Choosing Bone Graft Substitutes: Filling the Gaps on Evidence and Pricing

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Choosing Bone Graft Substitutes: Filling the Gaps on Evidence and Pricing

ECRI Institute Webinar
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What do you need to know to find the most clinically sound and best-priced bone substitute products in today's crowded market?
To Answer These Questions Today’s Presentation Will Help You

- Appreciate the benefits and limitations of autologous bone graft material
- Be aware of the biological properties of various bone substitute categories
  - How well do they match autologous bone grafts?
- Understand the clinical evidence, cost and safety data, and regulatory issues for specific products
- Learn about market share

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Understanding Bone Graft Substitutes

Today’s presentation has some very technical and clinical content.

- We hope that covering these unfamiliar topics will help you engage with orthopedic clinicians and surgeons.
- For supply chain or material management positions, we hope this presentation helps you understand clinician concerns when using these products.
Autologous Bone Grafts

- Osseous (bone) material is harvested from one site and transplanted to another in the same patient.
- It is used to fill bone voids, promote spinal fusion, and promote healing of nonunion fractures.
- It is considered the gold standard because it has all the properties necessary for bone healing and regeneration:
  - Osteoconduction
  - Osteoinduction
  - Osteogenesis
Benefits of Autologous Bone Grafts

Osteoconduction

- Structure of the graft material passively promotes ingrowth of host blood vessels, cells, and tissue

Osteoinduction

- Exogenous growth factors present in the graft material promote differentiation of host mesenchymal stem cells (MSCs) to form chondroblasts and osteoblasts that form new bone tissue.
- Bone morphogenetic proteins (BMPs), platelet-derived growth factor, fibroblast growth factor, and others
Benefits of Autologous Bone Grafts

- **Osteogenesis**
  - Cells derived from the graft material or the host synthesize new bone.
  - MSC, osteoblasts (form new bone), osteocytes (form new bone cells).
  - Most bone graft substitutes do not provide this important property.
Limitations of Autologous Bone Grafts

- Morbidities
  - Donor site pain – most common, up to 50%
  - Increased blood loss and operative time
  - Donor site infection

- Limited supply of graft material from a single patient
  - Often obtained from iliac crest bone

- Cancellous bone provides the best mix of cells and growth factors but has little structural support

- Cortical bone provides better structural support but has limited cellular material

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The limitations of autologous bone graft have led to a search for substitute materials with the same properties.
What Is the Ideal Bone Graft Substitute?

- Easy to obtain and use
- Has the properties of autologous bone graft that promote the healing process
- Biocompatible – nontoxic
- Ultimately leads to natural bone development and restoration of bone to its original healthy state

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Potential Bone Graft Substitutes

- **Synthetic bone grafts**
  - Calcium phosphate and calcium sulfate

- **Allografts** – obtained from human cadaver bone
  - Processed to remove cells – whole bone and demineralized bone matrix

- **Cell-based combinations**
  - Mesenchymal stem cells

- **BMP-based**
  - InFuse
Potential Bone Graft Substitutes

Two things to keep in mind when evaluating potential bone graft substitutes:

- The results of in vitro, cadaver, animal, and laboratory studies may not be indicative of clinical performance.
  - Poor indicator of safety issues
- The success or failure of a bone graft substitute in one orthopedic procedure does not transfer to other orthopedic procedures.
  - Filling a bone void is not the same as aiding spinal fusion.
Synthetic Bone Grafts

- Calcium salt-based compounds
  - Calcium phosphates and calcium sulfate
  - Ceramics – crystalline structure
- Primarily osteoconductive properties
  - No immediate structural support
  - Often combined with autologous bone graft material
Synthetic Bone Grafts

- Mono-, di-, and tri-calcium phosphates and hydroxyapatite
  - Combinations of calcium phosphates available as powders, pellets, and injectable forms
    - Mixed with water, the paste hardens with a strength equal to bone
  - Slowly absorbed in six months or longer
  - Pores in structure allows for good blood vessel incorporation

- Calcium sulfate
  - Readily absorbed within 4 to 12 weeks
  - Rapid degradation may weaken structural support
  - May cause postoperative wound drainage
Synthetic Bone Grafts

Regulated under FDA’s 510(k) process for marketing clearance

- Resorbable calcium salt bone void filler device
- “A resorbable implant intended to fill bony voids or gaps of the extremities, spine, and pelvis that are caused by trauma or surgery and are not intrinsic to the stability of the bony structure.”
- May be combined with autologous blood and/or bone marrow
Synthetic Bone Graft Examples

Actifuse Bone Graft Substitute Silicate Substituted Calcium Phosphate (Baxter Healthcare Corp.)

- Addition of silicon is believed to accelerate bone formation
- Two randomized controlled trials (RCT) reported Actifuse was not as effective as rhBMP-2 in patients undergoing single-level lumbar interbody fusion but still achieved a high rate of fusion.
  - Study 1: 65% vs. 92% at 1 year
  - Study 2: 100% at 36 months, but Actifuse patients took longer
Synthetic Bone Graft Examples

ChronOS™ (DePuy Synthes)

- Consists of pure β-tricalcium phosphate (β-TCP). Putty form is mixed with a non-animal-derived sodium hyaluronate.
- Single nonrandomized comparison study reported 100% fusion with ChronOS for patients undergoing anterior cervical interbody fusion.
- Case series reported 86% anterior lumbar interbody fusion when used with pedicle screw fixation.
- Several case series report success using ChronOS as a bone void filler.
Synthetic Bone Graft Examples

► MasterGraft® Granules and Matrix (Medtronic, Inc.)
  ■ Biphasic, resorbable ceramics composed of hydroxyapatite (HA) and β-TCP
  ■ In granule form or combined with a type I collagen in putty matrix form
  ■ One small case series in dental extraction patients reported benefit for repairing bone defects

► Norian® SRS® (skeletal repair system) (DePuy unit of Johnson & Johnson)
  ■ Injectable calcium phosphate cement
  ■ Case series evidence for use in nonunions
Synthetic Bone Graft Examples

- OsteoSet® resorbable mini-beads and Pro-Dense bone graft substitute (Wright Medical Technology)
  - OsteoSet is made of calcium sulfate.
  - Pro-Dense is composed of 75% calcium sulfate and 25% tricalcium phosphate.
  - In an RCT of patients undergoing one-level lumbar posterolateral fusion, OsteoSet plus bone marrow aspirate was inferior to autologous iliac crest bone graft
    — Fusion rate of 46% compared to 90%.

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Synthetic Bone Graft Examples

Pro Osteon® Bone Graft Substitute (Biomet, Inc.)

- Underlying hydroxyapatite calcium carbonate covered with a thin layer of calcium phosphate. Calcium phosphate is slowly reabsorbed.
- Comparison study reported similar results to autologous bone graft for internal fixation of tibia plateau fractures.
- Several case series report successful use in a variety of orthopedic procedures: acetabular reconstruction, anterior cervical fusion, posterolateral and interbody lumbar fusion, treatment of bone defects and fractures.
Synthetic Bone Graft Examples

- Vitoss® Bone Graft Substitute (Stryker Corp.)
  - β-TCP, also available combined with collagen or collagen and bioactive glass.
  - 2 RCTs suggest that Vitoss works for repairing bone defects and correcting adolescent idiopathic scoliosis.
Synthetic Bone Grafts

Bottom Line

- Overall, evidence from systematic reviews supports using calcium sulfate for bone defects.
- Calcium phosphate is useful for bone defects and adolescent idiopathic scoliosis.
- Calcium phosphate can be used as an extender (combined with autologous bone graft) in lumbar fusion.
- Few comparative studies of the many different varieties of synthetic bone grafts are available.
- No evidence is available to distinguish one product as superior to another.

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Allografts

- Allograft bone is harvested from human cadavers
  - Processing and sterilization removes cells; therefore, allografts have no osteogenic properties and reduced osteoinductive properties.
  - Allograft bone undergoes serologic testing, which has a small risk of transmission of infectious disease.
- Cancellous allograft bone chips offer osteoconduction but little structural support.
  - Healing may be slowed by local inflammation.
- Cortical allograft bone offers more structural support.
Allografts

Considered tissues for transplantation

- FDA: “Minimally manipulated human bone for transplantation: Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P.”

If combined with other materials, the resulting product is considered a device and regulated by the FDA as a medical device.
Musculoskeletal Transplant Foundation

- A nonprofit organization responsible for donor screening, tissue collection, cryopreservation, and prerelease testing
- Processes cancellous and cortical chips, granules, various size spacers
- Registered with FDA as an organization producing human cellular and tissue-based products (HCT/Ps)
  - Not required to demonstrate the safety or efficacy of HCT/Ps
Allograft Examples

- **Cornerstone™ machined allograft tissue (Medtronic)**
  - Freeze-dried cortical allograft bone blocks in different shapes.
  - Some are a combination of cortical (for structural support) and cancellous bone (provides scaffold for bone in-growth) or dense cancellous bone only.
  - **RCT:** InFuse placed inside a Cornerstone allograft compared to autologous iliac crest bone graft placed inside a Cornerstone allograft in anterior cervical discectomy and interbody fusion.
    - All patients achieved fusion by 24 months.
Allograft Examples

- Plexur M (Medtronic) moldable
  - Contains processed human bone particles that are mixed with resorbable/biodegradable nontissue components.
  - Small case series shows use in treating bone defects caused by tumor removal.
Demineralized Bone Matrix (DBM)

- Human bone processed with hydrochloric acid to remove mineral content
  - Retains collagen, other bone proteins, and bone morphogenetic proteins
- High osteoinductive properties with some osteoconductive
  - Offers no structural support
Allografts - DBM

DBM

- Readily available and popular bone graft substitute
  - Used as an autologous bone graft extender in spinal and trauma surgery
- Often combined with cortical and cancellous bone chips to add osteoconductive properties
- Also combined with calcium sulfate or calcium phosphates
Allografts - DBM

- DBM is usually regulated by FDA’s 510(k) marketing clearance process
  - If not combined with other material, DBM is considered human tissue for transplantation.
  - Most commercial DBM is combined with some other material and considered by FDA to be a device
    -- FDA product code MBP: Filler, Bone Void, Osteoinduction (Without human growth factor)
  - Indications for use are similar to synthetic bone void fillers
Allografts – DBM Examples

Allomatrix® Custom Bone Graft Putty (Wright Medical Technology)

- Combination of DBM and cancellous bone chips with a binding medium of calcium sulfate and carboxymethylcellulose.
- RCT reported Allomatrix plus autologous bone in treating unstable distal radial fracture provided no benefit over autologous bone alone.
- Case-series study of patients requiring bone grafting for atrophic/avascular nonunions reported unacceptably high rate of complications with Allomatrix.
- Other case series report benefit of using Allomatrix as a bone void filler.
Allografts – DBM Examples

Grafton® DBM products (developed by Osteotech, Inc., and purchased by Medtronic)

- **RCT** comparing Grafton combined with local bone (n = 30) vs. autologous iliac crest bone graft (ICBG) (n = 16) for instrumented single-level lumbar fusion
  - After 2 years, fusion rates were similar (92% ICBG vs. 86% DBM).
- Other studies showed successful use in hip reconstruction, idiopathic scoliosis, and anterior cervical discectomy and fusion.
Allografts – DBM Examples

► Osteosponge® (Bacterin)
  ■ DBM processed to be compressible and flexible but has no additives
  ■ Case series report benefit in fusion of foot and ankle bones

► Puros® DBM putty or putty with cortico-cancellous allograft chips (Zimmer Carolinas)
  ■ Nonrandomized comparison study reported that Puros worked as well as autologous bone for augmentation of the maxillary sinus.
Allografts – DBM Examples

Other DBMs with little or no clinical literature

- Accell /Evo3® (Integra) is DBM mixed with poloxamer resorbable reverse-phase medium to make it moldable.

- Allofuse® DBM Gel and Putty (AlloSource) and Stimublast™ DBM (Arthrex, Inc.) is the same product – DBM mixed with a carrier.

- DBX® DBM (processed by Musculoskeletal Transplant Foundation, sold through Synthes, Inc.) contains DBM combined with sodium hyaluronate.
Allografts – DBM Examples

Other DBMs with little or no clinical literature

- InterGro® DBM products (InterGro DBM Putty, InterGro DBM Paste, and InterGro DBM Plus) is DBM mixed with a lipid carrier (lecithin).
- Magnifuse® and Magnifuse® II Bone Graft (Medtronic) is DBM mixed with nondemineralized cortical bone fibers sealed in an absorbable polyglycolic acid mesh pouch.
- OsteoSelect® DBM Putty (Bacterin International Biologics) is DBM plus carboxymethylcellulose carrier.
- Progenix™ Plus and Progenix putty (Medtronic) contains DBM combined with type-1 bovine collagen and sodium alginate and contains bone chips.
Allografts

Bottom Line

- Lots of products to choose from but only a few have published evidence of effectiveness for orthopedic procedures.
- Allograft bone offers osteoconduction plus support.
- DBM offers osteoinduction but no support.
- Allograft bone and DBM are often combined to provide both osteoconduction and osteoinduction properties.
Cell-based Combinations

- Allografts and synthetic bone graft materials all lack osteogenic properties and offer varying degrees of osteoconduction and osteoinduction.

- Cell-based combinations add MSCs to a osteoconductive scaffold in the hope of creating properties similar to autologous bone graft material.
Cell-based Combinations - Examples

**AlloStem® Stem Cell Bone Growth Substitute (AlloSource)**
- Adipose-derived MSCs combined with partially demineralized allograft bone
- Both materials are obtained from a single donor
- No published clinical evidence of efficacy in orthopedic procedures

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Cell-based Combinations

AlloStem Stem Cell Bone Growth Substitute (AlloSource)

- FDA warning letter sent to AlloSource in September 2011
  - FDA advised AlloSource that AlloStem does not meet the HCT/P requirements because “it is dependent upon the metabolic activity of living cells for its primary function.
- We have identified no further follow-up to the warning letter.
- Product is still available on company website.
Cell-based Combinations - Examples

▶ Osteocel® Bone Graft (NuVasive, Inc.)

- According to the company, Osteocel is “an allograft cellular bone matrix that retains its native bone-forming cells, including mesenchymal stem cells and osteoprogenitors.”
- Regulated as HCT/Ps
- Four cases series of lumbar interbody spinal fusion surgery —at a median follow-up of 12 months (5 to 18 months), fusion ranged from 88.0% to 92.3% across the 4 studies.
Cell-based Combinations - Examples

Trinity® Evolution™ and Trinity Elite™ Allografts (Orthofix International)

- Orthofix claims “cancellous bone containing viable adult stem cells and osteoprogenitor cells within the matrix and a demineralized bone component.”
  - “viable osteogenic cells retained within the cancellous matrix”
- Processed by Musculoskeletal Transplant Foundation
- Regulated as HCT/Ps
- No published clinical research but studies in progress

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Cell-based Combinations

**Bottom Line**

- Cell-based combinations attempt to create autologous-like bone graft substitutes.
  - BEWARE: a lot of hype but not much evidence

- Composition varies, and company websites provide very little information on components and their efficacy.

- FDA regulations may be evolving as these products do not fit the HCT/P classification as minimally processed.
Bone Morphogenetic Protein-based

BMPs

- Stimulate bone growth through all stages of healing
- Have to be combined with a carrier to slow turnover
  - Provide sufficient time to promote bone growth cell movement to the target site
  - Time for proliferation and differentiation during the healing process
- Commercially available product
  - Infuse® Bone Graft (Medtronic) contains rhBMP-2
Bone Morphogenetic Protein-based

► OP-1™ Putty and Implant (Olympus Biotech Corp.)

► As of August 29, 2014 stated, “Commercial operations and sales of the Olympus Biotech products were discontinued on May 31st. OP-1® IMPLANT, OP-1® PUTTY, BioEZE™, and BioVERSE™ are no longer available for sale.”
Bone Morphogenetic Protein-based

- Infuse Bone Graft (Medtronic)
  - rhBMP-2 applied to an absorbable collagen sponge
  - When used with Medtronic Titanium Threaded Interbody Fusion Device
    —Indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease at one level from L2-S1 using an anterior open or an anterior laparoscopic approach.
  - Also indicated for treating acute, open tibial shaft fractures that have been stabilized with intramedullary nail fixation

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Bone Morphogenetic Protein-based

Infuse Bone Graft

- Regulated under FDA premarket approval (PMA) process
- Contraindicated:
  - patients with a known hypersensitivity to rhBMP-2 bovine type I collagen or to other components of the formulation
  - should not be used in the vicinity of a resected or extant tumor
  - patients with any active malignancy or patients undergoing treatment for a malignancy
  - patients who are skeletally immature
  - pregnant women
  - patients with an active infection at the operative site
Bone Morphogenetic Protein-based

Infuse Bone Graft

- Many clinical studies, including RCTs of lumbar fusion.
- Clinical studies and systematic reviews suggest that Infuse when used in an anterior interbody lumbar fusion works as well as autologous bone graft material to promote lumbar spinal fusion.
- Clinical studies and systematic reviews suggest that Infuse also aids fusion when used in transforaminal interbody lumbar fusion and posterolateral lumbar fusion, which are off-label uses.
- An RCT of tibial fracture nonunion suggests that Infuse promotes healing and reduces secondary operations and infections.
Bone Morphogenetic Protein-based

Adverse Events Associated with Infuse Bone Graft

- The original industry-sponsored publications of Infuse use in spinal fusion may have under-reported the rate of adverse events.
- The rate could be 10 to 50 times higher.
- Adverse events include early and delayed infection, implant malposition, subsidence, retrograde ejaculation, and urogenital/bladder retention.
Bone Morphogenetic Protein-based

Adverse Events Associated with Infuse Bone Graft

- Ectopic bone growth and other complications have been noted when used in the cervical spine.

- FDA has warned against the off-label use in the cervical spine.
  —Associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck, and difficulty swallowing, breathing, or speaking
Bone Morphogenetic Protein-based

◆ Bottom Line
  ■ Systematic reviews of InFuse support use in tibial nonunions and for fusion when treating degenerative spondylolisthesis with spinal stenosis and spondylolysis
  ■ Restricted indications
  ■ Expensive
  ■ Associated with significant adverse events, especially when used off-label

◆ Recommend using only for approved indications and surgical approaches
Final Thoughts

Many bone graft substitutes are commercially available.

- Consider whether the bone graft substitute has the right properties for the site needing repair.

Each has pluses and minuses in how close they come to approximating the properties of autologous bone graft material.

- May be considered effective and useful if its fusion or repair rate is similar to that of autologous bone material and adverse events are limited.

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# Final Thoughts

You will likely want a few formulations from each category.

<table>
<thead>
<tr>
<th>Product</th>
<th>Best Uses</th>
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<tbody>
<tr>
<td>Calcium sulfate</td>
<td>As a bone void filler when void is due to trauma or removal of tumor. Due to rapid turnover, not used to treat large fractures or non-union fractures.</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>As a bone void filler when void is due to trauma or removal of tumor. As an autologous bone graft extender for correcting adolescent idiopathic scoliosis and for spinal fusion procedures. May have some use for nonunion fractures that are not load bearing.</td>
</tr>
<tr>
<td>Allograft bone</td>
<td>Adjunct in instrumented anterior lumbar and cervical spinal fusion surgeries to provide osteoconduction. May be combined with DBM in other orthopedic procedures.</td>
</tr>
<tr>
<td>DBM</td>
<td>As a bone void filler when void is due to trauma or removal of tumor. For treatment of nonunion fractures. As an autologous bone graft extender for spinal fusion and other orthopedic procedures. May be combined with synthetic bone graft substitutes and allograft bone.</td>
</tr>
</tbody>
</table>
Final Thoughts

Know what’s in the product.
- How do the components provide osteoconduction, osteoinduction, and osteogenesis?

Bone morphogenetic-based products such as InFuse are for special uses
- Beware of adverse events and avoid “off-label” uses.

Cell-based products have yet to show they are superior to other bone graft substitutes.
- Keep monitoring clinical literature for clinical study data on efficacy.
Further Information:
ECRI Institute Reports on Bone Graft Substitutes

► Synthetic bone grafts


► Allografts and DBM


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Further Information:
ECRI Institute Reports on Bone Graft Substitutes

► Cell-based combinations

► BMP-based
Bone Graft Substitutes: A Procurement Perspective

Tim Browne, Director, PriceGuide™ Advisory Service

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Bone Graft Substitutes
A Procurement Perspective

What patterns has ECRI Institute observed?

1. Market leaders
2. Market trends
3. Obstacles frequently encountered
4. Navigating obstacles
PriceGuide Database

Medical/Surgical Supplies and Implants

- 1,500 hospitals/ASCs
  - All regions and GPOs
- $19B+ in spend
- 1.6M + unique SKUs
- 4,600+ vendors
- 2,600+ product categories

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Suppliers

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Top 10 Suppliers

- Medtronic: 41%
- NuVasive: 7%
- LifeNet: 7%
- Stryker: 3%
- Bacterin: 3%
- DePuy Synthes: 3%
- Integra: 2%
- Baxter: 2%
- AlloSource: 2%
- MTF: 30%

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Within Top 10 Suppliers
Allografts-Whole Bone

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Within Top 10 Suppliers
Allografts-Demineralized Bone Matrix

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Within Top 10 Suppliers
Bone Morphogenetic Protein

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Within Top 10 Suppliers
Cell-based Combinations

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Within Top 10 Suppliers
Synthetic Bone Grafts

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Price Trends

Whole Bone Allograft
Prices Paid By All Contributing Priceguide Members

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Price Trends

Bone Morphogenetic Protein-Based
Prices Paid By All Contributing PriceGuide Members

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Obstacles Frequently Encountered

► Cost Containment
  ■ Costs are highly variable
  ■ Cost often erodes savings previously negotiated on related categories
    — Joints, spine, and trauma
  ■ Average potential savings opportunities
    — $50K to $300K

► Standardization
  ■ Rapidly growing number of options available
  ■ Inventories are difficult to manage
    — Not unusual to have 50+ different SKUs in use simultaneously
Before You Develop a Plan to Tackle the Obstacles, Establish Your Team

Establish *relationships* with the key players?

- Administration, especially the CFO
- Supply chain
- Clinicians and physicians
- Value analysis
- Suppliers
Suggested Plans of Attack

► Spend Analytics
  ■ Utilize “big data” to identify opportunities and formulate the story.

► Develop a pricing strategy that works for your organization
  ■ Standardization
  ■ Capitation
  ■ Line item pricing

► Functional Equivalents
  ■ Determine whether there is overlap of products currently in use
Spend Analytics

Aggregator your data with “big data” to reveal opportunities.

- Overall
- By facility
- By supplier
- By category
- By item
- By procedure

Presenting the data in this format levels the playing field for key stakeholders.

Internal politics: Consider the use of a third party.
Pricing Strategies

▲ Standardization
  ■ Pro: Limited number of suppliers results in greater price flexibility
  ■ Con: Requires physician engagement

▲ Capitation
  ■ Pro: Sets consistent price across vendors
    — Multi-tier primary vs. secondary suppliers
    — Variations based on unit size/CC
  ■ Con: Rapid introduction of new products erodes savings opportunities

▲ Line Item Pricing
  ■ Pro: More flexibility with pricing models and greater transparency
  ■ Con: More data to manage with each contract negotiation
Functional Equivalents

- Complete survey of product currently in use
  - Product indications for use
  - FDA clearance (510K or PMA)
  - Product recalls
  - Adverse events
## Market Overview

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Final Thoughts
A Procurement Perspective

- Bone graft substitutes are just like any other category.
- The same methodologies to cost reduction and standardization will apply.
- The major difference: the pace at which the technology is evolving and the number of players in this space.
THANK YOU