Introduction

Bioengineered skin and soft tissue substitutes are artificial alternatives to live skin grafts for wound care and tissue reconstruction. The products are made from various sources including human tissue (from the patient or others), nonhuman tissue (cows, pigs, horses), synthetic materials (man-made), or a combination of these materials. Some skin substitutes are labeled for specific uses such as for healing severe diabetic foot sores or during surgery for severe burns or breast reconstruction; other uses are being researched. This policy outlines when specific bioengineered skin and soft tissue substitutes might be medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Products</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Allogeneic Acellular Dermal Matrix Products, including but not limited to:  
• AlloDerm®*  
• AlloMend®  
• Cortiva® [AlloMax™]  
• DermACELL™  
• DermaMatrix™*  
• FlexHD®*  
• FlexHD® Pliable™  
• Graftjacket®*  
| Breast reconstructive surgery using allogeneic acellular dermal matrix products listed in the left column may be considered medically necessary when:  
• There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required  
OR  
• There is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis  
OR  
• The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed |
| • AlloPatch®*  
• Apligraft®**  
• Dermagraft®**  
• Integra® Flowable Wound Matrix  
• Integra® Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™)  
• Integra® Flowable Wound Matrix  
| Treatment of chronic, non-infected, full-thickness diabetic lower-extremity ulcers using the tissue-engineered skin substitute products listed in the left column may be considered medically necessary.  
Note: Criteria for using human amniotic membrane products are addressed in a separate medical policy (see Related Policies). |
| • Apligraf®**  
• Oasis™ Wound Matrix***  
| Treatment of chronic, non-infected, partial or full-thickness lower-extremity skin ulcers due to venous insufficiency using the tissue-engineered skin substitute products listed in the left column may be considered medically necessary when:  
• A one-month period of conventional ulcer therapy has failed to promote healing |
| • OrCel™****  
| Treatment of dystrophic epidermolysis bullosa using the tissue-engineered skin substitute product listed in the left column may be considered medically necessary when:  
• Standard wound therapy has failed for the treatment of mitten-hand deformity  
AND  
• When provided in accordance with the humanitarian device exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA)**** |
### Products

- **Epicel ®****
- **Integra ® Dermal Regeneration Template**

### Medical Necessity

Treatment of second- and third-degree burns using the tissue-engineered skin substitute products listed in the left column may be considered medically necessary when:

- **Epicel® only**: It is used for the treatment of deep dermal or full-thickness burns covering a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA****
- **Integra ® Dermal Regeneration Template**™**: No additional criteria required

All other uses of the bioengineered skin and soft tissue substitutes listed above are considered investigational.

*Banked human tissue; **FDA premarket approval; ***FDA 510(k) cleared; ****FDA-approved under an HDE

**Note:** Amniotic membrane and amniotic fluid products are reviewed in a Related Policy.

### Investigational

All other bioengineered skin and soft tissue substitute products not listed above are considered investigational, including, but not limited to:

- **ACell® UBM Hydrated Wound Dressing**
- **ACell® UBM Lyophilized Wound Dressing**
- **AlloSkin™**
- **AlloSkin™ RT**
- **Aongen™ Collagen Matrix**
- **Architect® ECM, PX, FX**
- **ArthroFlex™ (Flex Graft)**
- **Atlas Wound Matrix**
- **Avagen Wound Dressing**
- **AxoGuard® Nerve Protector (AxoGen)**
- **Biobrane®/Biobrane-L**
- **CollaCare®**
- **CollaCare® Dental**
- **Collagen Wound Dressing (Oasis Research)**
- **CollaGUARD®**
- **CollaMend™**
- **DermaSpan™**
- **DressSkin Durepair Regeneration Matrix®**
- **Endoform Dermal Template™**
- **ENDURAGen™**
- **Excellagen**
- **ExpressGraft™**
- **E-Z Derm™**
- **FlowerDerm**
- **GammaGraft**
- **Graftjacket® Xpress, injectable**
- **Helicoll™**
- **Hyalomatrix®**
- **Hyalomatrix® PA**
- **hMatrix®**
- **Integra™ Bilayer Wound Matrix**
- **Keramatrix®**
- **Oasis® Ultra**
- **Pelvicol®/PelviSoft®**
- **Permacol™**
- **PriMatrix™**
- **PriMatrix™ Dermal Repair Scaffold**
- **PuraPly™ Wound Matrix** (previously FortaDerm™)
- **PuraPly™ AM (Antimicrobial Wound Matrix)**
- **Puros® Dermis**
- **RegenePro™**
- **Repliform®**
- **Repriza™**
- **StrataGraft®**
- **Strattice™ (xenograft)**
- **Suprathel®**
- **SurgiMend®**
- **Talymed®**
- **TenoGlide™**
### Investigational

- CollaWound™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- Cymetra™ (Micronized AlloDerm™ Tissue [MAT])
- Cytal™ (previously MatriStem®)
- Dermadapt™ Wound Dressing
- DermaPure™
- Kerecis™
- MariGen ™/Kerecis™ Omega3™
- MatriDerm®
- Matrix HD™
- Mediskin®
- MemoDer™
- MicroDerm® biologic wound matrix
- NeoForm™
- NuCel
- Oasis® Burn Matrix
- TenSIX™ Acellular Dermal Matrix
- TissueMend
- TheraForm™ Standard/Sheet
- TheraSkin®
- TransCyte™
- TruSkin™
- Veritas® Collagen Matrix
- XCM Biologic® Tissue Matrix
- XenMatrix™ AB

### Documentation Requirements

For wound care, detailed history and physical, with the record to include the following:

- Associated medical comorbidities
- Description of wound (eg, full thickness [affecting all layers of the skin], deep dermal [deeper than a superficial wound but not a full thickness wound])
- Standard wound therapy treatment provided, including duration and effectiveness or failure of treatment

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
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<td>Integra Bilayer Matrix Wound Dressing (BMWD), per square centimeter</td>
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<td>Integra Dermal Regeneration Template (DRT), per square centimeter</td>
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<tr>
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<td>Q4107</td>
<td>Graftjacket, per square centimeter</td>
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<td>Q4122</td>
<td>DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq cm</td>
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<td>Q4128</td>
<td>FlexHD, Allopatch HD or Matrix HD, per square centimeter</td>
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**Investigational (Not Eligible for Coverage)**

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<tr>
<td>A6460</td>
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<td>Synthetic resorbable wound dressing, sterile, pad size more than 16 sq. in. but less than or equal to 48 sq. in., without adhesive border, each dressing</td>
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<td>Q4110</td>
<td>PriMatrix, per square centimeter</td>
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<td>Q4111</td>
<td>GammaGraft, per square centimeter</td>
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<tr>
<td>Q4113</td>
<td>Graftjacket Xpress, injectable, 1 cc</td>
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<tr>
<td>Q4114</td>
<td>Integra Flowable Wound Matrix, injectable, 1 cc</td>
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<td>Q4115</td>
<td>AlloSkin, per square centimeter</td>
</tr>
<tr>
<td>Q4117</td>
<td>Hyalomatrix, per square centimeter</td>
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<tr>
<td>Q4118</td>
<td>MatriStem micromatrix, 1 mg</td>
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<tr>
<td>Q4121</td>
<td>TheraSkin, per square centimeter</td>
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<tr>
<td>Q4123</td>
<td>AlloSkin RT, per square centimeter</td>
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<td>Q4124</td>
<td>Oasis Ultra Tri-Layer Wound Matrix, per square centimeter</td>
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<td>Q4125</td>
<td>Arthroflex, per square centimeter</td>
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<tr>
<td>Q4126</td>
<td>Memoderm, Dermaspan, Transgraft or Integuply, per square centimeter</td>
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<tr>
<td>Q4127</td>
<td>Talymed, per square centimeter</td>
</tr>
<tr>
<td>Q4130</td>
<td>Strattlice TM, per square centimeter</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Q4134</td>
<td>hMatrix, per square centimeter</td>
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<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
</tr>
<tr>
<td>Q4136</td>
<td>EZ-derm, per square centimeter</td>
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<td>Q4141</td>
<td>Alloskin AC, per square centimeter</td>
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<tr>
<td>Q4142</td>
<td>Xcm biologic tissue matrix, per square centimeter</td>
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<tr>
<td>Q4143</td>
<td>Repriza, per square centimeter</td>
</tr>
<tr>
<td>Q4146</td>
<td>TenSIX, per square centimeter</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
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<tr>
<td>Q4152</td>
<td>DermaPure per square centimeter</td>
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<td>Q4158</td>
<td>Kerecis Omega3, per sq cm</td>
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<tr>
<td>Q4161</td>
<td>Bio-ConneKt Wound Matrix, per square centimeter</td>
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<tr>
<td>Q4164</td>
<td>Helicoll, per square centimeter</td>
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<tr>
<td>Q4165</td>
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<td>Cytal, per square centimeter</td>
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<tr>
<td>Q4167</td>
<td>Truskin, per square centimeter</td>
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<td>Q4175</td>
<td>Miroderm, per square centimeter</td>
</tr>
<tr>
<td>Q4179</td>
<td>Flowerderm, per square centimeter</td>
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<tr>
<td>Q4182</td>
<td>Transcyte, per square centimeter</td>
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<tr>
<td>Q4193</td>
<td>Coll-e-derm, per square centimeter</td>
</tr>
<tr>
<td>Q4195</td>
<td>Puraply, per square centimeter</td>
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<tr>
<td>Q4196</td>
<td>Puraply am, per square centimeter</td>
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<tr>
<td>Q4197</td>
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<td>Q4200</td>
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<tr>
<td>Q4203</td>
<td>Derma-gide, per square centimeter</td>
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<tr>
<td>Q4220</td>
<td>BellaCell HD or Surederm, per sq cm (code effective 10/1/19)</td>
</tr>
</tbody>
</table>
Clinical input has indicated that the various acellular dermal matrix products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional acellular dermal matrix products may become available for this indication.

Benefit Application

Many states have mandates related to breast reconstruction that may impact the application of this policy.

Evidence Review

Description

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bioengineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and healing lower-extremity ulcers and severe burns. Acellular dermal matrix (ADM) products are also being evaluated for soft tissue repair.
Background

Skin and Soft Tissue Substitutes

Bioengineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (eg, dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix (ADM) products can differ in a number of ways, including the species source (human, bovine, porcine), tissue source (eg, dermis, pericardium, intestinal mucosa), additives (eg, antibiotics, surfactants), hydration (wet, freeze dried), and required preparation (multiple rinses, rehydration).

Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (eg, bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Bioengineered skin substitutes can be used as either temporary or permanent wound coverings.

Applications

There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (eg, breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second and third-degree burns are another indication in which artificial skin products may substitute for autografts or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (eg, bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. ADM products are
also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A systematic review found no difference in overall complication rates with ADM allograft compared with standard procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, the available evidence may inform patient decision making about reconstruction options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Tendon Repair

For individuals who are undergoing tendon repair who receive Graftjacket, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The RCT identified improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate consistency of the effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Surgical Repair of Hernias or Parastomal Reinforcement

For individuals who are undergoing surgical repair of hernias or parastomal reinforcement who receive acellular collagen-based scaffolds, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. The
evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Diabetic Lower-Extremity Ulcers

For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra (biosynthetic) over the standard of care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers who receive ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. Results from a multicenter RCT showed some benefit of DermACEll that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, TheraSkin, DermACEll, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lower-Extremity Ulcers Due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogenic Oasis Wound Matrix over the standard of care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive bioengineered skin substitutes other than Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary end points in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups
of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute versus the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Dystrophic Epidermolysis Bullosa**

For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (eg, 5 patients). The evidence is insufficient to determine the effects of the technology on health outcomes.

**Deep Dermal Burns**

For individuals who have deep dermal burns who receive bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell therapy) has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.
### Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT03285698</td>
<td>A Randomized, Prospective Trial Comparing the Clinical Outcomes for DermACELL® Compared With Integra® Bilayer Wound Matrix</td>
<td>100</td>
<td>Oct 2020</td>
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<tr>
<td>NCT02587403*</td>
<td>A Randomized, Prospective Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair</td>
<td>120</td>
<td>Oct 2020</td>
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<tr>
<td>NCT02322554</td>
<td>The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<td>NCT01987700*</td>
<td>Multi-Center Study To Examine The Use Of Flex HD® And Strattice In The Repair Of Large Abdominal Wall Hernias</td>
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<td>Aug 2018 (completed)</td>
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NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

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### Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### 2016 Input

In response to requests, input was received from two physician specialty societies and three academic medical centers while this policy was under review in 2016. Input was requested on the equivalency of products within the categories of amniotic membrane, living cell therapies, and biosynthetic skin substitutes for the treatment of diabetic foot ulcers and non-ocular burns (biosynthetic only). Input on the equivalency of products within these categories was mixed.
2014 Input

In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. In addition to questions on medical necessity for different indications, input was specifically requested on the equivalency of products within the different categories (eg, acellular dermal matrix [ADM], living cell therapy, xenogeneic collagen scaffold, amniotic membrane). Five reviewers addressed the use of ADM products for breast reconstruction, and most considered the various ADM products (AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bioengineered skin and soft tissue substitutes for diabetic and venous lower-extremity ulcers. Responses were mixed, although most reviewers considered living cell therapies to be equivalent for these indications. Most reviewers did not consider xenogeneic ADM products (eg, PriMatrix) or amniotic membrane (eg, EpiFix) to be medically necessary for any indication.

2012 Input

In response to requests, input was received from three physician specialty societies and two academic medical centers while this policy was under review in 2012. Most reviewers supported the indications and products described in this policy. Input was requested on the use of an interpositional spacer after parotidectomy. Support for this indication was mixed. Some reviewers suggested use of other products and/or additional indications; however, the input on these products/indications was not uniform. Reviewers provided references for the additional indications; these were subsequently reviewed.

2009 Input

In response to requests, input was received from one physician specialty society (two physicians) and one academic medical center while this policy was under review in 2009. All reviewers indicated that the use of AlloDerm in breast reconstruction surgery should be available for use during breast reconstructive surgery.
Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The Institute recommended that clinicians “consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.”

It was emphasized that none of these measures had been shown to improve the resolution of infection and that they were expensive, not universally available, might require consultation with experts, and reports supporting their utility were mostly flawed.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) issued the following national coverage determination: porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers.

In 2019, CMS reported that it is finalizing the proposal to continue the policy established in CY 2018 to assign skin substitutes to the low cost or high-cost group. In addition, CMS presented several payment ideas to change how skin substitute products are paid and solicited comments on these ideas to be used for future rulemaking.

Regulatory Status

A large number of artificial skin products are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy.

Acellular Dermal Matrix (ADM) Products

Allograft ADM products derived from donated human skin tissue are supplied by tissue banks compliant with standards of the American Association of Tissue Banks and U.S. Food and Drug
Administration (FDA) guidelines. The processing removes the cellular components (ie, epidermis, all viable dermal cells) that can lead to rejection and infection. ADM products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; FDA classifies ADM products as banked human tissue and therefore not requiring FDA approval for homologous use.

In 2017, FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).[^3]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

1. The HCT/P is minimally manipulated;

2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;

3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4. Either:

   i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

   ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use.

Although frequently used by surgeons for breast reconstruction, FDA does not consider this homologous use and has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery. The indication of surgical mesh for general use in “Plastic and reconstructive surgery” was cleared by the FDA before surgical mesh was described for breast reconstruction in 2005. FDA states that the specific use of surgical mesh in breast procedures represents a new intended use and that a
substantial equivalence evaluation via 510(k) review is not appropriate and a pre-market approval evaluation is required.4

- AlloDerm® (LifeCell Corp.) is an ADM (allograft) tissue-replacement product created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm® required refrigeration and rehydration before use. It is currently available in a ready-to-use product stored at room temperature. An injectable micronized form of AlloDerm® (Cymetra) is available.

- Cortiva® (previously marketed as AlloMax™ Surgical Graft, and before that as NeoForm™) is an acellular non-cross-linked human dermis allograft.

- AlloPatch® (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD® for postmastectomy breast reconstruction.

- FlexHD® and the newer formulation FlexHD® Pliable™ (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.

- DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.

- DermaMatrix™ (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.

- DermaPure™ (Tissue Regenix Wound Care) is a singlelayer decellularized human dermal allograft for the treatment of acute and chronic wounds.

- Graftjacket® Regenerative Tissue Matrix (also called Graftjacket Skin Substitute; KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure. Graftjacket Xpress® is an injectable product.

FDA product codes: FTM, OXF.

Xenogenic Products

- Cytal™ (previously called MatriStem®) Wound Matrix, Multilayer Wound Matrix, Pelvic Floor Matrix, MicroMatrix, and Burn Matrix (all manufactured by ACell) are composed of porcine-derived urinary bladder matrix.
• Helicoll (Encol) is an acellular collagen matrix derived from bovine dermis. In 2004, it was cleared for marketing by FDA through the 510(k) process for topical wound management that includes partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears), and surgical wounds including donor sites/grafts.

• Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is derived from acellular animal protein. In 2009, it was cleared for marketing by FDA through the 510(k) process under the name of Keratec. The wound dressings are indicated in the management of the following types of dry, light, and moderately exudating partial and full-thickness wounds: pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

• Kerecis™ Omega3 Wound (Kerecis) is an ADM derived from fish skin. It has a high content of omega 3 fatty acids and is intended for use in burn wounds, chronic wounds, and other applications.

• Permacol™ (Covidien) is xenogeneic and composed of cross-linked porcine dermal collagen. Cross-linking improves the tensile strength and long-term durability but decreases pliability.

• PriMatrix™ (TEI Biosciences, a subsidiary of Integra Life Sciences) is a xenogeneic ADM processed from fetal bovine dermis. It was cleared for marketing by FDA through the 510(k) process for partial and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds. FDA product code: KGN.

• SurgiMend® PRS (TEI Biosciences, a subsidiary of Integra Life Sciences) is a xenogeneic ADM processed from fetal and neonatal bovine dermis.

• Strattice™ Reconstructive Tissue Matrix (LifeCell Corp) is a xenogenic non-cross-linked porcine-derived ADM. There are pliable and firm versions, which are stored at room temperature and come fully hydrated.

• Oasis™ Wound Matrix (Cook Biotech) is a collagen scaffold (extracellular matrix) derived from porcine small intestinal mucosa. In 2000, it was cleared for marketing by FDA through the 510(k) process for the management of partial and full-thickness wounds, including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds. FDA Product code: KGN.
Living Cell Therapy

- Apligraf® (Organogenesis) is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. In 1998, it was approved by FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM.

- Dermagraft® (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by FDA for repair of diabetic foot ulcers. FDA product code: PFC.

- Epicel® (Genzyme Biosurgery) is an epithelial autograft composed of a patient's own keratinocytes cultured ex vivo and is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. FDA product code: OCE.

- OrCel™ (Forticell Bioscience; formerly Composite Cultured Skin) is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by FDA premarket approval for healing donor site wounds in burn victims and under a humanitarian device exemption (HDE) for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites. FDA product code: ODS.

- TheraSkin® (Soluble Systems) is a cryopreserved split-thickness human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSkin® is derived from human skin allograft supplied by tissue banks compliant with the AATB and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product by FDA.

Biosynthetic Products

- Biobrane®/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a
complex 3-dimensional structure of tri-filament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. FDA product code: FRO.

- Integra® Dermal Regeneration Template (also marketed as Omnigraft Dermal Regeneration Matrix; Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by FDA for use in the post-excisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient and for certain diabetic foot ulcers.

- Integra® Matrix Wound Dressing and Integra® Meshed Bilayer Wound Matrix are substantially equivalent skin substitutes and were cleared for marketing by FDA through the 510(k) process for other indications. Integra® Bilayer Wound Matrix (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

- TransCyte™ (Advanced Tissue Sciences) consists of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer and was approved by the FDA in 1997. TransCyte is intended as a temporary covering over burns until autografting is possible. It can also be used as a temporary covering for some burn wounds that heal without autografting.

**Synthetic Products**

- Suprathel® (PolyMedics Innovations) is a synthetic copolymer membrane fabricated from a tri-polymer of polylactide, trimethylene carbonate, and s-caprolactone. It is used to provide temporary coverage of superficial dermal burns and wounds. Suprathel® is covered with gauze and a dressing that is left in place until the wound has healed.

**References**


54. Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. Wounds, 2019 Feb 6;31(3). PMID 30720443


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>09/01/16</td>
<td>New policy, approved August 9, 2016. Add to Surgery section. Some bioengineered skin and soft tissue substitutes may be considered medically necessary when criteria are met. The use of bioengineered skin and soft tissue substitutes is investigational when criteria are not met. The effective date of this policy is December 1, 2016.</td>
</tr>
<tr>
<td>01/06/17</td>
<td>Updated effective date. The effective date of this policy has been updated to March 1, 2017.</td>
</tr>
<tr>
<td>02/17/17</td>
<td>Coding update. Added new HCPCS codes Q4166-Q4167 and Q4169-Q4175 with effective date 01/01/17. Removed HCPCS codes Q4137, Q4139, Q4151, and Q4163.</td>
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<td>Date</td>
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<tr>
<td>04/01/17</td>
<td>Annual Review, approved March 14, 2017. Policy updated with literature review through November 7, 2016; references 6, 19, 26, and 28-29 added; rationale revised and some references removed. Investigational products list updated: Microderm, TruSkin products added; MatriStem renamed Cytal; FortaDerm renamed PuraPly; Unite Biomatrix deleted (no longer available). AlloMend added to medically necessary statement for breast reconstructive surgery. AlloPatch added to medically necessary statement for diabetic lower-extremity ulcers. Criteria for human amniotic membrane products for diabetic foot ulcers moved to policy 7.01.149. Section on laryngoplasty removed. Coding updated, removed HCPCS codes Q4119-Q4120 and Q4129 as they terminated as of 1/1/17. CPT code table removed.</td>
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<tr>
<td>06/20/17</td>
<td>Coding update, removed HCPCS codes Q4148, Q4155, and Q4156 as they are applicable to policy 7.01.149.</td>
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<tr>
<td>08/09/17</td>
<td>Coding update, removed HCPCS codes Q4131-Q4133, Q4145, and Q4154 from policy as they are addressed on a separate medical policy. Moved HCPCS codes Q4104 and Q4108 from investigational to medically necessary.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Interim Review, approved October 10, 2017. CellerateRX® (CRXa™) and Integra® Omnigraft™ Dermal Regeneration Matrix removed from the investigational policy statement, may be considered medically necessary if criteria are met. The Evidence Review section was reformatted.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Minor update; added DermACELL® which was inadvertently left off of policy.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references 4-5, 7, 9, 15, 20, 29, 35, and 54 added; references 59 and 61 updated. DermACELL and FlexHD Pliable added to medically necessary statement on breast reconstructive surgery. Integra Flowable Wound Matrix added to medically necessary statement on use of Integra Dermal Regeneration Template for diabetic lower-extremity ulcers. Several products added to investigational list.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>Coding updated, added new HCPCS codes Q4193, Q4195, Q4196, Q4197, Q4200, Q4201, Q4202, Q4203, and Q4204 new codes effective 1/1/19).</td>
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<tr>
<td>02/01/19</td>
<td>Minor coding updates, Q4102 moved to the “Medically Necessary (Eligible for Coverage)” section. Minor formatting edits.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Annual Review, approved March 19, 2019. Policy updated with literature review through December 2018; references 28 and 43 added. Policy statements unchanged. Added HCPCS codes Q4179 and Q4182 to the “Investigational (Not Eligible for Coverage)” section. Removed HCPCS codes Q4138, Q4140, Q4153, Q4157, Q4159, Q4160, Q4169-Q4171, Q4173, Q4174, Q4201, and Q4202.</td>
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<tr>
<td>01/01/20</td>
<td>Coding update, removed HCPCS code Q4172 as it was terminated 1/1/19.</td>
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<tr>
<td>03/01/20</td>
<td>Coding update, removed HCPCS code Q4150 and Q4204 as they are applicable to a separate policy. Added HCPCS codes A6460 and A6461. Added new HCPCS codes Q4220, Q4222, and Q4226 (new codes effective 10/1/19).</td>
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### Date | Comments
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06/25/2020 | Coding update. Added HCPCS code Q4238 under investigative section.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Avi sila a gen Enfomasyon Enpōtan ladann.


Oromoo (Cushite):

Avi sila a gen enfomassyon enpōtan ladann. Avi sila a kapab genen enfomassyon enpōtan konsēnān aplikasyon w lan oswa konsēnān khuwëti asirans lan atravë Premera Blue Cross. Kapab genen dat ki enpōtan nān avi sila a. Oo ka gen pou pran kēk aksyon avan séten dat limit pou ka kente khuwitë asirans sante w la oswa pou yo ka ede w akèk depans yo. Se dwa w pou resewaa enfomassyon sa a ak asistans nan lang o pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Îloko (Ilocano):

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Italiano (Italian):

This document contains important information about how Premera Blue Cross covers certain health care services. It is intended for use by members who have a Premera Blue Cross plan.

Romanian (Romanian):

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Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaring nagagamit ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakin sa pamamagitan ng Premera Blue Cross. Maaaring maayos o makapal sa pagsacket ng kanilang impormasyon, at dapat mahuhulaan ng mga hangar ng ikakailangan ng mga paraan ng kagalangan at impormasyon, at dapat nanguna ang akong impormasyon at pag-unawa sa mga impormasyon sa kanilang pagsacket. 

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