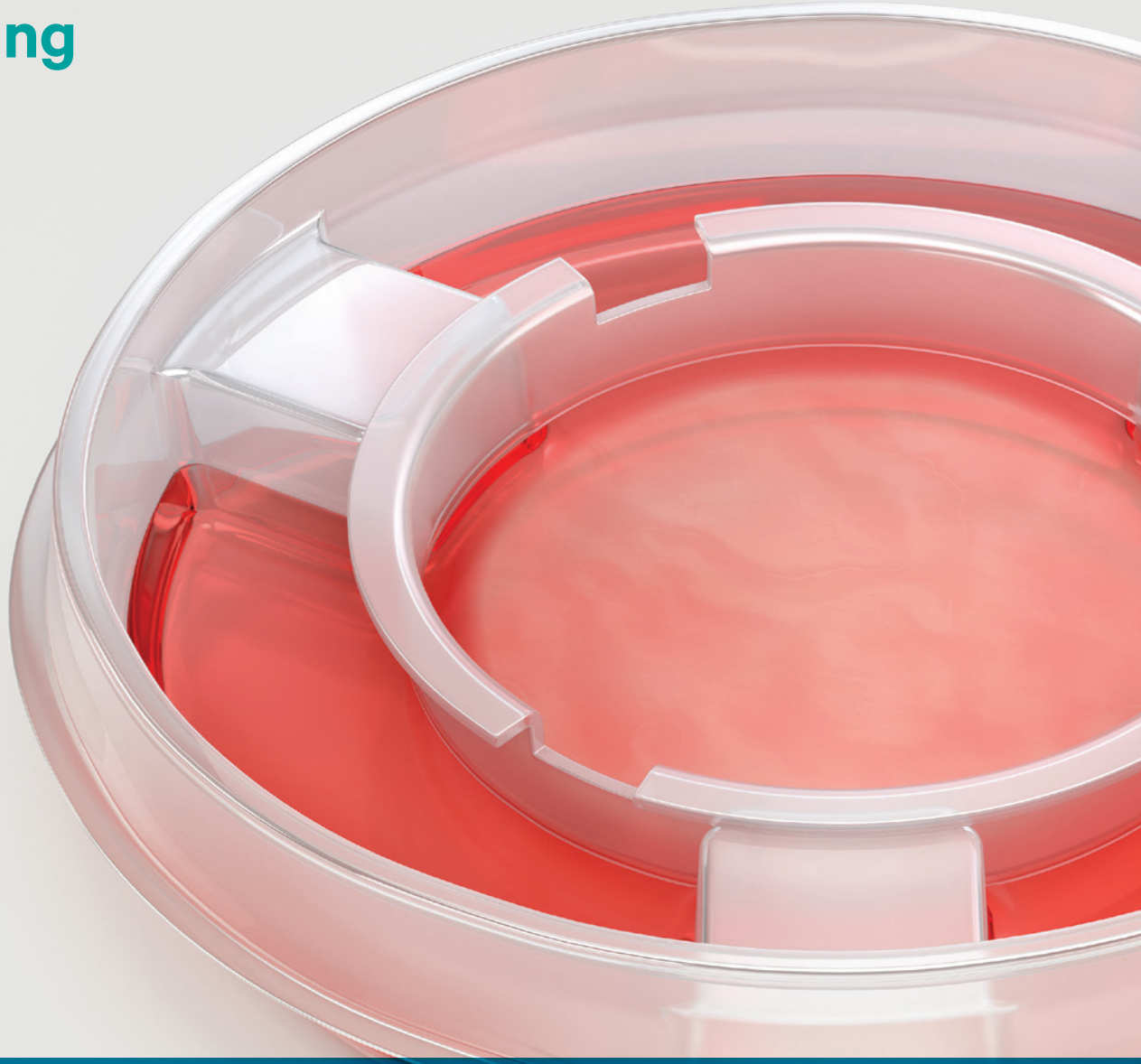
The timeless quality of proven results in healing VLUs and DFUs.

VLU = venous leg ulcer; DFU = diabetic foot ulcer



Organogenesis

Apligraf®

Living Cellular Skin Substitute

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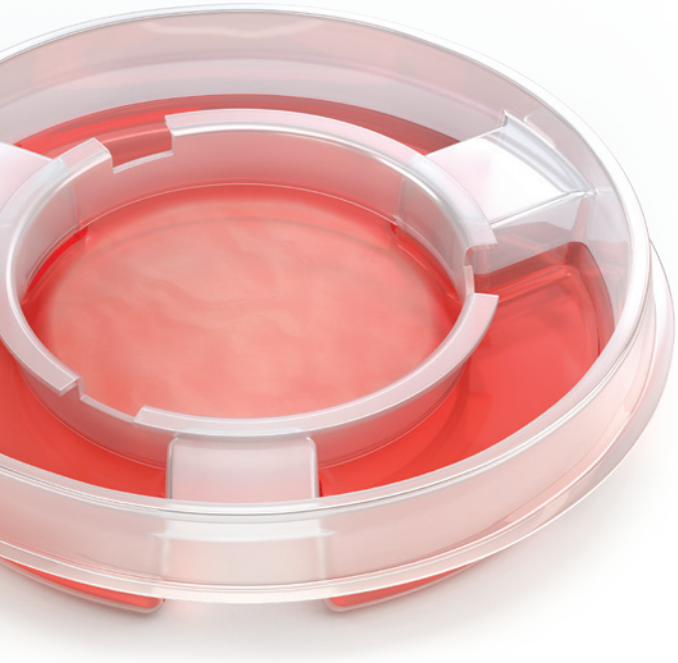
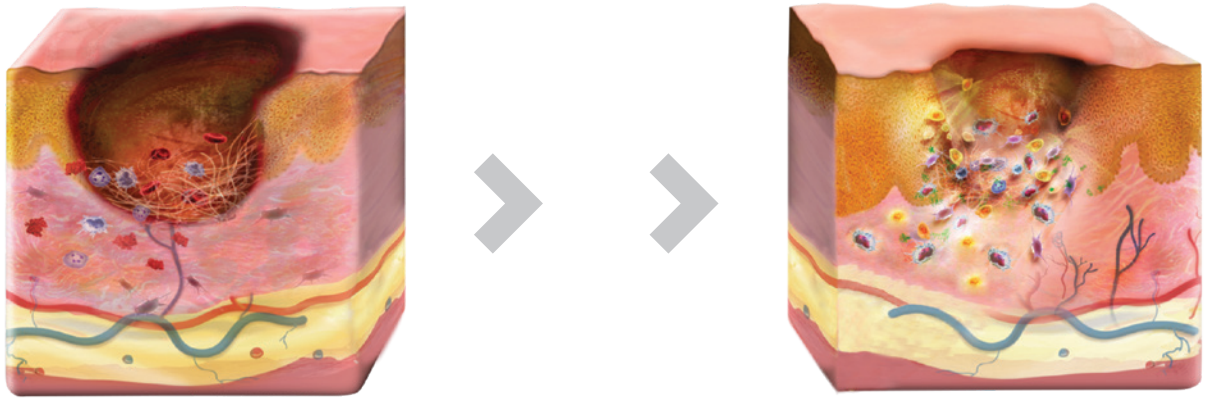


Apligraf® transforms wounds from chronic to acute.

The living cells of Apligraf stimulate a potent healing mechanism, helping to restore normal healing functions and putting the wound back on track to heal.[1-4]



Before Apligraf treatment

- Keratinocytes and fibroblasts unresponsive/dysfunctional[5-8]
- ECM disorganized and MMPs imbalanced[8-10]
- Growth factor signaling dysfunctional[11,12]
- Fibrosis present[13,14]

After Apligraf treatment

- Activated keratinocytes at the wound edge[1]
- Restored fibroblast function at the wound base, thus normalizing ECM production and MMP balance[15]
- Corrected and regulated growth factor signaling[1,2,4]
- Downregulated fibrosis formation[15]

Randomized clinical trial[1,15]

PURPOSE

To investigate Apligraf's mechanism of action (MOA) in patients with chronic, nonhealing VLUs.

METHODOLOGY

- Patients were treated with Apligraf plus conventional therapy (sharp debridement and compression) or conventional therapy alone
- Biopsies were obtained at baseline and week 1 following a single application of Apligraf; biopsies were taken at both the wound edge (n=24) and the wound base (n=19)

ANALYSIS

Changes in gene expression were compared between groups.

ECM = extracellular matrix; MMP = matrix metalloproteinases

Apligraf®: Extensive, reliable, unmatched clinical evidence proving it heals more VLUs and DFUs faster.

Reliable data equals:

Randomized controlled trials (RCTs)[16,17]

- Strongest method for proving efficacy and safety
- Required to obtain FDA approval

Real-world observational studies[16,17]

- Provide evidence of health benefit in real-world use
- Demonstrate effectiveness in patients with significant comorbidities

Apligraf's evidence is extensive, reliable, and unmatched:

RCTs for FDA approval*

- ✓ **VLUs** (N=240)[18,19]
- ✓ **DFUs** (N=208)[20]

Real-world observational studies

- ✓ **3 in VLUs** (N=3621)[21-23]
- ✓ **1 in DFUs** (N=226)[24]

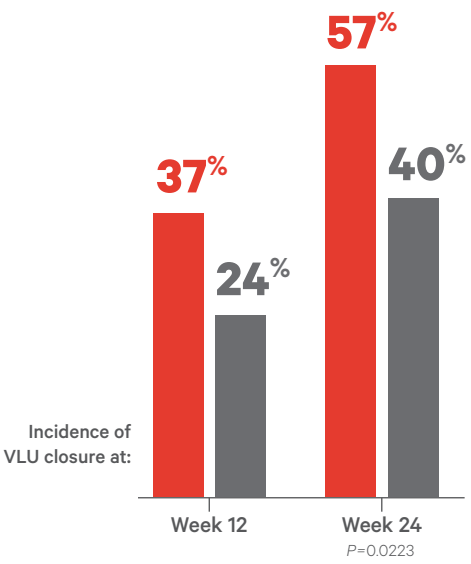
***Only Apligraf has conducted RCTs resulting in FDA approval for VLUs and DFUs.[18-20]**

Ns for RCTs = number of patients; Ns for real-world observational studies = number of wounds

An RCT and real-world observational studies have proven time and again that Apligraf® closes more VLUs faster.

RCT required for FDA approval[18,19]

Apligraf (n=130 patients) **vs Control** (n=110 patients)



Median time to wound closure

99 vs 184 days

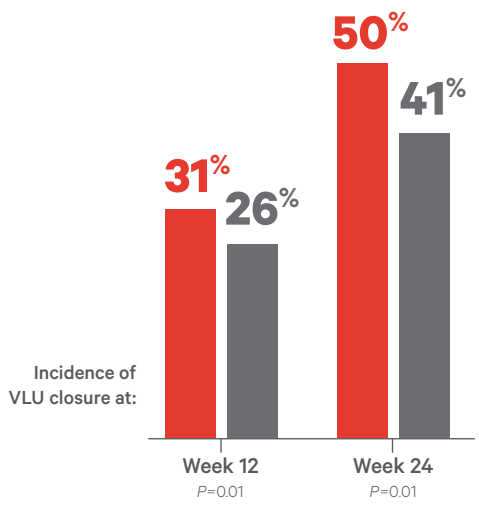
P=0.0073

85 DAYS FASTER

A prospective, randomized, controlled, multicenter, multispecialty, unmasked study was conducted to evaluate the safety and effectiveness of Apligraf and compression therapy in comparison to an active treatment-concurrent control of zinc paste gauze and compression therapy. Wound closure defined as 100% epithelialization without drainage.

Observational comparative effectiveness studies*

Apligraf (n=1451 wounds) **vs Oasis®[21]** (n=350 wounds)



Median time to wound closure

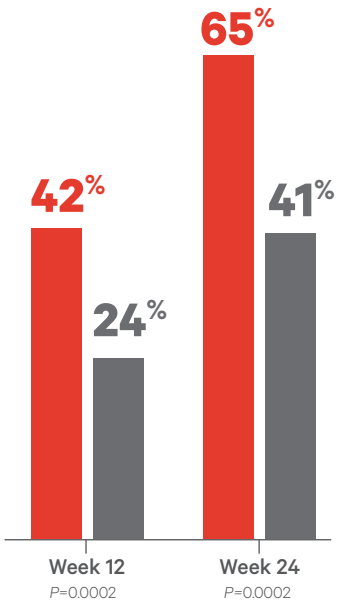
24 vs 43 weeks

P=0.01

44% FASTER HEALING

For the Apligraf vs Oasis analysis, incidence of and median time to wound closure were determined by Kaplan-Meier analysis with two-tailed log-rank test. The hazard ratio along with its 95% confidence interval (CI) and *P* value is based on a Cox proportional hazards regression model with one term for treatment group. Wound closure defined as an ulcer achieving an area between 0 and 0.25 cm^2.

Apligraf (n=688 wounds) **vs TheraSkin®[22]** (n=111 wounds)



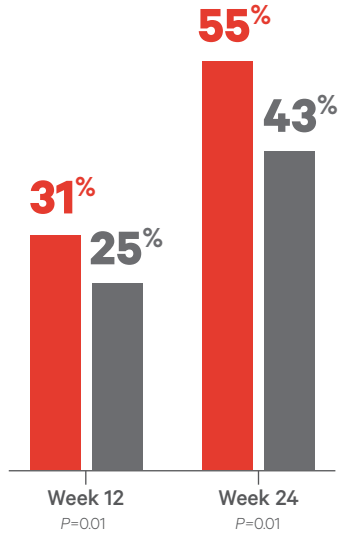
15 vs 31 weeks

P=0.0002

52% FASTER HEALING

For the Apligraf vs TheraSkin analysis, the estimated incidence of wound closure and the estimated median time to wound closure are from a Cox regression model with terms for treatment, baseline wound area, baseline wound duration, baseline wound depth, and patient age at first visit. Wound closure defined as an ulcer achieving an area between 0 and 0.25 cm^2.

Apligraf (n=893 wounds) **vs PriMatrix®[23]** (n=128 wounds)



19 vs 30 weeks

P=0.01

37% FASTER HEALING

For the Apligraf vs PriMatrix analyses, the estimated incidence of wound closure and estimated median time to wound closure are from a Cox regression model with terms for treatment, baseline wound area, baseline wound duration, baseline wound depth, patient age at first treatment, sex, and body mass index. Wound closure defined as an ulcer achieving an area between 0 and 0.25 cm^2.

***Effectiveness is the extent to which an intervention produces an overall health benefit in routine clinical practice (real-world situations). Effectiveness studies do not establish efficacy or comparative superiority.** Based on data obtained from a large wound care–specific Electronic Medical Record (EMR) database (WoundExpert®, Net Health, Pittsburgh, PA). For the Apligraf vs Oasis analysis, data are from July 2009 through July 2012. For the Apligraf vs TheraSkin analysis, data are from January 1, 2014 through March 31, 2015. For the Apligraf vs PriMatrix analysis, data are from January 2015 through January 2017. De-identified patient data released to Organogenesis were consistent with the terms and conditions of Net Health's participating client contracts and the requirements of HIPAA. Net Health was not involved in any way in the analyses, interpretation, or reporting of the data.

Overview of Apligraf® VLU case studies

Patient demographics, comorbidities, and wound specifics

- 9 patients (5 females; 4 males)
- Mean patient age: 65 years (range, 44 to 81 years)
- Wound duration
  - 33.9 weeks (mean)
  - 18 weeks (median)
  - 12 to 104 weeks (range)
- Wound area
  - 79.4 cm^2 (mean)
  - 17.5 cm^2 (median)
  - 3.2 to 350.0 cm^2 (range)

Prevalence of comorbidities

Patients (%)

CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease

VLU healed at 8 weeks with 3 applications of Apligraf® in a patient with significant comorbidities.

74-year-old male with a chronic VLU on the right leg

WOUND SPECIFICS

- Initial wound area was 3.2 cm^2
- Wound was present for 12 weeks (3 months)
- Wound infection treated with antibiotics prior to Apligraf treatment

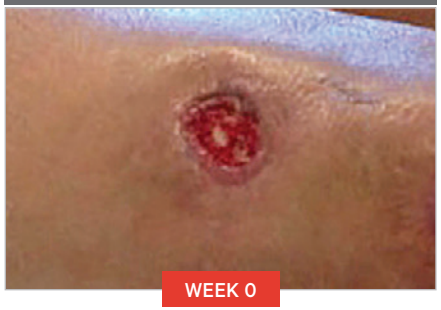
COMORBIDITIES

Coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, hypertension, peripheral vascular disease, surgery for bowel obstruction, and smoking

APLIGRAF APPLICATION SCHEDULE

- 3 applications over 6 weeks
- 2-layer compression wrap applied during Apligraf treatment

1st Apligraf application

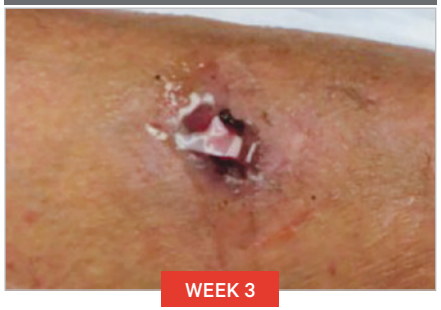


WEEK 0

Post-debridement

Date: 03/25/11
Wound size: 1.9 x 1.7 x 0.3 cm
Wound area: 3.2 cm^2

2nd Apligraf application

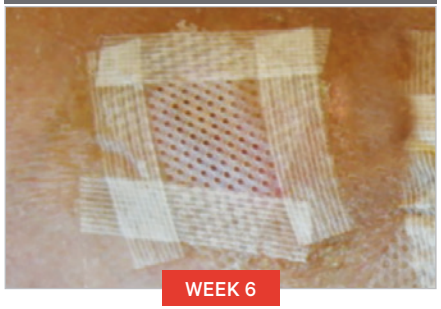


WEEK 3

Pre-debridement

Date: 04/15/11
Wound size: 0.9 x 0.9 x 0.1 cm
Wound area: 0.8 cm^2

3rd Apligraf application

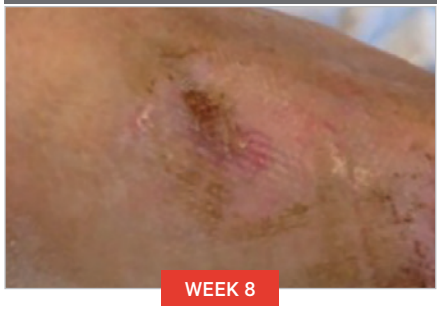


WEEK 6

Post-application

Date: 05/06/11
Wound size: 0.4 x 0.3 x 0.1 cm
Wound area: 0.1 cm^2

Complete wound closure



WEEK 8

Date: 05/20/11

Case initially presented in 2011.

VLU CASE 2 Courtesy of Ronald Belczyk, DPM

VLU healed at 9 weeks with 4 applications of Apligraf® after failing a split-thickness skin graft.

44-year-old female with a chronic VLU on the right leg

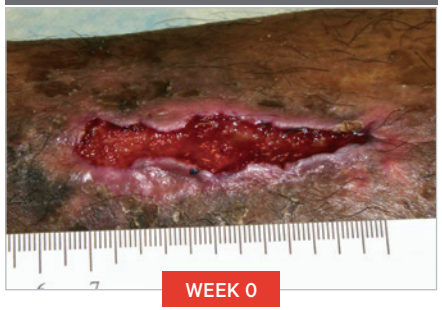
WOUND SPECIFICS
- Initial wound area was 7.8 cm^2
- Wound was present for 104 weeks (2 years)

COMORBIDITIES
Diabetes, peripheral vascular disease, venous stasis, varicosities, edema, hypertension, obesity, and infection

PREVIOUS TREATMENTS
Patient failed split-thickness skin graft, compression wrap, collagen dressing, silver sulfadiazine, and antibiotics to treat previous infection

APLIGRAF APPLICATION SCHEDULE
- 4 applications over 6 weeks
- 3-layer compression wrap applied during Apligraf treatment

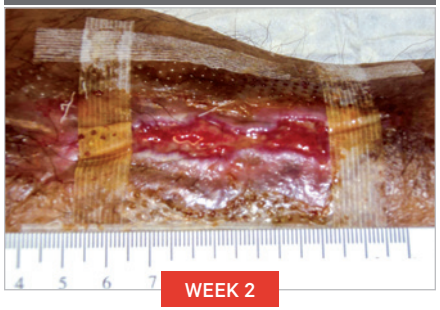
1st Apligraf application



WEEK 0

Post-debridement
Date: 05/17/12
Wound size: 6.0 x 1.3 x 0.1 cm
Wound area: 7.8 cm^2

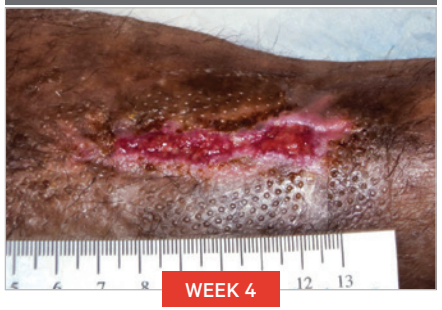
2nd Apligraf application



WEEK 2

Pre-debridement
Date: 05/31/12
Wound size: 5.0 x 1.0 x 0.1 cm
Wound area: 5.0 cm^2

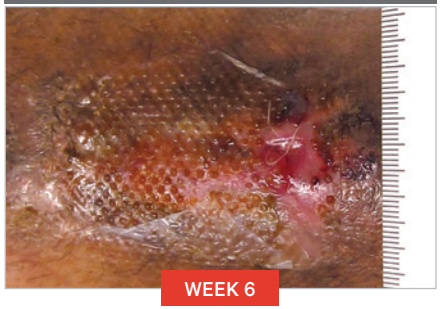
3rd Apligraf application



WEEK 4

Post-debridement
Date: 06/13/12
Wound size: 4.3 x 0.9 x 0.1 cm
Wound area: 3.9 cm^2

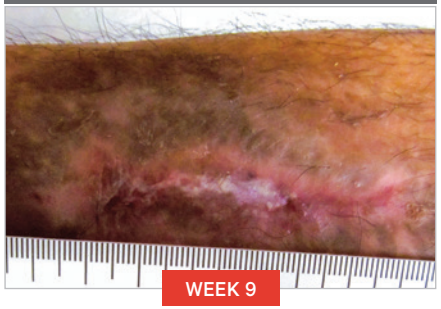
4th Apligraf application



WEEK 6

Post-debridement
Date: 06/28/12
Wound size: 0.6 x 1.0 x 0.0 cm
Wound area: 0.6 cm^2

Complete wound closure



WEEK 9

Date: 07/19/12

Case initially presented in 2012.

VLU healed at 8 weeks with 4 applications of Apligraf® in a patient with reflux in the great saphenous vein.

77-year-old female with a chronic VLU on the lower right ankle

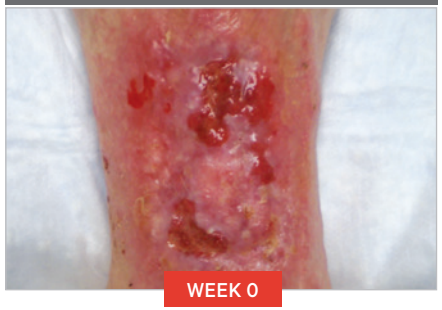
WOUND SPECIFICS
- Initial wound area was 14.4 cm^2
- Wound was present for 24 weeks (6 months)

COMORBIDITIES
Hypertension, hepatitis C, superficial venous insufficiency, and reflux in the great saphenous vein

PREVIOUS TREATMENTS
Debridement, compression, negative pressure wound therapy (NPWT), and hyperbaric oxygen therapy

APLIGRAF APPLICATION SCHEDULE
- 4 applications over 5 weeks
- 2-layer compression wrap applied during Apligraf treatment

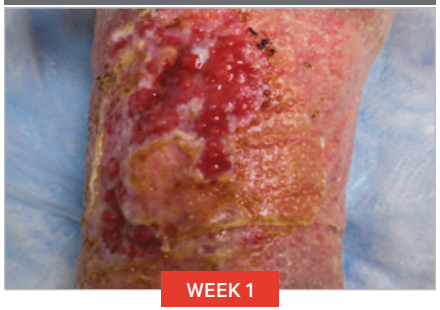
1st Apligraf application



WEEK 0

Pre-debridement
Date: 03/27/12
Wound size: 7.2 x 2.0 x 0.2 cm
Wound area: 14.4 cm^2

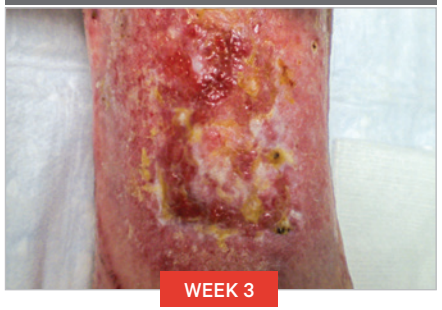
2nd Apligraf application



WEEK 1

Pre-debridement
Date: 04/03/12
Wound size: 6.5 x 4.0 x 0.1 cm
Wound area: 26.0 cm^2

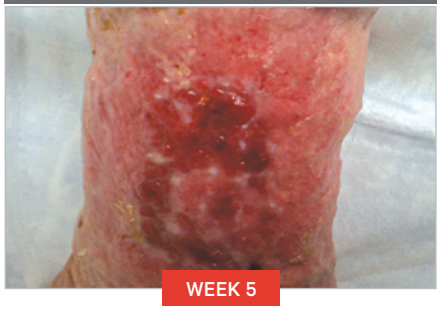
3rd Apligraf application



WEEK 3

Pre-debridement
Date: 04/17/12
Wound size: 5.0 x 3.5 x 0.2 cm
Wound area: 17.5 cm^2

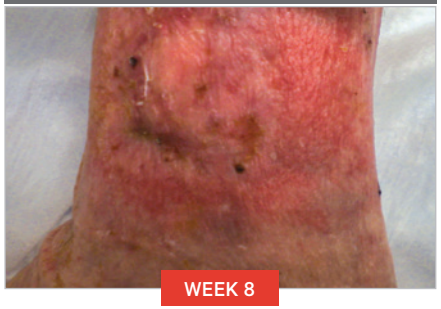
4th Apligraf application



WEEK 5

Pre-debridement
Date: 05/01/12
Wound size: 5.8 x 2.5 x 0.1 cm
Wound area: 14.5 cm^2

Complete wound closure



WEEK 8

Date: 05/22/12

Case initially presented in 2012.

VLU CASE 4 Courtesy of Antonio J. Carrasco, PhD, MD

VLU healed at 11 weeks with a combination of PuraPly® AM and Apligraf®

59-year-old male with a chronic VLU on the left distal lateral calf

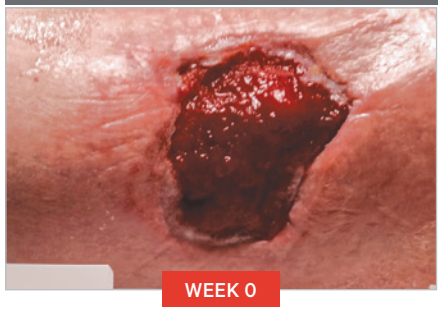
WOUND SPECIFICS
- Initial wound area (at time of Apligraf treatment) was 16.8 cm^2
- Wound was present for 16 weeks, including 5 weeks of PuraPly AM application

COMORBIDITIES
Hypertension, diabetes, and obesity; previous abscess and cellulitis, which were treated with antibiotics

PREVIOUS TREATMENTS
Collagen and NPWT; PuraPly AM was used for 5 consecutive weeks to control bioburden and prevent biofilm re-formation prior to Apligraf treatment

APLIGRAF APPLICATION SCHEDULE
- 5 applications over 6 weeks
- Compression wrap applied during Apligraf treatment

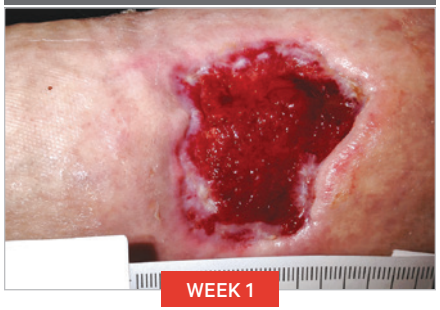
1st Apligraf application



WEEK 0

Post-debridement
Date: 11/04/15
Wound size: 4.0 x 4.2 x 0.4 cm
Wound area: 16.8 cm^2

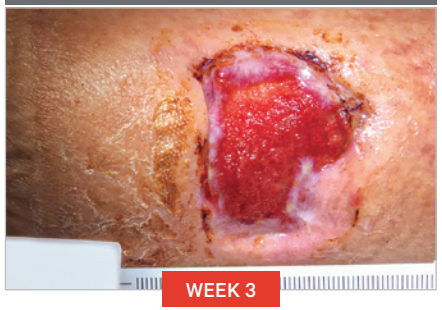
2nd Apligraf application



WEEK 1

Post-debridement
Date: 11/10/15
Wound size: 3.6 x 4.3 x 0.3 cm
Wound area: 15.5 cm^2

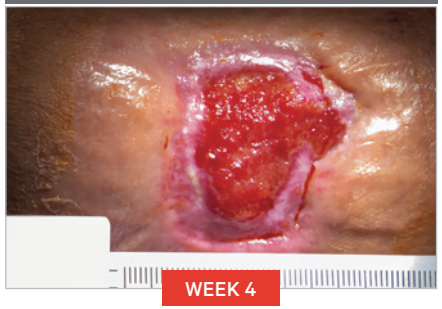
3rd Apligraf application



WEEK 3

Post-debridement
Date: 11/24/15
Wound size: 2.6 x 3.0 x 0.2 cm
Wound area: 7.8 cm^2

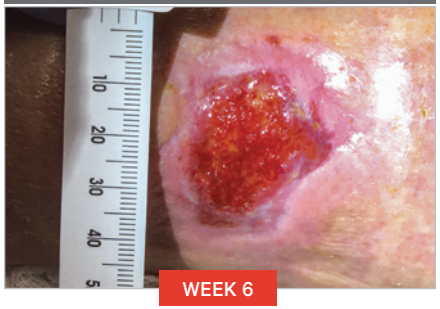
4th Apligraf application



WEEK 4

Post-debridement
Date: 12/01/15
Wound size: 2.6 x 2.8 x 0.2 cm
Wound area: 7.3 cm^2

5th Apligraf application



WEEK 6

Post-debridement
Date: 12/15/15
Wound size: 2.3 x 2.2 x 0.2 cm
Wound area: 5.1 cm^2

Significant reduction in wound size and depth was achieved following 5 applications of Apligraf. Wound was on an excellent healing trajectory, and the physician decided to reinitiate PuraPly AM to manage biofilm re-formation. Following 2 PuraPly AM applications, complete wound closure was achieved on 01/19/16.

Case initially presented in 2016.

VLU healed at 7 weeks with a combination of PuraPly® AM and Apligraf®

58-year-old female with a chronic VLU on the distal lateral aspect of the left leg

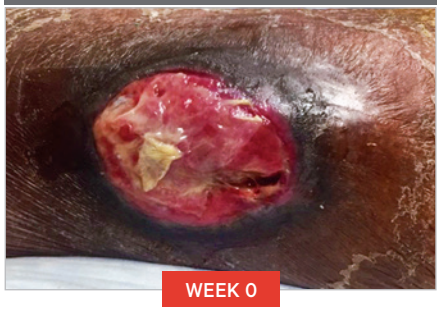
WOUND SPECIFICS
- Initial wound area (at time of Apligraf treatment) was 17.5 cm^2
- Wound was present for 17 weeks, including 4 weeks of PuraPly AM application

COMORBIDITIES
Congestive heart failure, peripheral vascular disease, hypertension, and diabetes

PREVIOUS TREATMENTS
Wet-to-dry dressings and Unna's boot compression; PuraPly AM was used for 4 consecutive weeks to control bioburden and prevent biofim re-formation prior to Apligraf treatment

APLIGRAF APPLICATION SCHEDULE
- 3 applications over 5 weeks
- Compression wrap applied during Apligraf treatment

1st Apligraf application



WEEK 0

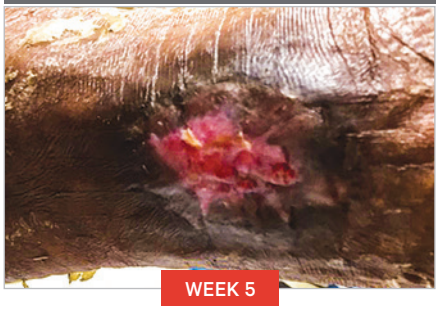
Pre-debridement
Date: 06/16/16
Wound size: 5.0 x 3.5 x 0.5 cm
Wound area: 17.5 cm^2

2nd Apligraf application

WEEK 3

Pre-debridement
Date: 07/05/16
Wound size: 4.0 x 3.5 x 0.5 cm
Wound area: 14.0 cm^2

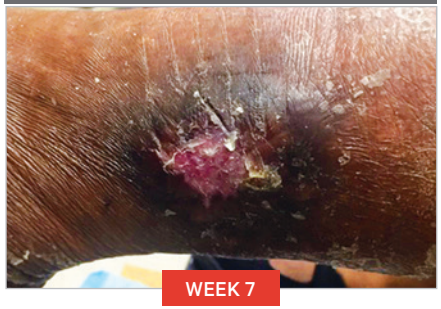
3rd Apligraf application



WEEK 5

Pre-debridement
Date: 07/19/16
Wound size: 3.0 x 2.5 x 0.2 cm
Wound area: 7.5 cm^2

Complete wound closure



WEEK 7

Date: 08/02/16

Case initially presented in 2016.

VLU healed at 6 weeks with 3 applications of Apligraf®—patient initially presented with an exposed arterial graft.

78-year-old female with a chronic VLU on the lower left leg

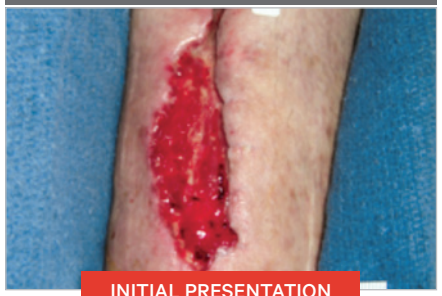
WOUND SPECIFICS
- Initial wound area was 20.8 cm^2
- Wound was present for 18 weeks (4.5 months)

COMORBIDITIES
Hypertension, diabetes, and peripheral vascular disease

PREVIOUS TREATMENTS
Femoropopliteal bypass surgery 2 years prior to initial visit; patient did not respond adequately to standard of care

APLIGRAF APPLICATION SCHEDULE
- 3 applications over 3.5 weeks
- 3-layer compression wrap applied during Apligraf treatment

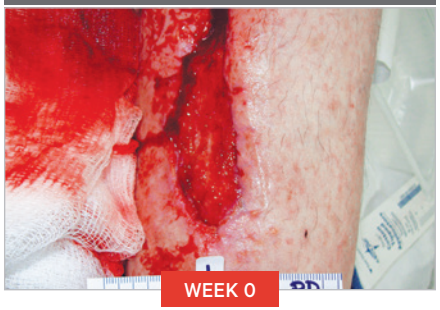
Exposed arterial graft



INITIAL PRESENTATION

Post-debridement
Date: 01/27/12
Wound size: 10.5 x 2.5 x 0.8 cm
Wound area: 26.2 cm^2

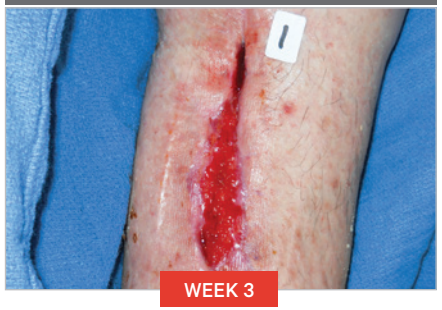
1st Apligraf application



WEEK 0

Post-debridement
Date: 02/17/12
Wound size: 9.9 x 2.1 x 0.5 cm
Wound area: 20.8 cm^2

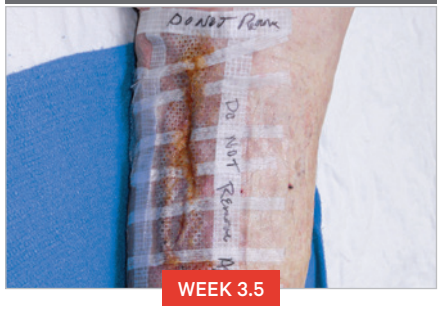
2nd Apligraf application



WEEK 3

Pre-debridement
Date: 03/05/12
Wound size: 9.4 x 1.0 x 0.5 cm
Wound area: 9.4 cm^2

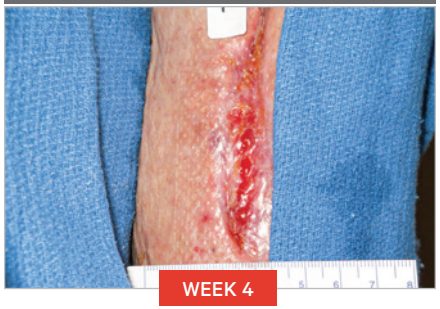
3rd Apligraf application*



WEEK 3.5

Pre-debridement
Date: 03/09/12
Wound size: 9.5 x 0.9 x 0.5 cm
Wound area: 8.6 cm^2

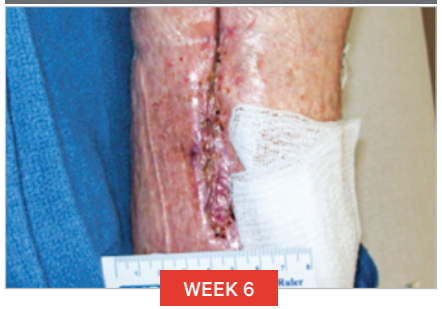
Reassessment



WEEK 4

Post-debridement
Date: 03/16/12
Wound size: 3.5 x 0.7 x 0.1 cm
Wound area: 2.4 cm^2

Complete wound closure



WEEK 6

Date: 03/30/12

*Apligraf was reapplied to speed wound closure.

Case initially presented in 2012.

Large VLU of long duration healed at 11 weeks with 4 applications of Apligraf® and remained healed at 23 weeks.

63-year-old male with a large, shallow, chronic VLU on the lower right leg

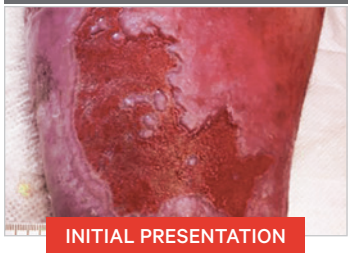
WOUND SPECIFICS
- Initial wound area was 100.0 cm^2
- Wound was present for 64 weeks (16 months)

COMORBIDITIES
Obesity, hypertension, and cellulitis (staph) at initial presentation

PREVIOUS TREATMENTS
Cellulitis was treated with oral antibiotics; patient did not respond adequately to standard of care

APLIGRAF APPLICATION SCHEDULE
- 4 applications over 9 weeks
- Unna's boot used during Apligraf treatment

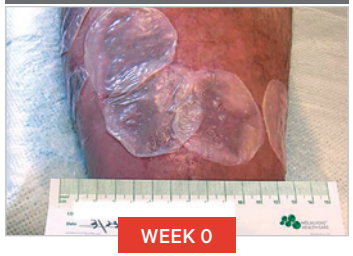
Cellulitis confirmed



INITIAL PRESENTATION

Pre-debridement
Date: 03/16/11
Wound size: 10.0 x 10.0 x 0.1 cm
Wound area: 100.0 cm^2

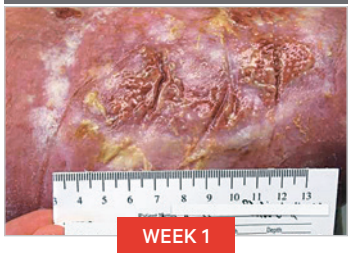
1st Apligraf application



WEEK 0

Post-application
Date: 03/23/11
Wound size: 10.0 x 10.0 x 0.1 cm
Wound area: 100.0 cm^2

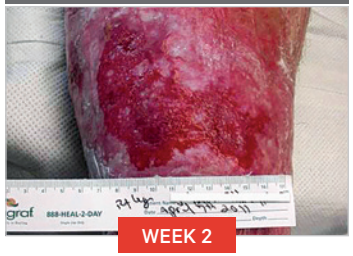
2nd Apligraf application



WEEK 1

Pre-debridement
Date: 03/29/11
Wound size: 6.5 x 6.0 x 0.1 cm
Wound area: 39.0 cm^2

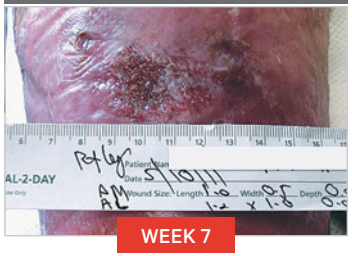
3rd Apligraf application



WEEK 2

Post-debridement
Date: 04/07/11
Wound size: 6.5 x 6.0 x 0.1 cm
Wound area: 39.0 cm^2

Reassessment



WEEK 7

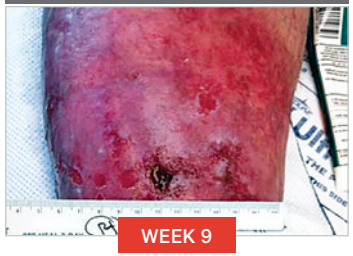
Post-debridement
Date: 05/10/11
Wound size: 1.2 x 1.0 x 0.0 cm
Wound area: 1.2 cm^2

Reassessment

WEEK 8

Date: 05/17/11
Wound size: 1.0 x 1.0 x 0.0 cm
Wound area: 1.0 cm^2

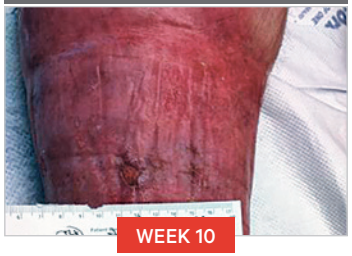
4th Apligraf application



WEEK 9

Post-debridement
Date: 05/24/11
Wound size: 0.9 x 0.5 x 0.1 cm
Wound area: 0.4 cm^2

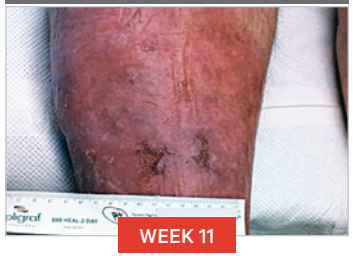
Reassessment



WEEK 10

Post-debridement
Date: 05/31/11
Wound size: 0.8 x 0.7 x 0.0 cm
Wound area: 0.6 cm^2

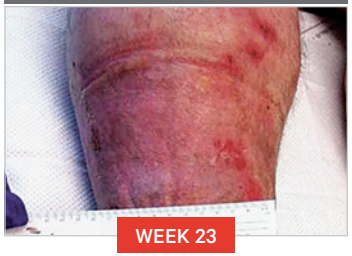
Complete wound closure



WEEK 11

Date: 06/07/11

Wound remained closed



WEEK 23

Date: 08/31/11

Case initially presented in 2011.

VLU CASE 8 Courtesy of Michael S. Robinowitz, MD, FAPWOA, FACOG and Kim Prescott, PT, CWS

Large VLU healed at 13 weeks with 5 applications of Apligraf® and remained healed at 21 weeks.

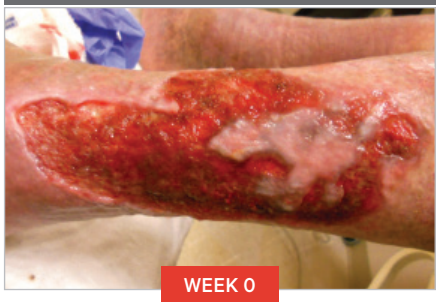
81-year-old male with a chronic VLU on the left lateral leg

WOUND SPECIFICS
- Initial wound area was 184.2 cm^2
- Wound was present for 36 weeks (9 months)

COMORBIDITIES
Peripheral vascular disease and a history of recurrent ulcerations and infections on the left leg

APLIGRAF APPLICATION SCHEDULE
- 5 applications over 9 weeks
- Multi-layer compression applied during Apligraf treatment

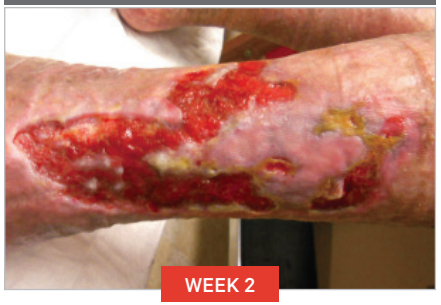
1st Apligraf application



WEEK 0

Post-debridement
Date: 12/02/11
Wound area: 184.2 cm^2

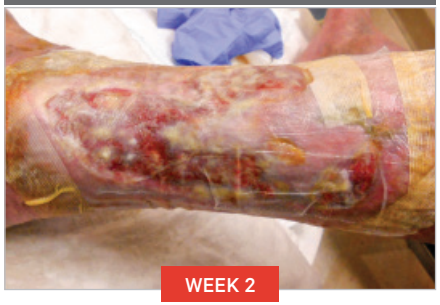
2nd Apligraf application



WEEK 2

Post-debridement
Date: 12/16/11
Wound area: 115.5 cm^2

Reassessment



WEEK 2

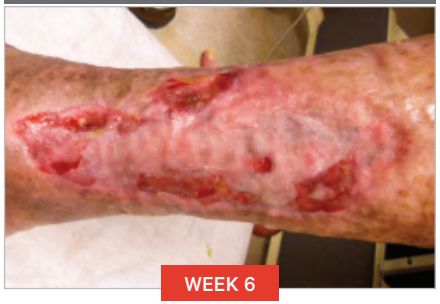
Date: 12/19/11
No wound measurements available.

3rd Apligraf application

WEEK 3

Date: 12/30/11
Apligraf application documented, but no photo or wound measurements available.

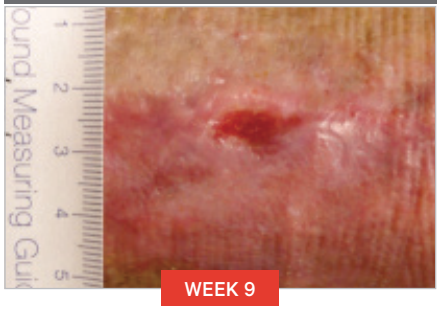
4th Apligraf application



WEEK 6

Post-debridement
Date: 01/17/12
Wound area: 3.94 cm^2

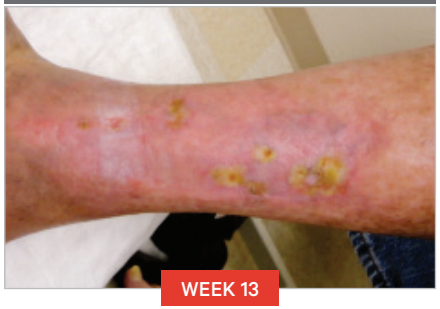
5th Apligraf application



WEEK 9

Post-debridement
Date: 02/07/12
Wound area: 0.28 cm^2

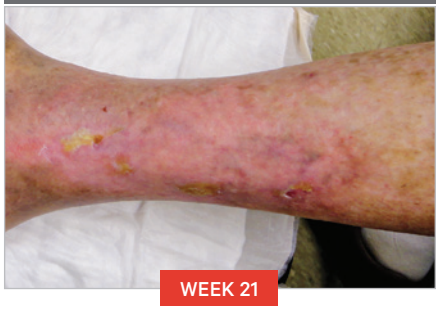
Complete wound closure



WEEK 13

Date: 03/06/12

Wound remained closed



WEEK 21

Date: 05/03/12

Case initially presented in 2012.

Large VLU healed at 12 weeks with 4 applications of Apligraf® and showed evidence of repigmentation by 28 weeks.

50-year-old female with a large, shallow, chronic VLU on the lower right leg

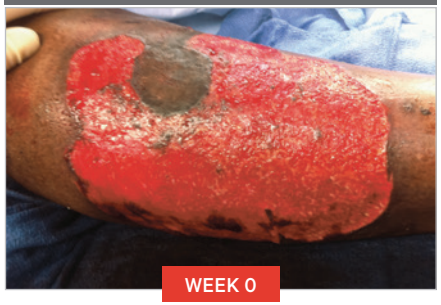
WOUND SPECIFICS
- Initial wound area was 350.0 cm^2
- Wound was present for 14 weeks (3.5 months)

COMORBIDITIES
Peripheral vascular disease, multiple myeloma, anemia, and MRSA at initial presentation

PREVIOUS TREATMENTS
MRSA was resolved prior to Apligraf treatment; patient did not respond adequately to standard of care

APLIGRAF APPLICATION SCHEDULE
- 4 applications over 10 weeks
- 4-layer compression applied from week 0 to week 9; low-level compression applied from week 10 to week 12

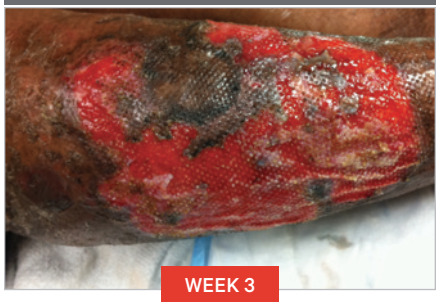
1st Apligraf application



WEEK 0

Post-debridement
Date: 06/28/11
Wound size: 20.0 x 17.5 x 0.2 cm
Wound area: 350.0 cm^2

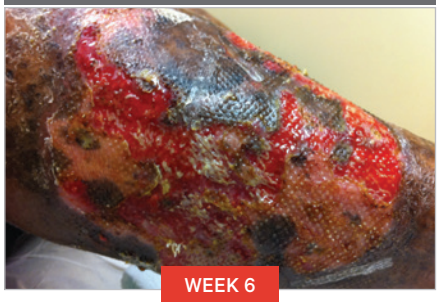
2nd Apligraf application



WEEK 3

Pre-debridement
Date: 07/20/11
Wound size: 17.0 x 15.0 x 0.1 cm
Wound area: 255.0 cm^2

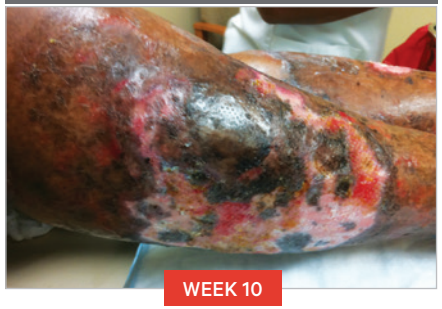
3rd Apligraf application



WEEK 6

Pre-debridement
Date: 08/10/11
Wound size: 12.0 x 9.0 x 0.1 cm
Wound area: 108.0 cm^2

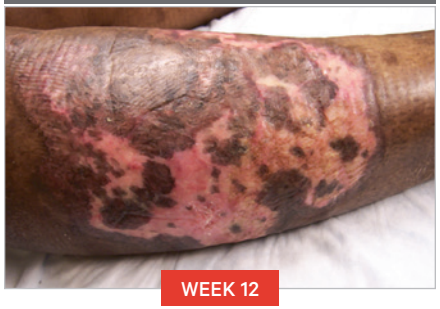
4th Apligraf application



WEEK 10

Pre-debridement
Date: 09/07/11
Wound size: 3.0 x 2.0 x 0.0 cm
Wound area: 6.0 cm^2

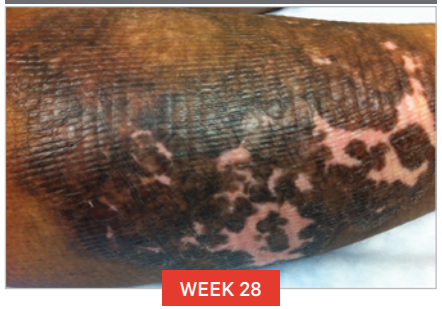
Complete wound closure



WEEK 12

Date: 09/21/11

Wound remained closed



WEEK 28

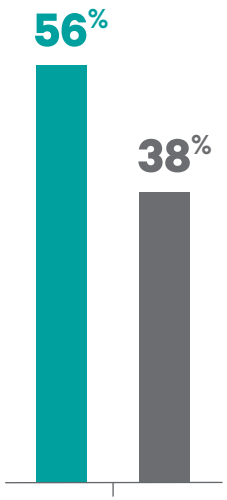
Date: 01/12/12

MRSA = methicillin-resistant *Staphylococcus aureus*
Case initially presented in 2011.

An RCT and real-world observational study have proven that Apligraf® closes more DFUs faster and helps patients avoid complications.

RCT required for FDA approval[20]

Apligraf (n=112 patients) **vs** **Control** (n=96 patients)



Incidence of DFU closure at **Week 12**
P=0.0042

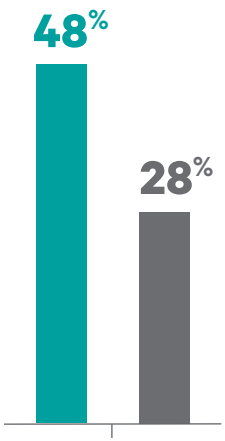
Median time to wound closure **65 vs 90 days**
P=0.0026

25 DAYS FASTER

A prospective, randomized, controlled, multicenter unmasked study was conducted to evaluate the safety and efficacy of Apligraf in comparison to control treatment, saline-moistened gauze, in the treatment of diabetic neuropathic foot ulcers. Wound closure was defined as 100% epithelialization without drainage.

Observational comparative effectiveness study[24]

Apligraf (n=163 wounds) **vs** **EpiFix®** (n=63 wounds)



Incidence of DFU closure at **Week 12**
P=0.01

Median time to wound closure **13 vs 26 weeks**
P=0.01

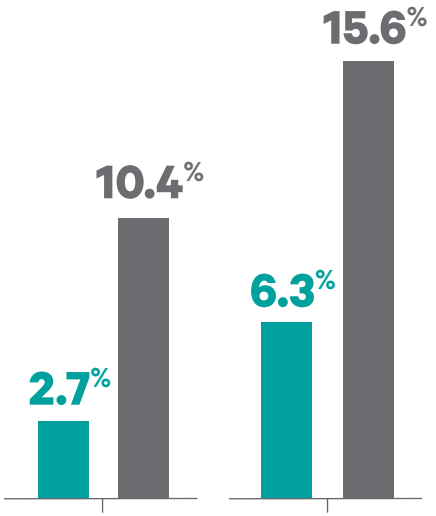
49% FASTER HEALING

Estimated incidence of and median time to wound closure and *P* value are from a Cox regression model with terms for treatment, baseline wound area, duration, depth, and location. *P*=0.01. Wound closure defined as an ulcer achieving an area between 0 and 0.25 cm^2. Although more patients received Apligraf treatment vs EpiFix in the database, there were no preferential exclusion/inclusion criteria applied. Additionally, the statistical methods employed ensure no bias for number of patients in either treatment group. The primary analyses were frequency of wound closure by week 12 and week 24, and median time to wound closure. As patients with healed wounds do not always follow up, wound closure was defined as an ulcer achieving area ≤0.25 cm^2.

Effectiveness is the extent to which an intervention produces an overall health benefit in routine clinical practice (real-world situations). Effectiveness studies do not establish efficacy or comparative superiority. Based on data obtained from a large wound care–specific Electronic Medical Record (EMR) database (WoundExpert®, Net Health, Pittsburgh, PA). Data are from January 1, 2014, through December 31, 2014.

In DFUs, Apligraf has been shown to avoid serious complications, including osteomyelitis and amputations[20]

Apligraf (n=112 patients) **vs** **Control** (n=96 patients)



Incidence of osteomyelitis at **6 months**
P=0.04

Incidence of amputation (on study limb) at **6 months**
P=0.028

This study was not designed to determine the incidence of osteomyelitis or amputations. These data were acquired through evaluation of clinical trial adverse events.

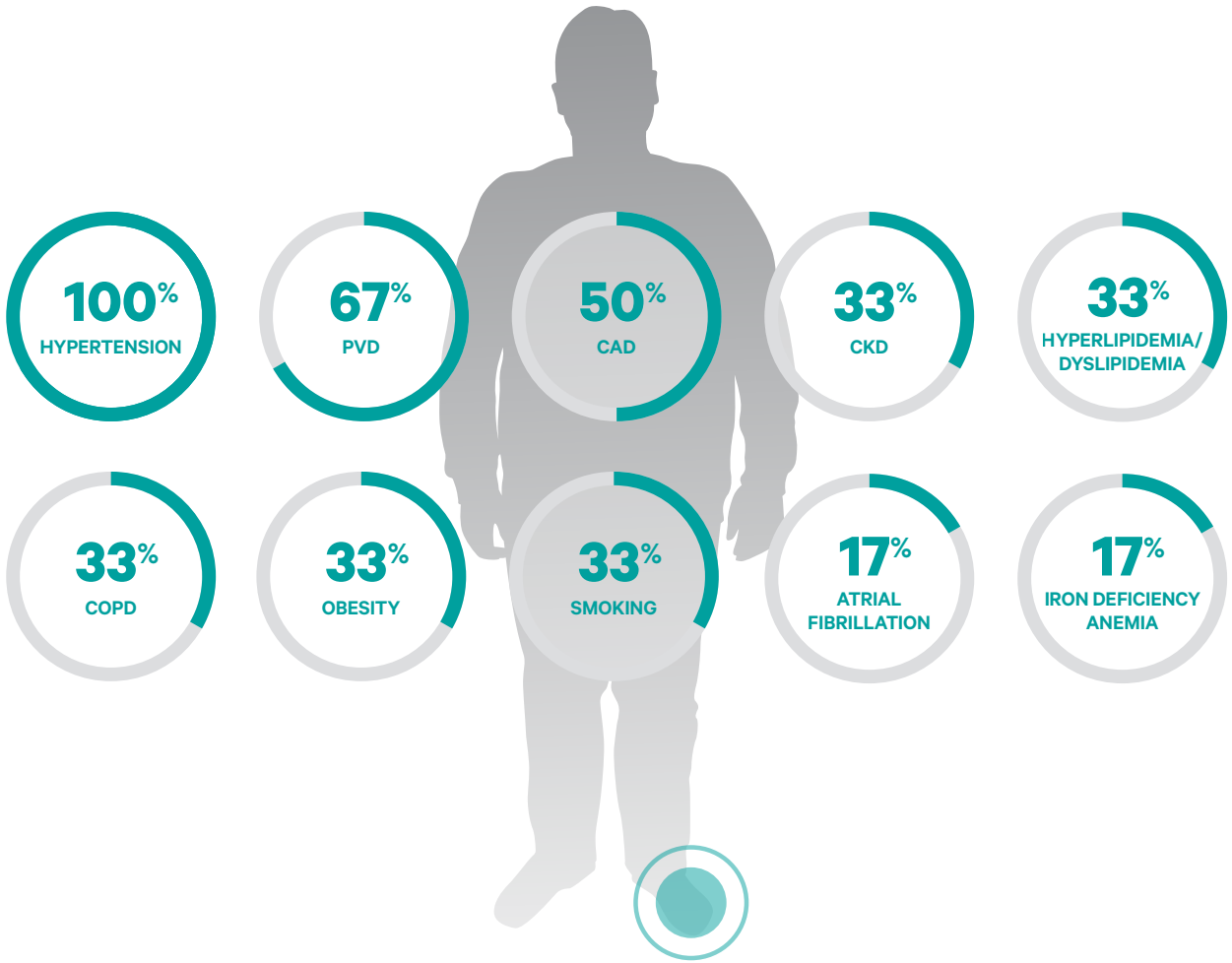
Overview of Apligraf® DFU case studies

Patient demographics, comorbidities, and wound specifics

- 6 patients (5 males; 1 female)
- Mean patient age: 68 years (range, 45 to 80 years)
- Wound duration
  - 22.8 weeks (mean)
  - 24.8 weeks (median)
  - 4 to 35 weeks (range)
- Wound area
  - 31.6 cm^2 (mean)
  - 8.4 cm^2 (median)
  - 1.2 to 140.0 cm^2 (range)

Prevalence of comorbidities

Patients (%)



CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease

DFU CASE 1 Courtesy of Reynald Allam, MD

DFU on the plantar surface and of long duration healed at 5 weeks with 2 applications of Apligraf®

71-year-old male with a DFU on the plantar surface of the right foot

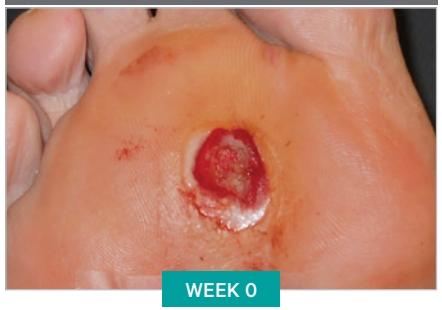
WOUND SPECIFICS
- Initial wound area was 1.2 cm^2
- Wound was present for 35 weeks (8 months)

COMORBIDITIES
Coronary artery disease, coronary angioplasty, hypertension, obesity, and smoking

PREVIOUS TREATMENTS
Calcium alginate nonadherent dressing, knee walker scooter, and an offloading shoe

APLIGRAF APPLICATION SCHEDULE
- 2 applications over 3 weeks
- Walking boot used for offloading during Apligraf treatment

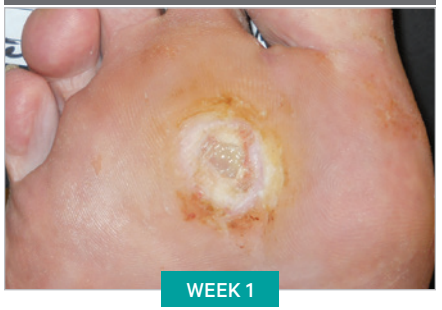
1st Apligraf application



WEEK 0

Post-debridement
Date: 03/27/12
Wound size: 1.2 x 1.0 x 0.5 cm
Wound area: 1.2 cm^2

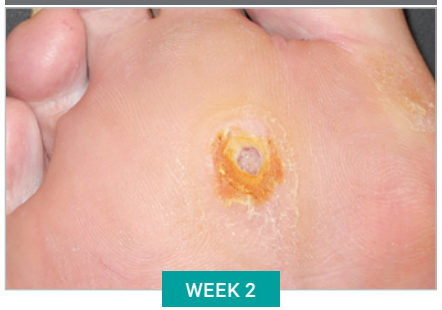
Reassessment



WEEK 1

Pre-debridement
Date: 04/03/12
Wound size: 0.8 x 0.5 x 0.1 cm
Wound area: 0.4 cm^2

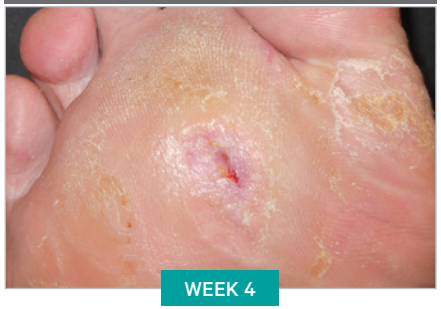
2nd Apligraf application



WEEK 2

Pre-debridement
Date: 04/13/12
Wound size: 0.5 x 0.4 x 0.2 cm
Wound area: 0.2 cm^2

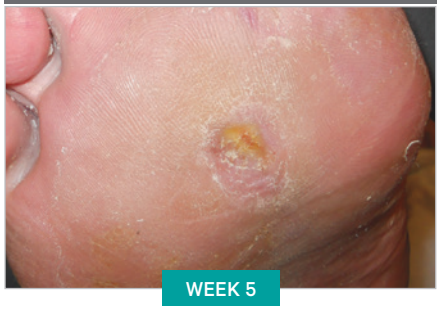
Reassessment



WEEK 4

Post-debridement
Date: 04/24/12
Wound size: 0.1 x 0.1 x 0.01 cm
Wound area: 0.01 cm^2

Complete wound closure



WEEK 5

Date: 05/01/12

Case originally presented in 2013.

DFU healed at 7 weeks with a combination of PuraPly® AM and Apligraf®

80-year-old male with a Wagner Grade 2 DFU on the medial aspect of the 1st left metatarsal head

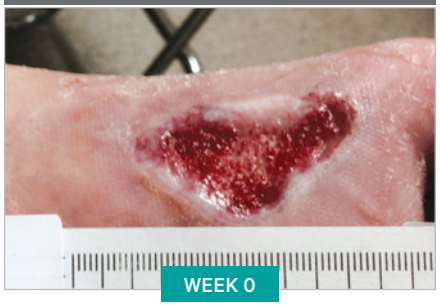
WOUND SPECIFICS
- Wound area (at time of Apligraf treatment) was 3.4 cm^2
- Wound was present for 44 weeks (9+ months), including 5 weeks of PuraPly AM

COMORBIDITIES
Atrial fibrillation, chronic obstructive pulmonary disease, hypertension, iron deficiency anemia, and peripheral vascular disease

PREVIOUS TREATMENTS
Conventional care followed by 5 consecutive weeks of PuraPly AM applications to control bioburden and prevent biofilm re-formation prior to Apligraf treatment

APLIGRAF APPLICATION SCHEDULE
- 5 applications over 5 weeks
- Offloading shoe used during Apligraf treatment

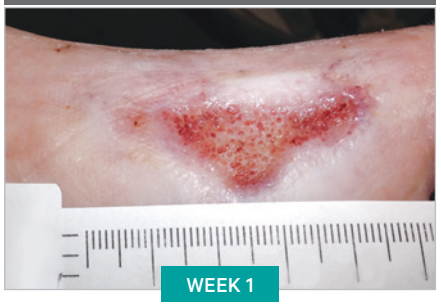
1st Apligraf application



WEEK 0

Post-debridement
Date: 10/26/15
Wound size: 2.6 x 1.3 x 0.1 cm
Wound area: 3.4 cm^2

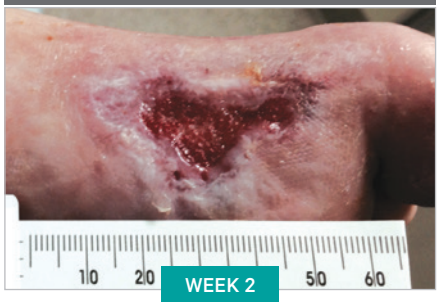
2nd Apligraf application



WEEK 1

Post-debridement
Date: 11/02/15
Wound size: 2.6 x 1.1 x 0.1 cm
Wound area: 2.9 cm^2

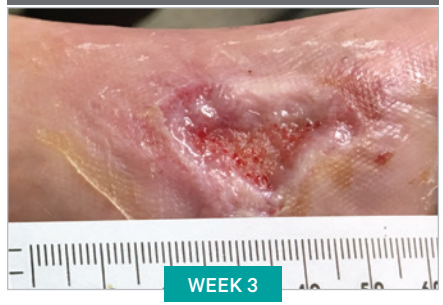
3rd Apligraf application



WEEK 2

Post-debridement
Date: 11/09/15
Wound size: 2.5 x 1.1 x 0.1 cm
Wound area: 2.8 cm^2

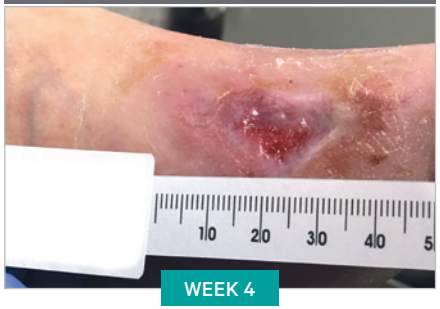
4th Apligraf application



WEEK 3

Post-debridement
Date: 11/16/15
Wound size: 1.7 x 1.1 x 0.1 cm
Wound area: 1.9 cm^2

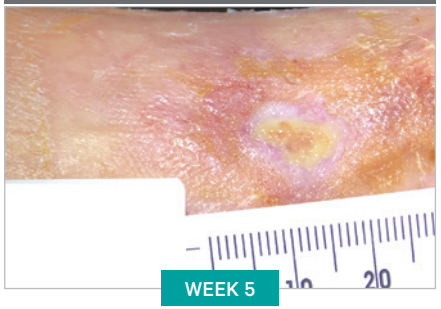
5th Apligraf application



WEEK 4

Post-debridement
Date: 11/23/15
Wound size: 1.0 x 0.5 x 0.1 cm
Wound area: 0.5 cm^2

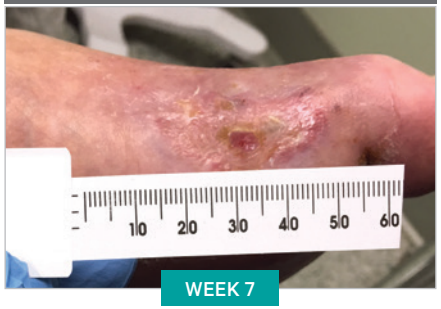
Reassessment



WEEK 5

No debridement required
Date: 11/30/15
Wound size: 0.5 x 0.5 x 0.1 cm
Wound area: 0.25 cm^2

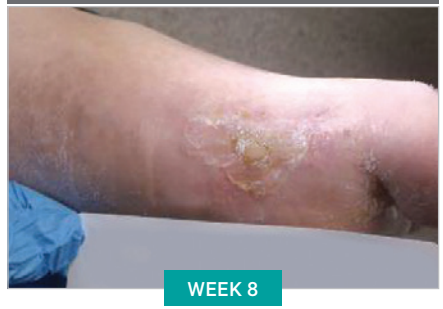
Complete wound closure



WEEK 7

Date: 12/16/15

Wound remained closed



WEEK 8

Date: 12/21/15
Wound remained closed as of 5/10/16.

Case originally presented in 2016.

DFU CASE 3 Courtesy of Robert C. Oram, MD and Stephanie K. Estrada, APRN

DFU healed at 6 weeks with 5 applications of Apligraf® in a patient with multiple comorbidities and previous amputation.

45-year-old female with a DFU on the right foot

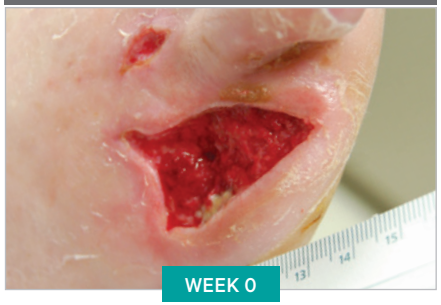
WOUND SPECIFICS
- Initial wound area was 5.7 cm^2
- Wound was present for 4 weeks (1 month)

COMORBIDITIES
Peripheral arterial disease, dyslipidemia, hypertension, obesity, chronic pain, heart attack, stroke, OCD, chronic smoking, right forefoot cellulitis, and gas gangrene on the fifth toe

PREVIOUS TREATMENTS
Right fifth toe amputation, atherectomy, balloon angioplasty and stent placement, negative pressure therapy, and conventional wound care

APLIGRAF APPLICATION SCHEDULE
- 5 applications over 6 weeks
- Front offloading shoe used during Apligraf treatment

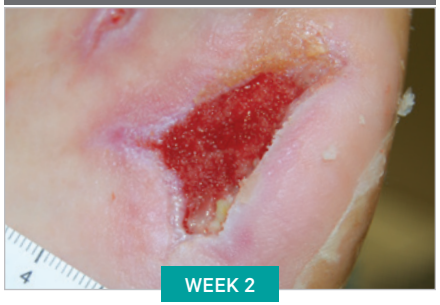
1st Apligraf application



WEEK 0

Post-debridement
Date: 03/15/13
Wound size: 1.9 x 3.0 x 0.7 cm
Wound area: 5.7 cm^2

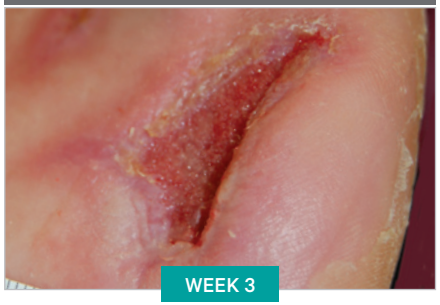
2nd Apligraf application



WEEK 2

Post-debridement
Date: 03/29/13
Wound size: 1.2 x 2.7 x 0.3 cm
Wound area: 3.2 cm^2

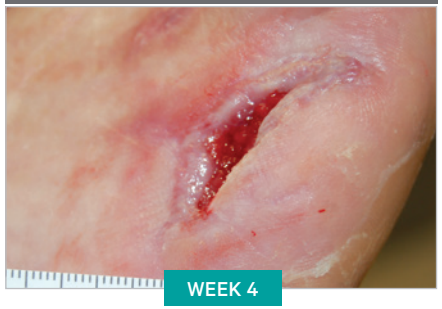
3rd Apligraf application



WEEK 3

Post-debridement
Date: 04/05/13
Wound size: 1.0 x 2.6 x 0.1 cm
Wound area: 2.6 cm^2

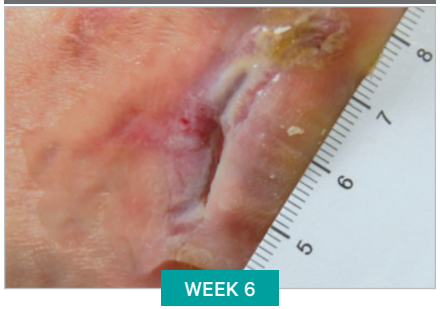
4th Apligraf application



WEEK 4

Post-debridement
Date: 04/12/13
Wound size: 0.5 x 2.3 x 0.2 cm
Wound area: 1.2 cm^2

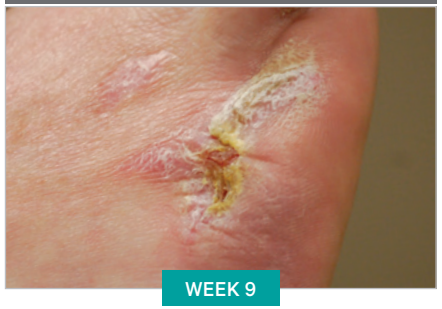
5th Apligraf application



WEEK 6

Pre-debridement
Date: 04/22/13
Wound size: 1.1 x 0.2 x 0.2 cm
Wound area: 0.2 cm^2

Complete wound closure



WEEK 9

Date: 05/15/13

Case originally presented in 2014.

DFU at amputation site healed at 7 weeks with a combination of PuraPly® AM and Apligraf®

73-year-old male with a DFU on the amputation site of the right foot

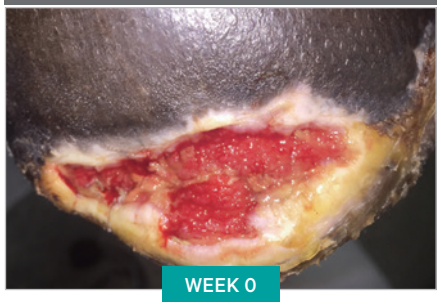
WOUND SPECIFICS
- Wound area (at time of Apligraf treatment) was 11.0 cm^2
- Wound was present for 15.5 weeks (4+ months), including 7 weeks of PuraPly AM

COMORBIDITIES
Coronary artery disease, chronic kidney disease (end stage and on dialysis), COPD, peripheral vascular disease, hypertension, venous insufficiency, and former smoker

PREVIOUS TREATMENTS
NPWT, Santyl, and foam dressings, followed by 6 applications of PuraPly AM over 7 weeks to control bioburden and prevent biofilm re-formation prior to Apligraf treatment

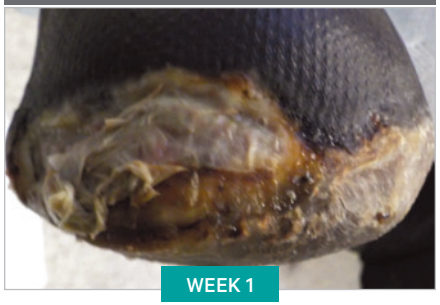
APLIGRAF APPLICATION SCHEDULE
- 5 applications over 6 weeks
- Patient was non-weight bearing during Apligraf treatment

1st Apligraf application



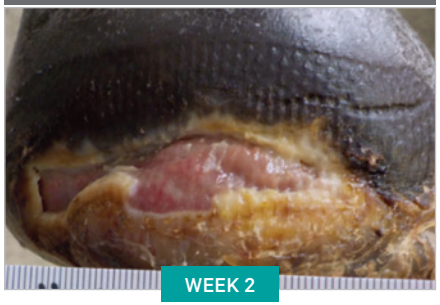
Post-debridement
Date: 11/14/16
Wound size: 2.0 x 5.5 x 0.2 cm
Wound area: 11.0 cm^2

2nd Apligraf application



Pre-debridement
Date: 11/21/16
Wound size: 1.5 x 5.5 x 0.2 cm
Wound area: 8.2 cm^2

3rd Apligraf application

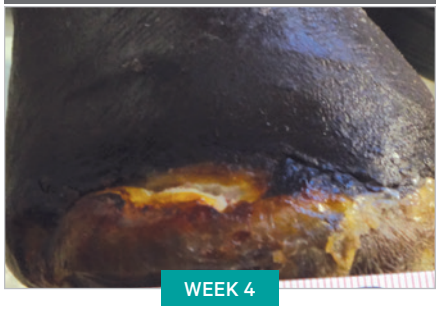


Pre-debridement
Date: 11/28/16
Wound size: 1.4 x 5.2 x 0.2 cm
Wound area: 7.3 cm^2

4th Apligraf application

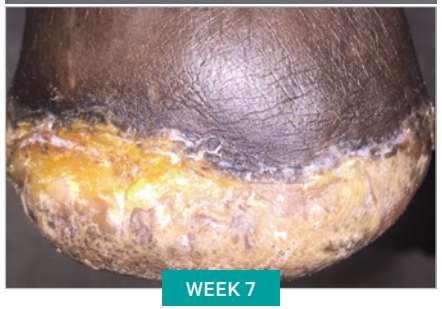
Pre-debridement
Date: 12/05/16
Wound size: 1.0 x 4.3 x 0.1 cm
Wound area: 4.3 cm^2

5th Apligraf application



Pre-debridement
Date: 12/12/16
Wound size: 1.0 x 3.5 x 0.1 cm
Wound area: 3.5 cm^2

Complete wound closure



Date: 01/04/17

Case originally presented in 2017.

DFU CASE 5 Courtesy of Debra Hammers-Bennett, LPN, WCC and Alex Kor, DPM, MS

DFU healed by 11 weeks with 4 applications of Apligraf® in a patient with multiple comorbidities and previous amputation.

66-year-old male with non-healing DFU at site of right foot amputation surgery

WOUND SPECIFICS
- Initial wound area was 28.0 cm^2
- Wound was present for 4 weeks (1 month)

COMORBIDITIES
Peripheral vascular disease, venous insufficiency, hypertension, and chronic kidney disease

PREVIOUS TREATMENTS
Wound infection treated prior to Apligraf application; daily peroxide scrubs and wet-to-dry dressing changes

APLIGRAF APPLICATION SCHEDULE
- 4 applications over 7 weeks
- Wedge forefoot shoe used for offloading during Apligraf treatment

1st Apligraf application

WEEK 0

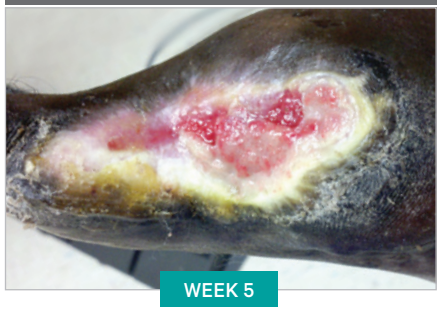
Post-debridement
Date: 06/07/11
Wound size: 4.0 x 7.0 x 1.0 cm
Wound area: 28.0 cm^2

2nd Apligraf application

WEEK 2

Pre-debridement
Date: 06/21/11
Wound size: 3.0 x 6.0 x 0.5 cm
Wound area: 18.0 cm^2

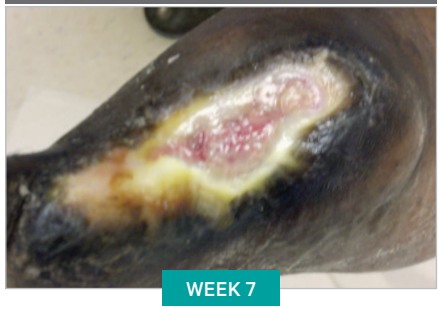
3rd Apligraf application



WEEK 5

Post-debridement
Date: 07/13/11
Wound size: 2.0 x 4.0 x 0.1 cm
Wound area: 8.0 cm^2

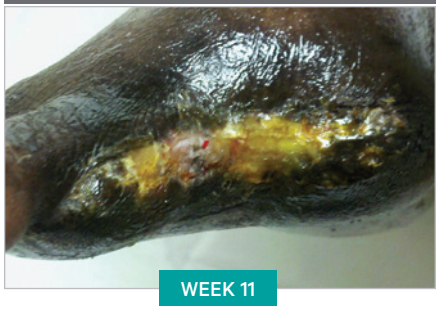
4th Apligraf application



WEEK 7

Pre-debridement
Date: 07/26/11
Wound size: 2.0 x 1.3 x 0.1 cm
Wound area: 2.6 cm^2

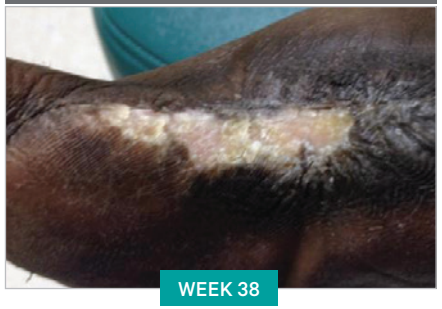
Complete wound closure



WEEK 11

Date: 08/23/11

Wound remained closed



WEEK 38

Date: 02/28/12
Note evidence of re-pigmentation.

Case initially presented in 2012.

DFU healed at 13 weeks with 5 applications of Apligraf® after failing a fasciocutaneous flap and a split-thickness skin graft.

74-year-old male with a chronic DFU on the left foot

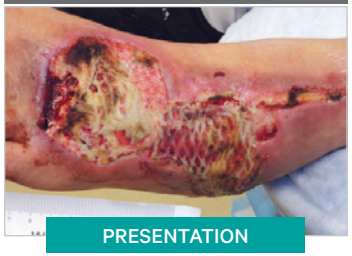
WOUND SPECIFICS
- Initial wound area was 140.0 cm^2
- Wound was present for 34 weeks

COMORBIDITIES
Hypertension and elevated cholesterol

PREVIOUS TREATMENTS
Radical excision and reconstruction with a fasciocutaneous flap; flap necrosis occurred and wound was then debrided and treated with a meshed split-thickness skin graft (STSG), which subsequently failed

APLIGRAF APPLICATION SCHEDULE
- 5 applications over 10 weeks
- Offloading shoe and 2-layer compression used during Apligraf treatment

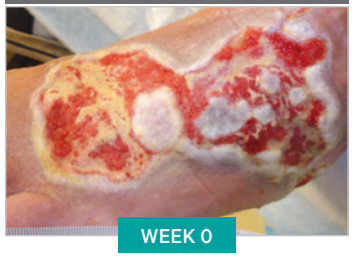
Post-STSG failure



PRESENTATION

Date: 05/31/11

1st Apligraf application

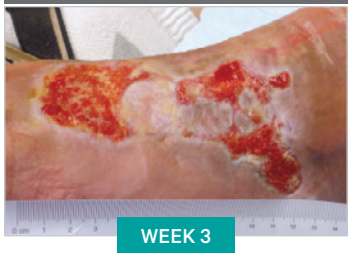


WEEK 0

Pre-debridement

Date: 07/05/11
Wound size: 10.0 x 14.0 x 0.3 cm
Wound area: 140.0 cm^2

2nd Apligraf application

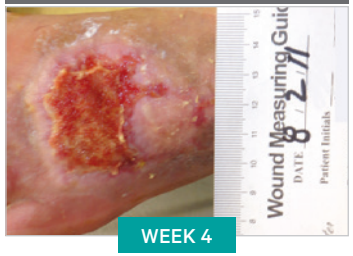


WEEK 3

Pre-debridement

Date: 07/21/11
Wound size: 10.0 x 12.0 x 0.3 cm
Wound area: 120.0 cm^2

3rd Apligraf application

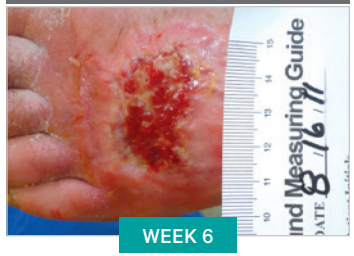


WEEK 4

Pre-debridement

Date: 08/02/11
Wound size: 8.0 x 4.4 x 0.0 cm
Wound area: 35.2 cm^2

Reassessment



WEEK 6

Pre-debridement

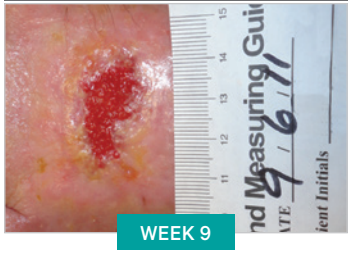
Date: 08/16/11
Wound size: 2.3 x 3.1 x 0.2 cm
Wound area: 7.1 cm^2

4th Apligraf application

WEEK 7

Apligraf application documented, but no photo or wound measurements available.

Reassessment

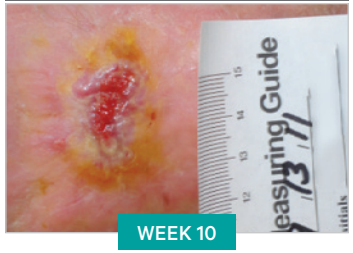


WEEK 9

Pre-debridement

Date: 09/06/11
Wound size: 1.2 x 2.1 x 0.0 cm
Wound area: 2.5 cm^2

5th Apligraf application

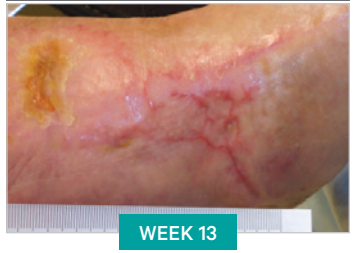


WEEK 10

Pre-debridement

Date: 09/13/11
Wound size: 1.2 x 0.6 x 0.0 cm
Wound area: 0.7 cm^2

Complete wound closure



WEEK 13

Date: 10/04/11

Case initially presented in 2012.

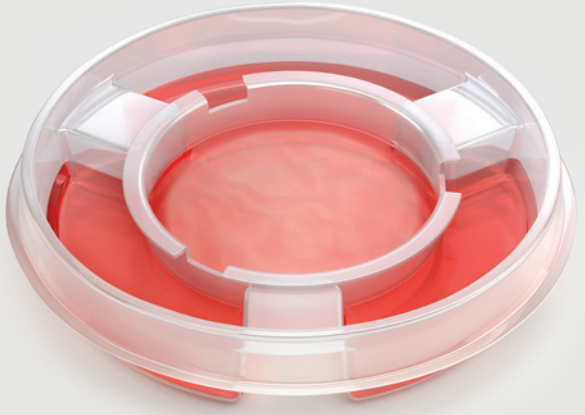
Take a closer look at Apligraf® and its timeless quality of proven results.

Bioengineered with living cells
Restores normal healing functions to actively transform wounds from chronic to acute[1]

Backed by unmatched clinical proof
Extensive studies have demonstrated time and again its ability to heal more VLUs and DFUs faster[18-24]

Unsurpassed access for patients
Quality, proven results plus universal coverage for 100% of Medicare contractors and commercial medical policies[19]

When a VLU or DFU stalls, give your patients the gold standard that heals faster.[18-24]



APLIGRAF ESSENTIAL PRESCRIBING INFORMATION.

Visit Apligraf.com for complete prescribing information and contraindications.

Numbers in parentheses ( ) refer to sections in the main part of the product labeling. Device Description: Apligraf is supplied as a living, bi-layered skin substitute manufactured from cells processed under aseptic conditions using neonatal foreskin-derived keratinocytes and fibroblasts with bovine Type I collagen. (1) Intended Use/Indications: Apligraf is indicated for use with standard therapeutic compression in the treatment of uninfected partial and/or full-thickness skin loss ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. (2) Apligraf is indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness foot ulcers of neuropathic etiology of at least three weeks duration, which have not adequately responded to conventional ulcer therapy and extend through the dermis but without tendon, muscle, capsule or bone exposure. (2) Contraindications: Apligraf is contraindicated for use on clinically infected wounds or in patients with known allergies to bovine collagen or with known hypersensitivity to the components of the Apligraf agarose shipping medium. (3, 4, 5, 8) Warnings and Precautions: If the expiration date or product pH (6.8-7.7) is not within the acceptable range DO NOT OPEN AND DO NOT USE the product. A clinical determination of wound infection should be made based on all of the signs and symptoms of infection. (4, 5)

References: 1. Stone RC, et al. *Sci Transl Med.* 2017;9(371). doi:10.1126/scitranslmed.aaf8611. **2.** Milstone LM, et al. *Wounds.* 2000;12(5 suppl A):12A-19A. **3.** Falanga V, et al. *J Invest Dermatol.* 2002;119(3):653-660. **4.** Brem H, et al. *Surg Technol Int.* 2003;11:23-31. **5.** Wall IB, et al. *J Invest Dermatol.* 2008;128(10):2526-2540. **6.** Hunt TK, et al. *Adv Skin Wound Care.* 2000;13(2 suppl):6-11. **7.** Mendez MV, et al. *J Vasc Surg.* 1998;28(5):876-883. **8.** Cook H, et al. *J Invest Dermatol.* 2000;115(2):225-233. **9.** Kim BC, et al. *J Cell Physiol.* 2003;195(3):331-336. **10.** O'Donnell TF Jr, et al. *J Vasc Surg.* 2014;60(2 suppl):3S-59S. **11.** Barrientos S, et al. *Wound Repair Regen.* 2008;16(5):585-601. **12.** Vande Berg JS, et al. *Surg Clin North Am.* 2003;83(3):509-520. **13.** Smith PC. *Int J Low Extrem Wounds.* 2006;5(3):160-168. **14.** Werner S, et al. *J Invest Dermatol.* 2007;127(5):998-1008. **15.** Stone RC, et al. *Wound Repair Regen.* 2020;28(2):164-176. **16.** Carter MJ, et al. *Adv Skin Wound Care.* 2009;22(7):316-324. **17.** Horn SD. *JAMA.* 2006;296(22):2731-2732. **18.** Apligraf [package insert]. Canton, MA: Organogenesis Inc; 2017. **19.** Data on file. Organogenesis Inc. **20.** Veves A, et al. *Diabetes Care.* 2001;24(2):290-295. **21.** Marston WA, et al. *Wound Repair Regen.* 2014;22(3):334-340. **22.** Treadwell T, et al. *Adv Wound Care.* 2018;7(3):69-76. **23.** Sabolinski ML, et al. *J Comp Eff Res.* 2018;7(8):797-805. **24.** Kirsner RS, et al. *Wound Repair Regen.* 2015;23(5):737-744.

Organogenesis
Apligraf®
Living Cellular Skin Substitute