NOVOMEDICS
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A GUIDE TO BONE GRAFTING

There are many options for bone grafting and each option has unique features and benefits.

"THE GOLD STANDARD"

Autograft, which is also referred to as autologous bone or autogenous bone is, and has been, the gold standard for grafting procedures for many years. Much of its attraction comes from the avoidance of graft rejection because the graft is harvested and implanted from the same patient.

Autograft also has the three essential elements of bone formation: **osteoconduction**, **osteoinduction** and **osteogenesis**. These advantages make autograft an attractive solution. However, autograft comes with a significant disadvantage—donor-site morbidity. This has led to the introduction of other bone grafting options.

THREE ESSENTIAL ELEMENTS OF BONE FORMATION

Osteoconductive Properties
Any material that acts as a passive scaffold or matrix that supports new bone formation and bone growth. The ideal osteoconductive scaffold will have enough porosity to allow for vascular ingrowth and cellular attachment.

nanOss® Advanced Bone Graft Substitute

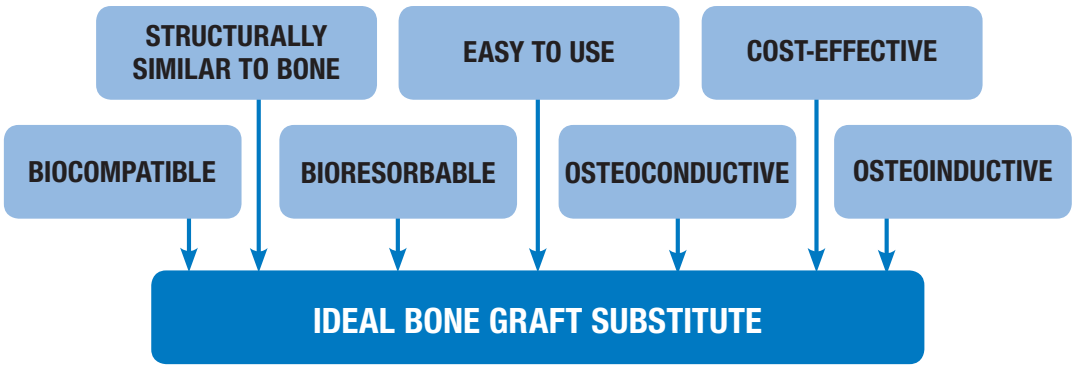
Osteoinductive Properties
Materials have the potential to form new bone through the active recruitment of host mesenchymal stem cells from the surrounding tissue, which differentiate into bone-forming osteoblasts. This is facilitated by the presence of growth factors (BMPs).

BioReady™ DBM

Osteogenic Properties
Materials that contain viable stem cells with the potential to support new bone growth at the recipient site.

map3® Cellular Allogeneic Bone Graft

While autografts have the ability to support new bone formation through all three elements, the presence of all three elements are not always necessary to be clinically effective. The American Academy of Orthopaedic Surgeons described the ideal bone graft substitute as having the following characteristics:[1]



The health of the patient, location and size of the defect play an important role in determining appropriate graft selection. Bone graft substitutes are alternatives to autograft and typically contain one or two of the three elements for bone formation: osteoconduction, osteoinduction and/or osteogenesis.

Osteoconductive scaffolds such as materials made from synthetic sources (e.g. calcium phosphate) provide a passive scaffold for cell infiltration. However, osteoconductive materials can also act as a vehicle for delivering bioactive agents, such as those contained in bone marrow aspirate (BMA).

The Importance of BMA

Surgeons will often mix autologous BMA with an osteoconductive allograft or synthetic-based scaffold because BMA is a rich source of bioactive agents (e.g. regenerative cells) needed for new bone formation. Typically, BMA is harvested from the iliac crest because it has the richest concentration of osteoprogenitor cells. Adding bone marrow aspirate to enrich orthopaedic grafting scaffolds is becoming more popular and the use of BMA is evolving as many surgeons are using concentration methods to isolate the regenerative cells. Concentration methods can be used to enhance the quality of the BMA being obtained.

Concentration of BMA can be achieved through various methods and is referred to as Bone Marrow Aspirate Concentrate or BMAC. Concentration allows for the isolation of stem cells within the bone marrow and allows the physician to return the concentrated stem cells to the patient to provide autologous healing properties to the body. Once the cells are separated they can be injected and/or mixed with the graft, resulting in a graft that is osteoinductive and/or conductive, and also potentially osteogenic.

Select the appropriate graft

The Bone Graft Classification chart below describes the various bone grafting options available and the RTI Surgical offering in each category.

The Grafting Materials chart on the following page describes the properties of each graft type.

BONE GRAFT CLASSIFICATION

Classification	Definition	Types	RTI Offering**
Autograft Bone Grafts	Bone is transferred within the same person; considered the gold standard	Iliac crest, fibula, tibia, calcaneous	N/A
Allografts – Conventional	Bone is processed in a way that exposes the bone morphogenetic proteins (BMPs) and transferred from one person to another (usually cadaveric).	Fresh, frozen, freeze-dried (lyophilized*)	Cancellous Chips, Cortical Cancellous Chips, Unicortical Dowels, Bicortical Blocks, Strips, Wedges and other structural bone grafts
Allografts – Demineralized Bone Matrix	Bone is processed in a way that exposes the bone morphogenetic proteins (BMPs) and is transferred from one person to another (usually cadaveric).	Grafts that have been demineralized most come frozen or freeze-dried	BioReady™ DBM BioSet® DBM*** BioAdapt® DBM DBM Powder
Xenografts	Bone is transferred between species	Bovine, Porcine	N/A
Synthetic-based Bone Grafts	Product is manufactured from non-human materials but has biomechanical properties and structure similar to that of bone and may be used as a bone graft substitute.	Calcium phosphates (e.g. hydroxyapatite and tricalcium phosphate), Bioglass and Calcium Sulfate[2]	nanOss® Advanced Bone Graft Substitute****
Growth Factors	Naturally occurring growth factors are manufactured (genetically engineered) and combined with various scaffolds.	Bone morphogenic protein, platelet-derived growth factor (PRP)	N/A
Cellular Allogeneic Bone Grafts	Live cells are added to various scaffolds	Mesenchymal stem cells, Multipotent adult progenitor cells (MAPC®)	map3® Cellular Allogeneic Bone Graft

**Lyophilized: Undergoes a dehydration process to remove water under vacuum pressure.*

***See labeling for specific instructions for use.*

****BioSet DBM contains allograft.*

*****Composed of hydroxyapatite granules and a gelatin based carrier.*

GRAFTING MATERIALS AND THEIR COMPARATIVE PROPERTIES*

Graft Type	Structural Strength	Osteoconductive	Osteoinductive	Osteogeneic
Autograft (Gold Standard)				
– Cancellous	++	+++	+++	+++
– Cortical	+++	++	++	++
Allograft (Conventional)				
– Frozen cancellous	++	++	+	No
– Freeze dried cancellous	++	++	+	No
– Frozen cortical	+++	+	No	No
– Freeze dried cortical	++	+	No	No
Structural Allograft (wedges, strips, shafts, etc.)	+++	+	No	No
Demineralized Bone Matrix (DBM) no chips	No	++	++	No
DBM with Cortical and Cancellous chips	+	+++	++	No
Cellular Allogeneic Bone Grafts	No	+	+++	+++
Growth Factors	No	No	+++	No
Synthetic-based Bone Grafts				
– Self-Setting	+++	++	No	No
– Non-self-setting	No	+++	No	No

+ = somewhat comparative properties; ++ = comparative properties; +++ = strong or similarly comparative properties

AVAILABLE BONE GRAFTING OPTIONS

Bone Graft Option: Cellular Allogeneic Bone Grafts

Cellular allogeneic bone grafts contain live cells which are recommended as part of the treatment for severe conditions such as non-unions. These grafts are most similar to autograft because they contain all three elements needed for bone formation but are not associated with donor site morbidity. These grafts have shown favorable outcomes, however they are typically more expensive than other grafting options.

Patients who have benefitted most from cellular allogeneic bone graft implants, such as map3® Cellular Allogeneic Bone Graft, have been shown to need support for bone healing due to trauma, tumor, infection, failed surgery, smoking, diabetes or other difficult-to-heal circumstances.

Competitor Cellular Allogeneic Bone Grafts

- Osteocel® Plus (AlloSource / NuVasive®)
- Trinity Evolution® (MTF / Orthofix)
- Trinity Elite® (MTF / Orthofix)
- Cellentra™ VCBM (TBI / Biomet)
- AlloStem® (AlloSource)

RTI Option: *map3® Cellular Allogeneic Bone Graft*

Bone Graft Option: Synthetic-based Bone Graft Substitutes

There are various types of synthetic-based bone grafting materials each with their own distinctive features. They most commonly consist of a synthetic component comprised of calcium phosphate, calcium sulfate, tricalcium phosphate and/or hydroxyapatite while some also include a collagen carrier component. These bone graft substitutes can be grouped into two general categories: self-setting bone grafts, or bone cements, and non-self setting bone graft substitutes.

**A majority of the Information obtained in this chart is from the American Academy of Orthopaedic Surgeons Annual Meeting, 2010, "The Evolving Role of Bone-Graft Substitutes."*

Category 1: Self-Setting Bone Cements

Some synthetic-based bone grafts are referred to as bone cements or self-setting grafts because they have the ability to set into a solid structure with a very rigid consistency. Bone cements consist of two components, a powder and a liquid constituent that are supplied in separate containers and must be mixed prior to implantation. Once the components are combined a chemical reaction takes place which allows the material's structure to become very rigid. Some forms may also accommodate screw augmentation or drilling.

BENEFIT

- The main benefit is the initial strength of the graft in situ after it has set or cured. The solid rigid structure is great for space maintenance and the ability to drill or place screws (very few grafts have an indication for drilling), however, these are still viewed as bone void fillers and only serve as temporary support, not to provide structural support during the healing process.

DISADVANTAGES

There are several disadvantages associated with self-setting grafts including:

- The majority of self-setting bone grafts lack remodeling ability due to very little porosity.
- Components are also pre-packaged and pre-measured therefore other constituents such BMA to enhance the biological activity of the graft cannot be added.
- There is some concern regarding migration of the graft after implantation because over time the material begins to lose its strength and will dissipate before remodeling occurs.
- Strict timing guidelines must be adhered to from the time mixing occurs to the time the implant site is closed. Once the components interact with each other there is no option to keep the material from activating.

Competitor Self-Setting Synthetic-based Bone Grafts or Bone Cements

- Norian® Drillable - DePuy Synthes
- HydroSet® - Stryker
- OsteoVation® - Osteomed
- Callos® - Skeletal Kinetics / Acumed
- Alpha-BSM®, Beta-BSM® and Gamma-BSM® - ETEX Corporation

RTI Option: *RTI does not offer a self-setting synthetic-based bone graft/cement.*

Polymethylmethracrlyte (PMMA)

PMMA is another type of synthetic-based self-setting bone cement which is sometimes confused with other self-setting bone cements described above. The main difference between a PMMA and traditional self-setting bone cement is the composition.

The material is supplied in two separate components, a polymer (powder) and a monomer (liquid). The components are combined causing an exothermic chemical reaction. This means that heat is produced as the chemical reaction occurs. (This is a disadvantage because the heat can cause necrosis or damage to the surrounding tissue.) *Note: Non PMMA self-setting grafts are isothermic, meaning that they do not produce heat during application.*

BENEFIT

- Product variations include combination with antibiotics such as tobramycin and gentamicin.

DISADVANTAGES

- This material does not remodel.
- Exothermic reaction, may cause tissue necrosis

NOTE: Not all bone graft substitutes can be mixed with BMA or other types of diluents. You must refer to each product's package insert or instructions for use. Please refer to implant labeling for clinical applications, warnings, precautions and other important information.

Competitor Polymethylmethacrylate (PMMA) Implants

- Palacos® - Heraeus Kulzer / Zimmer
- Cortoss® - Stryker
- Simplex™ P - Stryker

RTI Option: *RTI does not offer or have alternative options for PMMA products.*

Category 2: Non-Self-Setting Bone Grafts

Non-self-setting bone grafts are typically composed of calcium phosphate (e.g. hydroxyapatite and tricalcium phosphate), bioglass and/or calcium sulfate. These products do not set or harden, rather they remain in a putty or paste-like consistency throughout their application.

Non-self-setting bone grafts have much higher porosity and therefore are more likely to remodel. A majority of these grafts can be mixed with BMA, blood or other fluids to achieve other elements conducive to bone formation.

BENEFITS*

- Ability to remodel
- Easy to follow mixing guidelines
- Some can be mixed with BMA

DISADVANTAGE

- These grafts will not harden and therefore will not obtain a rigid structure for drilling etc. during implantation

Competitor Non-Self-Setting Synthetic-based Bone Grafts

- Vitoss® - Stryker
- NovaBone® - NovaBone
- ActiFuse® - Baxter
- Inetgria Mozaik™ - Integria
- chronOs® - DePuy Synthes

RTI Option: *nanOss® Advanced Bone Graft Substitute*

**Not all bone graft substitutes can be mixed with BMA or other types of diluents. You must refer to each product's package insert or instructions for use. Please refer to implant labeling for clinical applications, warnings, precautions and other important information.*

NOTE: Please refer to the "Bone Grafting Options by Implant" chart for a complete list of implants.

IMPORTANT TERM

Bioactive glass: When bioactive glass comes in contact with bodily fluids, the bioactive glass particles release sodium, silicon and calcium ions into the environment. This is estimated to promote deposits of calcium phosphate on the surface of the graft/scaffold. The calcium phosphate surface has the potential of attracting or promoting osteoblast attachment and direct bone apposition. Products with bioactive glass claim to increase the rate of bone formation.

Demineralized Bone Matrix

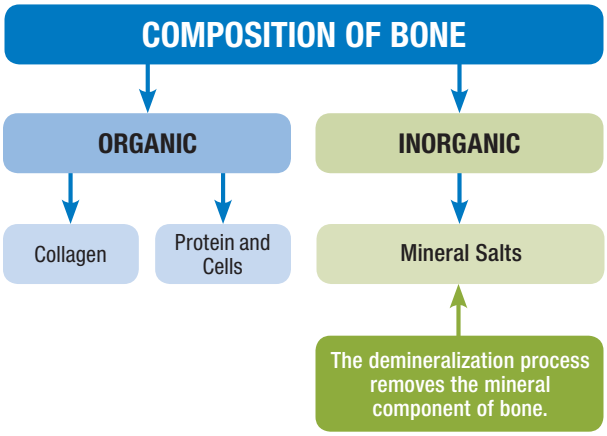
Demineralized Bone Matrix (DBM) is typically comprised of cortical allograft bone that has been processed to remove the mineral component. In very general terms bone is divided into two categories: organic and inorganic components.

During the demineralization process the inorganic component is removed leaving behind the organic component and exposing the bone morphogenetic proteins (BMPs). By exposing the BMPs, the graft has the potential to have osteoinductive properties. Manufacturers typically test DBMs through either in vitro or in vivo testing methods to ensure some level of osteoinductivity prior to the release of the grafts.

Competitor Demineralized Bone Matrix (DBMs)

- DBX™ - MTF / DePuy Synthes
- Grafton® - Osteotech / Medtronic
- Accell Evo 3® - Integra LifeSciences
- AlloMatrix® / AlloSource - Wright Medical
- InterGro® - BioMet / Integra LifeSciences

RTI DBM Options: *BioReady™ DBM, BioSet® DBM, BioAdapt® DBM (Pre-formed shapes)*



Bone Graft Option: Growth Factors

Infuse® is the most well-known product in this category and has two very distinctive properties:

- An osteoconductive scaffold made of bovine collagen which provides the framework for new bone growth.
- rhBMP-2, which is very similar to the BMP-2 protein found in the body and in DBM implants, however the protein in Infuse is synthetic and has been engineered to replicate the protein found in natural bone.

The amount of rhBMP-2 found in Infuse is more concentrated than in DBM. Infuse has been suggested to be associated with male sterility, cancer complications and unethical practices in clinical trials. Because of this, surgeons who were using Infuse have researched alternative options, which include DBMs and synthetic materials, or have been reverting to methods that were used prior to the release of Infuse.

Competitor Growth Factors

- Infuse® (commonly referred to as BMP-2) - Medtronic

RTI Option: *RTI does not have a direct offering for a growth factor based implant.*

BONE GRAFTING OPTIONS BY IMPLANT

This chart is restricted to gels, pastes and putties and does not include pre-formed shapes such as BioAdapt® DBM or nanOss® 3D Advanced Bone Graft Substitute.

SYNTHETICS-BASED BONE GRAFT SUBSTITUTES

Self-Setting Bone Cements
(Does not include PMMA products)

COMPETITORS:
Norian® Products: DePuy Synthes
HydroSet®: Stryker
Bone Source®: Stryker
GeneX® Putty: Biocomposites
Calcibon®: Biomet
Strucsure® CP: Smith & Nephew

Synthetic Materials Claiming Remodeling Ability
Cerament®: Bone Support/Biomet
Pro-Dense®: Wright Medical

Non-Self-Setting Bone Grafts

nanOss® Advanced Bone Graft Substitute: RTI Surgical

COMPETITORS:
Vitoss® & Vitoss® BA: Stryker
Actifuse®: Baxter
NovaBone®: NovaBone
Integra Mozaik™ Putty also branded as OsteoStrux Strip: Integra Orthobiologics
OsteoStrux®: Integra Spine
chronOS® Inject: Synthes
FormaGraft®: NuVasive
Healos® Fx: DePuy Synthes

ALLOGRAFT

Demineralized Bone Matrix

BioSet® DBM, BioReady™ DBM & BioAdapt® DBM: RTI Surgical**

COMPETITORS:
DBX™: MTF/DePuy Synthes
Grafton®: Medtronic
AlloFuse® (contains RPM*): AlloSource/Zimmer and Biomet
Accell Evo3®: (contains RPM* and is branded as OsteoSurge 300 by Integra Spine): AlloSource/Integra
Accell 100™ (contains RPM*): AlloSource/Integra
Accell Connexus® (contains RPM* and is branded as OsteoSurge 100 by Integra Spine): AlloSource/Integra
Accell TBM® (contains RPM*): AlloSource/Integra
DynaGraft® II/OsteoSparx (contains RPM*): AlloSource/Integra
OrthoBlast® II/OsteoSpark C (contains RPM*): AlloSource/Integra
OsteoSet® 2 DBM: AlloSource/ Wright Medical
AlloMatrix®: AlloSource/ Wright Medical
Optium® DBM: LifeNet/DePuy Synthes
InterGro® GBM: Biomet
Stimublas® (contains RPM*): AlloSource/Arthrex

Cellular Allogeneic Bone Grafts

map3® Cellular Allogeneic Bone Graft: RTI Surgical

COMPETITORS:
Osteocel Plus®: AlloSource/ NuVasive®
Trinity Evolution® & Trinity Elite®: MTF/OrthoFix
Cellentra: Tissue Banks International (TBI)/Biomet
AlloStem®: AlloSource

**RPM (reverse phase medium): Enables the product to flow at operating room temperature but thicken to a gel when placed in the body and warmed to body temperature.[3]*

***BioSet DBM contains allograft.*

WITH SO MANY BONE GRAFTING OPTIONS, HOW DO YOU SELECT THE CORRECT GRAFT?

The rationale and the proper selection for the ideal graft should be made according to the patient's needs and local surgical site and in consideration of the implant labeling. Challenging orthopedic procedures combined with poor patient health can lead to inadequate healing and impaired local factors that can affect soft tissue and vascularity.

Several local factors can compromise bone healing in a healthy patient including: prior surgery/revision site, osteopenia disuse or poor bone stock, trauma affecting the soft tissue causing poor perfusion to the area and infections. A good patient is typically a healthy active individual with normal blood values, and not a smoker. A good surgical site has adequate bone stock with healthy soft tissue structures and normal vascular perfusion.

POOR PATIENT

- Smoker
- Steroid use
- Obesity
- Chemotherapy
- Osteoporosis
- Renal disease
- Low vitamin D or low calcium
- Low protein levels
- Rheumatoid arthritis

GOOD SURGICAL SITE

- Adequate bone
- Healthy soft tissue
- Structures with normal vascular perfusion

POOR SURGICAL SITE

- Prior surgery on the site
- Osteopenia disuse or poor bone stock
- Trauma affecting the soft tissue causing poor perfusion to the area
- Prior infections to the area
- Non-union

GOOD PATIENT

- Healthy active individual with normal blood values
- Non-smoker

Please refer to implant labeling for clinical applications, warnings, precautions and other important information.

REFERENCE:

1. The evolving role of bone graft substitutes. American Academy of Orthopedic Surgeons 77th Annual Meeting, 2010.
2. Nguyen, Ngoc Hung (2012). Basic Knowledge of Bone Grafting, Bone Grafting, Dr. Alessandro Zorzi (Ed.), InTech.
3. IsoTis Receives US Patent Related to Reverse Phase Medium Technology. PR Newswire. 2007.

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