTOGRAFT

Cancellous allograft, the category which **PRESERVE** bone grafts belong to, has demonstrated comparable fusion rates to the gold standard of autograft.

An independent study conducted by researchers at Harvard, Brown, Vanderbilt and OrthoCarolina found the fusion rate for cancellous allograft was effectively equal to that of the "gold standard", cancellous autograft (93.3% vs 93.7%), and higher than structural allograft or those who did not receive a graft of any type.⁵



Foster reviewed 26 subjects who received a tricortical allograft that was fashioned intraoperatively from an iliac crest bone block.¹² They found 15.4% non-union, 30.8% hardware removal and 3.8% infection rate. The median time to union was 12 weeks.

Vosseller reviewed records from 126 lateral column lengthening (LCL) procedures from five surgeons.¹³ In total, 13.7% of the autograft group and 17.3% of the tricortical iliac crest allograft group failed.

		Data from Vosseller, et al.
	Tricortical Iliac Crest Autograft	Tricortical Iliac Crest Allograft
# of Procedures	51	75
Non-Union	4 (7.8%)	9 (12.0%)
Loss of Correction	3 (5.9%)	4 (5.3%)
Failures	7 (13.7%)	13 (17.3%)

Muller found a non-union rate of 20% for subjects who underwent an LCL procedure with an iliac crest autograft.³

Luk reported a 13.3% non-union rate using hand-reamed tricortical iliac crest allograft in revision first MTP arthrodesis procedures.¹⁴



CUSTOMIZED ASEPTIC PROCESSING

"Irradiation is not a substitute for careful donor screening and viral assays." $$\rm Ng^{15}$$

What is aseptic processing?

Aseptic processing requires that sterile tissue handling is employed in a controlled environment throughout all stages of processing.⁸ The fundamental methods to achieve this include: the utilization of sterile handling techniques during donor bone recovery, thorough graft debridement and cleansing, and the use of treatment solutions such as surfactants, alcohol and antibiotic solutions during cleaning while maintaining strict environmental and quality controls.⁸

How does aseptic processing differ from terminal sterilization?

In many situations, **some controls during processing using terminal sterilization are reduced,** and a sterilization technique (such as gamma irradiation) is employed to achieve sterility.⁸

Why wouldn't a surgeon want a terminally sterilized graft?

Terminal sterilization may alter biologic and biomechanical features of the graft and cause them to perform differently.^{8,10,16-20} This may lead to graft failure or non-union of the graft and subsequent revision surgeries.⁸

Paragon 28°'s customized aseptic processing technique narrows the donor pool to only the highest quality bone in terms of safety and performance.

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PROCESSING EFFECTS ON BIOMECHANICAL PROPERTIES

"Processing techniques also can have a undesirable effect on graft strength, stiffness and the amount of energy absorbed." — Boyce, et al.⁸

Gamma Irradiation:

- Makes bone more brittle¹⁰
- Reduces functional life of bone¹⁰
- Reduces fatigue crack propagation resistance¹⁶

Not all tissue processing methods are equal

Some tissue processes have been proven to compromise the biomechanical and biological properties of the allograft. **Thus, seemingly similar grafts may perform differently as a result of the processing procedures**.⁸

Currey studied the effects of radiation on human bone and concluded that even at relatively low doses, radiation makes bone more brittle and reduces its energy-absorbing capacity.²¹

Akkus compared gamma irradiated bone samples to non-irradiated bone samples from three young male donors (≤38 years old).¹⁰ They found that irradiated bone samples had reduced biomechanical properties.

$igstyle ext{Yield strain}$ (9.9% less)	✓ Post-yield energy (70.0%)
✓ Max stress (10.2% less)	\checkmark Energy to fracture (86.4% less)
Ψ Fracture strain (60.5% less)	↓ Low-cycle fatigue (99.5% less)
↓ Elastic energy (14.3% less)	$igstyle ext{High-cycle fatigue (99.0\% less, estimated)}$

Gamma irradiation has also been shown to **reduce fatigue crack propagation resistance, shear strength, bending strength and compression strength** in cortical bone compared to non-irradiated bone.^{16,22}

Dux compared gamma irradiated bovine dense cancellous bone to controls and found that **irradiated samples had** significantly more mircrofractures and an increase in residual strain.²³



PROCESSING EFFECTS ON BIOLOGIC PROPERTIES

Hydrogen Peroxide

Negatively impacts osteoinductivity of bone ^{17, 24, 25}

Gamma Irradiation

- Inhibits osteoinductivity¹⁷⁻¹⁹
- Delays graft incorporation²⁰

In 2005, DePaula found that osteoinductivity decreased as hydrogen peroxide soak time increased.²⁴ Russell determined that hydrogen peroxide and gamma irradiation harm the osteoinductive properties of bone.¹⁷ Carpenter similarly concluded that hydrogen peroxide can damage osteoinductive capacity.²⁵



Osteoinductivity with and without hydrogen peroxide (H_2O_2)



Arjmand studied the effect of gamma irradiation on the osteoinductivity of bone and compared it to aseptically processed samples.¹⁸ Histopathology showed that new bone formation, chondrocytes, osteoblasts and angiogenesis all favored the aseptic allograft.

Han concluded that gamma irradiated demineralized bone matrix *"loses a significant degree of osteoinductivity"* when compared to non-irradiated samples.¹⁹ At 25kGy, all bone formation activity was virtually lost.

Voggenreiter used an animal model to investigate the incorporation of extracorporeal irradiated autogeneic cortical bone compared to controls and found: ²⁰

- At 25 kGy, graft incorporation was delayed at 6, 9 and 12 weeks
- At 9 and 12 weeks, all irradiated groups showed less cortical bone formation, worse revitalization of the grafts and delayed incorporation
- Fracture was seen in 71.4% of the grafts irradiated at 50 kGy

In a comprehensive literature review, Nguyen stated that: ²⁶

- > The activity of osteoclasts is reduced when they are cultured onto irradiated bone slices
- > Peroxidation of marrow fat increases apoptosis of osteoblasts
- Bacterial products remain after irradiation and induce inflammatory bone resorption following macrophage activation

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REASONS FOR ALLOGRAFT BONE

There are many reasons why iliac crest harvesting should be avoided.²⁷

- Previous operations at or near the potential harvest area
- Systemic bony or neurological diseases
- Long standing treatments with steroids
- Immunosuppressive drugs
- Chemotherapy in the previous two months
- Drug misuse in the previous three months

Other factors that may elevate surgical risk or impact bone quality that should be taken into consideration prior to introducing a second surgical site to harvesting an autograft.

- Age²⁸
- Gender²⁸
- Tobacco use^{29,30}
- ▶ Diabetes^{31,32}

Surgical Site Infection

Increasing risk of surgical site infection is associated with increasing operative time.³³ Several factors linked to prolonged surgical time may further increase the risk of infection. ^{34,35}

> "Currently, there are also commercially available sizers and preconfigured allografts (Paragon 28°). I prefer these systems in these bone block fusion scenarios, as they save operating room time and are less challenging to work with." Schuberth and Hamilton³⁶



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ILIAC CREST BONE HARVESTING: PAIN AND MORBIDITY

Complications Associated with Iliac Crest Bone Harvesting:

- Pain^{6,38,39}
- ► Fracture^{4,6,38}
- ▶ Infection⁶
- ▶ Hematoma⁶
- ► Seroma⁶
- ► Nerve injury^{6,38,40,41}
- Arterial injury^{6,38}
- Peritoneal perforation³⁸
- Sacroiliac joint instability³⁸
- Herniation of abdominal contents through defects in the ilium³⁸
- ▶ Wound Dehiscence⁶
- ► Scarring^{6,41}

Kim published findings from a prospective study looking at iliac crest bone graft harvest site pain and morbidity.⁴¹

At 1 year post-op:

- 16.5% had more severe pain from harvest site than from primary surgical site
- 29.1% had noticeable numbress
- ▶ 11.3% had bothersome numbness
- ▶ 3.9% were bothered by scar appearance



A systematic literature review of 6,449 patients to assess complications after bone graft harvesting from the iliac crest showed that 19.4% of patients experienced donor site complications, including 91 cases of infection. 7.8% of the patients had chronic pain at the harvest site.⁶

Huang reported a 30% complication rate at the harvest site for subject undergoing an anterior iliac crest autograft procedure including harvest site fracture.⁴

Injury to the lateral femoral cutaneous nerve can occur in up to 20% of patients during iliac crest bone harvesting.⁴⁰

Patients also experienced functional disability due to persistent harvest site pain.

- 15.1% difficulty walking
- ▶ 5.2% difficulty with their job
- ▶ 12.9% difficulty with recreational activities,
- ▶ 14.1% difficulty with household chores
- 7.6% difficulty with sexual activity
- ▶ 5.9% irritation from clothing

Bone Harvesting in Pediatric Patients

Bone grafts are commonly used in pediatric patients who require corrective skeletal surgery. It has been stated that pediatric autograft can sometimes lead to "disastrous consequences".⁴² In addition to the typical complications associated with iliac crest bone harvesting, children and adolescents may also experience disturbance in the growth of the iliac wing.⁴³ Kager et al. reported that 10% of adolescents had harvest site pain at 1 year after undergoing an iliac crest autograft procedure.³⁹



DESIGNED COMPATIBILITY WITH THE BUN-YO-MATIC LAPIDUS CLAMP SYSTEM

The Bun-Yo-Matic[™] Lapidus Clamp System is used to assist with the de-rotation, IM angle reduction, and joint closure in a Lapidus arthrodesis. The system is equipped with cutting guides designed to remove minimal bone from the base of the first metatarsal and the medial cuneiform to prepare the joint for fusion. The guides help establish parallel cut surfaces to improve apposition and arthrodesis following correction.

While the Bun-Yo-Matic Lapidus Clamp System is designed to minimize shortening of the 1st ray during a Lapidus arthrodesis, in some cases the surgeon may wish to introduce a minor amount of lengthening correction to improve soft tissue tensioning. **The 4 mm Parallel Lapidus Wedge** was designed precisely for this purpose:

- 4 mm length: Add a small amount of lengthening that may improve medial soft tissue tensioning
- **Parallel surfaces:** Maintains the deformity correction achieved by the Bun-Yo-Matic Lapidus Clamp, fits within the parallel-cut surfaces
- **PRESERVE Bone Graft Advantages:** Still has all the advantages of the PRESERVE Bone Graft system, including high structural integrity, rapid incorporation, and low rates of non-union



DENSE CANCELLOUS ALLOGRAFTS

(GRAFT	SIZE OFFERING	PRIMARY DONOR SITE	FEATURES
Evans		4 mm 6 mm 8 mm 10 mm 12 mm	• Patella • Talus • Femoral Calcar	 Patented dorsal to plantar taper and lateral to medial taper allows for multiplane correction while avoiding higher stresses to the long plantar ligament. Rounded corners dorsally and plantarly help prevent soft tissue irritation. Donor bone is cut to allow for the dorsolateral corner to have the highest density—allows the surgeon to tamp on the bone graft in this area to facilitate insertion.
Cotton	\bigcirc	5 mm 6 mm 7 mm 8 mm 9 mm 10 mm	• Patella • Talus • Femoral Calcar	 Patented shape has a rounded dorsomedial corner to match the curvature of the medial cuneiform. Donor bone is cut to allow for the dorsal portion of the graft to have the highest density—allows the surgeon to tamp on the bone graft in this area to facilitate insertion.
Lapidus	\bigcirc	4 mm x 0° 5 mm x 5° 8 mm x 8° 10 mm x 10° 12 mm x 12° 14 mm Universal (Parallel)	• Distal Femur	 Patented kidney bean shape provides biplanar correction from dorsal to plantar and medial to lateral along an axis to provide plantarflexion and abduction of the 1st metatarsal. Donor bone is cut to allow for the dorsomedial portion of the graft to have the highest density—allows the surgeon to tamp on the bone graft in this area to facilitate insertion.
MTP	\bigcirc	19 x 5 mm 19 x 8 mm 19 x 10 mm 19 x 15 mm 19 x 20 mm 21 x 5 mm 21 x 8 mm 21 x 10 mm	• Distal Femur	 Patented convex/concave design allows the hallux position to be adjusted in all 3 planes, without having to re-cut to adjust planar correction. Convex and concave shapes maximize surface area interaction between recipient bone and graft.
Subtalar		10 mm 12 mm 14 mm 16 mm 18 mm Universal (Parallel)	• Distal Femur • Talus • Patella • Femoral Calcar	 10 mm-16 mm grafts add height and varus/valgus correction. Angle of correction is proportional to the height of the graft. The round shape allows the wedge to be rotated to the desired correction to accommodate a wide range of anatomical shapes.
Calcaneo- Cuboid	\bigcirc	8 mm 10 mm 12 mm 14 mm 16 mm 18 mm Universal (Parallel)	• Distal Femur • Talus • Calcaneus • Femoral Calcar	 Tapered from medial to lateral to allow for ease of insertion. As width of wedge increases medial to lateral taper of wedge proportionally increases.
SMO		One concentric wedge size of 21° pre-shaped and up to 25° shaped or 15.5 mm tall	 Talus Proximal Femur Distal Femur Calcaneus Distal Tibia Proximal Tibia Femoral Calcar 	 Harvested from dense cancelleous bone Designed for medial opening SMO procedures The outer perimeter of the wedge was designed for the metaphyseal region of the distal tibia
Avitrac™ MTP Revision Graft		Ø9 mm Ø11 mm Ø13 mm	 Proximal Femur Distal Femur Calcaneus Distal Tibia Proximal Tibia 	 Designed to provide structural rigidity to the 1st metatarsal head following removal of a failed synthetic cartilage implant (SCI) Shape and size of the graft were optimized to fill the bony void Reamers included to provide reproducible preparation allowing for press fit of the graft

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PROCEDURE SPECIFIC INSTRUMENTATION

Evans & Cotton Allograft Trial Caddy



Lapidus Allograft Trial Caddy



MTP Allograft Trial Caddy



Subtalar & Calc-Cuboid Allograft Trial Caddy





MTP Trials

Trial handles, K-wires and patented spin guard reamers (Patent # 10,064,631) are included in the PRESERVE MTP Allograft Trial Caddy.



Trial handles, K-wires and a curved bone tamp are included in the PRESERVE Subtalar & Calc-Cuboid Allograft Trial Caddy.

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PRESERVE BONEGRAFT SYSTEM

Patent Numbers

D691,272 D813,394 D720,456 9,452,057 D740,424 9,848,893 D720,457

Additional patents pending

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Paragon 28's PRESERVE™ Bone Graft System is a human cell, tissue, and cellular and tissue-based product (HCT/P) that is regulated under 21 CFR 1271.3(d)(1) and Section 361 of the Public Health Service Act and is intended for homologous use only.

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