CYGNUS®

MONOGRAPH

VIVEX® BIOLOGICS

VIVEX® INTRODUCTION AND COMPANY OVERVIEW

VIVEX® Biologics is a commercial stage, regenerative solutions company improving patient care through the innovation of tissue-based therapies. During more than 50 years of safe and effective operations, VIVEX has sourced millions of allograft products throughout the US and eighteen countries worldwide. VIVEX is registered with the Food and Drug Administration (FDA) and accredited by the American Association of Tissue Banks (AATB), continuously since 1992. VIVEX's strong processes, manufacturing expertise, and operational excellence is the result of continuously monitoring and improving its performance and systems.

Theodore I. Malinin, MD

VIVEX strives to create treatment options and solutions that will improve clinical, surgical, and therapeutic patient outcomes. Under the guidance of experienced and successful health care professionals, VIVEX tasks the brightest minds from the medical and material science industries to explore innovative ways to help others. VIVEX works with partners that are committed to providing care and compassion to donor families while inspiring communities to share life through their donation. Partnering with families in the prospect of regenerative treatments, VIVEX assures appropriate options are available to support translation of their gifts.

VIVEX operates the oldest civilian tissue bank in the country, which it acquired in 2014. The University of Miami Tissue Bank (UMTB) was founded in 1970 as the US Navy Tissue Bank was curtailing its service to civilian patients. Theodore I. Malinin, MD, who was trained and experienced in tissue banking at the US Navy Tissue Bank Naval Medical Research Institute, adopted those protocols and tissue banking techniques when founding UMTB. By the 1990s, UMTB was not only one of the oldest, but recognized as one of the largest and most well-respected tissue banks in the country. Over its tenure, UMTB assisted in the organization of new tissue banks throughout the US and abroad. UMTB also provided training for personnel from other tissue banks in the US and foreign countries and for surgeons interested in bone transplantation and tissue banking. Throughout its history, UMTB has been a worldwide leader in bone transplantation and tissue banking, with multiple firsts in clinical and scientific achievements.

H. Thomas Temple, MD

H. Thomas Temple, MD, joined UMTB in 1998. As a world leader in the field of Musculoskeletal Oncology, Dr. Temple is an enthusiastic advocate of the proposition that clinical challenges respond to therapeutic solutions. With a reputation for clinical insight and medical innovations, his patient care initiatives continue to offer novel treatments that are unmatched. As the current Chief Medical Officer for VIVEX, Dr. Temple's commitment to matching quality and safety serve as impeccable guides to tissue product development.

50 years of regeneration

Dr. Temple earned a Bachelor of Arts degree from Harvard University in Cambridge, Massachusetts, and a Doctor of Medicine from Jefferson Medical College in Philadelphia, Pennsylvania. He completed his residency in orthopedic surgery at Walter Reed Army Medical Center in Washington, D.C., and his musculoskeletal oncology fellowship at Harvard University– Massachusetts General Hospital–Boston Children's Hospital. He is board certified by the American Board of Orthopedic Surgery. Dr. Temple was a member of the United States Army Reserve for 15 years, where he held the titles of second lieutenant, captain, and major, and received an honorable discharge. He received numerous Army Achievement Medals and Army Commendation Medals.

Today, VIVEX focuses on core products and new technologies to meet the evolving needs of surgeons and patients while sustaining its 50-year commitment to serving and honoring both tissue donors and recipients. The VIVEX business is focused on the development and commercialization of new regenerative medicine solutions through increased research and development efforts as well as the expansion of manufacturing capabilities. Due to its leadership in the field, VIVEX maintains the trend of safely delivering over 2 million allografts with no disease transmission, an unmatched history of safety in the industry.

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CLINICAL HISTORY OF AMNIOTIC TISSUE

Amniotic allograft tissues in the clinical setting have over a century of documented use in many different surgical applications. The first reported use of an amniotic allograft tissue as a wound covering was in 1910.[1] Amniotic allografts were specifically used as a barrier against adhesion in ophthalmology procedures[2] and nerve wraps as early as the 1940s. Amniotic allograft tissues have been used as a wound covering, including for diabetic wound ulcers and burn victims[3], spinal and abdominal surgeries, and other applications[4-7] where it is desirable to maintain a plane of separation between tissue types in the body during wound repair. Amniotic allografts are used in a wide variety of surgical situations to provide mechanical protection to surgically traumatized tissues.

AMNIOTIC ALLOGRAFT TISSUE SOURCES

Amniotic allografts are derived from specific amniotic tissues, which include the placental disc, the umbilical cord membrane, and the amniotic sac. The amniotic sac has two main layers, each of which is subdivided into many layers of different tissue composition. From the perspective of the fetus, the inner layer is called the amnion and the outer layer is chorion.[8] During consenting healthy full-term births, after the baby has been delivered, the amniotic tissues are removed from the mother.

As shown in Figure 1, the amnion layer is comprised of five sub-layers. The epithelium, the closest layer to the fetus, is a single layer of epithelial cells, followed by the basement membrane of collagens III, IV, and V coupled with glycoproteins laminin and fibronectin. The compact layer maintains structural integrity of the membrane with collagens I, III, V, and VI. The fibroblast layer is the thickest part of the amnion section and is a loose collagen network with abundant proteoglycans and glycoproteins.[9-10] The final layer of the amnion portion of the amniotic sac is the intermediate spongy layer. The spongy layer is retained by VIVEX's Integrity Processing™ methodology, unlike other cleaning processes where the spongy layer is lost when the amnion layer is separated from the chorion layer. This preserved spongy layer contains a meshwork of mostly type III collagen, a protein that has a prominent role in wound repair.[11-12]

The chorion layer, which is 4X thicker than the amnion layer, is comprised of three sub-layers, of which the reticular layer is the second thickest and comprised of collagens I and III-VI.[13-14] The basement membrane layer anchors the thick trophoblast layer to the reticular layer with collagen IV, fibronectin, and laminin.[13-14]

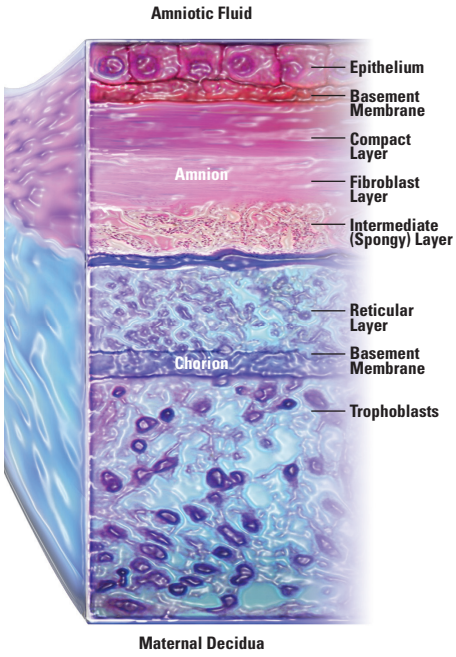


Figure 1: The Layers of the Amniotic Sac

The amniotic sac acts as a biologically active and mechanically robust barrier between the mother and the fetus during pregnancy. The sac contains the developing fetus and amniotic fluid, so this thin membrane must possess sufficient structural integrity to support the growing fetus to term.[5] The metabolically active tissue must continually remodel to accommodate the increasing volume of fetus and fluid. Tissue remodeling is governed by mechanical response and growth factors, cytokines, and extracellular matrix produced by cells. One of the inherent values attributed to amnion and chorion layers comes from the scope of tissue expansion without scar tissue. The biologically active nature of this barrier is evidenced in the low levels of antigens.[15]

PRODUCT DESCRIPTION

VIVEX offers multiple amniotic allograft options to meet the needs of the surgical community. These products include a single amnion-only layer tissue, which is the thinnest amniotic allograft product. The medium thickness allograft tissue is composed of the amnion and chorion membranes, which are never separated during processing. Finally, the thickest amniotic allograft tissue offered by VIVEX is an umbilical cord membrane product.

CYGNUS® Matrix is an amniotic tissue allograft composed of intact human amniotic membranes, where the amnion and chorion layers are never separated, that preserves and contains multiple extracellular matrix proteins, growth factors, collagen, cytokines, and other specialty proteins that are intrinsic to wound repair.[16-17] Extracellular matrix provides three-dimensional scaffold support for cellular migration and attachment to facilitate proliferation and integration.[18-21] Growth factors guide cell signaling processes that affect cellular growth, proliferation, and healing through activities such as angiogenesis and immune modulation.[22-23] CYGNUS® Solo is an amnion-only single layer membrane ideal for superficial wounds and topical applications. CYGNUS® Max is an umbilical cord membrane robust enough to be sutured in place. CYGNUS® Max XL is a fenestrated umbilical cord membrane, increasing the available allograft size to cover a larger wound while also allowing the wound to drain.

CYGNUS amniotic allograft products are intended for homologous use to provide a mechanical barrier and soft tissue protection for wound repair. VIVEX processes this scaffold material with its proprietary Integrity Processing™ that protects the components of the amniotic tissue to leave the matrix intact. The result is a durable dehydrated allograft with inherent barrier properties which may be stored at ambient conditions for up to 5 years. CYGNUS products have excellent handling properties that hydrate in place and sheets are available in a wide variety of sizes and thickness to optimize the donor gift. CYGNUS products are processed in accordance to guidelines established by the Food and Drug Administration (FDA) and by the American Association of Tissue Banks (AATB).

CYGNUS® MATRIX

CYGNUS® SOLO

CYGNUS® MAX

CYGNUS® MAX XL

CYGNUS® CRYO MAX

KEY FEATURES AND BENEFITS

- Effective allograft with excellent handling characteristics
- Hydrates quickly in surgical site
- Ideal for internal or external applications
- Contains many identified growth factors, cytokines, and extracellular matrix proteins

AMNIOTIC ALLOGRAFT TISSUE, PROCESSING, SAFETY, PACKAGING

VIVEX's amniotic tissues are supplied through a donation process in multiple states across the US. Industry standards require that donated tissue only come from healthy and consenting mothers delivering full-term babies via live births. Prospective donors learn of the amniotic tissue donation process through their obstetrician.

Prior to the birth of their healthy child, mothers are informed of the program and must sign an informed consent form. Each donor must fill out a medical questionnaire and have a blood sample drawn. Serology performed from the blood sample include testing for human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), syphilis, West Nile Virus, Hepatitis B and Hepatitis C. There are other medical conditions that can disqualify a donor, including active cancer and infectious diseases. All donor interactions and tests are consistent with the guidelines issued by the AATB.

After delivery of the baby, VIVEX partners with acquisition specialists who work with the obstetric team to acquire the donated amniotic tissue. The donor mother has no further requirements, and after the tissue is acquired, it is transported to a VIVEX processing facility. Once reviewed and released by a Medical Director in accordance with both FDA and AATB regulations and standards, the amniotic allograft is processed using VIVEX's Integrity Processing™. This is an innovative process methodology focused on protecting donated amniotic tissue from harmful cleaning agents to maintain its natural state and characteristics to support the patient's regenerative potential.

The goal of the Integrity Processing™ is to clean the amniotic tissue of any blood components, while retaining the inherent properties of the original tissue. Aseptic processing was developed to minimize risk of contamination during preparation and reduce the presence of microorganisms. Integrity Processing™ is a gentle process that removes blood remnants, while preserving the allograft composition without compromising structural integrity. All VIVEX amniotic allograft tissue products are processed within cGTP conditions at VIVEX's state-of-the-art manufacturing facility in Miami, Florida. The allografts are sized to be specific for various clinical uses and then packaged for storage. Selected dehydrated tissues are terminally sterilized, subjected to a small, validated dose of electron beam irradiation after being packaged.

VIVEX's CYGNUS amniotic allograft tissues are packaged in 5-year, room temperature, shelf stable forms. One of VIVEX's amniotic tissues, CYGNUS Cryopreserved Max, is aseptically processed and available in a cryopreserved format, which should be stored at -65°C or colder and has a shorter shelf life. All tissues undergo multiple, separate quality assurance checks prior to release to ensure utmost quality and safety. Traceability is maintained for all tissues from recovery through testing, processing, packaging, and distribution.

VIVEX has an impeccable record of quality that exemplifies its robust manufacturing processes with millions of allografts distributed over its 50 years of service. Measures integrated in processing ensure that regulatory compliance and the final allograft products maintain the safety record VIVEX has established.

DONOR TESTING

TEST	SYMBOL
Human Immunodeficiency Virus (HIV)	
HIV-1/2 Plus O Antibodies	HIV-1/2 Plus O Ab
Nucleic Acid Test for HIV-1 RNA	HIV-1 NAT
Hepatitis B (HBV)	
HBV Surface Antigen	HBsAg
HBV Core Antibody (IgG & IgM)	HBcAb
Nucleic Acid Test for HBV DNA (if performed)	HBV NAT
Hepatitis C Virus (HCV)	
HCV Antibody	HCVAb
Nucleic Acid Test for HCV RNA	HCV NAT
Syphilis*	
Rapid Plasma Reagin Screen	RPR
T. Pallidum IgG	T. Pallidum IgG
West Nile Virus (WNV)	
Nucleic Acid Test for WNV RNA	WNV NAT

*A donor whose blood specimen is unsuitable for the non-treponemal screening assay, such as the RPR test, or with a reactive result from the non-treponemal screening assay, is cleared for transplantation use only when the result from the treponemal-specific (confirmatory) assay is nonreactive.

CYGNUS CONFIGURATIONS

VIVEX offers five different configurations of amniotic allograft tissues, all under the CYGNUS product brand. CYGNUS is intended for use as a wound covering or barrier in soft tissue applications. The CYGNUS amniotic allografts can help provide mechanical protection to damaged tissues.[18-21] VIVEX's proprietary Integrity Processing™ retains inherent growth factors that are essential for signaling as well as maintaining the intact extracellular matrix of the tissue itself.

CYGNUS® MATRIX

Multi-layer membrane allograft, maintaining the amnion layer, its intermediate/spongy layer, and the chorion layer of the amniotic sac, containing inherent growth factors, collagen, cytokines, and extracellular matrix.[17,24]

- Multi-layer amniotic membrane allografts, ~400µm (0.4mm) thick, up to 4X thicker than the single amnion layer
- 5-year shelf life at room temperature storage
- No upfront preparation – hydrates rapidly in surgical site
- Ideal for both internal and external application
- Available in a variety of sizes to meet clinical needs and allow use throughout the course of wound repair
- Available circular shape saves time by reducing the need to trim and associated potential to waste tissue

SIZE RECTANGLES	SIZE DISKS
2×2cm	15mm Disk
2×3cm	25mm Disk
3×3cm	35mm Disk
4×4cm	45mm Disk
4×6cm	55mm Disk
7×7cm	65mm Disk

CYGNUS® SOLO

Single layer membrane allograft, featuring the amnion layer of the amniotic sac, offering inherent growth factors, cytokines, chemokines, and extracellular matrix of the amnion layer.[17,24]

- Thin amniotic membrane allograft, ~100µm (0.1mm) thick
- 5-year shelf life at room temperature storage
- No upfront preparation – hydrates rapidly in surgical site
- Ideal for superficial wounds and topical application
- Burn treatment, acute wounds, non-healing/chronic wounds, diabetic ulcers

SIZE	SIZE
2×2cm	4×6cm
2×3cm	4×8cm
3×3cm	7×7cm
4×4cm	

CYGNUS® MAX

Comprised of the umbilical cord membrane, this tissue is the thickest of the VIVEX dehydrated amniotic allograft products and is robust enough to be sutured in place.

- Thick umbilical cord membrane, ~400µm (0.4mm), up to 4X thicker than the single amnion layer
- 5-year shelf life at room temperature storage
- No upfront preparation – hydrates rapidly in surgical site
- Tissue can be sutured into place
- Excellent handling properties

SIZE

2×2cm
2×3cm
2×4cm

CYGNUS® MAX XL

Comprised of fenestrated umbilical cord membrane, increasing the available allograft size to cover a larger wound while also allowing the wound to drain.

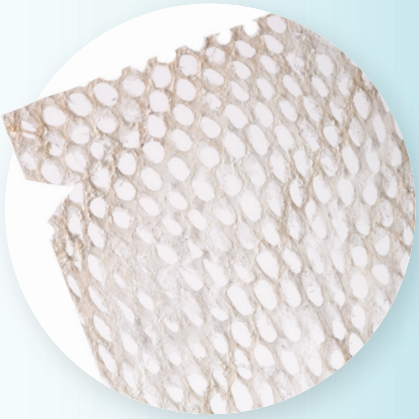
- Thick umbilical cord membrane, 400µm (0.4mm) thick, up to 4X thicker than amniotic membrane allografts
- 5-year shelf life at room temperature storage
- No upfront preparation – hydrates rapidly in surgical site
- Tissue can be sutured into place
- Excellent handling properties
- Fenestrated to allow for wound drainage and increases the size of the umbilical cord membrane

SIZE

2×3cm
3×3cm
3×8cm
4×4cm

SIZE

4x6cm
4x8cm
5x7cm



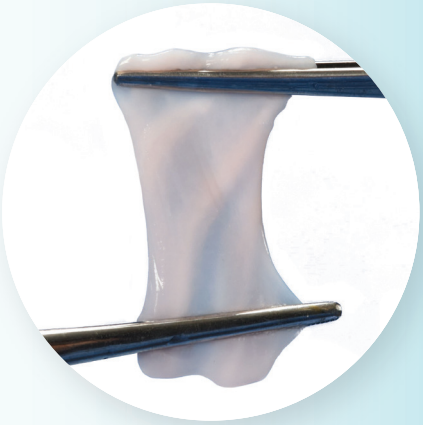
CYGNUS® CRYO MAX

Comprised of the cryopreserved umbilical cord membrane, this tissue is the thickest amniotic allograft of the VIVEX products and is robust enough to be sutured in place.

- Thick umbilical cord membrane, ~800–2,000µm (0.8-2.0mm) thick, up to 8X thicker than the single amnion layer
- 9-month shelf life at temperature of -65°C or colder
- Thaws quickly in 3-5 minutes
- Tissue can be sutured into place

SIZE

2x2cm
2x4cm
3x4cm



SCIENTIFIC EVIDENCE

GROWTH FACTORS FUNCTIONS

The following list of growth factors and cytokines[24-40] are present within amniotic allograft tissues. Some of the most notable and commonly mentioned are: epidermal growth factor (EGF), transforming growth factors alpha and beta (TGF-α&β), fibroblast growth factor (FGF), platelet derived growth factors (PDGF AA & BB), and vascular endothelial growth factors (VEGF).[16,25]

REGULATORS OF WOUND HEALING VIA ANGIOGENESIS, CELLULAR GROWTH, MIGRATION, PROLIFERATION, AND DIFFERENTIATION

ABBREVIATION	GROWTH FACTOR	FUNCTION
Ang	Angiogenin	Stimulates migration, proliferation, and vessel formation by endothelial and smooth muscle cells
Ang-2	Angiopoietin-2	Regulates neovascularization in conjunction with angiopoeitin-1 and VEGF
bFGF	Basic Fibroblast Growth Factor	Regulates neovascularization in conjunction with angiopoeitin-1 and VEGF
βFGF	Beta Fibroblast Growth Factor	Has a role in smooth muscle cell production and regulation
βNGF	Beta Nerve Growth Factor	Important for growth and apoptosis cycle maintenance of neurons
BMP-5	Bone Morphogenic Protein 5	Has a role in bone and cartilage development
BDNF	Brain Derived Neurotrophic Factor	Has a role in bone and cartilage development
EG-VEGF	Endocrine Gland-Derived Vascular Endothelial Growth Factor	Stimulates endothelial cell migration, proliferation, and survival; Potent stimulator
EGF	Epidermal Growth Factor	Stimulates proliferation, differentiation, and survival in numerous cell types, including epithelial cells
FGF	Fibroblast Growth Factor	22 members of FGF family regulate cell proliferation, survival, migration & differentiation in skin, blood vessels, muscle, adipose, tendon/ligament, cartilage, bone, tooth, and nerve
GH	Growth Hormone	Stimulates body growth through IGF-1 production, involved in anabolic activity
GRO-α	Growth Related Oncogene - alpha	Multiple functions affecting angiogenesis and inflammation systems
HB-EGF	Heparin Binding EGF-like Growth Factor	Causes keratinocytes and fibroblasts to migrate to the wound and proliferate, promotes angiogenesis

ABBREVIATION	GROWTH FACTOR	FUNCTION
HGF	Hepatocyte Growth Factor	Regulates cell growth and cell migration of hematopoietic stem cell and epithelial cells, promotes angiogenesis
IGF-1&2	Insulin-like Growth Factor	Part of a general growth-promoting system, regulates cellular processes and promotes angiogenesis
IGFBP (-1 thru 6)	Insulin-like Growth Factor Binding Proteins	Binds and stabilizes IGF-1 as a carrier protein
KGF	Keratinocyte Growth Factor	Promotes proliferation and migration of epithelial cells and keratinocytes
PIGF	Placental Growth Factor	Promotes angiogenesis through the stimulation of proliferation and migration of endothelial cells
PDGFα, β, AA, BB	Platelet Derived Growth Factors	Attract macrophages, aid in migration, proliferation and differentiation of target cells to support angiogenesis
TGFα, β1, β2	Transforming Growth Factors alpha, beta	Family with multiple roles in stimulating growth, proliferation, migration, and apoptosis of numerous cell types; potent stimulator of angiogenesis
TIMP-1,-2,-3,-4	Tissue Inhibitor of Metalloproteinase	Binds to and inactivates metalloproteinases to halt the degradation of ECM, affects cell growth and migration
TNF-α	Tumor Necrosis Factor alpha	Produced by macrophages to regulate cell functions including cell proliferation, survival, differentiation, and apoptosis
VEGF	Vascular Endothelial Growth Factor	Stimulates endothelial cell migration and activation for the formation of blood vessels

REGULATORS OF INFLAMMATION AND IMMUNE MODULATION

ABBREVIATION	GROWTH FACTOR	FUNCTION
GCSF	Granulocyte Colony-Stimulating Factor	Stimulates the proliferation, differentiation, and growth of neutrophils
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor	Stimulates the differentiation and proliferation of monocytes and granulocytes
GDF-15	Growth Differentiation Factor	Regulates the apoptosis and inflammation responses in injured tissues
IFNy	Interferon Gamma	Macrophage activator, regulates early inflammation process
IL-1α, 1β	Interleukin 1 Alpha & Beta	Affects lymphocyte proliferation, differentiation, and apoptosis
IL-1ra	Interleukin 1 receptor antagonist	Central role in regulation of immune and inflammatory responses
IL-4	Interleukin 4	Promotes proliferation of B & T cells
IL-5	Interleukin 5	Promotes B cell growth, increases immunoglobulin secretion
IL-6	Interleukin 6	Promotes proliferation and growth of neutrophils and B cells
IL-7	Interleukin 7	Promotes proliferation and apoptosis of B cells, T cells, and natural killer cells
IL-10	Interleukin 10	Promotes B cell proliferation and antibody production
IL-15	Interleukin 15	Promotes proliferation of T lymphocytes and natural killer cells
IL-17	Interleukin 17	Increases and supports proliferation of chemokines
MCP-1	Monocyte Chemoattractant Protein-1	Regulates migration and of monocytes and macrophages
MCSF	Macrophage Colony-Stimulating Factor	Promotes Monocyte and Macrophage proliferation and differentiation
OPG	Osteoprotegerin	Inhibits osteoclast activation, limits osteo-ECM degradation
TGF-β1 & β2	Transforming Growth Factor beta 1&2	Growth-enhancing or growth inhibiting immunomodulator

GROUPING SOME WELL-STUDIED GROWTH FACTORS INTO THEIR MULTIPLE FUNCTIONS

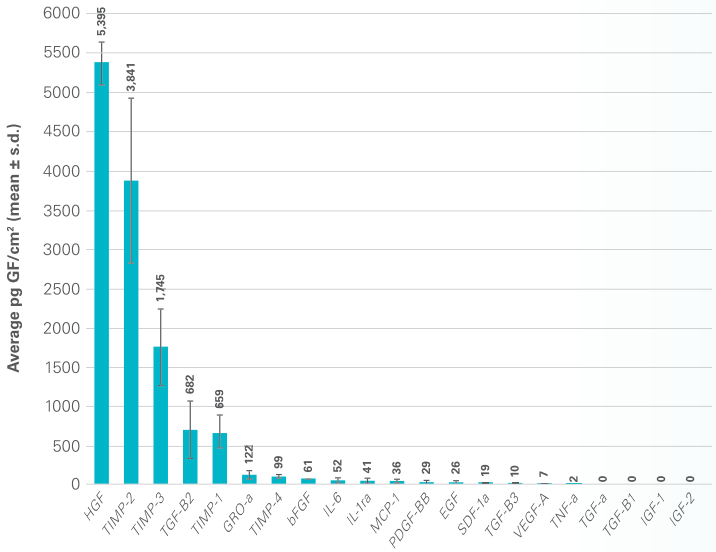
GROWTH FACTOR	ROLE
MCP-1[39], IL1-RA[22], TGF-β1&2[32], IL6[22]	Immune Modulation / Anti-Inflammatory
TNF-α[40], GRO-α[38], HGF[28], IGF1&2[29,31], VEGF[33], βFGF[34], PDGFα&β[30], Ang[32]	Angiogenesis
EGF[35], FGF[34], TGFβ[32], TIMP(1-4)[26], HGF[27]	Cell Growth
PDGFα&β[36], EGF[35], TIMP-2&-3[26], HGF[27], Ang[23], KGF[37]	Cell Migration
PDGFα&β[36], EGF[35], FGF[34], TGF-β1&2[32], IGF1&2[30], Ang[23], KGF[37]	Cell Proliferation
PDGFα&β[36], EGF[1], TIMP-2& -3[26], TGF-β1&2[32]	Cell Differentiation

HIGHLIGHTS OF GROWTH FACTORS MEASURED IN CYGNUS ALLOGRAFT TISSUE

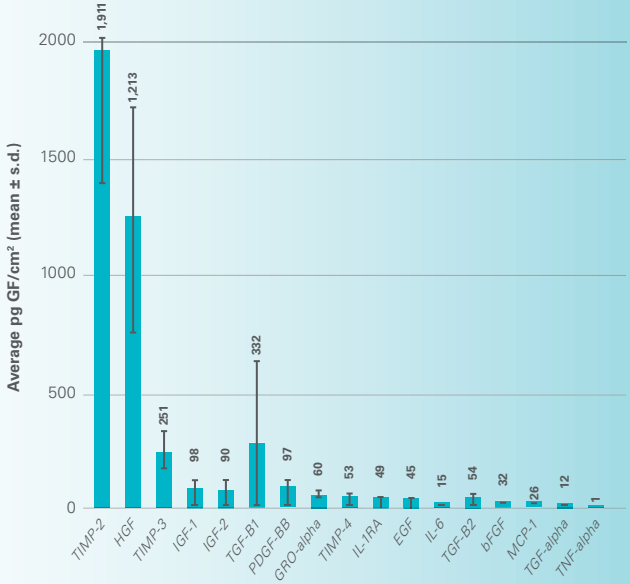
VIVEX's proprietary Integrity Processing™ methodology helps to maintain the inherent levels of key extracellular matrices, including proteins, carbohydrates, growth factors and cytokines.[17,24] Amniotic tissues recovered from live births, once reviewed and released by a Medical Director in accordance with FDA and AATB regulations and standard, were processed via the Integrity Processing™ gentle cleansing procedure and then dried for long-term room temperature storage. **The propriety Integrity Processing preserves up to 600+ signaling proteins in CYGNUS Matrix, Max and Solo.**[41]

ELISA assays were used to analyze the content of key growth factors and cytokines released from the amniotic allograft tissues from four donors. Tissue was placed in DPBS media and incubated for 24 hours at 37°C. The supernatant was evaluated to quantify the concentration of growth factors / cytokines. The data was normalized with respect to the dried weight of the tissue. Testing was performed pre- and post-processing to ensure that select molecules were preserved after processing. The figures below and on the next page present the data for the products in the CYGNUS family.

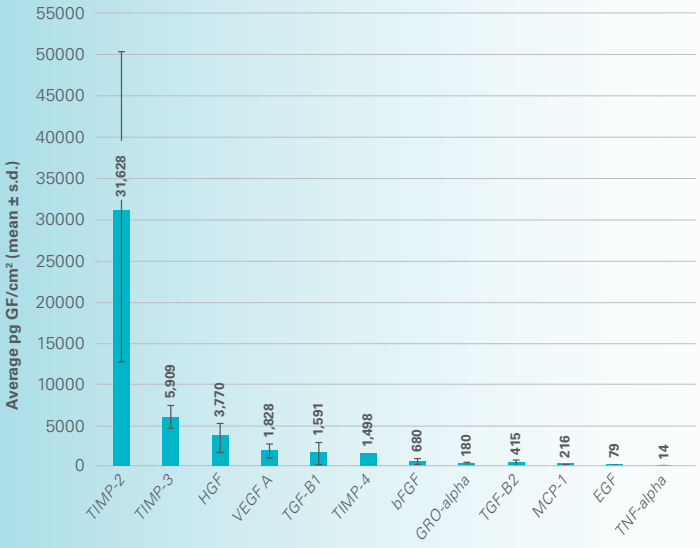
CYGNUS MATRIX GROWTH FACTORS RELEASED AFTER 24 HOURS AT 37°C



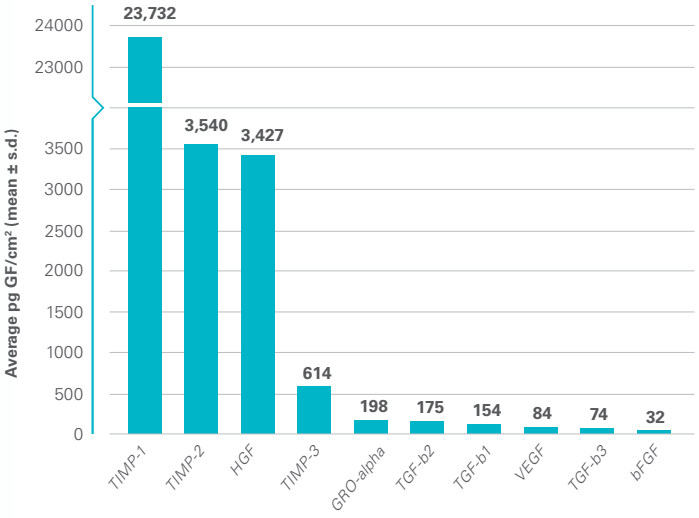
CYGNUS SOLO GROWTH FACTORS RELEASED AFTER 24 HOURS AT 37°C



CYGNUS MAX GROWTH FACTORS RELEASED AFTER 24 HOURS AT 37°C



CYGNUS CRYOPRESERVED MAX GROWTH FACTORS RELEASED AFTER 24 HOURS AT 37°C



EXTRACELLULAR MATRIX COMPONENTS & FUNCTIONS

Amniotic allografts are natural barriers, and the sheet-like three-dimensional matrix is comprised of many proteins recognized as important in the complex wound repair process. The extracellular matrix (ECM) of the amniotic allograft is a biological surface that provides a familiar and natural scaffold for cells to attach, migrate, and proliferate upon during the progression of the wound repair process.[22,23] The components of the ECM in the amniotic allografts are proteins found in a variety of tissue types in the human body.[42,43]

The main protein components in amniotic allografts are collagens (I, II, III, IV, VII), fibronectin, laminin, and hyaluronic acids (HA).[42] Additionally, the ECM of amniotic allografts tissues include proteoglycans, cytokines, and amnio acids. Collagen is the main structural component in amniotic allografts and also in the body in general. In fact, 25-35% of the whole human body protein content is a type of collagen. In amniotic allografts, type I collagen is 90% of the extracellular matrix. Type III collagen, predominant in the intermediate/spongy layer and expressed in early granulation tissue, has been proposed to play a prominent role in cutaneous wound repair.[12] Other collagen protein structures in amniotic tissues include type IV and type VII collagen. Cells in the human body recognize collagen as a protein that is advantageous to adhere to, and supportive of cellular activities, such as migration and proliferation.

ECM COMPONENT	DESCRIPTION
Collagen, type I	Main structural protein component in the body
Collagen, type II–VII	Structural protein component of the body
Fibronectin	Binding protein agent, supports initial cell attachment
Laminin	High molecular weight protein to which cells easily bind and migrate across
Hyaluronic Acid	Lubricating hydrophilic protein that coats cells and aids in hydrodynamic movements
Proteoglycans	Connective proteins that fill the spaces between cells in tissue and affect the stability of the proteins and growth factors
Cytokines	Small proteins produced by a broad range of cells and embedded into the ECM of tissues
Amino Acids	Small proteins produced by a broad range of cells and embedded into the ECM of tissues

Fibronectin is another commonly occurring protein in amniotic allografts and plays a role in holding the extracellular matrix of tissues together by aiding in initial cell attachment. Laminin is a high molecular weight protein of the ECM to which cells easily bind and migrate across. Proteoglycans are connective proteins that fill the spaces between cells in tissue and affect the stability of the proteins and growth factors in the ECM.[43] Cytokines and amnio acids are small proteins produced by a broad range of cells and embedded into the ECM of tissues.

Hyaluronic acid (HA) is an important component of the ECM in human tissues.[44] It is a lubricating smooth protein that coats cells, aiding in the cell's hydrodynamic movements.[45] The ability of cells to migrate across an ECM and thus proliferate during the wound healing cascade is aided by this smooth protein. HA has a range of molecular weights, however, which affects the manner in which cells utilize its lubricious benefits.[46]

HYALURONIC ACID – THE BENEFIT OF HEAVY CHAIN HA

HA ranges from 200-10,000 kDa in molecular weight.[44] Research in the last decade has increased our understanding of cellular reaction to the presence of HA. There is evidence that low molecular weight HA incites different cellular responses than high molecular weight HA.

Low molecular weight HA are now understood to induce pro-inflammatory gene expression[45] as specific cells preferentially interact with this protein. On the other hand, high molecular weight HA, called heavy chain or HC-HA, are shown to interact with cells that inhibit pro-inflammatory gene expressions. It is now understood that HC-HA is an active component responsible for some of the clinically observed anti-inflammatory and anti-scarring actions[46] of the naturally occurring extracellular matrix of amniotic membranes. Additionally, HC-HA is stabilized by pentraxin 3 (PTX3), which is expressed and secreted by amniotic membrane cells. Thus, the HC-HA-PTX3 complex contributes to the function of amniotic membranes as anti-inflammatory and anti-scarring[46] in the native use as a protective mechanical barrier between the mother and developing fetus.

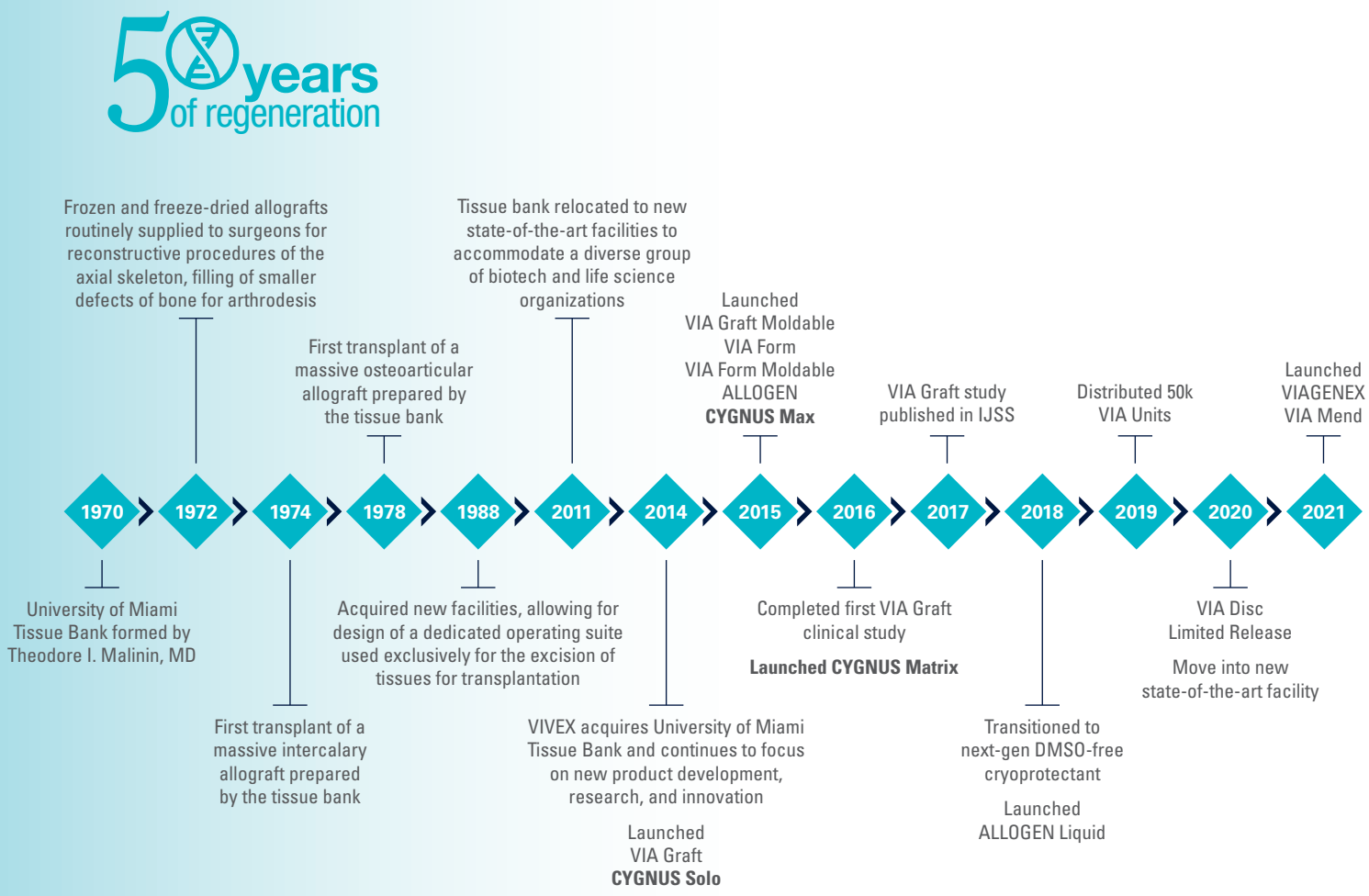
VIVEX's Integrity Processing™, by which donated amniotic tissues are processed into allografts, prepared for homologous use as a natural barrier, is gentle enough to retain the naturally occurring components of the ECM.[41]

CLINICAL EVIDENCE

The underpinnings of VIVEX's regenerative medicine solutions technology date back 50 years to the founding of UMTB. There have been multiple firsts in clinical and scientific achievement leading up to 2014, when VIVEX acquired UMTB's assets and intellectual property and repositioned the business to focus on the development and commercialization of new regenerative medicine solutions. Shortly after VIVEX acquired UMTB, the amniotic tissue allograft products were introduced, with CYGNUS Solo launching in 2014, CYGNUS Max in 2015, and CYGNUS Matrix in 2016. The graphic below highlights key milestones in our innovative history.

SAFE AND TRUSTED PARTNER

VIVEX is a regenerative solutions company focused on the innovation of tissue-based therapies. Our amniotic allografts and other signature VIVEX products, including demineralized bone matrices, cortical and cancellous bone in strips, sponges, fibers, and pastes, and skin and intervetebral disc tissue allografts, support Wound Care, Ortho-Fusion, and Interventional Pain Therapies. During more than 50 years of safe and effective operations, VIVEX has safely delivered over 2 million allografts with no disease transmission throughout the US and eighteen countries worldwide.

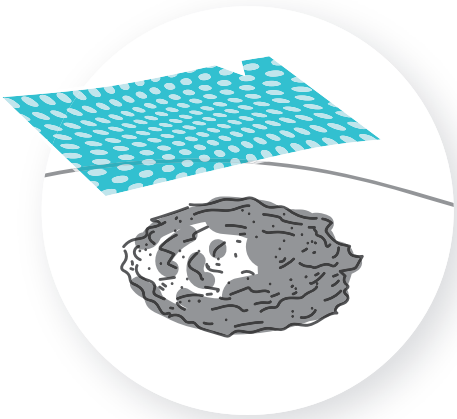


CONCLUSION

With over a century of clinical use, amniotic allografts provide a well-documented benefit for patients during the wound repair phase of post-event healing. Scientific research has taken a deep dive into and supplied a thorough grasp of the interactions of proteins and growth factors within the tissue. Amniotic allografts have shown to be a reasonable option as a mechanical barrier for traumatized tissues and safe for use in a variety of settings. VIVEX is proud to offer several options of amniotic allografts in multiple sizes to meet the needs of both the surgeons and their patients.

POTENTIAL CLINICAL APPLICATIONS

In general wound care, such as diabetic foot ulcers, venous leg ulcers, pressure wounds, hard-to-heal wounds, and surgical wound dehiscence, CYGNUS has been used as a protective barrier to provide essential mechanical protection for wounds. Other potential clinical applications include general orthopedics, arthroplasty, hand and wrist, and foot and ankle procedures.



WOUND

BURN

WOUND DEHISCENCE

PRESSURE WOUND

FREQUENTLY ASKED QUESTIONS

HOW SAFE IS AN AMNIOTIC TISSUE GRAFT?

VIVEX's Integrity Processing™ for cleaning, packaging and sterilization of amniotic membranes follows the regulations and standards laid out by the FDA and the AATB. Eligible donors are mothers delivering full term, live births who also go through a strict donor screening process based on FDA and AATB guidelines. Serologic blood tests are performed to investigate the potential for infectious diseases. The complete process concludes with sterilization and culture results analysis by an outside source and internal final release review and verification of all results to assess that the procedural process results in a safe implant.

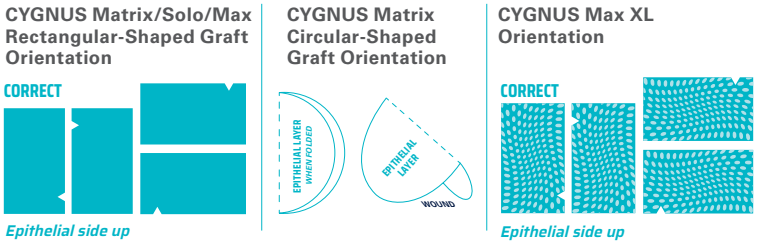
IS AMNIOTIC TISSUE PERMANENT OR RESORBABLE?

Amniotic membrane grafts, such as CYGNUS, are resorbable and will resorb depending on the specific application, patient, and location in which it is placed.

ARE THE SIZES AND FORMS OF CYGNUS SPECIFIC TO AN INDICATION?

No, all sizes perform the same function, that of a mechanical barrier for protection; however, the variety of sizes and forms of CYGNUS allow a surgeon to tailor the amniotic barrier to the need of the patient.

IS THERE A SPECIFIC SIDE THAT GOES UP OR DOWN?



CAN THE TISSUE BE CUT?

Yes.

DOES THE TISSUE NEED TO BE HYDRATED BEFORE BEING PLACED IN SITU?

No, the tissue will hydrate once in place.

WILL THE TISSUE STAY IN PLACE?

The side that goes down is 'tackier,' yet any irrigation should be performed prior to laying down the tissue.

CAN THE TISSUE BE SUTURED OR USED WITH A GLUE-LIKE FIBRIN?

The tissue is not indicated specifically for suturing or with glues. If a surgeon desires to place a suture, the thicker tissue of CYGNUS Max provides easier handling with a small suture, such as a 4-0. Try not to create tension in the graft with a suture.

WHAT IS THE PROCEDURE FOR PLACING AN AMNIOTIC TISSUE GRAFT?

a. Complete surgical preparation of site

b. Follow orientation placement guidelines

c. Cut tissue, if desired, then apply to wound site

d. Suture, if desired

e. Close wound site

i. If the amniotic allograft is placed over a surface wound, follow physician advice for site treatment and dressing

CYGNUS® MATRIX

Product HCPCS Code: Q4170 (CYGNUS) per square centimeter

ITEM NUMBER	DESCRIPTION	SIZE	SQ. CM
CAP020200S	CYGNUS® Matrix Amnion Allograft	2x2cm	4
CAP020300S	CYGNUS® Matrix Amnion Allograft	2x3cm	6
CAP030300S	CYGNUS® Matrix Amnion Allograft	3x3cm	9
CAP040400S	CYGNUS® Matrix Amnion Allograft	4x4cm	16
CAP040600S	CYGNUS® Matrix Amnion Allograft	4x6cm	24
CAP070700S	CYGNUS® Matrix Amnion Allograft	7x7cm	49
CAP015000S	CYGNUS® Matrix Amnion Allograft Disk	15mm Disk	2
CAP025000S	CYGNUS® Matrix Amnion Allograft Disk	25mm Disk	5
CAP035000S	CYGNUS® Matrix Amnion Allograft Disk	35mm Disk	10
CAP045000S	CYGNUS® Matrix Amnion Allograft Disk	45mm Disk	16
CAP055000S	CYGNUS® Matrix Amnion Allograft Disk	55mm Disk	24
CAP065000S	CYGNUS® Matrix Amnion Allograft Disk	65mm Disk	33

CYGNUS® SOLO

ITEM NUMBER	DESCRIPTION	SIZE	SQ. CM
CAS020200S	CYGNUS® Solo Amnion Allograft	2x2cm	4
CAS020300S	CYGNUS® Solo Amnion Allograft	2x3cm	6
CAS030300S	CYGNUS® Solo Amnion Allograft	3x3cm	9
CAS040400S	CYGNUS® Solo Amnion Allograft	4x4cm	16
CAS040600S	CYGNUS® Solo Amnion Allograft	4x6cm	24
CAS040800S	CYGNUS® Solo Amnion Allograft	4x8cm	32
CAS070700S	CYGNUS® Solo Amnion Allograft	7x7cm	49

CYGNUS® MAX

ITEM NUMBER	DESCRIPTION	SIZE	SQ. CM
CAM020200S	CYGNUS® Max Umbilical Cord Membrane	2x2cm	4
CAM020300S	CYGNUS® Max Umbilical Cord Membrane	2x3cm	6
CAM020400S	CYGNUS® Max Umbilical Cord Membrane	2x4cm	8

CYGNUS® MAX XL

ITEM NUMBER	DESCRIPTION	SIZE	SQ. CM
CAX020300S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	2x3cm	6
CAX030300S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	3x3cm	9
CAX030800S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	3x8cm	24
CAX040400S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	4x4cm	16
CAX040600S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	4x6cm	24
CAX040800S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	4x8cm	32
CAX050700S	CYGNUS® Max XL Fenestrated Umbilical Cord Membrane	5x7cm	35

CYGNUS® CRYOPRESERVED MAX

ITEM NUMBER	DESCRIPTION	SIZE	SQ. CM
CUC020200	CYGNUS® Cryopreserved Max Umbilical Cord Membrane	2x2cm	4
CUC020400	CYGNUS® Cryopreserved Max Umbilical Cord Membrane	2x4cm	8
CUC030400	CYGNUS® Cryopreserved Max Umbilical Cord Membrane	3x4cm	12

VIVEX Biologics will use reasonable efforts to provide accurate and complete information herein, but this information should not be construed as providing clinical advice, dictating reimbursement policy or as a substitute for the judgment of a health care provider. It is the health care provider's responsibility to determine the appropriate treatment, codes, charges for services and use of modifiers for services rendered and to submit coverage or reimbursement-related documentation.

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