Executive Summary

<table>
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<th>CLINICAL VALUE</th>
<th>ViviGen Solution</th>
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<tr>
<td><strong>Challenges with Current Bone Graft Materials</strong></td>
<td><strong>Patient-Centered Care</strong></td>
<td><strong>Economic Value</strong></td>
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<tr>
<td>Clinical Effectiveness</td>
<td>• In vitro studies show that ViviGen contains all the properties required for bone formation and can be used as an alternative to an autograft.</td>
<td>• Complications associated with ICBG and rhBMP-2 can be avoided with use of ViviGen because it represents a composite allograft that can be considered a viable alternative to autograft.</td>
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<td>• Successful bone grafting requires 3 properties:</td>
<td>• ViviGen contains lineage-committed bone cells(^1) – it is the first cellular allograft focused on bone cells.(^2)</td>
<td>• Complications associated with ICBG and rhBMP-2 can be avoided with use of ViviGen because it represents a composite allograft that can be considered a viable alternative to autograft.</td>
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<tr>
<td>1. Osteogenesis (osteoprogenitor cells)</td>
<td>• ViviGen cells have been shown to exponentially proliferate post-thawing.(^3)</td>
<td>• ViviGen bone cells in vitro do not elicit an immune response.(^4)</td>
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<td>2. Osteoinduction (bone morphogenic proteins (BMPs) and other growth factors)</td>
<td></td>
<td>• Every donor for ViviGen must meet LifeNet Health’s strict medical and behavioral risks assessment in addition to microbial and serological testing.(^5)</td>
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<td>3. Osteoconduction (scaffold)</td>
<td></td>
<td>• The availability of an alternative to an autograft or rhBMP-2 could increase the patient population eligible for bone grafting interventions.</td>
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<td>Operating Room Efficiency</td>
<td>• The packaging for ViviGen enables a rapid thaw time of 5 minutes or less – crucial for cell viability and optimizing OR time.(^6)</td>
<td>• Use of ViviGen represents a viable alternative to autograft, and thereby, eliminates the possibility of costly complications associated with the use of ICBG and rhBMP-2.</td>
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<td>• Estimating the amount of bone graft prior to the surgical procedure, may lead to a delay in operating room time if additional graft material is needed and the duration of surgical time is increased to accommodate thawing time.</td>
<td></td>
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\(^1\) ViviGen\(^2\) rhBMP-2
\(^3\) ViviGen\(^4\) ViviGen\(^5\) ViviGen\(^6\) ViviGen
BACKGROUND

The use of bone graft technology is routinely employed within Orthopedic trauma surgery to promote a biological response that will assist the timely healing of musculoskeletal injuries. An ideal bone graft substitute possesses osteoconductive, osteoinductive, and osteogenic properties to facilitate bone healing.

Epidemiology

The need for bone graft is rising in orthopedic reconstructive surgery with the increasing number of arthroplasties, fusions, and limb salvage procedures. It has been estimated that more than 500,000 allograft bone grafts are being recovered annually in the United States alone. Fresh autogenous cancellous and, to a lesser degree, cortical bone are benchmark graft materials that allograft and bone substitutes attempt to match in in vivo performance. The availability of autograft is, however, limited, and recovery is often associated with donor-site morbidity and increased healthcare costs. Hence, there is a substantial need for autograft alternatives for orthopedic applications.

Clinical Burden

Fracture nonunions of long bones represent a significant clinical challenge and socioeconomic burden, associated with high complication rates and the potential for poor long-term outcomes. Nonunions are defined as fractures that fail to heal. Despite advances in surgical technique, fracture fixation, and adjuncts to healing, femoral nonunion continues to be a significant clinical problem. Fractures may fail to unite because of the severity of the injury, damage to the surrounding tissues, inadequate initial fixation, and demographic characteristics of the patient. A retrospective study of a U.S. managed care medical claims database showed that, from a retrospective cohort of 853 patients with tibial shaft fractures, 99 (12%) had a nonunion diagnosis associated with their tibia fracture treatment. Greater than 70,000 hospitalizations, 800,000 office visits, and 500,000 hospital days have been attributed to tibial shaft fractures in the U.S. annually.

One epidemiology study in Rochester MN in 1987 demonstrated that the incidence of ankle fractures is approximately 187 fractures per 100,000 people each year. This rate is increasing in many industrialized countries, most likely due to growth in the number of people involved in athletics and in the size of the elderly population. The incidence of more complex foot and ankle fracture patterns is also increasing, and failure to achieve anatomic fracture reduction results in poor functional outcomes. Open injury, diabetes, and peripheral vascular disease are strong risk factors predicting a complicated short-term postoperative course.

Economic Burden

Nonunions in tibial shaft fractures are associated with substantial healthcare resource use, common use of NSAIDs or opioids, and high per-patient costs. All categories of care (except emergency room costs) were more expensive in nonunion patients than in those that achieved bony union: median total care cost $25,556 vs. $11,686 (p<0.001).

The estimated economic burden of foot and ankle surgery in the Medicare population was estimated to be $11 billion in 2011, up 38.2% since 2000. Considerable healthcare costs and productivity losses are associated with foot and ankle surgery, and trends in chronic disease indicate that the cost of foot and ankle fractures is likely to increase.
Challenges with Existing Interventions for Bone Grafting

Iliac Crest Bone Graft (ICBG)

The most common source of cortical and cancellous bone has been the iliac crest, frequently called iliac crest bone graft (ICBG). This is due to the availability of adequate quantity of bone graft with progenitor cells, growth factors, and structural support. However, the recovery of ICBG requires an additional surgical step during the index procedure which often results in complications and discomfort for the patient. The incidence of morbidity and complications associated with recovering bone from the iliac crest has been reported to range between 6% and 30%. Potential complications include infection, hematoma/seroma, fracture, nerve and vascular injuries, chronic donor site pain, hernias, scars, and poor cosmetic outcome. The complications and morbidity may persist regardless of the recovery site or technique, or even the surgeon’s skills; and they often come with a substantial cost, especially when hospitalization is prolonged or complications occur that require further management.

Bone Morphogenic Protein (BMP)

Despite the excellent spinal fusion rates promoted by recombinant human bone morphogenic protein (rhBMP)-2, the increasingly reported adverse outcomes associated with rhBMP-2 usage have created real concerns. rhBMP-2 was approved in 2002 by the U.S. Food and Drug Administration (FDA) as a bone graft substitute for a single-level anterior lumbar interbody fusion, and in 2004 for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. However, rhBMP-2 has been used in other ways that have not been reviewed or cleared by the FDA. Several years following FDA approval, a series of publications surfaced that detailed the serious adverse events associated with rhBMP-2 including heterotopic ossification, osteolysis, seroma/hematoma, infection, allergic reaction, scar formation, arachnoiditis, dysphagia and life threatening retropharyngeal swelling (anterior cervical surgery), increased incidence of neurologic deficits (radiculopathy, myelopathy), retrograde ejaculation, and cancer.

Traditional Allografts

Traditional allografts have osteoconductive and osteoinductive properties, however they lack viable osteogenic cells. These allografts depend on native stem cells/precursors and osteoblasts from the recipient to populate the allograft and can be influenced by the recipient’s health conditions.

Mesenchymal Stem Cells (MSCs)

Processing methods have been developed to attempt to retain viable bone precursors such as mesenchymal stem cells (MSCs) within the donor’s original bone niche to stimulate bone formation. MSCs are the progenitors of osteoblasts, which drive the synthesis and mineralization of the bone matrix. The number of MSCs and their physiological function have been shown to progressively decline with age and disease state of an individual and, therefore, poses a challenge for effective clinical application of these cells to repair bone defects in individuals receiving traditional allograft bone products. Moreover, since MSCs are capable of differentiation into multiple cell types, it is difficult to precisely control the differentiation of MSCs into a specific cell type. In addition to differentiating into bone cells, MSCs are also capable of differentiating into other mesenchymal cell types including fibroblasts, chondrocytes, and adipocytes dependent on the growth factors provided (Figure 1).
OPPORTUNITIES FOR IMPROVED CLINICAL EFFECTIVENESS WITH VIVIGEN

BENEFITS OF LINEAGE-COMMITTED BONE CELLS

Since they are human derived, lineage-committed bone cells, (i.e. osteoblasts and osteocytes), offer a better potential for bone repair than MSCs by:

- depositing high quality, differentiated bone;\(^2,3\)
- promoting vascularization of the scaffold;\(^4\)
- secreting chemotactic factors to recruit host osteoblasts;\(^5\) and
- stimulating osteogenesis in already resident MSCs.\(^6\)

ViviGen contains lineage-committed bone cells\(^1\) – it is the first cellular allograft focused on bone cells.\(^7\)

The osteogenic property of a graft is imparted by living cells capable of producing new bone. Mesenchymal stem cells (MSCs) can differentiate into several types of cell lineages including bone, cartilage, muscle, marrow, and tendons or ligaments. ViviGen represents a paradigm shift in the field of bone and tissue repair because it is the first cellular allograft to be focused on recovering, processing, and protecting viable lineage-committed bone cells (Figure 2).\(^1,7\)

The processing of bone for ViviGen involves depleting the bone of bone marrow and MSC’s from the bone retaining essential, viable bone cells including osteoblasts, osteocytes, and bone lining cells (Figure 3).

FIGURE 2: Proliferation of mesenchymal stem cells (MSCs).

FIGURE 3: ViviGen contains lineage-committed bone cells, including bone lining cells, osteoblasts, and osteocytes.
Pre-clinical studies suggest bone cells remain at the defect site longer, directly participate in the bone formation process, and deposit a higher quality of bone than MSCs.

- Tortelli et al. (2010) seeded ceramic scaffolds with green fluorescent protein (GFP)-labeled murine MSCs or GFP-labeled murine osteoblasts and implanted them into immunocompromised mice. MSCs directed the formation of bone of host origin by activating the endochondral ossification process, whereas osteoblasts directly participated in the formation of new bone through an intramembranous ossification process. Only osteoblast-seeded implants contained bone-depositing cells of donor origin. MSC-seeded implants showed no cells of donor origin after 30 days and led to the development of a tissue-engineered bone of host origin (Figure 4).

**FIGURE 4:** Osteoblasts out-performed MSCs in both bone quantity and bone quality.

- Reichert et al. (2011) seeded TCP scaffolds with ovine-marrow derived MSCs or osteoblasts and implanted them into a severe combined immunodeficiency mouse. Ectopic bone formation (i.e., bone volume, maturation, and density) was found to be much more robust in the scaffold seeded with osteoblasts compared to MSCs. The scaffolds seeded with osteoblasts also had higher mineralization than those seeded with MSCs and BMP-7 combined.

**FIGURE 5:** Human osteoblasts promote vascularization.

- The ability of bone cells to promote vascularization was demonstrated in a study of primary human osteoblasts pre-seeded on silk fibroin micronets by Ghanaati et al. (2011). Osteoblasts were shown to migrate throughout the entire scaffold and produce extensive bone matrix in vitro (Figure 5). Osteoblasts induced a more rapid and significantly higher level of vascularization of the scaffold, with microvessels homogeneously distributed throughout the scaffold, than silk fibroin alone with no pre-cultivation (Figure 5). The findings showed that osteoblasts can produce not only bone matrix but also soluble factors which can serve to instruct host endothelial cells to migrate, proliferate, and initiate the process of scaffold vascularization, which is critical to bone healing (Figure 5).

**Note:** In vitro performance is not necessarily indicative of clinical performance in human subjects.

**OSTEONECROSSES PROMOTE HIGH QUALITY BONE FORMATION AND VASCULARIZATION**

**Difference between groups is statistically significant (p<0.05)**
The ViviGen lineage-committed bone cells are already committed and ready to produce calcium deposition. When stimulated with a standard osteogenic differentiation media, a substantial deposition of calcium was seen in the ViviGen derived cells as early as day 7. When allowed to differentiate to 14 - 21 days, extensive matrix deposits were evident by their positive red staining for calcium in the entire well (Figure 6).

**FIGURE 5:** ViviGen lineage-committed bone cells are already committed and ready to produce calcium deposition, days 7, 14, and 21.

**ViviGen** contains all the properties required for bone formation and can be used as an alternative to an autograft.¹

ViviGen Cellular Bone Matrix comprises the 3 essential components required for bone formation:¹

1. Corticocancellous chips provide the natural scaffold for bone formation
2. Demineralized bone provides osteoinductive properties due to naturally-occurring BMPs
3. Live lineage-committed bone cells capable of directly facilitating bone synthesis

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**DONOR RECOVERY AND PROCESSING TIME DIRECTLY AFFECTS CELL VIABILITY**

The cells within ViviGen are maintained in a viable state during processing and cryopreservation.³

**RECOVERY AND PROCESSING METHODS PROTECT BONE CELL**

**Viability**

- ViviGen is only recovered from the hemi-pelvis and femoral heads based on clinical publications citing those areas contain the highest population of cells.¹⁻¹⁵
- At every step of the processing of ViviGen, LifeNet Health has focused on maintaining the highest level of bone cell viability by decreasing the time required for recovery and processing (see figure 7).⁷
- ViviGen is recovered, processed and placed into cryopreservation within 72 hours.
- Cell atrophy begins at the time of donor death and continues at an increasing rate as time passes. By achieving the cryopreservation 24 hours sooner than competitive MSC-based cellular allografts, more cells are preserved.⁷⁻¹⁵

**FIGURE 7:** Timing of ViviGen cryopreservation.

- **Recovery:** ≤ 24 HRS
- **Processing:** ≤ 48 HRS
- **Cryopreservation:** ≤ 72 HRS

- LifeNet Health developed a Xeno-free cryo solution to optimize cell viability.¹⁵
- Cells can be left in thawed cryopreservant for up to two hours and maintain 96% cell viability.¹⁵
IMPROVED PROCEDURAL EFFICIENCY

The packaging for ViviGen enables a thaw time of 5 minutes or less – rapid thawing is crucial for cell viability.

PACKAGING OF VIVIGEN OPTIMIZES CELL VIABILITY

The basic principle for successful cryopreservation while maintaining cell viability is a controlled slow freeze and a rapid thaw. The packaging design of ViviGen (see Figure 8) is unique:

- The thin walls of the ViviGen packaging allow for efficient energy transfer, which facilitates a slow freeze and rapid thaw.
- The rapid heat transfer of the ViviGen packaging not only allows pouches of all sizes to thaw in 5 minutes, but is also essential for cell viability.
- The rapid thaw prevents ice crystals from forming intracellularly during thawing, ultimately maintaining viability.
- The port at the end of the ViviGen pouch allows for the quick and efficient removal of the cryopreservation media and rinsing solutions.

ViviGen cells have been shown to exponentially proliferate post-thawing.

THAWED VIVIGEN CELLS HAVE A ROBUST PROLIFERATION PROFILE

In vitro studies have demonstrated the growth potential of cryopreserved ViviGen bone matrix from multiple donors using a highly sensitive cell viability assay. Bone particles cryopreserved in ViviGen packaging were thawed and rinsed according to the Instructions for Use (IFU). Three replicates of 1 mL of bone particles from each donor were placed in individual wells in a 24 well plate for viability studies. The bone cells within ViviGen demonstrated a robust proliferation profile over time, showing a sigmoidal growth pattern (Figure 9).

FIGURE 8: ViviGen cryopreserved in custom-manufactured packaging.

FIGURE 9: Exponential proliferation of bone cells was observed with ViviGen from 2 different donors post-thawing:

- The viable bone tissue is cryopreserved in a specialized packaging system to preserve cell viability as well as growth potential and bone formation upon thawing.
- Consistent results demonstrating cell viability and proliferation were seen for ViviGen bone matrix from multiple donors.
- Due to the proprietary processing methods, ViviGen maintains a population of viable bone cells capable of exponential growth.
The rapid thaw time of ViviGen helps ensure clinical efficiency. The 5-minute or less thaw time optimizes product availability as needed and avoids waste associated with waiting for thawing, and waste with excess allograft.

**USE OF VIVIGEN REDUCES THE NEED TO DISCARD UNUSED DONOR MATERIAL**

The rapid heat transfer of the ViviGen packaging allows pouches of all sizes to thaw in 5 minutes.³

- The rapid thawing of ViviGen enables surgeons to prepare ViviGen in situ as needed rather than trying to estimate the amount of allograft needed ahead of surgery, which may lead to under- or over-estimation, and ultimately waste.
  - Over-estimation: product in excess wastes money, time, and space.
  - Under-estimation: inadequate product leads to wasted time for more thawing or potentially reduced effectiveness of the grafting.
- The port at the end of the ViviGen pouch allows for the quick and efficient removal of the cryopreservation media and rinsing solutions.³

**FIGURE 10: Thawing time with ViviGen.³**

The availability of an alternative to an autograft or rhBMP-2 could increase the patient population eligible for bone grafting interventions.

Complications Associated with Bone Grafting Interventions

- The morbidity associated with ICBG recovery, the limited supply for fusions, and the variability of graft quality resulted in the development of alternative osteobiologic materials such as rhBMP-2.³
- Chronic ICBG recovery site pain and discomfort is reported by a significant percentage of patients undergoing this procedure more than three years following surgery, and these complications are associated with worse patient-reported disability.³
  - Over-estimation: product in excess wastes money, time, and space.
  - Under-estimation: inadequate product leads to wasted time for more thawing or potentially reduced effectiveness of the grafting.

- The port at the end of the ViviGen pouch allows for the quick and efficient removal of the cryopreservation media and rinsing solutions.³

**FIGURE 11: Patient-reported effects of ICBG recovery that persisted more than 3 years³**

ViviGen is an alternative when autograft (ICBG) or rhBMP-2 are undesirable for use. Complications associated with ICBG or rhBMP-2 can be avoided with use of ViviGen.³

**INCREASED PATIENT POPULATION FOR BONE GRAFTING INTERVENTIONS**

Use of rhBMP-2 is contraindicated in certain patient populations (refer to IFU for full details). Recovery of autologous bone is undesirable in certain patient populations. The availability of an alternative to an autograft or rhBMP-2 could increase the patient population eligible for bone grafting interventions.

**COMPILATIONS OF AUTLOGOUS BONE GRAFTING INTERVENTIONS AVOIDED**

- The morbidity associated with ICBG recovery, the limited supply for fusions, and the variability of graft quality resulted in the development of alternative osteobiologic materials such as rhBMP-2.³
- Chronic ICBG recovery site pain and discomfort is reported by a significant percentage of patients undergoing this procedure more than three years following surgery, and these complications are associated with worse patient-reported disability.³
  - At a mean of greater than 3 years following surgery, a large percentage of patients continued to report being troubled by numbness (24%), and chronic harvest site pain resulted in difficulty with household chores (19%), recreational activity (18%), walking (16%), sexual activity (16%), their job (10%), and irritation from clothing (9%) (Figure 11).³

**FIGURE 10: Thawing time with ViviGen.³**
• Reports of serious and potentially life-threatening complications associated with rhBMP-2 began emerging after its approval in 2002.13,14

• An independent published review of reported data on the safety and effectiveness of rhBMP-2 versus ICBG by the Yale University Open Data Access (YODA) Project determined the following:
  - The risks of any adverse event were high (77%-93% at 2 years) and similar for both groups.40
  - At or shortly following surgery, pain was more common in the rhBMP-2 group (odds ratio, 1.78 [CI, 1.06–2.95]).40
  - Heterotopic bone formation, dysphagia, and osteolysis may be more common with rhBMP-2.40
  - In anterior cervical spinal fusion, rhBMP-2 was associated with increased risk of wound complications and dysphagia.40
  - At 24 months, cancer risk was increased with rhBMP-2 (HR, 3.45 [95% CI, 1.98–6.00], however, the event rates were low and the increased risk was no longer apparent at 4 years.40

ViviGen bone cells, in vitro, do not elicit an immune response.45

ABSENCE OF IMMUNE RESPONSE WITH VIVIGEN BONE CELLS IN VITRO15

• An in vitro analysis demonstrated that the processing with ViviGen reduces the number of potentially immunogenic cells from the bone marrow, also reducing the risk of eliciting an immune response (Figure 12).15
  - Staining for CD45, a protein present on all hematopoietic cells and distributed throughout the immune system, confirmed the presence of hematopoietic cells in the bone matrix prior to processing.15
  - Post processing, cryopreservation and thawing, marrow components and CD45 positive cells were absent, which confirmed that the marrow components were negligible.15

FIGURE 12: Immunohistochemistry staining of CD45 positive cells (brown color) preprocessing and post cryopreservation and thawing.15

• Bone cells derived from ViviGen in vitro were shown to be non-immunogenic using a mixed lymphocyte reaction (MLR) assay (Figure 13).15 Lymphocytes from ViviGen donors were combined with peripheral blood mononuclear cells (PBMCs) to elicit an immune reaction (lymphocyte proliferation) as the positive control.15 ViviGen-derived bone cells from the same donors were mixed with PBMC, but rather than showing an immune reaction like the lymphocytes, they reacted similarly to PBMC alone (no proliferation of cells), which was the negative control.15

FIGURE 13: Non-immunogenicity of ViviGen bone cells was demonstrated with mixed lymphocyte reaction (MLR) assay.15

Note: In vitro performance is not necessarily indicative of clinical performance in human subjects.
Donors must meet strict medical and behavioral risks assessment in addition to microbial and serological testing.\(^{16}\)

### STRICT TESTING OF VIVIGEN DONORS

Every donor for ViviGen must meet LifeNet Health’s strict medical and behavioral risks assessment in addition to microbial and serological testing (Figure 14).\(^{16}\)

- LifeNet Health is a leading, federally designated Organ Procurement Organization. LifeNet Health only accepts donors from federally designated Organ Procurement Organizations and qualified tissue recovery partners.\(^{16}\)
- These partners are regularly audited to document that their recovery process meets current FDA regulations.

![Figure 14: ViviGen donor suitability and release criteria.](image)

#### FIGURE 14: ViviGen donor suitability and release criteria.\(^{16}\)

### 1. Initial Screening

- **POTENTIAL DONORS**

- **AGE**

  All tissue is evaluated to meet appropriate age limits. ViviGen donors must adhere to specific age limits.

- **PAST MEDICAL HISTORY AND CURRENT ILLNESSES**

  LifeNet Health reviews the potential ViviGen donor’s past medical history for specific rule outs including cancer, diabetes, renal disease, CJD, auto-immune diseases as well as numerous other diseases and illnesses. LifeNet Health utilizes a medical conditions database of over 1,500 diseases and medical conditions that affect donor suitability.

- **REPORT BEHAVIORAL AND SOCIAL RISK FACTORS**

  LifeNet Health will review the medical history reports along with an Incidence-Window Period Model to identify donors who are at risk of having a recent infection that may not be detected by routine serology or NAT testing. The model evaluates possible high risk behaviors based on drug use, tattoos, body art, body modifications, and sexual behaviors. This is to minimize the risk of a donor having a false negative screening test result for hepatitis B, hepatitis C, and/or HIV.\(^{16}\)

- **POTENTIAL MEDICALLY-SUITABLEDONORS**

  Once the initial screening is complete, the potential ViviGen donor is recovered and a stringent medical screening is performed.

### 2. Recovery

Recovery technicians do positive identification and review all medical documents. A physical inspection of the deceased donor is administered to make sure physical evidence matches medical information provided prior to recovery. LifeNet Health has trained its recovery personnel as well as LifeNet Health Partners’ recovery personnel to take pictures and obtain biopsies of any suspicious lesions.

In 2004, the first known national recovery biopsy program was initiated by LifeNet Health and included all of their tissue recovery partners. Its purpose is to identify any possible occult infection or cancer in the donor. Biopsies taken at recovery are processed by an independent pathology lab.

Evidence of any unexpected cancer or infection will prevent the tissue from being released.\(^{42}\)

Not only does LifeNet Health hold the longest continuous accreditation from the American Association of Tissue Banks, but we have a comprehensive range of measures in place to ensure the safety of ViviGen, including stringent donor screening methods and release criteria. To obtain suitable donors, LifeNet Health maintains an extensive network of recovery partners. Additionally, LifeNet Health is a leading, Federally designated Organ Procurement Organization (OPO) that coordinates recovery and transplants of organs in Virginia and part of West Virginia.

### 3. Medical Screening/Processing

- **POTENTIAL MEDICALLY-SUITABLE DONORS**

  After the initial screening process, the potential medically-suitable ViviGen donor goes through a more in-depth medical screening. Due to the sensitive nature of ViviGen, the donor is processed in tandem with the in-depth medical screening.

- **CULTURE AND SEROLOGY POSITIVE RESULTS**

  Blood cultures and independent tissue cultures are collected. Tests for HIV and Hepatitis are administered. Biopsy results and the initial chart are reviewed.

- **QUALITY CONTROL QUALITY ASSURANCE**

  LifeNet Health performs the following quality control testing on each lot of ViviGen. The finished product must pass USP<71> Sterility Tests. Each lot is tested to contain >16,000 viable bone cells per cubic centimeter (cc) post thaw. Finally, calcium content in the demineralized bone is measured to ensure average residual calcium levels in the optimal range of 1% to 4%. Quality assurance compiles and places all relevant technical and medical chart information for final review by the Medical Director.

- **MEDICAL DIRECTOR REVIEW**

  The final disposition of tissue is the responsibility of the Medical Director who makes their determination based on all relevant information including autopsy results, medical chart, recovery and quality records. The Medical Directors Advisory Group, a cross-departmental team unique to LifeNet Health, meets quarterly to discuss and provide decisions regarding any technical, medical, or social issue relevant to donor suitability. It is responsible for reviewing and modifying donor suitability criteria and establishing new donor suitability criteria as needed.

- **MEDICALLY-SUITABLE DONOR**

  The ViviGen donor is acceptable for release.
ECONOMIC VALUE

Reduced Cost of Complications of Other Bone Grafting Interventions

The healthcare cost, duration of surgery, and length of hospital stay of ICBG and rhBMP-2 are important concerns for physicians, hospitals, and payers. ICBG recovery and ICBG and rhBMP-2 complications have been shown to be associated significant costs. 17, 18, 19, 20

- Data from a randomized controlled trial examining inpatient and outpatient costs for up to 2 years post-operatively showed significant costs for both ICBG and rhBMP-2 (Figure 15). 20

**FIGURE 15:** Healthcare costs of ICBG (n=52) and rhBMP-2 (n=50) over 2 years.

<table>
<thead>
<tr>
<th>2-year total cost of ICBG</th>
<th>$42,286</th>
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<td>2-year total cost of rhBMP-2</td>
<td>$39,967</td>
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<tr>
<td>Cost of a major complication</td>
<td>$10,888</td>
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<tr>
<td>Cost of a revision surgery for non-union</td>
<td>$46,852</td>
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- In the ICBG group (n=52), 8 patients had complications; 20 had additional interventions, 5 of whom required revision for nonunion. In the rhBMP-2/ACS group, 6 patients had complications, 10 had additional interventions, and 1 required revision for nonunion. 20

- ViviGen may eliminate the need for ICBG and BMP-2, which may result in a reduction in costly complications and revisions.

ViviGen is the first cellular allograft focused on lineage-committed bone cells and contains all the properties required for bone formation. 1 The morbidity and complications associated with ICBG and rhBMP-2 may be avoided with use of ViviGen because it represents a composite allograft that can be considered a viable alternative to autograft. 1

FEATURES AND BENEFITS

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<tr>
<th>FEATURES</th>
<th>BENEFITS</th>
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<tr>
<td>Osteogenic</td>
<td>Contains viable lineage committed bone cells that are able to proliferate in vitro post cryopreservation and thaw</td>
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<tr>
<td>Osteoconductive</td>
<td>Contains corticocancellous chips that provide a natural scaffold for cell attachment, cell migration and cell proliferation.</td>
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<td>Osteoinductive</td>
<td>Demineralization of the cortical bone exposes the natural growth factors within the matrix</td>
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<td>Safety</td>
<td>Every lot is aseptically processed and all final product is tested for sterility using USP &lt;71&gt; standards</td>
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<tr>
<td>Packaging</td>
<td>The rapid heat transfer not only allows for all sizes to thaw in less than 5 minutes but is also vital for cell viability</td>
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<tr>
<td>Processing Time</td>
<td>ViviGen reaches cryopreservation within 72 hours maximizing cell viability 24 hours sooner than competitive products</td>
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<td>Maximized Cell Viability</td>
<td>The processing of ViviGen is focused on protecting viable lineage committed bone cells from recovery to implantation¹</td>
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*Please refer to the package insert for a complete list of indications, contraindications, precautions and warnings. For further information on DePuy Synthes products, please contact your local DePuy Synthes representative.
REFERENCES


DEPUY SYNTHES TRAUMA: FOCUSED ON PATIENTS AND HOSPITALS

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