UPDATES ON CGS MEDICARE

NOVEMBER 19 2022

OHFAMA ANNUAL BUSINESS MEETING

ANIMESH BHATIA DPM

CARRIER ADVISORY REP TO CGS MEDICARE

- Proposed Local Coverage Determination (LCD): Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DL36690) and Proposed Local Coverage Article (LCA): Billing and Coding: Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DA56696)

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

Skin substitute defined:

Per the Current Procedural Terminology (CPT®) codebook definition, skin substitute grafts include non-autologous human skin (dermal or epidermal, cellular and acellular) grafts (e.g., homograft, allograft), nonhuman skin substitute grafts (i.e., xenograft), and biological products that form a sheet scaffolding for skin growth.

Skin substitute graft application codes are not to be reported for application of non-graft wound dressings (e.g., gel, powder, ointment, foam, liquid) or injected skin substitutes.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

Skin substitute Grafts

In order to qualify as skin substitute graft the product must be:

1. Non-autologous human skin OR
2. Non-human skin substitute grafts (“i.e., xenograft”), OR
3. form a sheet scaffolding for skin growth

The graft is intended to remain on the recipient and grow in place or have the recipient’s cells grow into the implanted graft material. Products that require regular replacement (i.e., weekly) do not meet this definition.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

- This is revision to policy previously titled ‘Wound Application of Cellular and/or Tissue Based Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers.’
- The ‘History/Background and/or General Information’ section of the LCD has been revised to clearly describe the services addressed in the LCD and additional regulatory information has been included for skin substitute products.
- The following sections of the LCD have been reworded and revised to be consistent with the evidence: ‘Covered Indications’ and ‘Limitations’. The following sections were added: ‘Provider Qualifications’, ‘Summary of Evidence’, ‘Societal Input’ and ‘Analysis of Evidence’.
- Documentation Requirements are located in the associated billing and coding article (DA56696).
- The Utilization Guidelines have been incorporated into the ‘Limitations’ section.
- The ‘Bibliography’ section has been updated to include all literature utilized in the development of this LCD.
- Formatting changes have been made throughout the LCD.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers Coverage

If the patient meets all the criteria as outlined in this LCD, application of a skin substitute graft for lower extremity DFU or VLU is considered medically reasonable and necessary for the following:

1. The presence of a chronic, non-infected DFU having failed to respond to documented conservative wound care measures for greater than four weeks with documented compliance.
2. The presence of a chronic, non-infected VLU having failed to respond to documented conservative wound care measures for greater than four weeks with documented compliance.
    - Conservative wound care measures defined in LCD
3. An implemented treatment plan demonstrating all of the following: debridement, offloading for DFUs and some form of compression for VLUs, infection control, management of exudate, smoking cessation actions.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers Coverage

4. The skin substitute graft is applied to an ulcer that has failed to respond (defined in LCD) to documented conservative wound care measures.
5. The medical record documentation addresses **why** the wound has failed to respond to standard wound care treatment of greater than 4 weeks and includes **specific interventions** that have failed.
6. Skin substitute grafts utilized per the approved FDA intended use.
7. The patient is under the care of a qualified physician/NPP for their underlying chronic condition.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers Limitations

These are not considered reasonable and necessary (therefore non-covered):

1. Exceeding maximum of 4 applications of skin substitute graph product within an episode of skin replacement surgery defined as 12 weeks from the first application and consistent with product labeling. Must use fewest repeat applications and amount required to heal the wound.
2. Switching skin substitute graft products in a 12-week episode of skin replacement surgery
3. Use of application of a skin substitute graft product beyond 12-weeks.
4. Repeat applications of skin substitute grafts when a previous application was unsuccessful as defined in policy.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers Limitations

5. Application of skin substitute grafts in patients with inadequate control of underlying conditions or exacerbating factors, or other contraindications.
6. Use of surgical preparation services (for example, debridement), in conjunction with routine, simple and/or repeat skin replacement surgery with a skin substitute graft.
7. Excessive wastage (discarded amount).
    - The skin substitute graft must be used in an efficient manner utilizing the smallest package size available for purchase from the manufacturer that could provide the appropriate amount for the patient.
8. All liquid skin substitute products for wound care.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

Frequency

- There is paucity of evidence to address how frequently skin substitutes should be reapplied.
- One study reports median time-to-heal of 16 weeks using an average of 1.24 applications of NEOX Wound Allograft. Couture reported using an average of 3.43 NEOX applications with an average healing time of 5.53 weeks in a single-center retrospective study.
- A retrospective chart review by Raphael reported median time to heal 13.79 weeks with an average 1.68 applications.
- Armstrong and colleagues presented a retrospective analysis at the 2021 Wounds UK annual Conference reporting skin substitutes were applied every 7-14 days.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

- An extensive variety of wound care products are available for providers to select from when treating chronic wounds. Many of these products may simulate or substitute for some aspect of the skin's structure and function to promote healing and wound closure. The materials used to create these products may be derived from human or animal tissue and may undergo extensive or minimal processing to generate the finished product. The degree of processing and the source of the material used in the product also governs which regulatory pathway may be required before the product may be marketed.
- The LCD reviews the various pathways.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

- Coverage will be provided for products in the associated billing and coding guideline meeting the necessary FDA regulatory requirements as of publication. Each product has specific designated approved usage.
- New products will be considered for coverage if meeting the regulatory requirements and criteria. Satisfactory evidence of FDA regulatory requirements include:
  1. A copy of the FDA's letter to the drug's manufacturer approving the new drug application (NDA),
  2. A listing of the drug or biological in the FDA's "Approved Drug Products" or "FDA Drug and Device Product Approvals",
  3. A copy of the manufacturer's package insert approved by the FDA as part of the labeling of the drug, containing its recommended uses and dosage, as well as possible adverse reactions and recommended precautions in using it, or
  4. Information from the FDA's Website.

Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

- For skin substitutes classified as HCT/Ps, a letter from the FDA indicating that the HCT/P has met regulatory guidance is acceptable evidence of the FDA regulatory compliance for HCT/Ps regulated under section 361 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act.
- It is recommended that the manufacturer of the particular skin substitute graft or CTP product obtain the appropriate information and send to the MAC along with evidence-based literature, if available. Once this information has been received by the MAC, the product will be considered for coverage and placed into the appropriate Code Group in the associated article.

Open Comment Period

JURISDICTION 15 **DRAFT LCD COMMENT SUBMISSION FORM**

METHODS FOR SUBMISSION OF DRAFT LCD COMMENT FORM

Draft LCD Comment submissions may be sent via one of three methods: Email (preferred), fax, or hard copy by mail. Pertinent information is listed below for each of the three methods.

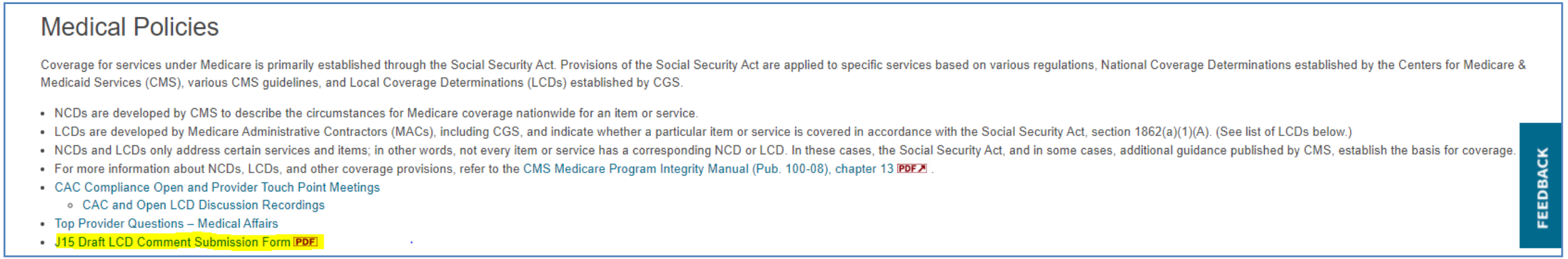
Type	Contact	Details
Email to (preferred method):	CMD.INQUIRY@cgsadmin.com	• Electronic requests should be sent with "Draft LCD Comment Submission – [Name of LCD]" in the subject line. • If the attachment size for clinical citations exceeds 15 MB, the requestor must send the articles and supporting documents via multiple, smaller emails. • Please contact CMD.INQUIRY@cgsadmin.com for alternative methods for submitting large electronic files or if you have difficulty submitting a Draft LCD Comment form.
Fax to:	1.615.664.5971	Please address your fax cover sheet to: Draft LCD Comment Submission – [Name of Draft LCD] - Attn: Chief Medical Director
Mail to:	CGS Administrators, LLC Attn: Chief Medical Director J15 A/B MAC Draft LCD Comment 26 Century Blvd, STE ST610 Nashville, TN 37214-3685	N/A

Open Comment Period: Preferred Method

- Comment period for these policies is 10/6/22-11/20/22.
- To submit comments, go to: https://www.cgsmedicare.com/pdf/j15/j15_draft_lcd_comment_submission_form.pdf
- Complete the PDF form and send attachments to CMD.INQUIRY@cgsadmin.com
- Must provide supporting literature for the comments in full-text PDF
- Supporting literature must be published
  - In press and abstracts cannot be considered

Open Comment Period: Preferred Method

The comment link can be found on the CGS website under Medical Policies



Medical Policies

Coverage for services under Medicare is primarily established through the Social Security Act. Provisions of the Social Security Act are applied to specific services based on various regulations, National Coverage Determinations established by the Centers for Medicare & Medicaid Services (CMS), various CMS guidelines, and Local Coverage Determinations (LCDs) established by CGS.

- NCDs are developed by CMS to describe the circumstances for Medicare coverage nationwide for an item or service.
- LCDs are developed by Medicare Administrative Contractors (MACs), including CGS, and indicate whether a particular item or service is covered in accordance with the Social Security Act, section 1862(a)(1)(A). (See list of LCDs below.)
- NCDs and LCDs only address certain services and items; in other words, not every item or service has a corresponding NCD or LCD. In these cases, the Social Security Act, and in some cases, additional guidance published by CMS, establish the basis for coverage.
- For more information about NCDs, LCDs, and other coverage provisions, refer to the CMS Medicare Program Integrity Manual (Pub. 100-08), chapter 13 PDF .
- CAC Compliance Open and Provider Touch Point Meetings
  - CAC and Open LCD Discussion Recordings
- Top Provider Questions – Medical Affairs
- J15 Draft LCD Comment Submission Form PDF

FEEDBACK

Draft Article - Billing and Coding: Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DA56696)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Posted: 10/20/2022
Placement of Q4229 in Group 2 was an inadvertent error and placement in group 3 is the correct location of Q4229 for this policy. We apologize for any confusion this has caused. Q4229 like similar amniotic membrane based products, do not meet the coverage requirements outlined in DL36690.

Draft Article
Draft Articles are works in progress and not necessarily a reflection of the current billing and coding practices. Revisions to codes are carefully and thoroughly reviewed and are not intended to change the original intent of the LCD.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
CGS Administrators, LLC	MAC - Part A	15101 - MAC A	J - 15	Kentucky
CGS Administrators, LLC	MAC - Part B	15102 - MAC B	J - 15	Kentucky
CGS Administrators, LLC	MAC - Part A	15201 - MAC A	J - 15	Ohio
CGS Administrators, LLC	MAC - Part B	15202 - MAC B	J - 15	Ohio

Draft Article Information

General Information

Source Article ID
A56696

Draft Article ID
DA56696

Draft Article Title
Billing and Coding: Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

Article Type
Billing and Coding

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

CMS National Coverage Policy

Internet-Only Manuals (IOMs):

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual*,
  ~ Chapter 15, Section 50.4.1 Approved Use of Drug
- CMS IOM Publication 100-04, *Medicare Claims Processing Manual*,
  ~ Chapter 17, Section 40 Discarded Drugs and Biologicals

Social Security Act (Title XVIII) Standard References:

- Title XVIII of the Social Security Act, Section 1833(e) states that no payment shall be made to any provider of services or other person under this part unless there has been furnished such information as may be necessary in order to determine the amounts due such provider or other person under this part for the period with respect to which the amounts are being paid or for any prior period.

Code of Federal Regulations (CFR) References:

- CFR, Title 21, Volume 8, Chapter 1, Subchapter L, Part 1271.10 Human cells, tissues, and cellular and tissue-based products

Article Guidance

Article Text

This Billing and Coding Article provides billing and coding guidance for Proposed Local Coverage Determination (LCD) DL36690 Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers. Please refer to the LCD for reasonable and necessary requirements.

Coding Guidance

Notice: It is not appropriate to bill Medicare for services that are not covered (as described by the entire LCD) as if they are covered. When billing for non-covered services, use the appropriate modifier.

Per the Current Procedural Terminology (CPT®) codebook definition, skin substitute grafts include non-autologous human skin (dermal or epidermal, cellular and acellular) grafts (e.g., homograft, allograft), non-human skin

substitute grafts (i.e., xenograft), and biological products that form a sheet scaffolding for skin growth. Skin substitute graft application codes are not to be reported for application of non-graft wound dressings (e.g., gel, powder, ointment, foam, liquid) or injected skin substitutes.

Do not report non-graft wound dressings or injected skin substitute HCPCS codes with skin substitute graft application codes as this would be considered incorrect coding. Such products are bundled into other standard management procedures if medically necessary and are not separately payable.

Removal of a current graft and/or simple cleansing of the wound and other surgical preparation services are included in the skin substitute graft application codes. Active wound care management (CPT code 97602) procedures should never be reported in conjunction with skin substitute graft application codes.

One would not expect an evaluation and management (E/M) service with each skin replacement surgical procedure (application of skin substitute graft) in an episode of care unless the patient's condition required a separately identified service.

If reporting a skin substitute product with HCPCS code Q4100 (Skin substitute, not otherwise specified), the product name, package size purchased, amount applied and amount wasted must be reported in the claim narrative/remarks or the claim will be returned to the provider. [HCPCS code A4100 (Skin substitute, FDA cleared as a device, not otherwise specified) will become effective 04/01/2022 and will be added to this paragraph upon finalization of this draft article.]

Skin substitute HCPCS codes included in Group 2 below reported with any application or administration service NOT included in Group 1 below will be denied.

Application codes billed **must** use the appropriate modifier (e.g., RT, LT) to identify the location where the skin substitute was applied, or the service will be denied.

The appropriate application code must be reported on the same claim as the skin substitute graft code. When the skin substitute graft is denied, the related application code will also be subject to denial.

Skin Substitute Grafts

In order to qualify as skin substitute graft the product must be:

1. Non-autologous human skin OR
2. Non-human skin substitute grafts ("ie, xenograft"), OR
3. form a sheet scaffolding for skin growth

The graft is intended to remain on the recipient and grow in place or have the recipient's cells grow into the implanted graft material. Products that require regular replacement (i.e. weekly) do not meet this definition.

Utilization Parameters

Application frequency must follow the product labeling. A maximum of four skin substitute graft product applications per wound will be allowed for the episode of skin replacement surgery for wound care (defined as 12-weeks from the first application of a skin substitute graft) for those products recommended per the labeling to require a second application.

Application of a skin substitute graft product beyond the 12-week episode of skin replacement wound care will not be allowed.

Documentation Requirements

1. All documentation must be maintained in the patient's medical record and made available to the contractor upon request.
2. Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, dates of service[s]). The documentation must include the legible signature of the physician or non-physician practitioner responsible for and providing the care to the patient.
3. The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must describe the service performed.
4. The medical record must clearly document that the criteria listed in the LCD has been met, as well as the appropriate diagnosis and response to treatment. Description of the wound(s) must be documented at baseline (prior to beginning conservative wound care measures) relative to size, location, stage, duration, and presence of infection, in addition to the type of conservative treatment given and the response. This information must be updated in the medical record throughout the episode of skin replacement surgery for wound care. The wound description must also be documented pre- and post- treatment with the skin substitute graft being used. The reason(s) for any repeat application should be specifically addressed in the medical record.
5. Documentation must include an assessment outlining the plan for skin replacement surgery and the choice of skin substitute product for the 12-week period as well as any anticipated repeat applications within the 12-week period. An operative note must support the procedure (e.g., application of skin substitute graft to legs) for the relevant date of service (first application starts the 12-week episode of care) and include the reason for the procedure and a complete description of the procedure including product used (with identifying package label in the chart), and relevant findings.
6. Any amount of wasted skin substitute must be clearly documented in the procedure note with ALL of the following information (at a minimum): Date, time and location of ulcer(s) treated; Name of skin substitute and

   package size: Approximate amount of product unit used; Approximate amount of product unit discarded; Reason for the wastage (including the reason for using a package size larger than was necessary for the size of the wound, if applicable); Manufacturer's serial/lot/batch or other unit identification number of graft material. When the manufacturer does not supply unit identification, the record must document such.

7. The HCPCS code of the applicable skin substitute and the units billed must be consistent with the medical record regarding wound description and size.
8. Satisfactory evidence of the U.S. Food and Drug Administration (FDA) regulatory requirements for the skin substitute products included in this billing and coding article includes:

- A copy of the FDA's letter to the drug's manufacturer approving the new drug application (NDA),
- A listing of the drug or biological in the FDA's "Approved Drug Products" or "FDA Drug and Device Product Approvals",
- A copy of the manufacturer's package insert approved by the FDA as part of the labeling of the drug, containing its recommended uses and dosage, as well as possible adverse reactions and recommended precautions in using it, or
- Information from the FDA's Website.

9. For skin substitutes classified as human cells, tissues, and cellular and tissue-based products (HCT/Ps), a

letter from the FDA indicating that the HCT/P has met regulatory guidance is acceptable evidence of the FDA regulatory compliance for HCT/Ps regulated under section 361 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act.

Coding Information

CPT/HCPCS Codes

Group 1 Paragraph:

Note: Providers are reminded to refer to the long descriptors of the CPT codes in their CPT book.

Group 1 Codes: (16 Codes)

CODE	DESCRIPTION
15271	APPLICATION OF SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; FIRST 25 SQ CM OR LESS WOUND SURFACE AREA
15272	APPLICATION OF SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; EACH ADDITIONAL 25 SQ CM WOUND SURFACE AREA, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
15273	APPLICATION OF SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; FIRST 100 SQ CM WOUND SURFACE AREA, OR 1% OF BODY AREA OF INFANTS AND CHILDREN
15274	APPLICATION OF SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; EACH ADDITIONAL 100 SQ CM WOUND SURFACE AREA, OR PART THEREOF, OR EACH ADDITIONAL 1% OF BODY AREA OF INFANTS AND CHILDREN, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
15275	APPLICATION OF SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; FIRST 25 SQ CM OR LESS WOUND SURFACE AREA
15276	APPLICATION OF SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; EACH ADDITIONAL 25 SQ CM WOUND SURFACE AREA, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
15277	APPLICATION OF SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; FIRST 100 SQ CM WOUND SURFACE AREA, OR 1% OF BODY AREA OF INFANTS AND CHILDREN

CODE	DESCRIPTION
15278	APPLICATION OF SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; EACH ADDITIONAL 100 SQ CM WOUND SURFACE AREA, OR PART THEREOF, OR EACH ADDITIONAL 1% OF BODY AREA OF INFANTS AND CHILDREN, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
A2001	INNOVAMATRIX AC, PER SQUARE CENTIMETER
C5271	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; FIRST 25 SQ CM OR LESS WOUND SURFACE AREA
C5272	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; EACH ADDITIONAL 25 SQ CM WOUND SURFACE AREA, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
C5273	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; FIRST 100 SQ CM WOUND SURFACE AREA, OR 1% OF BODY AREA OF INFANTS AND CHILDREN
C5274	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO TRUNK, ARMS, LEGS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; EACH ADDITIONAL 100 SQ CM WOUND SURFACE AREA, OR PART THEREOF, OR EACH ADDITIONAL 1% OF BODY AREA OF INFANTS AND CHILDREN, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
C5276	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA UP TO 100 SQ CM; EACH ADDITIONAL 25 SQ CM WOUND SURFACE AREA, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
C5277	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; FIRST 100 SQ CM WOUND SURFACE AREA, OR 1% OF BODY AREA OF INFANTS AND CHILDREN
C5278	APPLICATION OF LOW COST SKIN SUBSTITUTE GRAFT TO FACE, SCALP, EYELIDS, MOUTH, NECK, EARS, ORBITS, GENITALIA, HANDS, FEET, AND/OR MULTIPLE DIGITS, TOTAL WOUND SURFACE AREA GREATER THAN OR EQUAL TO 100 SQ CM; EACH ADDITIONAL 100 SQ CM WOUND SURFACE AREA, OR PART THEREOF, OR EACH ADDITIONAL 1% OF BODY AREA OF INFANTS AND CHILDREN, OR PART THEREOF (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)

Group 2 Paragraph:

A CPT/HCPCS code from the Group 1 Codes above **must be reported with** a HCPCS code from the Group 2 Codes in the table below.

The HCPCS codes included in this list meet the necessary FDA regulatory requirements for indications addressed in this article as of publication. Each product has specific designated approved usage. New products and HCPCS codes will be considered for coverage if meeting the FDA regulatory requirements and criteria.

Group 2 Codes: (81 Codes)

CODE	DESCRIPTION
A2002	MIRRAGEN ADVANCED WOUND MATRIX, PER SQUARE CENTIMETER
A2007	RESTRATA, PER SQUARE CENTIMETER
A2009	SYMPHONY, PER SQUARE CENTIMETER
A2010	APIS, PER SQUARE CENTIMETER
A2011	SUPRA SDRM, PER SQUARE CENTIMETER
A2012	SUPRATHEL, PER SQUARE CENTIMETER
Q4101	APLIGRAF, PER SQUARE CENTIMETER
Q4102	OASIS WOUND MATRIX, PER SQUARE CENTIMETER
Q4104	INTEGRA BILAYER MATRIX WOUND DRESSING (BMWD), PER SQUARE CENTIMETER
Q4105	INTEGRA DERMAL REGENERATION TEMPLATE (DRT) OR INTEGRA OMNIGRAFT DERMAL REGENERATION MATRIX, PER SQUARE CENTIMETER
Q4106	DERMAGRAFT, PER SQUARE CENTIMETER
Q4107	GRAFTJACKET, PER SQUARE CENTIMETER
Q4108	INTEGRA MATRIX, PER SQUARE CENTIMETER
Q4110	PRIMATRIX, PER SQUARE CENTIMETER
Q4111	GAMMAGRAFT, PER SQUARE CENTIMETER
Q4115	ALLOSKIN, PER SQUARE CENTIMETER
Q4117	HYALOMATRIX, PER SQUARE CENTIMETER
Q4121	THERASKIN, PER SQUARE CENTIMETER
Q4122	DERMACELL, DERMACELL AWM OR DERMACELL AWM POROUS, PER SQUARE CENTIMETER
Q4123	ALLOSKIN RT, PER SQUARE CENTIMETER
Q4124	OASIS ULTRA TRI-LAYER WOUND MATRIX, PER SQUARE CENTIMETER
Q4127	TALYMED, PER SQUARE CENTIMETER

CODE	DESCRIPTION
Q4132	GRAFIX CORE AND GRAFIXPL CORE, PER SQUARE CENTIMETER
Q4133	GRAFIX PRIME, GRAFIXPL PRIME, STRAVIX AND STRAVIXPL, PER SQUARE CENTIMETER
Q4136	EZ-DERM, PER SQUARE CENTIMETER
Q4137	AMNIOEXCEL, AMNIOEXCEL PLUS OR BIODEXCEL, PER SQUARE CENTIMETER
Q4141	ALLOSKIN AC, PER SQUARE CENTIMETER
Q4147	ARCHITECT, ARCHITECT PX, OR ARCHITECT FX, EXTRACELLULAR MATRIX, PER SQUARE CENTIMETER
Q4148	NEOX CORD 1K, NEOX CORD RT, OR CLARIX CORD 1K, PER SQUARE CENTIMETER
Q4151	AMNIOBAND OR GUARDIAN, PER SQUARE CENTIMETER
Q4152	DERMAPURE, PER SQUARE CENTIMETER
Q4153	DERMAVEST AND PLURIVEST, PER SQUARE CENTIMETER
Q4154	BIOVANCE, PER SQUARE CENTIMETER
Q4156	NEOX 100 OR CLARIX 100, PER SQUARE CENTIMETER
Q4157	REVITALON, PER SQUARE CENTIMETER
Q4158	KERECIS OMEGA3, PER SQUARE CENTIMETER
Q4159	AFFINITY, PER SQUARE CENTIMETER
Q4160	NUSHIELD, PER SQUARE CENTIMETER
Q4161	BIO-CONNEKT WOUND MATRIX, PER SQUARE CENTIMETER
Q4163	WOUNDEX, BIOSKIN, PER SQUARE CENTIMETER
Q4164	HELICOLL, PER SQUARE CENTIMETER
Q4165	KERAMATRIX OR KERASORB, PER SQUARE CENTIMETER
Q4166	CYTAL, PER SQUARE CENTIMETER
Q4169	ARTACENT WOUND, PER SQUARE CENTIMETER
Q4170	CYGNUS, PER SQUARE CENTIMETER
Q4173	PALINGEN OR PALINGEN XPLUS, PER SQUARE CENTIMETER
Q4175	MIRODERM, PER SQUARE CENTIMETER
Q4178	FLOWERAMNIOPATCH, PER SQUARE CENTIMETER
Q4179	FLOWERDERM, PER SQUARE CENTIMETER
Q4180	REVITA, PER SQUARE CENTIMETER
Q4182	TRANSCYTE, PER SQUARE CENTIMETER
Q4183	SURGIGRAFT, PER SQUARE CENTIMETER

CODE	DESCRIPTION
Q4186	EPIFIX, PER SQUARE CENTIMETER
Q4187	EPICORD, PER SQUARE CENTIMETER
Q4188	AMNIOARMOR, PER SQUARE CENTIMETER
Q4190	ARTACENT AC, PER SQUARE CENTIMETER
Q4191	RESTORIGIN, PER SQUARE CENTIMETER
Q4193	COLL-E-DERM, PER SQUARE CENTIMETER
Q4194	NOVACHOR, PER SQUARE CENTIMETER
Q4199	CYGNUS MATRIX, PER SQUARE CENTIMETER
Q4200	SKIN TE, PER SQUARE CENTIMETER
Q4203	DERMA-GIDE, PER SQUARE CENTIMETER
Q4204	XWRAP, PER SQUARE CENTIMETER
Q4205	MEMBRANE GRAFT OR MEMBRANE WRAP, PER SQUARE CENTIMETER
Q4209	SURGRAFT, PER SQUARE CENTIMETER
Q4214	CELLESTA CORD, PER SQUARE CENTIMETER
Q4216	ARTACENT CORD, PER SQUARE CENTIMETER
Q4222	PROGENAMATRIX, PER SQUARE CENTIMETER
Q4229	COGENEX AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER
Q4232	CORPLEX, PER SQUARE CENTIMETER
Q4234	XCELLERATE, PER SQUARE CENTIMETER
Q4235	AMNIOREPAIR OR ALTIPLY, PER SQUARE CENTIMETER
Q4237	CRYO-CORD, PER SQUARE CENTIMETER
Q4238	DERM-MAXX, PER SQUARE CENTIMETER
Q4239	AMNIO-MAXX OR AMNIO-MAXX LITE, PER SQUARE CENTIMETER
Q4247	AMNIOTEXT PATCH, PER SQUARE CENTIMETER
Q4248	DERMACYTE AMNIOTIC MEMBRANE ALLOGRAFT, PER SQUARE CENTIMETER
Q4249	AMNIPLY, FOR TOPICAL USE ONLY, PER SQUARE CENTIMETER
Q4251	VIM, PER SQUARE CENTIMETER
Q4252	VENDAJE, PER SQUARE CENTIMETER
Q4253	ZENITH AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER

Group 3 Paragraph:

The following HCPCS codes are Non-Covered:

Group 3 Codes: (79 Codes)

Group 3 Codes: (65 Codes)

CODE	DESCRIPTION
A2001	INNOVAMATRIX AC, PER SQUARE CENTIMETER
A2004	XCELLISTEM, 1 MG
A2005	MICROLYTE MATRIX, PER SQUARE CENTIMETER
A2006	NOVOSORB SYNPATH DERMAL MATRIX, PER SQUARE CENTIMETER
A2008	THERAGENESIS, PER SQUARE CENTIMETER
A2013	INNOVAMATRIX FS, PER SQUARE CENTIMETER
Q4103	OASIS BURN MATRIX, PER SQUARE CENTIMETER
Q4112	CYMETRA, INJECTABLE, 1 CC
Q4113	GRAFTJACKET XPRESS, INJECTABLE, 1 CC
Q4114	INTEGRA FLOWABLE WOUND MATRIX, INJECTABLE, 1 CC
Q4116	ALLODERM, PER SQUARE CENTIMETER
Q4118	MATRISTEM MICROMATRIX, 1 MG
Q4125	ARTHROFLEX, PER SQUARE CENTIMETER
Q4126	MEMODERM, DERMASPAN, TRANZGRAFT OR INTEGUPLY, PER SQUARE CENTIMETER
Q4128	FLEX HD, OR ALLOPATCH HD, PER SQUARE CENTIMETER
Q4130	STRATTICE TM, PER SQUARE CENTIMETER
Q4134	HMATRIX, PER SQUARE CENTIMETER
Q4135	MEDISKIN, PER SQUARE CENTIMETER
Q4138	BIODFENCE DRYFLEX, PER SQUARE CENTIMETER
Q4139	AMNIOMATRIX OR BIODMATRIX, INJECTABLE, 1 CC
Q4140	BIODFENCE, PER SQUARE CENTIMETER
Q4142	XCM BIOLOGIC TISSUE MATRIX, PER SQUARE CENTIMETER
Q4143	REPRIZA, PER SQUARE CENTIMETER
Q4145	EPIFIX, INJECTABLE, 1 MG
Q4146	TENSIX, PER SQUARE CENTIMETER
Q4149	EXCELLAGEN, 0.1 CC
Q4150	ALLOWRAP DS OR DRY, PER SQUARE CENTIMETER
Q4155	NEOXFLO OR CLARIXFLO, 1 MG
Q4162	WOUNDEX FLOW, BIOSKIN FLOW, 0.5 CC

CODE	DESCRIPTION
Q4167	TRUSKIN, PER SQUARE CENTIMETER
Q4168	AMNIOBAND, 1 MG
Q4171	INTERFYL, 1 MG
Q4174	PALINGEN OR PROMATRX, 0.36 MG PER 0.25 CC
Q4176	NEOPATCH OR THERION, PER SQUARE CENTIMETER
Q4177	FLOWERAMNIOFLO, 0.1 CC
Q4181	AMNIO WOUND, PER SQUARE CENTIMETER
Q4184	CELLESTA OR CELLESTA DUO, PER SQUARE CENTIMETER
Q4185	CELLESTA FLOWABLE AMNION (25 MG PER CC); PER 0.5 CC
Q4189	ARTACENT AC, 1 MG
Q4192	RESTORIGIN, 1 CC
Q4195	PURAPLY, PER SQUARE CENTIMETER
Q4196	PURAPLY AM, PER SQUARE CENTIMETER
Q4197	PURAPLY XT, PER SQUARE CENTIMETER
Q4198	GENESIS AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER
Q4201	MATRION, PER SQUARE CENTIMETER
Q4202	KEROXX (2.5G/CC), 1CC
Q4206	FLUID FLOW OR FLUID GF, 1 CC
Q4208	NOVAFIX, PER SQUARE CENITMETER
Q4210	AXOLOTL GRAFT OR AXOLOTL DUALGRAFT, PER SQUARE CENTIMETER
Q4211	AMNION BIO OR AXOBIOMEMBRANE, PER SQUARE CENTIMETER
Q4212	ALLOGEN, PER CC
Q4213	ASCENT, 0.5 MG
Q4215	AXOLOTL AMBIENT OR AXOLOTL CRYO, 0.1 MG
Q4217	WOUNDFIX, BIOWOUND, WOUNDFIX PLUS, BIOWOUND PLUS, WOUNDFIX XPLUS OR BIOWOUND XPLUS, PER SQUARE CENTIMETER
Q4218	SURGICORD, PER SQUARE CENTIMETER
Q4219	SURGIGRAFT-DUAL, PER SQUARE CENTIMETER
Q4220	BELLACELL HD OR SUREDERM, PER SQUARE CENTIMETER
Q4221	AMNIOWRAP2, PER SQUARE CENTIMETER
Q4224	HUMAN HEALTH FACTOR 10 AMNIOTIC PATCH (HHF10-P), PER SQUARE CENTIMETER

CODE	DESCRIPTION
Q4225	AMNIOBIND, PER SQUARE CENTIMETER
Q4229	COGENEX AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER
Q4230	COGENEX FLOWABLE AMNION, PER 0.5 CC
Q4256	MLG-COMPLETE, PER SQUARE CENTIMETER
Q4257	RELESE, PER SQUARE CENTIMETER
Q4258	ENVERSE, PER SQUARE CENTIMETER

CPT/HCPCS Modifiers

N/A

ICD-10-CM Codes that Support Medical Necessity

Group 1 Paragraph:

It is the provider's responsibility to select codes carried out to the highest level of specificity and selected from the ICD-10-CM code book appropriate to the year in which the service is rendered for the claim(s) submitted.

The following ICD-10-CM codes support medical necessity and provide coverage for the HCPCS codes in Group 2 above.

Group 1 Codes: (21 Codes)

CODE	DESCRIPTION
E08.621*	Diabetes mellitus due to underlying condition with foot ulcer
E09.621*	Drug or chemical induced diabetes mellitus with foot ulcer
E10.621*	Type 1 diabetes mellitus with foot ulcer
E11.621*	Type 2 diabetes mellitus with foot ulcer
E13.621*	Other specified diabetes mellitus with foot ulcer
I87.311*	Chronic venous hypertension (idiopathic) with ulcer of right lower extremity
I87.312*	Chronic venous hypertension (idiopathic) with ulcer of left lower extremity
I87.313*	Chronic venous hypertension (idiopathic) with ulcer of bilateral lower extremity
I87.331*	Chronic venous hypertension (idiopathic) with ulcer and inflammation of right lower extremity
I87.332*	Chronic venous hypertension (idiopathic) with ulcer and inflammation of left lower

CODE	DESCRIPTION
	extremity
I87.333*	Chronic venous hypertension (idiopathic) with ulcer and inflammation of bilateral lower extremity
L97.112	Non-pressure chronic ulcer of right thigh with fat layer exposed
L97.122	Non-pressure chronic ulcer of left thigh with fat layer exposed
L97.212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97.222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97.312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed

Group 1 Medical Necessity ICD-10-CM Codes Asterisk Explanation:

*When reporting E08.621, E09.621, E10.621, E11.621, E13.621, I87.311, I87.312, I87.313, I87.331, I87.332 or I87.333, one of the L97 ICD-10 codes in the above table **must** also be reported (the L97 codes are standalone codes if they are listed in the table above).

ICD-10-CM Codes that DO NOT Support Medical Necessity

N/A

ICD-10-PCS Codes

N/A

Additional ICD-10 Information

N/A

Bill Type Codes

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the article does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the article should be assumed to apply equally to all claims.

CODE	DESCRIPTION
999x	Not Applicable

Revenue Codes

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the article, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the article should be assumed to apply equally to all Revenue Codes.

N/A

Other Coding Information

N/A

Associated Documents

Related Local Coverage Documents

LCDs

DL36690 - Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DL)

Related National Coverage Documents

N/A

Statutory Requirements URLs

N/A

Rules and Regulations URLs

N/A

CMS Manual Explanations URLs

N/A

Other URLs

N/A

Public Versions

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Keywords

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Proposed LCD - Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DL) (DL36690)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Proposed LCD
Proposed LCDs are works in progress that are available on the Medicare Coverage Database site for public review.
Proposed LCDs are not necessarily a reflection of the current policies or practices of the contractor.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
CGS Administrators, LLC	MAC - Part A	15101 - MAC A	J - 15	Kentucky
CGS Administrators, LLC	MAC - Part B	15102 - MAC B	J - 15	Kentucky
CGS Administrators, LLC	MAC - Part A	15201 - MAC A	J - 15	Ohio
CGS Administrators, LLC	MAC - Part B	15202 - MAC B	J - 15	Ohio

Proposed LCD Information

Document Information

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Proposed LCD Title
Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DL)

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

Issue

Issue Description

This LCD outlines limited coverage for this service with specific details under **Coverage Indications, Limitations and/or Medical Necessity**.

CMS National Coverage Policy

This LCD supplements but does not replace, modify or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for skin substitutes for the treatment of diabetic foot ulcers and venous leg ulcers. Federal statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy. They are not repeated in this LCD. Neither Medicare payment policy rules nor this LCD replace, modify or supersede applicable state statutes regarding medical practice or other health practice professions acts, definitions and/or scopes of practice. All providers who report services for Medicare payment must fully understand and follow all existing laws, regulations, and rules for Medicare payment for skin substitutes for the treatment of diabetic foot ulcers and venous leg ulcers and must properly submit only valid claims for them. Please review and understand them and apply the medical necessity provisions in the policy within the context of the manual rules. Relevant CMS manual instructions and policies may be found in the following Internet-Only Manuals (IOMs) published on the CMS Web site:

IOM Citations:

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual*,
  ~ Chapter 15, Section 50.4.1 Approved Use of Drug
- CMS IOM Publication 100-04, *Medicare Claims Processing Manual*,
  ~ Chapter 17, Section 40 Discarded Drugs and Biologicals
- CMS IOM Publication 100-08, *Medicare Program Integrity Manual*,
  ~ Chapter 13, Section 13.5.4 Reasonable and Necessary Provision in an LCD
- CMS IOM Publication 100-03, *National Coverage Determinations Manual, Chapter* 1, Sections 270.3, 270.4 & 270.5

Social Security Act (Title XVIII) Standard References:

- Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment may be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury.
- Title XVIII of the Social Security Act, Section 1862(a)(7). This section excludes routine physical examinations.

Code of Federal Regulations (CFR) References:

- CFR, Title 21, Volume 8, Chapter 1, Subchapter L, Part 1271.10 Human cells, tissues, and cellular and tissue-based products

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Compliance with the provisions in this LCD may be monitored and addressed through post payment data analysis and subsequent medical review audits.

History/Background and/or General Information

This LCD addresses the medically reasonable and necessary threshold for coverage of skin replacement surgery for application of skin substitute grafts for diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).

Application of skin substitute grafts for wound care indications other than for DFU or VLU are not addressed by this LCD. Use of skin substitute grafts must meet the medically reasonable and necessary threshold for coverage and these devices must be used in accordance with their approved United States (U.S.) Food and Drug Administration (FDA) intended use.

Chronic wounds of the lower extremities, including venous stasis ulcers, DFUs and pressure sores, are a major public health problem. While lower extremity ulcers have numerous causes such as burns, trauma, mixed venous-arterial disease, immobility, and vasculitis, nutritional or other neuropathy, over 90% of the lesions in the U.S. are related to venous stasis disease and diabetic neuropathy.[1-3]

Generally, depending on the purpose of the product and how it functions, skin substitutes are regulated by the FDA premarket approval (PMA) process, FDA 510(k) premarket notification process, or the FDA regulations for human cells, tissues, and cellular and tissue-based products (HCT/Ps). Although skin substitutes have attributes of both biologicals and devices, the current position is that these products are best characterized as surgical supplies or devices because of their required surgical application and their similarity to other surgical supplies. It has been noted that there are instances in which certain products might have a wound healing indication but may not necessarily meet the definition of skin substitutes. Therefore, FDA classification and indication alone does not determine if a product meets the definition of skin substitute and/or meets the medically reasonable and necessary threshold for coverage.

Amniotic/chorionic-based products are HCT/Ps as defined in 21 CFR 1271.3(d) and must meet criteria in 21 CFR 1271 and 361 of the Public Health Service Act (PHS Act). The HCT/Ps not regulated under 361 are regulated as drugs as defined under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. In order to lawfully market a drug that is also a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after a showing of safety and efficacy for the product's intended use.[4-6]

Standard treatment of lower extremity ulcers (e.g., DFUs and/or VLUs) may include mechanical offloading, infection control, mechanical compression, limb elevation, debridement of necrotic tissue, management of systemic disease and medications, nutrition assessment, tissue perfusion and oxygenation, and counseling on the risk of continued tobacco use. In addition, maintenance of a moist wound environment through appropriate dressings facilitates development of healthy granulation tissue and epithelialization and thus may potentiate complete healing at a wound site. Dressings are an integral part of wound management by not only maintaining a moist environment but by stopping contamination and absorbing exudate.[7-12]

Despite advancements in various synthetic occlusive dressings some ulcers fail to heal. The development of skin substitutes has been employed as an adjunct to established wound care methods to increase the chances of healing.[1,13]

Chronic wounds and frequently recurring wounds related to DFUs and VLUs are a challenge to treat effectively. Chronic wounds may be unresponsive to initial therapy or persist despite additional care. A wound that has not healed within one to three months may be considered chronic and the application of a skin substitute graft, an advanced treatment modality, may be considered medically reasonable and necessary for certain patients.[1-3]

Patients receiving skin replacement surgery with a skin substitute graft should be under the care of a physician/non-physician practitioner (NPP) for the treatment of their systemic disease process (e.g., diabetes mellitus, chronic venous insufficiency, and/or peripheral vascular disease). It is imperative that their systemic disease be monitored/treated in order to ensure adequate healing of the wound site.[3,9]

It is the expectation that a specific skin substitute graft product will be used for the episode of skin replacement surgery for wound care (defined as 12 weeks from the first application of a skin substitute graft) assuming its use is not in conflict with the FDA assessments (e.g., indications, contraindications, how supplied and directions for use, etc.) and/or the American Association of Tissue Banks (AATB) approved use and assuming there is one related wound. Repeat application of a skin substitute graft within the 12-week episode of skin replacement surgery for wound care may be appropriate per the package insert based on wound re-assessment and must be supported in the medical record documentation for that encounter. Additional applications of a skin substitute product beyond the 12-week episode of skin replacement wound care are not expected if the wound has responded to the skin replacement surgery with epithelialization and other progression. This LCD does not endorse particular products for separate payment. The medical record documentation must support the medical necessity for skin replacement surgery and that the product is being used within its approved FDA indications.

Covered Indications

If the patient meets all of the criteria as outlined in this LCD, application of a skin substitute graft for lower extremity DFU or VLU is considered medically reasonable and necessary for the following:

1. The presence of a chronic, non-infected DFU having failed to respond to documented conservative wound care measures (outlined below) for greater than four weeks with documented compliance.[7]
2. The presence of a chronic, non-infected VLU having failed to respond to documented conservative wound care measures (outlined below) for greater than four weeks with documented compliance.[10]

- For purposes of this LCD, conservative wound care measures include, but are not limited to[2,7-12]:

  Comprehensive patient assessment (history, exam, Ankle-Brachial Index [ABI]) and diagnostic tests as indicated) and implemented treatment plan.

  For patients with a DFU - assessment of Type 1 vs. Type 2 diabetes and management history with attention to certain comorbidities (e.g., vascular disease, neuropathy, osteomyelitis), review of current blood glucose levels/hemoglobin A1c (HbA1c), diet and nutritional status, activity level, physical exam that includes assessment of skin and wound, ABI, and check of off-loading device or assessment of appropriate footwear.[3]

  For patients with a VLU - assessment of clinical history (prior ulcers, thrombosis risks), physical exam (edema, skin changes), ABI, diagnostic testing to verify superficial or deep venous reflux, perforator incompetence, and chronic (or acute) venous thrombosis. In this regard, venous duplex ultrasound is recommended to confirm the Clinical class, Etiology, Anatomy, and Pathophysiology (CEAP) classification and categorize the patient's chronic venous disorder to guide the analysis of management alternatives. The Venous Clinical Severity Score (VCSS) is used to assess changes in response to therapy.

3. An implemented treatment plan demonstrating all of the following:

- Debridement as appropriate.
- Some form of offloading for DFUs and some form of compression for VLUs.

- Infection control.
- Management of exudate - maintenance of a moist environment (moist saline gauze, other classic dressings, bioactive dressing, etc.).
- Patient is a nonsmoker or has refrained from smoking for at least 6 weeks prior to planned skin replacement surgery or has received counseling on the effects of smoking on surgical outcomes and treatment for smoking cessation.

4. The skin substitute graft is applied to an ulcer that has failed to respond to documented conservative wound care measures. "Failed response" is defined as an ulcer that has increased in size or depth, or no change in baseline size or depth, or no sign of improvement or indication that improvement is likely (such as granulation, epithelialization, or progress towards closing). Documentation of response requires measurements of the initial ulcer, measurements at the completion of at least four weeks of conservative wound care measures, and measurements immediately prior to placement of the skin substitute graft for a DFU. For VLUs, conservative wound care measures must continue for no less than four weeks and include on-going compression therapy.[7,10,13]

5. The medical record documentation specifically addresses the circumstances regarding why the wound has failed to respond to standard wound care treatment of greater than 4 weeks and references the specific interventions that have failed based on the prior wound evaluation. The record must include an updated medication history, review of pertinent medical problems that may have arisen since the previous wound evaluation, and explanation of the planned skin replacement surgery with choice of skin substitute graft product. The procedure risks and complications must also be reviewed and documented.[7,10,13-14]
6. Skin substitute grafts utilized per the approved FDA intended use.
7. The patient is under the care of a qualified physician/NPP for their underlying chronic condition.[3,9]

Limitations

The following are considered not medically reasonable and necessary[1-3,9-10]:

1. Not to exceed four applications of a specific skin substitute graft product within the episode of skin replacement surgery for wound care defined as 12 weeks from the first application and consistent with product labeling.
    - The expectation is treatment will consist of the fewest repeat applications and amount of product to heal the wound. It is expected that products are used per the labeling. It is not expected that every ulcer, in every patient will require the maximum number of applications listed on the product label. This utilization pattern may be subject to focused medical review.

2. Switching skin substitute graft products in a 12-week episode of skin replacement surgery for wound care. Exceptions should be rare and may be considered on appeal when the medical necessity of the change is clearly documented in the medical record.
3. Application of a skin substitute graft product beyond 12-weeks.
4. Repeat applications of skin substitute grafts when a previous application was unsuccessful. Unsuccessful treatment is defined as increase in size or depth of an ulcer, or no change in baseline size or depth and no sign of improvement or indication that improvement is likely (such as granulation, epithelialization, or progress towards closing).
5. Application of skin substitute grafts in patients with inadequate control of underlying conditions or exacerbating factors, or other contraindications (e.g., uncontrolled diabetes, active infection, active Charcot arthropathy of the ulcer extremity, active vasculitis).
6. Use of surgical preparation services (for example, debridement), in conjunction with routine, simple and/or repeat skin replacement surgery with a skin substitute graft.

7. Excessive wastage (discarded amount).

    - The skin substitute graft must be used in an efficient manner utilizing the smallest package size available for purchase from the manufacturer that could provide the appropriate amount for the patient.

8. All liquid skin substitute products for wound care.[15]
9. Refer to the CFR, Title 21, Volume 8, Chapter 1, Subchapter L, Part 1271.10 for Human-derived products regulated as human cells, tissues, or cellular or tissue-based product (HCT/P) for additional limitations.

Provider Qualifications

Services provided within the LCD coverage indications will be considered medically reasonable and necessary when all aspects of care are within the scope of practice of the provider's professional licensure; and when all procedures are performed by appropriately trained providers in the appropriate setting.

Notice: Services performed for any given diagnosis must meet all the indications and limitations stated in this LCD, the general requirements for medical necessity as stated in CMS payment policy manuals, any and all existing CMS national coverage determinations, and all Medicare payment rules.

Summary of Evidence

A literature search was conducted using the following key words: Non-healing; wound; chronic; diabetic foot; foot ulcer; venous leg ulcer; guidelines; wound healing; skin substitutes; dermal skin substitute; human skin allograft; randomized trial; standard of care; venous leg ulcer; skin grafts; wound dressing; human derived products; animal derived products; FDA regulations. The literature search was filtered to locate articles within 5-10 years, full-text articles, clinical trials, and systematic reviews. In general, improved health outcomes of interest include patient quality of life and function.

Introduction

Chronic wounds are described as wounds which have been unable to re-epithelialize after 1 to 3 months of treatment. More than 90% of chronic wounds in the United States (U.S.) are a result of diabetic ulcers, venous stasis ulcers, and decubitus ulcers. Chronic wounds may be described as vascular ulcers (e.g., venous and arterial), diabetic ulcers, and pressure ulcers (local tissue hypoxia). These types of chronic wounds impact patient quality of life due to impaired mobility, pain, and substantial morbidity.[1-3]

Evidence-Based Guidelines for Standard of Care

Evidence-based guidelines indicate that standard of care (SOC) treatment of lower extremity ulcers (e.g., diabetic foot ulcers [DFUs] and/or venous leg ulcers [VLUs]) may include mechanical offloading, infection control, mechanical compression, limb elevation, debridement of necrotic tissue, management of systemic disease and medications, nutrition assessment, tissue perfusion and oxygenation, education regarding care of the foot, callus, and nail and fitting of shoes, and counseling on the risk of continued tobacco use. In addition, maintenance of a moist wound environment through appropriate dressings facilitates development of healthy granulation tissue and epithelialization and thus may potentiate complete healing at a wound site. Dressings are an integral part of wound management by not only maintaining a moist environment but by stopping contamination and absorbing exudate.7-12

A comprehensive assessment of patients and their wounds will also facilitate appropriate care by identifying and correcting systemic causes of impaired healing. The presence of a severe illness or systemic disease and drug treatments such as immunosuppressive drugs and systemic steroids may inhibit wound healing by changes in immune functioning, metabolism, inflammation, nutrition, and tissue perfusion. Therefore, this information in conjunction with a detailed history of the wound itself is essential.[3,9]

A vascular evaluation is also vital for all chronic wounds. Palpation of pulses may be problematic in cases of medial arterial calcification. An ankle-brachial index (ABI) should be taken for patients with a questionable pulse deficit although the ABI levels may be falsely elevated with medial arterial calcification. The patient is considered to have impaired arterial perfusion when the ABI is below 0.9. To supplement ankle-brachial studies, toe blood pressure readings, pulse volume recordings, transcutaneous oxygen measurements (TCOMs), and skin perfusion pressure measurements have been suggested as acceptable benchmarks for the prediction of wound healing.[3]

Venous ulcers require a series of diagnostic testing to verify superficial or deep venous reflux, perforator incompetence, and chronic (or acute) venous thrombosis. In this regard, venous duplex ultrasound is recommended and if the venous duplex ultrasound does not provide definitive diagnostic information, a venous plethysmography is recommended. Patients with mixed arterial and venous disease require a combination of arterial and venous noninvasive testing. The use of a Class 3 (most supportive) high-compression method is strongly recommended in the treatment of venous ulcers. High strength compression may be applied using techniques such as multilayered elastic compression, inelastic compression, Unna boot, compression stockings, and others. The extent of compression should be modified for patients with mixed venous/arterial disease.[3,10]

The clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum[10] recommend that patients with VLUs have the ulcer classified using the Clinical class, Etiology, Anatomy, and Pathophysiology (CEAP) classification (confirmed by duplex scan). The Venous Clinical Severity Score (VCSS) is recommended to assess changes in response to therapy. Specific classification of venous disease is essential for standardization of venous disease severity and evaluation of treatment efficiency.

The Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine has recommended a SOC treatment schedule for DFUs that includes weekly to monthly wound evaluations of wound size and healing progress, infection control, debridement of all devitalized tissue and surrounding callus material, dressings that maintain a moist wound environment, control of exudate, and avoiding maceration of adjacent intact skin. Adequate glycemic control of hemoglobin A1c (HbA1c < 7%) is also recommended to reduce the incidence of DFUs and infections and periodic assessments of appropriate footwear and/or off-loading device.[7,13]

Regulation of Skin Substitute

Despite standard of care and advancements in various moisture retaining synthetic occlusive dressings, many chronic wounds fail to heal. The development of skin substitutes has been employed to be used as an adjunct to established chronic wound care methods to increase the chances of healing.[1,13] Skin substitute can be organized into the following groups: 1) Human-derived products regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps); 2) Human and human/animal-derived products regulated through premarket approval (PMA) by the U.S. Food and Drug Administration (FDA); and 3) Animal-derived products regulated under the 510(k) process; and 4) Synthetic products regulated under the 510(k) process.[4-6]

Human tissue can be obtained from human donors, processed, and used in exactly the same role in the recipient, such as a dermal replacement to be placed in a wound as a skin substitute (regulated as HCT/Ps). These products may be regulated under the Biologics License Application (BLA) (under the Public Health Service Act [PHS Act]) or

PMA (under the Federal Food, Drug, and Cosmetic Act [FD&C Act]), depending on their composition and primary mode of action. Amniotic/chorionic-based products are HCT/Ps as defined in 21 CFR 1271.3(d) and must meet criteria in 21 CFR 1271 and 361 of the PHS Act. The HCT/Ps not regulated under 361 are regulated as drugs as defined under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. In order to legally market a drug that is also a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after a showing of safety and efficacy for the product's intended use.[6]

Evidence-Based Guidelines for Skin Substitute

Skin substitute are a heterogeneous group of biological and/or synthetic elements that allow the temporary or permanent occlusion of wounds. Dermal substitutes may vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, but all have a mutual goal to attain resemblance with an individual's skin to the greatest extent possible.[13] Skin substitute are recommended as an adjunct to the established SOC treatment protocols for wound care to increase the chances of healing. In this regard, evidence-based guidelines recommend wound bed preparation prior to the application of any biologically active dressing which includes complete removal of slough, debris and/or necrotic tissue.[14] Skin substitutes are recommended in conjunction with SOC treatment for DFUs that have failed to demonstrate more than 50% wound area reduction after a minimum of four weeks of standard wound care measures.[7] For VLUs, if substantial wound improvement is not demonstrated after a minimum of four-six weeks of standard wound care measures, skin substitutes are recommended in addition to SOC treatment and compression therapy.[10]

Technology Assessment

The Agency for Healthcare Research and Quality (AHRQ) provided an evidenced-based technical brief for skin substitutes for treating chronic wounds.[2] This technical brief was developed to describe assorted products that may be considered skin substitutes in the U.S., which are utilized for the treatment of chronic wounds. In addition, systems utilized to classify skin substitutes were assessed, randomized controlled trials (RCTs) involving skin substitutes were reviewed, and recommendations were made regarding best practices for future studies. A systematic search of the published literature since 2012 was conducted for systematic reviews/meta-analyses, RCTs, and prospective nonrandomized comparative studies studying commercially available skin substitutes for individuals with DFUs, VLUs, pressure ulcers, and arterial leg ulcers.

Seventy-six skin substitutes were identified and categorized using the Davison-Kotler classification system, a method structured according to cellularity, layering, replaced region, material used, and permanence. Of these, 68 (89%) were categorized as acellular dermal substitutes, largely replacements from human placental membranes and animal tissue sources. Acellular dermal substitutes prepared from natural biological materials are the most common commercially available skin substitute product for treating or managing chronic wounds. Cellularity is a significant difference among skin substitutes as the presence of cells raises the rejection risk and production complexity. This category includes decellularized donated human dermis (14 products recognized), human placental membranes (28 products recognized), and animal tissue (21 products recognized). Less products are prepared from synthetic materials (two products recognized) or a blend of natural and synthetic materials (two products recognized). A limited number of skin substitute products are acellular replacements for both the epidermis and dermis (one product recognized). Only eight products were recognized that contain cells and would be classified in the cellular grouping.

Three systematic reviews and 22 RCTs studied the utilization of 16 distinct skin substitutes, comprising acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in DFUs, pressure ulcers, and VLUs. Twenty-one ongoing studies (all RCTs) assessed an additional nine skin substitutes with comparable classifications. It was noted that studies seldom reported clinical outcomes, such as amputation, wound recurrence at least two weeks after treatment ended, or patient-related outcomes, such as return to function, pain,

exudate, and odor. This review found that more studies are needed to assess the effectiveness of most skin substitutes and studies need to be better designed and include clinically relevant outcomes.

Of the 22 included RCTs, 16 studies contrasted a skin substitute with SOC. The SOC for each wound type involved sharp debridement, glucose control, compression bandages for VLUs, pressure redistribution support surfaces for pressure ulcers, infection control, offloading, and daily dressing changes with a moisture-retentive dressing, such as an alginate or hydrocolloid type dressing. Though 85% of the studies examining acellular dermal substitutes portrayed the experimental intervention as favorable over SOC for wound healing and quicker time to heal, inadequate data is available to determine whether wound recurrence or other sequela are less frequent with acellular dermal substitutes. Only three studies contrasted cellular dermal substitutes with SOC. Clinical evidence for cellular dermal substitutes may be limited by the lack of robust, well-controlled clinical trials.

Of the six head-to-head comparative studies, results from five studies did not show substantial differences between skin substitutes in outcomes measured at the latest follow-up (>12 weeks). One study concluding at 12 weeks described a substantial difference in wound healing favoring an acellular dermal skin substitute over a cellular epidermal and dermal skin substitute. Another study compared two acellular dermal substitutes and seemed to have deliberately underpowered one arm of the study as statistical significance was not sought or expected for this study arm. Of the two studies reporting on recurrence, one study described comparable recurrence, while the other study reported no recurrence at 26 weeks. The current evidence base, as portrayed by the authors for the literature reviewed, may be inadequate to determine whether one skin substitute product is superior to another.[2]

Industry sponsored most of the studies reviewed; 20 of the 22 RCTs in this review, which presents concerns regarding bias for these studies. This AHRQ technical brief also noted that a skin substitute's commercial availability is not a reflection of its legal status. Manufacturers self-determine whether their human cells, tissues, or cellular or tissue-based product (HCT/P) may be marketed without FDA preapproval and frequently misunderstand or mischaracterize the conditions they must meet for the product to be regulated solely for communicable disease risk.

The Code of Federal Regulations (CFR) was referenced; 21 CFR 1271.10(a). Also, the 'FDA Announces Comprehensive Regenerative Medicine Policy Framework'[5] was referenced.

Systemic Review and Meta-Analysis

Santema et al[16] provided a systematic review and meta-analysis to assess the efficiency of skin substitutes utilized for the treatment of DFUs regarding ulcer healing and limb salvage. Using the Cochrane Collaboration methodology, 17 clinical trials were identified, which included a total of 1,655 randomized study participants with diabetic foot ulceration. The number of study participants per clinical trial ranged from 23 to 314. Fourteen studies included chronic or difficult to heal ulcers that were present for a minimum of 2, 4, or 6 weeks.

Skin substitutes were contrasted with SOC in 13 trials. The results collectively demonstrated that SOC treatment, together with skin substitutes, enhance the chances of attaining complete ulcer closure in contrast to SOC alone after 6 to 16 weeks (risk ratio [RR] 1.55, 95% confidence interval [CI] 1.30 to 1.85, low quality of evidence). Apligraf/Graftskin, Epifix, and Hyalograft 3D were the only individual products that demonstrated a statistically substantial beneficial effect on complete ulcer closure (i.e., full epithelialization without any evidence of drainage or bleeding). Four clinical trials contrasted two different types of skin substitutes, although no product demonstrated a greater effect over another. Sixteen of the trials evaluated the efficacy of a bioengineered skin substitute. Only one trial evaluated the efficacy of a nonbioengineered skin graft.

The total occurrence of lower limb amputations was only reported for two trials and the results for these two trials collectively produced a substantially lower amputation rate for individuals treated with skin substitutes (RR 0.43,

95% CI 0.23 to 0.81), though the absolute risk difference (RD) was small (-0.06, 95% CI -0.10 to -0.01, very low quality of evidence). Of the included studies, 16 reported on adverse events (AEs) in different ways, although there were no reports of a substantial difference in the incidence of AEs between the intervention and the control group. Additionally, support of long-term effectiveness is lacking, and cost-effectiveness is unclear. Noted limitations included a variable risk of bias among the studies, the lack of blinding (i.e., study participants and investigators knew which patients were receiving the experimental therapy and which patients were receiving the standard therapy), and 15 of the studies conveyed industry involvement; the majority of which did not indicate if the industry applied any limitations regarding data analysis or publication.[16]

Jones et al[17] provided a fourth update for a systematic literature review to evaluate the effect of skin grafts for the treatment of VLUs. Using the Cochrane Collaboration methodology, one new trial was identified, generating a total of 17 RCTs, which included a total of 1,034 study participants. The studies comprised participants of any age, in any care setting, and with VLU. Given the process for diagnosis of venous ulceration differed between studies, a standard definition was not applied. The trials also involved study participants with arterial, mixed, neuropathic, and diabetic ulcers provided that the outcomes for patients with venous ulcers were conveyed separately. To be included in the review, trials also had to report at least one of the primary outcomes (i.e., objective measures of healing, such as relative or absolute rate of change in ulcer area, time for complete healing, or proportion of ulcers healed within the trial period).

Eleven studies contrasted a graft with SOC. Two of these studies (102 patients) contrasted an autograft with a dressing, three studies (80 patients) contrasted a frozen allograft with a dressing, and two studies (45 patients) contrasted a fresh allograft with a dressing. Two studies (345 patients) contrasted a tissue-engineered skin (bilayer artificial skin) with a dressing. In two studies (97 patients) a single-layer dermal replacement was contrasted with SOC.

Six studies contrasted alternative skin grafting techniques. The first study (92 patients) contrasted an autograft with a frozen allograft, a second study (51 patients) contrasted a pinch graft (autograft) with a porcine dermis (xenograft), the third study (110 patients) contrasted growth-arrested human keratinocytes and fibroblasts with a placebo, the fourth study (10 patients) contrasted an autograft delivered on porcine pads with an autograft delivered on porcine gelatin microbeads, the fifth study (92 patients) contrasted a meshed graft with a cultured keratinocyte autograft, and the sixth study (50 patients) contrasted a frozen keratinocyte allograft with a lyophilized (freeze-dried) keratinocyte allograft.

Overall, the results show that substantially more ulcers healed when treated with bilayer artificial skin than with dressings. There was inadequate evidence from the other trials to establish whether other types of skin grafting improved the healing of venous ulcers. The authors concluded that bilayer artificial skin, used together with compression bandaging, improves venous ulcer healing contrasted with a simple dressing plus compression.

It was noted that the overall quality of the studies reviewed was poor, thus affecting the risk of inherent bias. Many of the studies did not convey inclusion criteria, insufficient information was provided regarding randomization techniques, and withdrawals and AEs were inadequately reported. Deficient data regarding withdrawals and the inclination to perform per-protocol analyses rather than intention-to-treat (ITT) analyses signify that the outcomes in the original study documentation may be biased.[17]

Clinical Trials for Skin Substitutes for Diabetic Foot Ulcers

Barbul et al[18] conducted a retrospective, matched-cohort study to establish the efficacy of a cryopreserved human bioactive split-thickness skin allograft (BSA) (i.e., TheraSkin®) plus SOC when contrasted to SOC alone for the treatment of diabetic ulcers. Data was obtained from electronic medical records (EMRs) of an initial pool of 650,309

diabetic ulcers for patients treated at 470 outpatient wound care centers in the U.S. from January 1, 2012 to October 25, 2018.

Primary inclusion criteria included: 1) Adults ≥ 18 years of age; 2) DFU, Wagner grade 1-4 present for ≥ 30 days for individuals diagnosed with Type 1 or Type 2 diabetes; 3) Ulcer sited on foot, leg, or toe; and 4) Wound area ≥ 1 cm^2 and ≤ 50 cm^2. Primary exclusion criteria included: 1) Ulcers treated at skilled nursing facilities; 2) Ulcers treated with advanced biological products other than BSA; 3) Individuals in the control cohort who received any cellular and/or tissue-based products; and 4) Individuals who showed ≥ 50% closure of their wounds four weeks before the study treatment period.

Following elimination of ineligible patients and those missing important information (i.e., wound characteristics) and/or lack of treatment documentation, data included a total of 778 patients who were treated with the BSA (treatment cohort) (mean age 65.67) and these study participants were paired with 778 patients (mean age 62.95) drawn from a pool of 126,864 patients treated with SOC alone (control cohort), by utilizing propensity matching to create almost identical cohorts. Complications and comorbidities for both groups included Alzheimer's disease, coronary artery disease, cellulitis, chronic obstructive pulmonary disease, congestive heart failure, end stage renal disease, immunosuppressive conditions, morbid obesity, peripheral vascular disease (arterial and venous), smoking status, and venous insufficiency. Although the disparity in body mass index (BMI) improved with propensity matching, a noteworthy difference remained between groups with those in the BSA cohort having a substantially higher mean BMI than those in the control cohort ($p < 0.002$).

Both cohorts received SOC treatment involving debridement, offloading, and application of any kind of nonbiologic wound dressings, such as hydrogels, saline-moistened gauze, and antimicrobial dressings. Study participants who received a BSA may have utilized any or all of the same dressings.

Amputation rates and recurrence at 3 months, 6 months, and 1 year after wound closure were analyzed. Diabetic ulcers were 59% more likely to close in the treatment cohort contrasted to the control cohort (p=0.0045). The healing rates with the BSA were greater than with SOC across multiple subsets, but the most substantial improvement was noted in the worst wounds that had a duration of 90-179 days prior to treatment (p=0.0073), exposed deep structures (p=0.036), and/or Wagner Grade 4 ulcers (p=0.04). Additionally, the reduction in recurrence was substantial at 3 months, 6 months, and 1 year, with and without initially exposed deep structures ($p < 0.05$). The amputation rate in the treatment cohort was 41.7% less than that of the control cohort at 20 weeks (0.9% vs. 1.5%, respectively). This study showed that diabetic ulcers treated with a cryopreserved bioactive split-thickness skin allograft were more likely to heal and stay closed contrasted to ulcers treated with SOC alone.[18]

Cazzell et al[19] performed a prospective, randomized, controlled, open-label trial with a primary objective to contrast the healing rates of a human decellularized acellular dermal matrix (D-ADM) for chronic DFUs with a SOC arm and an active comparator, human acellular dermal matrix (ADM) arm for the treatment of DFUs. Secondary objectives studied differences in time to wound closure, economic burden, quality of life questionnaires and product utilization between D-ADM, SOC, and a second active comparator human ADM.

Inclusion criteria included, but was not limited to: 1) Enrolled study participants must have the capability to comply with offloading and dressing change requirements; 2) The wound of focus must have been open and receiving SOC for 30 days with an area ≥ to 1 cm^2 and < than 25 cm^2; 3) Patient must be between 21 and 80 years of age, have a single DFU of focus with a Wagner Ulcer Classification Grade of 1 or 2, and no infection present; and 4) Patients must have had acceptable circulation to the affected area, specified as having at least one of the following criteria within the past 60 days: TCOM at the dorsum of the foot ≥ 30 mmHg, ABI ranging from 0.8 - 1.2, or at least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries.

Exclusion criteria included, but was not limited to: 1) Patient had wound treatments including biomedical or topical growth factors within 30 days prior to screening; 2) Patient had circulating HbA1c > 12% within 90 days of the screening visit, serum creatinine concentrations of 3.0 mg/dL or > within 30 days before screening; 3) The presence of peripheral vascular disease, active infection or untreated malignancy, Charcot's disease, or necrosis, purulence, or sinus tracts unable to be removed by debridement; 4) Patient had a revascularization procedure aimed at improving blood flow in the target limb, or received a living skin equivalent within 4 weeks before screening; and 5) Patient has a sensitivity to lincomycin, gentamicin, polymyxin B, vancomycin, polysorbate 20, N-lauroyl sarcosinate, benzonase, or glycerol.

Patients with a diagnosis of diabetes mellitus on a stable treatment regimen (no modifications in treatment for 30 days prior to screening) who visited the clinic for care of a chronic lower extremity ulcer and met the above inclusion criteria and none of the exclusion criteria were asked to join the study. In this regard, the study enrolled 168 DFU patients in 13 centers across nine states in the U.S. Patients were randomized into one of three treatment arms; D-ADM (DermACELL®), SOC wound management, or GJ-ADM (GraftJacketTM) at a ratio of 2:2:1. The authors of this study indicated that the active comparator arm for GJ-ADM was not intended to compare the difference between the ADMs as several articles have reported the safety and efficiency of GJ-ADM; this arm was added to the study to determine a baseline ADM healing rate.

Numbered envelopes holding the treatment designation were arranged by an outside contract research organization and the study investigators were blinded to the randomization codes matching each envelope. After a patient successfully passed screening to be in the study, the investigator would open the envelope to ascertain which randomized arm the patient was assigned to. The ADM is visible upon application; therefore, it would have been impossible to continue blinding the investigator once treatment was applied. Therefore, as a secondary examination to avoid bias, a clinician, blinded to the treatment arm assessed the wound images for confirmation of healing condition.

Initially, the wound beds were debrided with a sharp blade, scissors or Versajet system to remove necrotic tissue for study participants in all three treatment groups. Wound size was recorded using an imaging system pre-and post-debridement as well as before dressing applications. The wound areas were calculated by the imaging system and utilized for subsequent analysis of the wound areas.

Patients in the D-ADM arm and the GJ-ADM arm had the appropriate ADM dressing applied and covered with a nonadherent dressing. A second ADM was applied between two weeks (at a minimum) and 12 weeks (at the latest) after the first D-ADM application. Patients could have a maximum of two ADM applications, which included the first application at baseline. Wounds in the conventional care arm were provided with wound therapy involving alginates, foams, or hydrogels. The treating provider then selected either a moist or dry gauze to be placed over the wound. In all three treatment arms, the dressing covered the wound for a minimum of 5 days, but no more than 9 days, (7 days ± 2 days) until the next visit and dressings were only changed by the study team. Also, during following weekly visits, debridement was used to remove necrotic tissue, as needed. In addition, off-loading utilizing a removable cast walker, diabetic shoe, surgical shoe, walker cast, or a total contact cast was essential for all treatment arms unless the investigator considered it to be inappropriate, such as situations involving a wheelchair bound patient or if the wound was located on the dorsal surface of the foot. Though either removable or nonremovable offloading techniques were permitted, 95% of all patients used some type of removable method; 68% of patients used removable boots and 16% of patients used surgical shoes.

Wounds were assessed on a weekly basis until wound closure was noted or the patient completed 24 weekly follow-up visits. Wound closure was defined as 100% re-epithelialization of the wound without drainage. A second visit was scheduled two weeks after the initial wound closure was noted to verify complete wound closure. Additionally, all healed wounds were followed at 4, 8, and 12 weeks after confirmation of complete wound closure to determine if the wound remained healed.

A total of 168 patients were included in this study: 71 patients in the D-ADM arm, 69 patients in the SOC arm, and 28 patients in the GJ-ADM arm. Patients that withdrew from the study prematurely because of severe adverse events (SAEs), which affected the ability to follow the wound of focus, offloading non-compliance, or ≥ 25% missed visits involved 18 patients in the D-ADM arm, 13 patients in the SOC arm, and 5 patients in the GJ-ADM arm. To this end, 53 patients remained in the D-ADM arm and 40 of these patients received one application, 56 patients remained in the SOC arm, and 23 patients remained in the GJ-ADM arm and 16 of these patients received only one application. The percentage of overall early withdrawals and the percentage of SAEs were comparable between the three treatment groups based on relative population size ($p \geq 0.05$).

Baseline ulcer features, including wound size, were comparable between the three ITT arms. The average age for patients in the D-ADM arm was 59.1, 56.9 in the SOC arm, and 58.5 in the GJ-ADM arm. The mean HbA1c at screening was 8.51% in the D-ADM arm, 8.38% in the SOC arm, and 7.63% in the GJ-ADM arm. Patients diagnosed with Type 2 diabetes involved 93.5% of the enrolled population, with 90.1% randomized to D-ADM, 97.1% randomized to SOC, and 92.9% randomized to GJ-ADM. The treatments prescribed for diabetes control were evenly dispersed across study arms, thus eliminating the potential confounding effect of insulin levels on cell responses and healing. Also, it was noted that almost half of the study participants (41.1%) were current or past smokers and 58.9% had never smoked. Additionally, the majority of patients in all three arms of the study had ulcers classified as Wagner class 2 (ulcers that extend into tendon or capsule); D-ADM arm (83.1%), SOC arm (79.7%), and GJ-ADM arm (82.1%).

Patients were followed for 24 weeks for all three treatment arms. Results for the per protocol population showed that a single application of D-ADM showed a substantially greater wound healing probability in comparison to SOC across all three endpoints at Week 12 (65.0% vs. 41.1%; HR = 1.969; 95% CI = 1.1–3.5; p=0.0123), Week 16 (82.5% vs. 48.1%; HR = 2.397; 95% CI = 1.4–4.1; p=0.0003), and Week 24 (89.7% vs. 67.3%; HR = 2.107; 95% CI = 1.3–3.5; p=0.0008). Patients in the D-ADM arm who received all applications also demonstrated a substantially greater wound healing probability over SOC during follow-up visits at Week 16 (67.9% vs. 48.1%; HR = 1.716; 95% CI =1.04–2.831; p=0.0283) and Week 24 (83.7% vs. 67.3%; HR = 1.546; 95% CI = 0.9821–2.435; p=0.0489). The patients in the D-ADM arm who received only one application exhibited wound healing in an average of 9 weeks, whereas patients in the conventional arm showed wound healing in an average of 16.5 weeks (p=0.0020). No substantial differences were observed between patients in the GJ-ADM arm and patients in the SOC arm or between patients in the D-ADM and GJ-ADM arms.

The SF-36 v2.0 (Optum, Inc.) was utilized to acquire the perception of general health in eight areas for each study participant. The average, overall SF-36 scores at the end of the study were 425 for D-ADM, 430 for SOC, and 404 for GJ-ADM. There were no substantial differences perceived between treatment arms for the overall total score or in any of the eight areas. Also, a limitation noted for this study indicates that the manufacturer of the D-ADM (DermACELL®) sponsored this trial.[19]

Driver et al[20] conducted The Foot Ulcer New Dermal Replacement Study (FOUNDER) to assess the safety and effectiveness of the Integra Dermal Regeneration Template (IDRT) (i.e., Omnigraft® Dermal Regeneration Matrix) for the treatment of nonhealing DFUs. The study was a multicenter, randomized, controlled, parallel group clinical trial performed under an Investigational Device Exemption. This study was designed based on guidelines from the FDA for creating products to treat chronic cutaneous ulcers. The FOUNDER study involved 32 clinical sites and 307 patients that were randomized into two parallel groups.

The primary inclusion criteria included: 1) Established Type 1 or Type 2 diabetes with a HbA1c ≤ 12%; 2) Patients ≥ 18 years of age; 3) Presence of a full-thickness neuropathic ulcer positioned distal to the malleolus; 4) The ulcer of focus must have been in existence for greater than 30 days with the ulcer area between 1 and 12 cm^2 post-debridement; and 5) Satisfactory vascular perfusion as defined by ABI ≥ 0.65 and ≤ 1.2 or toe pressure > 50 mmHg or transcutaneous oxygen pressure (TcPO2) > 40 mmHg or doppler ultrasound consistent with sufficient blood flow

to the affected extremity.

The primary exclusion criteria were active infection involving osteomyelitis, exposed capsule, tendon, or bone, and reduction of wound ≥ 30% during the screening interval. The trial was separated into three phases: screening/run-in, randomization/treatment, and follow-up. Patients entered the screening/run-in phase after providing written consent and underwent a series of screening evaluations and a 14-day run-in period in which patients received SOC treatment on the ulcer of focus to establish eligibility for the study. The following procedures were performed during the run-in period for the ulcer of focus: 1) Infection and exudate evaluation; 2) Sharp debridement; 3) Measurement of the deepest aspect (post-debridement); 4) Photograph (pre- and post-debridement); 5) Tracing for planimetric evaluation (post-debridement); 6) SOC that involved sharp debridement followed by application of a moist wound therapy consisting of 0.9% sodium chloride gel and a secondary dressing involving a nonadherent foam dressing, an outer gauze wrap, and an offloading/protective device (i.e., Active Offloading Walker [boot and/or shoe]); and 7) Patients were instructed on the SOC treatment for daily dressing changes.

Other patient evaluations conducted during the run-in period included: A medical history; medication usage; therapies; physical examination; and neuropathic, laboratory, and vascular perfusion assessments. Once the patients completed the screening/run-in phase, patients were then assessed to determine continued satisfaction of eligibility criteria. The ulcer of focus was then debrided using sharp debridement prior to the first treatment. Also, a planimetric evaluation was performed (blindly by a central laboratory).

Patients with study ulcers that had healed < 30% in the run-in period were randomized using a software algorithm at a central location in mixed blocks of 2 and 4 in a 1:1 ratio to the active or control treatment. Randomization was stratified by study location and wound size (≤ 3 cm^2 versus > 3 cm^2). Treatment started on the day of randomization as assigned and the treatment phase continued until the patient had 100% wound closure or for up to 16 weeks. The SOC was the control treatment and the IDRT was the active treatment. The SOC treatments were just as described in the screening/run-in phase and daily dressing changes were done either by the patient in the control group or by a trained caregiver.

For the active treatment group, fenestrating and meshing of the IDRT was acceptable to allow for drainage and in the presence of exudating wounds or hematomas. The IDRT was placed on the debrided wound, trimmed to size, and secured with sutures or staples, and covered with a secondary dressing. When the collagen layer was replaced by new tissue, typically in 14 to 21 days after application, the silicone layer of the IDRT was removed. Re-applications of the IDRT were done as deemed necessary by the investigator. The site personnel performed the secondary dressing changes for the active treatment group on a weekly basis.

Wounds were assessed on a weekly basis during the treatment phase or until wound closure was noted. A visit was scheduled one week after the initial wound closure was noted to verify complete wound closure. An additional visit was then scheduled for confirmation of wound closure. Following completion of the treatment phase, all patients were followed every four weeks during the 12-week follow-up phase.

Complete closure of the ulcer of focus during the treatment phase (16 weeks) (defined as 100% re-epithelialization of the wound surface with no discernable exudate and without drainage or dressing needs), was substantially greater in the active group (51%; 79/154) in contrast to the control group (32%; 49/153, p=0.001). Comparable results were observed when wound closure was evaluated by computerized planimetry: 50% (77/154) in the active group and 31% (48/153) in the control group (p=0.001). The probabilities of complete wound closure established at the end of the treatment phase were 2.2 times higher (95% CI = 1.4, 3.5; p=0.001) for the active group contrasted with the control group. Assessment using planimetric data to evaluate wound closure was consistent with an odds ratio of 2.2 (95% CI = 1.3, 3.5; p=0.001). When complete wound closure was evaluated at 12 weeks, the results were substantially different between the two groups (45% active [70/154] vs. 20% control [31/153]; $p < 0.001$). The

probabilities of complete wound closure at 12 weeks were 3.3 times higher (95% CI = 2.0, 5.4; $p < 0.001$) for the active group contrasted with the control group. The average number of applications per individual, including the initial application, for the active group was 1 (range 1–15).

The degree of decrease in wound size was 7.2% per week for the active group vs. 4.8% per week for the control group (p=0.012). At the end of the follow-up phase, ulcer recurrence was experienced by 19% of the active treatment group and by 26% of the control treatment group (p=0.32). Quality of life data demonstrated substantial improvements in physical functioning (p=0.047) and bodily pain (p=0.033) for the active group contrasted with the control group.

Most AEs in both groups were mild. Severe AEs were incurred by 15.6% of patients in the active group and by 26.8% in the control group (p=0.016). Moderate AEs were incurred by 31.8% of patients in the active group and by 42.5% of patients in the control group (p=0.053). The AEs possibly linked to study treatment were comparable in both treatment groups (7/154 [4.5%] in the active group vs. 8/153 [5.2%] in the control group). Also, a limitation noted for this study is the manufacturer of the IDRT used in the active treatment group sponsored this trial.[20]

Lavery et al[21] performed a prospective, multi-center, randomized, single-blinded study to contrast the effectiveness of a human viable wound matrix (hVWM) (i.e., Grafix®) to standard wound care in treating chronic DFUs from May 2012 to April 2013. The primary outcome was the percentage of patients with complete wound closure by 12 weeks. Complete wound closure was defined as 100% re-epithelialization with no wound drainage. Secondary outcomes encompassed the time to wound closure, AEs, and wound closure in a crossover phase.

Primary inclusion criteria included: 1) Established Type 1 or Type 2 diabetic patients 18-80 years of age; 2) Diabetic ulcer present for 4 to 52 weeks; and 3) Diabetic ulcer positioned below the malleoli on the plantar or dorsal surface of the foot and ulcer 1 to 15 cm^2 in size. Primary exclusion criteria included: 1) HbA1c above 12%; 2) Indication of active infection, including osteomyelitis or cellulitis; 3) Insufficient circulation to the affected foot defined by an ABI < 0.70 or > 1.30, or toe brachial index ≤ 0.50 or Doppler study with insufficient arterial pulsation; 4) Exposed muscle, tendon, bone, or joint capsule; and 5) Decrease of wound area by ≥ 30% during the screening period.

After a 1-week screening period, patients were randomized to the active treatment arm (i.e., hVWM) or control treatment arm (i.e., standard wound care) in a 1:1 ratio. Patients in the active treatment group received an application of hVWM once a week (± 3 days) for up to 84 days (blinded treatment phase). Patients in the control group received SOC wound therapy once a week (± 3 days) for up to 84 days and wounds were cleaned and surgically debrided to remove all non-viable soft tissue from the wound by scalpel, tissue nippers and/or curettes at each weekly visit.

Wounds in both groups received SOC that involved surgical debridement, off-loading and non-adherent dressings and either saline moistened gauze or an absorbent foam dressing for moderately draining wounds. Also, an outer dressing was applied. In addition, walking boots were provided for patients with wounds on the sole of the foot and post-op shoes were provided for patients with wounds on the dorsum of the foot or at the ankle.

Patients were evaluated weekly at the clinical site. Patients who attained complete wound closure then continued to be assessed during the follow-up phase, twice during the first month and then monthly for two additional visits. Patients in the control group whose wounds were not closed by the end of the blinded treatment phase were able to receive the hVWM in the open-label treatment phase, in which the hVWM was applied weekly for up to 84 days.

During screening, 139 patients were assessed. A total of 42 patients failed screening and of these, 6 were excluded due to a decrease of their wound areas by ≥ 30% during the screening period. A total of 97 patients were randomized: 50 to the active treatment arm and 47 to the control arm.

The percentage of patients who attained complete wound closure was substantially higher in the active treatment group (62%) compared with the control group (21%, *P*=0.0001). The average time for healing was 42 days in the active treatment arm contrasted with 69.5 days in the control arm (*P*=0.019). There were less AEs in the active arm (44% versus 66%, *P*=0.031) and less wound-related infections (18% versus 36.2%, *P*=0.044). Among the study participants that healed, ulcers remained closed in 82.1% of patients (23 of 28 patients) in the active group versus 70% (7 of 10 patients) in the control group (*P*=0.419). The authors concluded that treatment with the hVWM substantially improved DFU healing contrasted with SOC therapy. Also, a limitation noted for this study is the manufacturer of the hVWM used in the active treatment group sponsored this trial.[21]

Sanders et al[22] performed a prospective, multi-center, randomized, controlled trial to contrast an in vitro-engineered, human fibroblast-derived dermal skin substitute (HFDS) (i.e., Dermagraft®) to a biologically active cryopreserved human skin allograft (HSA) (i.e., TheraSkin®) in the treatment of DFUs. The primary objectives were to establish the relative number of DFUs healed (100% epithelization without drainage) and the number of grafts needed by week 12. Secondary objectives involved the percentage of DFUs healed at weeks 16 and 20, time to heal during the study and wound size progression.

Primary inclusion criteria included: 1) Established Type 1 or Type 2 diabetic patients > 18 years of age; 2) HbA1C < 12%; 3) Full-thickness foot ulcer existing > 30 days; 4) Ulcer > 1 cm^2 and < 10 cm^2 in size with at least 2 cm between study ulcer and other ulcers; and 5) ABI > 0.65, toe pressure > 50 mmHG, and TcPO2 > 20 mmHG. Primary exclusion criteria included: 1) Wound infection or gangrene of the foot; 2) Patient has received oral or parenteral corticosteroids, immune-suppressive or cytotoxic drugs within the last 12 months; and 3) Treatment with growth factors or bioengineered skin substitutes within the past 30 days.

A total of 23 patients participated in the study at two hospital-based wound care centers in three phases. During the first phase, screening was performed, and eligible patients were randomly assigned to the HFDS treatment group (12 patients) (mean age 57) or the HSA treatment group (11 patients) (mean age 60) using a series of sealed envelopes employing a block randomization technique that described the treatment to be applied. During the second phase (one week later), the treatment phase started and continued for 12 weeks. All wounds (both groups) were debrided to remove nonviable tissue and callous from the wound surface and adjacent wound perimeter and then cleansed with saline. Afterwards, the initial application of the biologically active product was applied as randomly assigned and all wounds were then covered with a non-adherent dressing and were offloaded with $^1/_2$ inch felt as part of an aperture type of device. All patients were then given a healing sandal developed from a surgical shoe or a fixed ankle boot.

Patients in the HSA group received a product application every other week and patients in the HFDS group were treated every week with wounds prepared as described above prior to application of the product. Since both products have a distinctive appearance, it was not possible to conceal the type of product used during wound assessments. Wounds were photographed at each visit and the margins of the wounds were traced along the inner edge of the margins.

At week 12, patients with an unhealed wound continued into the third phase (follow-up) for treatment and assessment for up to eight more weeks. After the week 12 visit, no additional biologically active products were used in either treatment group. In this phase, wounds were treated with saline-moistened gauze and debridement as needed.

Patients with ulcers verified to be healed were scheduled for a confirmatory visit. Patients with incomplete wound closure continued to be evaluated though week 20; subsequent treatment was then provided outside the scope of the study.

There were no substantial differences discerned between patient demographics and wound attributes at baseline in the two treatment groups. At week 12, seven (63.6%) wounds in the HSA treatment group versus four (33.3%) in the HFDS treatment group were healed (P=0.0498). At the end of week 20, 90.91% of wounds in the HSA group

versus 66.67% of wounds in the HFDS group were healed (P=0.4282). Among the subset of wounds that healed during the first 12 weeks of treatment, a mean of 4.36 (range 2-7) HSA grafts were applied versus 8.92 (range 612) in the HFDS subset group (P < 0.0001, SE 0.77584). Time to healing in the HSA group was substantially less (8.9 weeks) than in the HFDS group (12.5 weeks) (log-rank test, P=0.0323). The results of this study showed that, after 12 weeks of care, DFUs treated with HSA are probably twice as likely to heal as DFUs managed with HFDS with about half the number of grafts required. Limitations noted for this study are the small sample size and the manufacturer of the HSA product used in one of the active treatment groups sponsored this trial.[22]

Zelen et al[23] performed a prospective, randomized, controlled, multicenter study to evaluate the healing rates, safety, and cost using an open-structure human reticular acellular dermis matrix (HR-ADM) (i.e., AlloPatch® PliableTM) plus SOC to facilitate wound closure in DFUs compared to treatment with SOC alone. The trial was conducted from December 2014 to November 2015 at five outpatient wound care centers in Virginia and Ohio.

Primary inclusion criteria included: 1) Patients with Type 1 or Type 2 diabetes with a non-healing neuropathic foot ulcer that failed a minimum of 4 weeks of documented conservative care; 2) Adequate renal function as shown by a serum creatinine level < 3.0 mg/dl; and 3) Sufficient circulation to the affected extremity within the past 60 days as evidenced by TCOM with result ≥ 30 mmHg, ABI with result of ≥ 0.7 and ≤ 1.2 or Doppler arterial waveforms, which were triphasic or biphasic at the ankle of the affected leg.

All eligible patients meeting inclusion and exclusion criteria were treated with SOC alone, which included surgical debridement, for a 2-week screening period and patients whose index wound had not healed greater than 20% at 2 weeks were then considered eligible for the study. A total of 40 study participants were eligible for enrollment in the study and were randomized to HR-ADM plus SOC (n = 20) (HR-ADM applications weekly) or SOC alone (n = 20) (daily dressing changes). There were no significant group differences regarding patient and wound attributes, with the exception of the average wound area, which was larger in the HR-ADM group (4.7 cm^2) contrasted with the SOC group (2.7 cm^2).

The primary outcome of this study focused on a comparison of wound healing at 6 weeks using HR-ADM plus SOC versus SOC alone. Wounds were considered as healed if there was complete (100%) re-epithelization with no drainage and no need for a dressing. Secondary outcomes involved comparing healing at 12 weeks, time to heal at 6 and 12 weeks, graft count, wastage, and assessment of product cost to closure. An ITT method was utilized for all analyses. At 6 weeks, 65% (13/20) of the HR-ADM-treated ulcers had healed contrasted with 5% (1/20) of the ulcers treated with SOC alone (P=0.00028). The decrease in the wound area size between the groups changed significantly over time, with an average time to heal within 6 weeks of 28 days (95% CI: 22–35 days) for the HR-ADM group contrasted with 41 days (95% CI: 40–43 days) for the SOC group. After adjusting for area of wound at randomization, the hazard ratio (HR) for HR-ADM contrasted with SOC was 168 (95% CI: 10–2704), P=0.00036. Ten study participants from the SOC group (50%) and one patient from the HR-ADM group (5%) discontinued the study at 6 weeks per protocol as their wound failed to decrease in area by at least 50%.

At 12 weeks, 80% (16/20) of the HR-ADM-treated ulcers had healed contrasted with 20% (4/20) of the ulcers treated with SOC alone (P=0.00036). The average time to heal within 12 weeks was 40 days (95% CI: 27–52 days) for the HR-ADM group contrasted with 77 days (95% CI: 70–84 days) for the SOC group (P=0.00014).

The average number of HR-ADM grafts used to achieve closure per ulcer was 4.7 (SD=3.3). The average percentage of wastage (healed wounds only) was 51.7% (SD: 10.7; n = 16). There was no occurrence of increased AEs or SAEs between groups, or any AEs related to the graft. This study concluded that the use of HR-ADM plus SOC is more effective in the treatment of DFUs than with SOC alone. This study was limited by the patients unblinded to treatment allocation and the study was also funded by the manufacturer of the HR-ADM graft.[23]

Clinical Trials for Skin Substitutes for Venous Leg Ulcers

Cazzell[24] conducted a multicenter, randomized, controlled, open-label trial designed to evaluate the safety and efficacy of human decellularized acellular dermal matrices (D-ADM) contrasted with SOC management in patients with chronic VLUs. This exploratory pilot study included eight implanting surgeons from seven medical centers in five states that enrolled patients with VLUs. The study participants were randomly assigned to the D-ADM (i.e., Dermacell AWM®) treatment arm or a SOC treatment arm in a 2:1 ratio. Numbered envelopes holding the treatment designation were arranged by an outside contract research organization and the study investigators were blinded to the randomization codes matching each envelope. After a patient successfully passed screening to be in the study, the investigator would open the envelope to ascertain which randomized arm the patient was assigned to. The D-ADM is visible upon application; therefore, it would have been impossible to continue blinding the investigator once treatment was applied. Therefore, as a secondary examination to avoid bias, a blinded, independent adjudicator also assessed the healing condition of all wounds.

Primary inclusion criteria included: 1) Adults ≥ 21 and ≤ 80 years of age; 2) Presence of a single target VLU with a CEAP ulcer classification Grade 6; 3) Duration of the target VLU ≥ 60 days; 4) Absence of infection; 5) VLU area ≥ 1 cm^2 and < 25 cm^2, depth ≤ 9 mm; and 6) Able to comply with offloading and dressing change stipulations.

Primary exclusion criteria included: 1) HbA1c < 12% within 90 days of screening visit; 2) Serum creatinine ≥ 3.0 mg/dL within 30 days of screening; 3) Application of biomedical, topical growth factors or living skin equivalents to the target VLU within 30 days of screening; 4) Recent revascularization procedure to increase blood flow in the target limb; 5) Sensitivity to possible D-ADM processing reagents (e.g., gentamicin, polymyxin B, vancomycin, N-lauroyl sarcosinate, Benzonase, glycerol); and 6) Manifestation of severe peripheral vascular disease, active infection, untreated malignancy, active Charcot's disease, necrosis, purulence, or sinus tracts in the ulcer unable to be removed by debridement.

Eighteen patients were included in the D-ADM arm (mean age 64.6) and 10 patients in the control arm (mean age 61.8). Initially, all wounds for both groups were debrided to remove necrotic tissue utilizing a sharp blade, scissors, or Versajet system. Wound size was recorded using an imaging system pre-and post-debridement as well as before dressing application. Patients in the treatment arm had the D-ADM applied and covered with a nonadherent dressing. A second D-ADM was applied between two weeks (at a minimum) and 12 weeks (at the latest) after the first D-ADM application. Patients could have a maximum of two D-ADM applications, which included the first application at baseline.

Wounds in the SOC arm were provided with wound therapy involving alginates, foams, or hydrogels. The treating provider then selected either a moist or dry gauze to be placed over the wound and left in place for 7 ± 2 days, which was only to be removed during weekly visits. During the weekly visits, debridement was used to remove necrotic tissue, as needed.

Compression therapy was used in the treatment and control arms. Wounds were assessed on a weekly basis until wound closure was noted or the patient completed 24 weekly follow-up visits. Wound closure was defined as 100% re-epithelialization of the wound without drainage. A second visit was scheduled two weeks after the initial wound closure was noted to verify complete wound closure. Additionally, all healed wounds were followed at 4, 8, and 12 weeks after confirmation of complete wound closure to determine if the wound remained healed.

The primary outcome of the study contrasted the full wound closure rates between the two groups. The second outcome of the study involved contrasting the decrease in wound size over time, time to wound closure, and treatment-related AEs. Twenty-eight patients completed at least 12 weeks of follow-up; 18 patients in the D-ADM arm and 10 in the SOC arm. Of the 18 patients receiving the D-ADM, nine (50%) received a second application

during the study. At 24 weeks, patients in the D-ADM arm demonstrated a strong trend of reduction in the wound area, with a mean reduction of 59.6%, in comparison to the SOC arm, with a mean reduction of 8.1%. Also, the wound areas in the SOC arm increased more than 100% in size for one-third (3/9) of the patients. Furthermore, healed ulcers in the D-ADM arm stayed closed at a significantly greater rate after initial confirmation of complete wound closure than healed ulcers in the control arm. Limitations noted for this study included a small patient population with an unbalanced proportion between the 2 groups (2:1) that ensured a low probability of achieving statistical significance, the lack of blinding for the study investigators, and the study was funded by the manufacturer of the D-ADM graft.[24]

Harding et al[25] conducted an open label, prospective, multicenter, randomized controlled study that assessed the human fibroblast-derived dermal substitute (HFDS) (i.e., Dermagraft®) in addition to four-layer compression therapy contrasted with compression therapy alone in the treatment of VLUs. The primary outcome variable was the proportion of patients with completely healed study ulcers by 12 weeks. Complete healing was characterized by having a closed wound (with full epithelization and no exudate or scab) for two consecutive weekly visits.

Primary inclusion criteria included: 1) Individuals ≥ 18 years of age referred to participating facilities/clinics in the United Kingdom (UK), Canada or the U.S.; 2) Presence of a VLU between the knee and ankle existing for at least 2 months and ≤ 5 years prior to screening; 3) Size of VLU 3-25 cm^2 without exposure of muscle, tendon or bone; 4) Presence of a clean, granulating base with negligible adherent slough, suitable for a skin graft; and 5) ABI of 0.8 to 1.2 and reflux of > 0.5 seconds in saphenous, calf perforator or popliteal veins as confirmed by duplex ultrasonography.

Primary exclusion criteria included: 1) Individuals with ulcers caused by a medical condition other than venous insufficiency; 2) Presence of sinus tracts in ulcer; 3) Signs of a wound infection (purulence and/or odor), cellulitis and/or verified osteomyelitis; 4) Morbid obesity; 5) Skin disease near study ulcer; 6) Malignant disease within the past 5 years; and 7) Severe peripheral vascular disease or renal disease, congestive heart failure, cell anemia, thalassemia or uncontrolled diabetes. Also, individuals who had received immune suppressants, systemic corticosteroids, cytotoxic chemotherapy, or topical steroids for more than 2 weeks and within one month of initial screening or who had a history of radiation at the ulcer site were not eligible to participate in the study. In addition, patients who had received an investigational drug within 30 days of randomization or had been previously treated with an HFDS and/or other tissue-engineered materials were also excluded from the study.

All patients received a SOC dressing treatment during the screening period; each ulcer was covered with a layer of non-adherent dressing followed by a four-layer compression bandage. During the 2-week screening period, ulcers were evaluated weekly to establish absence of necrotic tissue and infection and the presence of a vascular bed. Ulcers that decreased in size (cm^2) by < 50% while under compression therapy during the 2-week screening period for the trial were eligible for randomization into the study.

Of the 573 patients screened, 207 failed screening (36%). The primary causes for screening failure were study ulcers decreasing in size by more than 50% during screening, study ulcers less than 3 cm^2 at randomization and patients without indication of venous reflux. The remaining 366 patients were randomized to receive treatment at a total of 25 centers: 19 in the UK, 1 in Canada and 5 in the U.S. The ITT population (patients who received treatment at baseline and had a follow-up visit post-baseline) included 186 patients in the HFDS group and 180 patients in the control group with a mean age of 68.5 years. Patients were randomized to receive an application of HFDS plus the four-layer compression bandage therapy (active) or the four-layer compression bandage therapy alone (control). Patients randomized to the active treatment group received the HFDS applied to the wound at weeks 0, 1, 4 and 8.

A total of 10% (19 of 186) of patients in the HFDS group discontinued the trial early contrasted with 23% (41 of 180) of patients in the control group. The causes for early discontinuation were AEs (3% in the HFDS group versus

6% in the control group), patient's own request (2% versus 9%), patient lost to follow-up (2% versus 3%) and 'other' (4% from each group).

Sixty-four (34%) of 186 patients in the HFDS group demonstrated healing by week 12 contrasted with 56 (31%) of 180 patients in the control group (P=0.235). For ulcers ≤ 12 months duration, 49 (52%) of 94 patients in the HFDS group contrasted with 36 (37%) of 97 patients in the control group healed at 12 weeks (P=0.029). For ulcers ≤ 10 cm^2, complete healing at week 12 was shown in 55 (47%) of 117 patients in the HFDS group contrasted with 47 (39%) of 120 patients in the control group (P=0.223). The most common AEs were wound infection, cellulitis, and skin ulcer. The occurrence of AEs was not significantly different between the treatment and control groups. Statistical significance was not achieved for the primary outcome of patients with VLUs completely healed by 12 weeks. Also, a limitation noted for this study is the manufacturer of the HFDS used in the control group helped sponsor this trial.[25]

Frequency

There is paucity of evidence to address how frequently skin substitutes should be reapplied. Few studies include the frequency of applications. A retrospective review by Caputo et al. reported seventy-eight percent of complex wounds achieved complete closure, with a median time-to-heal of 16 weeks using an average of 1.24 applications of NEOX Wound Allograft. Couture reported using an average of 3.43 NEOX applications with an average healing time of 5.53 weeks in a single-center retrospective study. A retrospective chart review by Raphael reported median time to heal 13.79 weeks with an average 1.68 applications. Armstrong and colleagues presented a retrospective analysis at the 2021 Wounds UK annual Conference reporting skin substitutes were applied every 7-14 days. While this is not peer-reviewed literature, and included authors who are paid speakers for MIMEDX, it is being included based on the patient population and lack of other evidence.

Societal Input

National Institute for Health and Care Excellence (NICE) Diabetic foot problems: prevention and management

The clinical guideline on diabetic foot problems considers 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. (NICE, published 2015; Updated October 2019).

International Working Group on the Diabetic Foot (IWGDF)

IWGDF recommends the consideration of placental-derived products as an adjunctive treatment to the best standard of care when standard care alone has failed to reduce the size of the wound. (GRADE Strength of recommendation: Weak; Quality of evidence: Low). This was based on a number of studies, including those of moderate bias, suggesting that placenta-derived products may have a beneficial effect on ulcer healing, but the authors also state that these findings need to be confirmed in large, randomized trials. They state there is insufficient evidence to support superiority of any particular products.

For use of topically applied treatments, the IWGDF recommends against the use of bioengineered skin products in comparison to standard of care.

For both of these recommendations, the IWGDF considered the available evidence to be of low quality, and their recommendation was weak (i.e., based on the quality of evidence, balance between benefits and harms, patient

values and preferences, and cost or resource utilization).

Wound Healing Society (WHS)

The WHS has published updated evidence-based guidelines on the treatment of diabetic ulcers. Regarding the use of skin substitutes, the WSH concluded that level I evidence suggests that cellular and acellular skin equivalents improve the healing of diabetes-related foot ulcers. In these guidelines Level I required at least two RCT supporting the intervention of the guidelines. The quality of evidence was not assessed (Lavery et al., 2016). 32

*In evidence-based guideline for venous ulcers, the WHS stated that there is evidence that a bilayered living human skin equivalent, used in conjunction with compression bandaging, increases the incidence and speed of healing for venous ulcers compared with compression and a simple dressing (Level I evidence). The WHS recommends adequate wound bed preparation and control of excess bioburden levels prior to application of a biologically active dressing. They also noted that cultured epithelial autografts or allografts have not been demonstrated to improve stable healing of venous ulcers (Level I). The WHS also stated that there is Level II evidence that a porcine small intestinal submucosal construct may enhance healing of venous ulcers (Marston et al., 2016).*33

Society for Vascular Surgery/American Podiatric Medical Association/Society for Vascular Medicine (SVS/APMA/SVM)

The SVS/APMA/SVM published a joint evidence-based guideline using Grades of Recommendation Assessment, Development, and Evaluation system for the management of patients with diabetes, including treatment of diabetes related chronic foot ulcers (Hingorani et al., 2016). 34

- These organizations recommendations for diabetic foot ulcers that fail to demonstrate improvement (> 50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, adjunctive wound therapy options include negative pressure therapy, biologics (platelet-derived growth factor, living cellular therapy, extracellular matrix products, amniotic membrane products) and hyperbaric oxygen therapy. The choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice (Grade 1B).
- Consideration of living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of diabetic foot ulcers when the individual is recalcitrant to standard therapy (Grade 2B).
- Consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for diabetic foot ulcers when the individual is recalcitrant to standard therapy (Grade 2C).

Analysis of Evidence (Rationale for Determination)

Chronic wounds can be very challenging for the provider as well as the patient and are described as wounds unable to re-epithelialize after one to three months of treatment. These wounds include vascular ulcers (e.g., venous and arterial), diabetic ulcers, and pressure ulcers and affect patient quality of life due to impaired mobility, pain, and substantial morbidity.

Standard treatment of lower extremity chronic wounds includes, but is not limited to, mechanical offloading, infection control, mechanical compression, limb elevation, debridement of necrotic tissue, management of systemic disease and medications, nutrition assessment, tissue perfusion and oxygenation, appropriate dressings, education regarding the care of the foot, callus, and nail and fitting of shoes, and counseling on the risk of continued tobacco use.

Nonhealing lower extremity ulcers should also have a vascular evaluation, including, but not limited to,

documentation of wound location, size, depth, drainage, and tissue type; palpation of pedal pulses; and measurement of the ankle-brachial index.

In the absence of underlying disease or non-adherence to prescribed basic treatment, skin substitute grafts are recommended in accordance with evidence-based guidelines for the following: 1) DFUs that have failed to demonstrate more than 50% wound area reduction after a minimum of four weeks of standard wound care measures, and 2) VLUs if substantial wound improvement is not demonstrated after a minimum of four to six weeks of standard wound care measures.

An extensive variety of wound care products are available for providers to select from when treating chronic wounds. Many of these products may simulate or substitute for some aspect of the skin’s structure and function to promote healing and wound closure. The materials used to create these products may be derived from human or animal tissue and may undergo extensive or minimal processing to generate the finished product. The degree of processing and the source of the material used in the product also governs which regulatory pathway may be required before the product may be marketed.

The regulation of tissue-engineered products in the U.S. occurs by one of several pathways established by the FDA, including a BLA, a 510(k) (Class I and Class II devices), PMA (Class III devices), or HCT/Ps (human cells, tissues, and cellular and tissue-based products) designation. Key differentiators among these regulatory classifications include the amount and type of data required to support a filing.

Amniotic/chorionic-based products that are HCT/Ps as defined in 21 CFR 1271.3(d) must meet criteria in 21 CFR 1271 and 361 of the PHS Act. Manufacturers of HCT/Ps should consult with the FDA Tissue Reference Group (TRG) or obtain a determination through a Request for Designation (RFD) on whether their HCT/Ps are appropriately regulated solely under section 361 of the PHS Act and the regulations in 21 CFR Part 1271 (85 FR 86058). The HCT/Ps that are drugs are defined under section 201(g) of the Federal FD&C Act [21 U.S.C. 321(g)] and biological products are defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. To lawfully market a drug that is also a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after a showing of safety and efficacy for the product's intended use. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug (IND) application in effect as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312].

The HCT/Ps which are more than minimally manipulated, or are intended for non-homologous use, may be subject to additional regulation as medical devices under the Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. section 301 et seq. (see 21 CFR section 1271.20). A manufacturer/distributor of HCT/Ps must register with the FDA as a "tissue establishment" and follow certain guidelines for designation of a product as an HCT/P (21 CFR sections 1271.10; 1271.21-22). The FDA imposes labeling requirements for HCT/Ps (refer to 21 CFR section 1271.370). The HCT/P labeling must include, inter alia, "instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases," and "other warnings, where appropriate" (21 CFR section 1271.370(c)(3)-(4)).

The FDA acceptance of an establishment registration and HCT/P listing does not constitute a determination that an establishment is in compliance with applicable rules and regulations or that the HCT/P is licensed or approved by the FDA (21 CFR 1271.27(b)). To establish compliance with the FDA requires a letter from the FDA indicating that the HCT/P has met regulatory compliance under section 361 of the Public Health Service Act and/or the Federal Food, Drug, & Cosmetic Act.

It is recommended that the manufacturer of the particular skin substitute graft or CTP product obtain the appropriate information and send to the MAC along with evidence-based literature, if available. Once this information has been

received by the MAC, the product will be considered for coverage and placed into the appropriate Code Group in the associated article. The literature would support the medially reasonable and necessary criteria for the product(s).

Studies are lacking for many wound care products (e.g., skin substitutes) which are essential to evaluate effectiveness and the impact that the product has on health outcomes. Available studies do not have a high level of evidence or even non-randomized prospective studies evaluating their effectiveness. The quality of current research for these products is moderate to low with high probability of publication bias and study limitations. Evidence is needed to show that the product(s) improve health outcomes or provide benefits relative to established alternatives or standard of care. Many of the current studies are noted to be funded by industry, which presents concerns regarding bias for these studies.

Despite the lack of studies, the moderate to low quality of current research and the likelihood of bias, coverage has been provided to increase the chances of improved health outcomes of interest which include patient quality of life and function. Coverage will be provided for products in the associated billing and coding guideline meeting the necessary FDA regulatory requirements as of publication. Each product has specific designated approved usage. New products will be considered for coverage if meeting the regulatory requirements and criteria. Satisfactory evidence of FDA regulatory requirements include: 1) A copy of the FDA's letter to the drug's manufacturer approving the new drug application (NDA), 2) A listing of the drug or biological in the FDA's "Approved Drug Products" or "FDA Drug and Device Product Approvals", 3) A copy of the manufacturer's package insert approved by the FDA as part of the labeling of the drug, containing its recommended uses and dosage, as well as possible adverse reactions and recommended precautions in using it, or 4) Information from the FDA's Website. For skin substitutes classified as HCT/Ps, a letter from the FDA indicating that the HCT/P has met regulatory guidance is acceptable evidence of the FDA regulatory compliance for HCT/Ps regulated under section 361 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act.

Proposed Process Information

Synopsis of Changes

CHANGES	FIELDS CHANGED
The name of the LCD has been changed from 'Wound Application of Cellular and/or Tissue Based Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers.' The 'History/Background and/or General Information' section of the LCD has been revised to clearly describe the services addressed in the LCD and additional regulatory information has been included for skin substitute products. The following sections of the LCD have been reworded and revised to be consistent with the evidence: 'Covered Indications' and 'Limitations'. The following sections were added: 'Provider Qualifications', 'Summary of Evidence', 'Societal Input' and 'Analysis of Evidence'. Documentation Requirements are located in the associated billing and coding article (DA56696). The Utilization Guidelines have been incorporated into the 'Limitations' section. The 'Bibliography' section has been updated to include all literature utilized in the development of this LCD. Also, formatting changes have been made throughout the LCD.	N/A

Associated Information

Please refer to the related Draft Local Coverage Article: Billing and Coding: Skin Substitutes for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (DA56696) for documentation requirements, utilization parameters and all coding information as applicable.

Sources of Information

N/A

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This bibliography presents those sources that were obtained during the development of this policy. The Contractor is not responsible for the continuing viability of Website addresses listed below.

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Open Meetings

MEETING DATE	MEETING STATES	MEETING INFORMATION
10/25/2022	Kentucky	Norton Women's & Children's Hospital 3999 Dutchmans Lane Plaza 1 Lower Leve; Room D Louisville, KY 40207
10/26/2022	Ohio	OSU Wexner Medical Center Biomedical Research Tower 460 W 12th Ave. Room 115 Columbus, Ohio 43210

Contractor Advisory Committee (CAC) Meetings

N/A

MAC Meeting Information URLs

N/A

Proposed LCD Posting Date

10/06/2022

Comment Period Start Date

10/06/2022

Comment Period End Date

11/19/2022

Reason for Proposed LCD

- Other (Creation of Uniform LCDs With Other MAC Jurisdiction)

Requestor Information

This request was MAC initiated.

Contact for Comments on Proposed LCD

Meredith Loveless, MD
Attn: Medical Review
26 Century Blvd., Ste ST610
Nashville, TN 37214-3685

cmd.inquiry@cgsadmin.com

Associated Documents

Attachments

N/A

Related Local Coverage Documents

N/A

Related National Coverage Documents

N/A

Keywords

N/A

APMA COMMENTS

Disagreement: Limitation of Four Applications

In the Limitations section of the Proposed LCD, the following is listed as not medically reasonable and necessary:

Not to exceed four applications of a specific skin substitute graft product within the episode of skin replacement surgery for wound care defined as 12 weeks from the first application and consistent with product labeling.

APMA COMMENTS

Disagreement: Required Use of RT or LT Modifier

The Proposed LCA contains this sentence:

- "Application codes billed must use the appropriate modifier (e.g., RT, LT) to identify the location where the skin substitute was applied, or the service will be denied."

- This guidance is contrary to current CPT®24 guidance. If two different contralateral ulcers from the same CPT code anatomic group receive application of a skin substitute graft, using an RT or LT Modifier would contradict CPT guidance regarding appropriate use of its codes and modifiers.

APMA COMMENTS

Disagreement: Set of Covered ICD-10-CM Codes

In the Proposed LCA, Group 1 of the "ICD-10-CM Codes that Support Medical Necessity" is missing multiple ICD-10-CM codes that are used to identify DFUs and VLUs. Among those missing are all L97.5- codes, which are used, in part, to identify DFUs of the forefoot (the area of the foot distal to the midfoot).

CMS POLICY CHANGE ON NAIL SURGICAL CODES 11730, 11732, 11750

- CPT codes 11730 and 11732 for nail avulsion will be denied if billed for the same finger less than 4 months (16 weeks) or the same toe lese than 8 months (32 weeks) following a previous avulsion. CPT code 11750 for nail excision permanent removal will be denied if billed for the same finger or toe following a previous excision,
- A medically reasonable and necessary repeat avulsion or excision of the same nail within 32 weeks of a previous avulsion, or excision, of the same nail, will be considered upon redetermination. The medical record must support the service, for example, there is an ingrown nail of the opposite border or a new significant pathology on the same border recently treated.

- Documentation Requirements
- 1. All documentation must be maintained in the patient's medical record and made available to the contractor upon request.
- 2. Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, dates of service[s]). The documentation must include the legible signature of the physician or non-physician practitioner responsible for and providing the care to the patient.
- 3. The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must describe the service performed.
- 4. The following information must be clearly documented in the patient's medical record:

- • Complete detailed description of the pre-operative findings. Include the patient's symptoms, the physical examination documenting the severity of the nail infection, injury or deformity, and the assessment and plan containing the rationale why surgical treatment is being selected over other treatment options.
- • Method of obtaining anesthesia (if not used, the reason for not using it).
- • A complete detailed description of the procedure performed.
- • Identify the specific digit(s) and make note to the nail margin(s) involved on which the procedure was performed.
- • Postoperative observation and treatment of the surgical site (e.g., minimal bleeding, sterile dressing applied).
- • Postoperative instructions given to the patient and any follow-up care (e.g., soaks, antibiotics, follow-up appointments).

- Sources of information: MCD (Medicare Coverage Database):

- LCDs
- L33833 - Surgical Treatment of Nails

- Articles
- A57666 - Billing and Coding: Surgical Treatment of Nails

CGS PRESENTATION

- Nail Debridement
- Prepare for Targeted Probe and Educate Pre-Payment Review

THANK YOU