# Development of a wound healing index for patients with chronic wounds

Susan D. Horn, PhD[1]; Caroline E. Fife, MD[2]; Randall J. Smout, MS[1]; Ryan S. Barrett, BS[1]; Brett Thomson, BS[2]

1. Institute for Clinical Outcomes Research, Salt Lake City, Utah, and
2. Intellicure Inc., Woodlands, Texas

**Reprint requests:**
Miss S. D. Horn, Institute for Clinical Outcomes Research, 669 East South Temple, Suite 300, Salt Lake City, UT 84102, USA.
Tel: +1 801 466 5595 x203;
Fax: +1 801 466 6685;
Email: shorn@isisicor.com

Manuscript received: May 26, 2013
Accepted in final form: August 17, 2013

DOI:10.1111/wrr.12107

## ABSTRACT

Randomized controlled trials in wound care generalize poorly because they exclude patients with significant comorbid conditions. Research using real-world wound care patients is hindered by lack of validated methods to stratify patients according to severity of underlying illnesses. We developed a comprehensive stratification system for patients with wounds that predicts healing likelihood. Complete medical record data on 50,967 wounds from the United States Wound Registry were assigned a clear outcome (healed, amputated, etc.). Factors known to be associated with healing were evaluated using logistic regression models. Significant variables ($p < 0.05$) were determined and subsequently tested on a holdout sample of data. A different model predicted healing for each wound type. Some variables predicted significantly in nearly all models: wound size, wound age, number of wounds, evidence of bioburden, tissue type exposed (Wagner grade or stage), being nonambulatory, and requiring hospitalization during the course of care. Variables significant in some models included renal failure, renal transplant, malnutrition, autoimmune disease, and cardiovascular disease. All models validated well when applied to the holdout sample. The "Wound Healing Index" can validly predict likelihood of wound healing among real-world patients and can facilitate comparative effectiveness research to identify patients needing advanced therapeutics.

Randomized controlled trials (RCTs) are the gold standard to determine clinical efficacy, defined as whether an intervention can be successful when properly implemented under controlled conditions.[1] Patients with chronic wounds suffer from a multitude of comorbid conditions that would have excluded them from nearly every RCT performed in the past 10 years.[2] A recent *Journal of the American Medical Association* article emphasized that future studies must include analyses of patients with comorbid conditions. Its authors state that multivariate, risk-stratified analyses based on easily obtainable clinical variables are "frequently feasible, but rarely performed."[3] In the field of wound care, the limiting factor for such studies has been the lack of a validated method to perform risk stratification.

The Centers for Medicare and Medicaid Services has acknowledged that there is benefit to analyzing real-world data to facilitate wound care research.[4] A byproduct of documenting care within electronic health records (EHRs) is the ability to mine these data for clinical research outcomes, a concept promoted by The Institute of Medicine.[5] Longitudinally linked EHR databases are a source of data for comparative effectiveness research strongly supported by The Federal Coordinating Council for Comparative Effectiveness Research.[6]

Nearly one third of patients in hospital-based outpatient wound centers may not heal their wounds even though they are cared for over a long period of time (outcomes include amputation, death, and failure to improve).[7] Numerous studies over the past two decades have identified specific wound and patient factors known to have a negative impact on healing. Predictive factors of failure to heal specific to the wound itself include size (depth, area, and diameter),[8–16] stage/grade,[7,17] wound "age" (duration since onset),[8] and bacterial load/presence of infection.[13,18,19] Numerous patient factors also known to negatively affect wound healing include renal failure,[7,16,20] age,[8,16,20] and peripheral arterial disease (PAD).[15,16,20] Important patient factors vary by wound type, such as PAD. The EURODIALE study of 1,088 patients in 14 European centers considered PAD, when comorbid with diabetic foot ulcers (DFUs), to be a separate disease state compared with DFUs alone, as infection was only a predictor of nonhealing in patients with both DFUs and PAD.[16] In addition, certain therapeutic interventions have been found to have a predictive effect on healing, including negative pressure wound therapy, hyperbaric oxygen therapy treatment number,

| | |
|---|---|
| CSI | Comprehensive Severity Index |
| DFU | Diabetic foot ulcer |
| EHR | Electronic health record |
| HITECH | Health Information Technology for Economic and Clinical Health |
| IRC | Intellicure Research Consortium |
| PAD | Peripheral arterial disease |
| PQRS | Physician Quality Reporting System |
| USWR | U.S. Wound Registry |
| WHI | Wound Healing Index |

endovascular revascularization, and electrical stimulation. Theoretical mathematical models have been developed to predict healing likelihood of chronic wounds that incorporate many of these predictive factors as their variables and/or parameters. Most of the early theoretical models from the 1980s and 1990s focused on a particular aspect of the healing process such as epidermal healing, extracellular matrix repair, wound contraction, or angiogenesis.[21] Recent models have been more complex and inclusive of multiple processes of healing, although more often than not inflammation has been the focus. It is not possible to incorporate these directly into patient care but they can be used to better understand the mechanism of action of some therapeutic interventions.

Many mathematical models have found ulcer size (area) and healing rates to be significantly correlated.[22–29] Cukjati and colleagues have done extensive work,[26–28] and their most recent model[26] addressed the use of wound area measurements to predict healing, as healing rates cannot be compared easily between wounds with different initial areas.

In general, prior efforts to model wound healing have been hampered by the lack of access to a sufficient volume of data with which to explore interactions, and even today, there are no models that were developed to specifically assess the design and optimization of treatments.[30] Until now, available models have only shown the potential to measure the probability of healing. No useable model exists with which to stratify chronic ulcer patients according to their likelihood of achieving healing.

We describe the use of a unique wound registry (the U.S. Wound Registry) comprised of linked, de-identified EHR data to develop a wound healing predictive model. We specifically did not evaluate the impact of therapeutic interventions (e.g., negative pressure wound therapy, hyperbaric oxygen therapy) but focused only on inherent patient and/or wound factors. The purpose of this model is to create a validated wound/patient risk stratification tool for patients with chronic wounds that is independent of treatments. Such a predictive model can facilitate the use of real-world data for wound healing research, either for prospective clinical trials or for retrospective comparative effectiveness research data analyses.

## MATERIALS AND METHODS

While the Centers for Medicare and Medicaid Services defines "wounds" and "ulcers" as different entities, there being no generic term encompassing both, unless otherwise specified, we use these two terms interchangeably with the same meaning.

### Settings and database description

The data come from an advanced EHR that has achieved a high degree of structured-language usage including one specific to wound care. It has been certified to meet the recent "HITECH" Act (Health Information Technology for Economic and Clinical Health Act)[31] standards. The EHR guides the physician through the pertinent International Classification of Diseases (9th revision) Clinical Modification (ICD-9-CM) diagnosis codes so that the correct diagnosis code is selected.[32] The majority of clinical data entry utilize standard vocabularies and "click and scroll" menu options, with limited use of "free text." Computers are present in every treatment location and point of service documentation is performed by both the nurse and the physician, with the program running off a server at the hospital or the EHR vendor's Computing Cloud. Improved documentation compliance and enhanced reimbursement motivate most facilities and physicians to use such an EHR.

Facilities usually require a year of use before their clinical data are accepted into the registry, with data being reviewed at intervals by vendor staff for consistency and completeness prior to a decision regarding registry data contribution. This national registry of wound care patients currently provides data to the Centers for Medicare and Medicaid Services as part of the Physician Quality Reporting System (PQRS). The Intellicure Research Consortium is a network of hospital-based outpatient wound centers across the United States and Puerto Rico, which agree to share de-identified data from patient electronic health records in exchange for benchmarking services. The aggregate national database known as the U.S. Wound Registry, a not-for-profit company, is recognized by Centers for Medicare and Medicaid Services for PQRS reporting. We used this extensive database to create and validate the Wound Healing Index (WHI) and determine its association with wound healing. At the initiation of this project, the U.S. Wound Registry consisted of approximately 56 clinics in 24 states. The U.S. Wound Registry has an independent Institutional Review Board (IRB) that ensures that research protocols conform to required standards of privacy and research ethics. The IRB determined that retrospective analysis of Health Insurance Portability and Accountability Act [HIPAA]-compliant data as described here was exempt from the requirement for patient consent.

Data from 256,671 wounds were examined. These wounds spanned from as early as July 2003 to July 2011. The breakdown of the data by year is as follows: 10.2% of the wounds occurred in 2003–2007; 12% of the wounds occurred in 2008; 22.4% of the wounds occurred in 2009; 33.4% of the wounds occurred in 2010; and the remaining 22% of the wounds occurred from January to July of 2011.

### Definition of wound type

We defined wound type by ICD-9-CM code. In some cases, multiple ICD-9-CM codes were required to establish a wound type. For example, surprisingly, there is no unique ICD-9-CM code for "diabetic foot ulcer." Clinicians must classify the patient as having a chronic ulcer "related to" the underlying disease of diabetes. A similar method is required to establish that a chronic ulcer is arterial in nature (chronic ulcer related to "atherosclerosis"). The opposite problem is true for venous ulcers that have three distinctly separate ICD-9-CM code sets, and also can be described as chronic ulcers related to venous insufficiency. In some cases, the ICD-9-CM codes are sufficiently detailed in order to specify location on the body (e.g., back, heels).

The Intellicure EHR uses structured language to capture ICD-9-CM data facilitating coding by the clinician and subsequent data extraction for this project. Thus, while the ICD-9-CM system is, in some ways, poorly designed for wound care research, clinicians practicing in the field are familiar with its limitations and were required at the time of data entry to specify the wound type insofar as possible. Clinicians, all of whom were performing point-of-care charting (in the room with the patient), also provided "free text" data entries designating the specific body location (e.g., "left lateral ankle").

We used text field searches when necessary to establish the location on the body of certain wound types if the ICD-9-CM code did not specify location. We also used text field searches when we performed analyses to evaluate left vs. right ulcerations. The wound types studied were defined as any codes with the following beginning digits:

- Amputation—codes 997.6
- Arterial—codes 440.23, 440.24, 443, or 444.2 or codes 707.1 and described as related to atherosclerosis
- Burns—codes 94X.X
- Diabetic Foot Ulcer—codes 250 and codes 707.13–707.15
- Flap or Graft—codes 996.52
- Pressure Ulcer—codes 707.0
- Surgical—codes 996.1, 996.4, 996.74, 998.32, 998.6, 998.83, or E878.8
- Traumatic—codes 707.1 and described as related to trauma or codes 87X.X-89X.X or E917.9 or E924.8
- Venous—codes 454, 459.31, 459.33, 459.81 or codes 707.1 and described as related to venous or venous ulcer

Pressure ulcers were further subdivided by those located on the heels and those not located on the heels, termed body pressure ulcers. This subdivision was warranted on the basis of prior research demonstrating that different risk factors affect the outcome of heel pressure ulcers (e.g., peripheral arterial disease).

These nine wound types included 106,272 wounds (41.4%) of the 256,671 wounds in the original database. Further requirements for inclusion in analyses were imposed by the trans-disciplinary Project Team. These included requiring (1) at least two clinician encounters for each wound; (2) at least 5 days between first and last encounter; (3) no gap longer than 60 days between any two wound encounters; (4) at least one area measurement or a clinician statement of wound outcome; (5) at least one wound assessment with a wound area larger than or equal to 0.25 $cm^2$; (6) wound age; and (7) a specified body location of the wound. Some additional wounds were excluded due to a clinician-assigned outcome considered to be lost to follow up. Imposing these restrictions reduced the sample to 50,967 wounds included for analyses.

## Definition of healed

In ideal circumstances, at the time of the final wound assessment, the clinician would assign an outcome to the wound (e.g., healed, amputated). In some cases, at the final visit the clinician might assign an outcome of "healing" although the wound was not yet closed. Thus, the first-level definition of outcome was that provided by the clinician. Wounds assigned an outcome of "not healed" by the clinician were considered not healed. If the patient died or a clinician-assigned outcome was missing, the wounds were included in the dataset. However, subsequent analysis was necessary to determine whether these unassigned wounds had in fact healed (but were not classified as such), were improving ("healing"), or were showing no evidence of healing. Thus, a hierarchical approach was created to determine whether a wound had healed. If the clinician did not assign an outcome, the second and third levels were size of last area and change in wound area from maximum to last. The fourth level of outcome assessment was last wound depth, and the fifth level was last exposed tissue type. The three categories of exposed tissue types included the following clinician descriptions. We used the worst tissue type category if a wound had descriptions from multiple categories during an encounter.

### *Mild*

This includes: callous, closed, epithelialized, no open areas, no exposed tissue, scar tissue, none, partial thickness, scab, epithelium, incision, external fixators, approximated, flap site, intact, first degree, stage 1, epidermis, suture line intact, blister, staple line intact, hyper granulation, tissue, surgical, suture, sutures, drainage tubes present, dermis, fibrin, second degree, suture line, open, slough, open suture line, graft site, engineered tissue.

### *Moderate*

This includes: subcutaneous, soft tissue, adipose, fat, third degree, full thickness, tunnel.

### *Severe*

This includes: fascia, muscle, unstageable, necrotic tissue, graft mesh, surgical mesh, tendon, joint capsule, cartilage, ligament, periosteum, fistula, bone, bowel, gangrene, hardware, exposed vasculature.

The outcome of healing was defined in a similar manner, with lower thresholds of change in area from maximum to last plus presence of granulation tissue, a decreasing depth of the wound, and improvement in last tissue exposed when available. The semi-hierarchical order of variables used to establish healed and healing wounds are depicted in Table 1 (healed) and Table 2 (healing).

## Data analysis phases

### *Descriptive statistics*

The first phase of analysis used descriptive statistics to examine frequencies of categorical patient, wound, and outcome measures, and average, median, quartiles, and amount of variation (standard deviation and range) for continuous measures.

### *Bivariate analyses*

We next conducted bivariate analyses to test the relationship between each candidate predictor and the outcomes of healed and healing. For discrete variables, we created contingency tables and used chi-square tests, Fisher's exact tests, Wilcoxon tests, or Kendall's tau (for ordered categories) to determine significance of bivariate associations. For continuous variables, we used correlation, two-sample *t*-tests, or analysis of variance. A two-sided $p$-value $<0.05$ was considered statistically significant. Once the dichotomous outcomes of healed and healing were defined, we randomly selected 10% of the wounds in each wound type category to use for model validation.

### *Multivariate logistic analyses*

We performed logistic regression for the dichotomous outcomes of healed and healing on the remaining 90% of wounds

**Table 1.** Hierarchical definition of a wound considered healed

| 1st level Clinician assigned wound outcome | 2nd level Size of last area ($cm^2$) | 3rd level Change from maximum area to last area (%) | 4th level Deep wound (last depth ≥0.5 cm) | 5th level Last exposed tissue type | WHI outcome |
|---|---|---|---|---|---|
| Healed, died, or missing | >2.5 | | | | Not healed |
| | 1.25–2.5 | >50 | Shallow | Mild | Healed |
| | | | | Moderate and change from maximum area to last area ≥80% | Healed |
| | | | Deep | | Not healed |
| | 0.25–1.25 | >30 | Shallow | Mild | Healed |
| | | | | Moderate and change from maximum area to last area ≥80% | Healed |
| | | | Deep | Mild and change from maximum area to last area ≥80% | Healed |
| | | | | Moderate | Not healed |
| | Missing | Missing | Shallow | Mild or (moderate and maximum area ≤2.5 $cm^2$) | Healed |
| Healing | >2.5 | | | | Not healed |
| | 1.25–2.5 | >50 | | | Not healed |
| | 0.25–1.25 | >30 | Shallow | Mild | Healed |
| | | | | Moderate and change from maximum area to last area ≥80% | Healed |
| | | | Deep | Mild and change from maximum area to last area ≥80% | Healed |
| | | | | Moderate | Not Healed |
| | Missing | Missing | Shallow | Mild and maximum area ≤1.25 $cm^2$ | Healed |

WHI, Wound Healing Index.

in each wound type category. In all models, we used data from two time frames: data available at the first visit for one model of likelihood of healed, or data available from all the visits that the wound was treated for the likelihood of healed for six common types of wounds. We did not include models for burns, arterial wounds, or flap or graft wounds due to either small sample sizes or questionable categorization descriptions by providers.

Using suggestions from the trans-disciplinary Project Team and the literature, potential predictors were allowed to enter the models with stepwise selection. From prior analyses, we identified the following patient and wound characteristics as being significantly associated with healing prediction:

- Wound area at first encounter
- Encounter ending with patient sent to the emergency department or hospital
- Patient chronological age
- Diabetes
- Location of wound
- Malnutrition
- Narcotic medications (used as a marker of possible ischemia or inflammatory diseases)
- Mobility of patients at arrival: bed bound, wheelchair, or able to ambulate
- Paralysis
- Peripheral arterial disease
- Pressure ulcer stage
- Number of previous or concurrent wounds or ulcers
- Renal failure
- Signs of inflammation and/or infection in the wound
- Transplant medications
- Wagner grade (for diabetic ulcers)
- Wound age at first encounter

The regression analyses identified patient and wound variables that were significantly associated with increased or decreased likelihood of the wound being healed. We confirmed through pairwise Spearman correlations that no independent variables in the final models were collinear. All correlations between independent variables were less than 0.75. Discrimination was measured by using the area under the receiver operator characteristic curve (c statistic) to evaluate how well the model distinguished wounds that did not achieve the specified outcome (healed or healing) from wounds that did achieve the specified outcome. This was measured on both the first visit and the all visits models using the 90% sample.

The WHI is the predicted probability of a specified wound becoming healed and is created from multiplying the logistic

**Table 2.** Hierarchical definition of a wound considered to be healing

| 1st level: If the wound healed, (see Table 1) then the wound is healing. | | | | | |
|---|---|---|---|---|---|
| 2nd level Clinician assigned wound outcome | 3rd level Size of last area | 4th level Change from maximum area to last area | 5th level Last exposed tissue type | 6th level Granulation and depth | WHI outcome |
| Healed, healing, died, or missing | Present in dataset | >50% | Last exposed < worst exposed | | Healing |
| | | | Last exposed was the same as first exposed and last exposed was mild or moderate | | Healing |
| | | | Last exposed was mild or moderate | Last granulation = 100% or granulation change from maximum to last is ≥50% or last depth ≤0.2 $cm^2$ or depth change from maximum to last is ≥1 $cm^2$ | Healing |
| | Missing from dataset | Missing | Last exposed < worst exposed | | Healing |
| | | | Last exposed was mild or moderate | Last granulation =100% or granulation change from maximum to last is ≥50% or depth change from maximum to last is ≥1 $cm^2$ | Healing |

WHI, Wound Healing Index.

regression parameter estimates by the values of the significant variables for each wound category type. The WHI was validated using the 10% validation sample. In addition, the Hosmer–Lemeshow goodness-of-fit test was used to evaluate the degree of correspondence between WHI-estimated probabilities of achieving the outcome (healed) and the actual outcome proportion over groups spanning the entire range of probabilities (calibration) in the 10% validation models.

Some predictor variables from previous literature were not allowed to enter any of the models; these included any variables related to documented wound treatment, as we did not want wound treatment administered to influence the WHI. If we allowed treatments to enter, then we could not use the WHI to determine which treatments were associated with more healing, as they would already be part of the index. A few other predictor variables (such as irritable bowel disease and chronic obstructive pulmonary disease) were not allowed because they were not significant in bivariate analyses. The Institute for Clinical Outcomes Research team performed analyses as directed by the trans-disciplinary Project Team members.

## RESULTS

Table 3 displays the direction of the bivariate association and its probability significance for each predictor variable with the outcome of healed for six common types of chronic wounds. A similar table was created for the outcome of healing, but the significance and direction of the associations were essentially the same. Predictor variables often were significant for one type of wound but not for other types.

We allowed the predictor variables that were at or near significance in bivariate associations to enter into the logistic regression models. We found a different model was predictive of a wound being healed for each wound type (venous stasis, diabetic foot ulcers, heel pressure ulcers, body pressure ulcers, chronic traumatic wounds, and chronic surgical wounds). Some variables were significant in nearly all models: wound size, age of wound, number of wounds, evidence of bioburden, tissue type exposed (Wagner grade or stage), being nonambulatory, and requiring hospitalization during the course of care. Variables that were significant in some, but not most models, included renal failure, renal transplant, malnutrition, and peripheral vascular disease. Malnutrition was indicated by any of the following three conditions: presence of a malnutrition ICD-9 code (262,263,995.84) found for that patient before or during the treatment episode; a score of 1 or 2 in the nutrition subscale of the Braden score (obtained either during the period of wound treatment or up to 120 days prior to the first wound encounter); or body mass index value less than 18.5 either during the course of wound treatment or, if missing, then during 1–120 days before the

**Table 3.** Variables included in each wound type (testing method inclusion, direction of bivariate association, and probability of significance for each predictor variable with outcome of healed for seven common types of chronic wounds)

| Variable | Used in bivariate testing | Allowed in regression testing | Significant in final regression models | Amputation *n* = 579 | Diabetic *n* = 6,440 | Body pressure ulcers *n* = 7,973 | Heel pressure ulcers *n* = 2,350 | Surgical *n* = 6,206 | Trauma *n* = 12,029 | Venous *n* = 11,773 |
|---|---|---|---|---|---|---|---|---|---|---|
| Infection/bioburden | Yes | Yes | Yes | (–)0.017 | (–)<0.001 | (–)<0.001 | (–)0.002 | (–)<0.001 | (–)<0.001 | (–)<0.001 |
| Patient admitted for acute hospital stay | Yes | Yes | Yes | (–)0.006 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 |
| First wound Area (–: healed wound associated with smaller area); | Yes | Yes | Yes | (–)0.077 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 |
| Malnutrition | Yes | Yes | Yes | (–)0.518 | (–)0.001 | (–)<0.001 | (–)<0.001 | (–)0.001 | (–)<0.001 | (–)0.134 |
| Patient age at first treatment (–: healed wound associated with younger age, +: healed wound associated with older age) | Yes | Yes | Yes | (–)0.022 | (–)<0.001 | (+)0.916 | (–)<0.001 | (+)0.442 | (+)<0.001 | (+)0.030 |
| Patient is on dialysis | Yes | Yes | Yes | (–)0.569 | (–)<0.001 | (–)0.131 | (–)<0.001 | (–)0.069 | (–)<0.001 | (–)0.181 |
| Insulin-dependent diabetes | Yes | Yes | Yes | (–)0.739 | (+)0.979 | (+)0.005 | (–)<0.001 | (–)0.657 | (+)0.095 | (+)<0.001 |
| Patient takes pain medications | Yes | Yes | Yes | (–)0.919 | (–)0.377 | (+)1.000 | (+)0.459 | (+)0.391 | (+)0.614 | (–)<0.001 |
| Paralyzed | Yes | Yes | Yes | (+)1.000 | (–)0.448 | (–)<0.001 | (+)0.495 | (–)<0.001 | (+)0.006 | (+)0.126 |
| Renal transplant or dialysis | Yes | Yes | Yes | (–)0.077 | (–)<0.001 | (–)0.103 | (–)<0.001 | (–)0.113 | (–)0.002 | (–)1.000 |
| Renal transplant | Yes | Yes | Yes | (–)0.110 | (–)0.382 | (+)0.593 | (–)0.052 | (–)0.026 | (+)0.133 | (–)1.000 |
| Wagner Grades* | Yes | Yes | Yes | N/A | <0.001 | N/A | N/A | N/A | N/A | N/A |
| Mobility of patients at arrival—bed bound vs. wheelchair or able to ambulate | Yes | Yes | Yes | (–)0.089 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (–)<0.001 |
| Peripheral vascular disease | Yes | Yes | Yes | (–)0.001 | (–)<0.001 | (+)0.406 | (–)<0.001 | (–)0.063 | (+)0.501 | (–)0.039 |
| Wound age at first encounter | Yes | Yes | Yes | (–)0.167 | (–)<0.001 | (–)<0.001 | (–)0.005 | (–)<0.001 | (–)<0.001 | (–)<0.001 |
| Number of previous or concurrent other wounds or ulcers (–: healed wound associated with fewer other wounds) | Yes | Yes | Yes | (–)0.034 | (–)<0.001 | (–)<0.001 | (–)<0.001 | (+)0.021 | (–)0.017 | (–)<0.001 |
| Stage III, IV, or unstageable | Yes | Yes | Yes | N/A | N/A | (–)<0.001 | (–)<0.001 | N/A | N/A | N/A |
| Wound location* | Yes | Yes | Yes | 0.658 | <0.001 | <0.001 | N/A | 0.063 | <0.001 | 0.577 |
| Days from first to last encounter (–: healed wound associated with shorter time, +: healed wound associated with longer time) | Yes | Yes | No | (+)<.001 | (+)<0.001 | (–)<0.001 | (+)<0.001 | (+)0.013 | (–)0.105 | (–)<0.001 |
| Worst Braden Score (+: healed wounds associated with higher score) | Yes | Yes | No | (+)0.353 | (+)<0.001 | (+)<0.001 | (+)<0.001 | (+)<0.001 | (+)0.014 | (+)0.006 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Braden Malnutrition subset (+: healed wounds associated with higher score) | Yes | Yes | No | (–)0.713 | (+)<0.001 | (+)<0.001 | (+)<0.001 | (+)0.002 | (+)<0.001 | (+)0.010 |
| Autoimmune disease | Yes | Yes | No | (+)0.366 | (+)0.014 | (+)0.013 | (+)0.015 | (–)0.271 | (+)0.425 | (–)0.094 |
| Patient on muscle relaxants | Yes | Yes | No | (–)0.585 | (+)0.005 | (+)0.291 | (+)<0.001 | (–)0.153 | (+)0.020 | (+)0.009 |
| Prior amputation | Yes | Yes | No | | (–)<0.001 | (+)<0.001 | (–)<0.001 | (–)0.001 | (–)0.003 | (+)0.964 |
| Patient resides in a nursing home or skilled nursing facility | Yes | Yes | No | (+)0.100 | (–)0.001 | (–)<0.001 | (–)0.070 | (–)<0.001 | (–)<0.001 | (–)0.297 |
| Dementia and Alzheimer's | Yes | Yes | No | (+)0.394 | (–)0.002 | (–)<0.001 | (–)<0.001 | (–)0.020 | (+)0.089 | (+)0.774 |
| Autoimmune disease and rheumatoid arthritis | Yes | Yes | No | (+)0.198 | (+)0.024 | (+)0.001 | (+)0.014 | (–)0.516 | (+)0.249 | (–)0.291 |
| Incontinence | Yes | Yes | No | (–)0.400 | (–)<0.001 | (–)<0.001 | (–)0.160 | (–)0.046 | (+)0.025 | (+)0.288 |
| Worst Braden Subscore for Mobility (+: healed wounds associated with higher score) | Yes | Yes | No | (+)0.690 | (+)<0.001 | (+)<0.001 | (+)0.001 | (+)<0.001 | (+)0.188 | (+)0.070 |
| Number of foot pulses obtained by Doppler rather than being palpable (+: healing associated with higher number) | Yes | Yes | No | (–)0.681 | (+)0.018 | (+)0.010 | (+)0.220 | (+)0.924 | (+)<0.001 | (+)0.125 |
| Patient is male | Yes | Yes | No | (–)0.258 | (–)0.265 | (–)0.266 | (–)0.730 | (–)0.018 | (+)0.201 | (+)0.589 |
| Patient takes transplant anti-rejection drugs | Yes | Yes | No | (–)0.019 | (+)0.884 | (+)0.065 | (+)0.862 | (–)0.115 | (+)0.335 | (+)1.000 |
| Any organ transplant | Yes | Yes | No | (–)0.121 | (–)0.528 | (+)1.000 | (–)0.124 | (–)0.095 | (+)0.872 | (+)0.046 |
| Alcoholic liver disease | Yes | Yes | No | (+)0.807 | (+)0.496 | (+)0.001 | (+)0.544 | (–)0.075 | (–)0.569 | (–)0.226 |
| Current smoker | Yes | Yes | No | (+)0.371 | (–)0.135 | (–)0.643 | (+)0.387 | (–)0.693 | (–)0.092 | (–)0.525 |
| Sleep apnea | Yes | Yes | No | (+)0.527 | (+)0.872 | (+)0.271 | (+)0.189 | (–)0.014 | (+)0.762 | (+)0.929 |
| Wound on left side | Yes | Yes | No | (–)0.356 | (–)0.559 | (+)0.007 | (–)0.762 | (+)0.472 | (+)0.220 | (–)0.105 |
| BMI category of patient at first treatment* | Yes | Yes | No | 0.826 | <0.001 | <0.001 | 0.402 | 0.032 | 0.244 | <0.001 |
| Sickle cell anemia | Yes | No | No | (–)0.458 | (+)0.368 | (+)0.012 | (+)0.097 | (–)0.390 | (+)0.459 | (+)0.548 |
| Chronic obstructive pulmonary disease | Yes | No | No | (+)0.882 | (–)0.798 | (+)0.449 | (–)0.387 | (–)0.804 | (+)0.116 | (+)0.874 |
| Chron's or irritable bowel disease | Yes | No | No | (+)1.000 | (+)1.000 | (+)0.884 | (–)0.532 | (+)0.506 | (+)0.821 | (+)0.142 |
| History of hip fracture | Yes | No | No | (–)0.420 | (–)0.085 | (+)0.259 | (–)0.846 | (–)0.156 | (+)0.245 | (–)0.684 |

*No direction of association provided because this variable has multiple categories.
Sign in parentheses tells the direction of the association.
BMI, body mass index; N/A, not applicable.

**Table 4.** Model fitting statistics to predict healed (yes/no) for development sample and validation sample for six common types of chronic wounds

| | Wound type | | | | | |
|---|---|---|---|---|---|---|
| | Diabetic | Venous | Pressure ulcer (body) | Pressure ulcer (heels) | Trauma | Amputation/ surgical |
| 90% development model | | | | | | |
| Number of wounds | 5,239 | 9,898 | 6,640 | 1,909 | 9,944 | 5,571 |
| Number healed | 3,462 | 7,498 | 4,300 | 1,240 | 7,706 | 3,906 |
| Whole course model c statistic | 0.668 | 0.636 | 0.736 | 0.703 | 0.632 | 0.619 |
| First encounter model c statistic | 0.648 | 0.603 | 0.702 | 0.697 | 0.62 | 0.612 |
| 10% validation model | | | | | | |
| Number of wounds | 555 | 1,044 | 709 | 203 | 1,055 | 594 |
| Number healed | 377 | 809 | 477 | 133 | 811 | 417 |
| Whole course model c statistic | 0.662 | 0.619 | 0.726 | 0.712 | 0.618 | 0.615 |
| First encounter model c statistic | 0.659 | 0.594 | 0.674 | 0.705 | 0.599 | 0.596 |
| Whole course model Hosmer–Lemeshow *p*-value | 0.489 | 0.332 | 0.398 | 0.615 | 0.532 | 0.422 |
| First encounter model Hosmer–Lemeshow *p*-value | 0.157 | 0.474 | 0.907 | 0.728 | 0.678 | 0.073 |

c Statistic, performance metric of model discrimination equivalent to the area under the receiver operating characteristic curve.

first wound encounter. All models were well validated when applied to the holdout validation 10% sample (Table 4).

As stated in the Methods section, in all models we used data from two time frames: data available at the first visit or data available from all the visits for the likelihood of healed for six common types of wounds (Table 4). Factors that were significant in nearly all first visit models and indicated less likelihood of the wound being healed were wound size, age of wound, and being nonambulatory.

## DISCUSSION

This study was designed to identify those characteristics inherent to the patient and the wound that affect the likelihood of healing, and *not* to assess the impact of treatments. Thus, it was not necessary to control for variations in care, although it is likely that the quality of patient care varies highly from one facility and provider to another.

The use of EHR data has certain advantages in this study. Because *all* the medical data collected for each patient are transmitted to the national registry, it is feasible to analyze many possible contributory factors, as this study shows. And because 100% of the patients seen at each participating clinic become part of the registry, there is no selection bias in patient enrollment to the U.S. Wound Registry.

A major challenge was the determination of whether a wound was "healed." An advantage of using the U.S. Wound Registry is that the data represent the patient's actual medical record, so there is no post hoc vetting of outcome information in order to improve the clinic's reported "healing rate" for purposes such as marketing; thus, outcomes were not artificially inflated to appear better than they were. However, while "healed" would seem to be a well-defined end point, in clinical practice it may not be. Some wounds may epithelialize with fragile skin and still continue to drain, so clinicians may be uncertain whether to designate the area as healed.

Also, among outpatients, dressing products are only covered for open wounds. If a patient requires protective dressings for some period of time until fragile skin matures, clinicians may continue to record wound measurements in order to justify products or services that the patient continues to require. The difficulty in establishing definitive wound closure, and the perverse disincentives for doing so, complicate wound healing research using EHR data. However, we feel that the manner in which we analyzed the longitudinal trends of wound characteristics at each visit (not size alone but also tissue type exposed and drainage characteristics) allowed us to correctly classify ulcer outcome.

We believe that these models will improve as more quantifiable data become available (e.g., laboratory data such as hemoglobin A1c). The progressive governmental requirements for "meaningful use" of certified EHRs will make more ancillary information available as clinics are incentivized to create interfaces with the hospital laboratory and other repositories of clinical data.

The approach we utilized had some similarities to that used to develop the Comprehensive Severity Index (CSI).[32] CSI employed the characteristics of patients' diseases (signs, symptoms, and physical findings from the principal and all secondary diagnoses) and no treatments to develop the severity score for each time window. In contrast to the development of the WHI, however, the development of the CSI did not use any database to model an outcome or outcomes. CSI was created by using medical literature, medical text books, and clinician expertise to define the levels of each severity indicator for a disease. Also, the CSI score incorporated disease-specific indicators and not just the diagnosis codes.

We anticipate that these predictive models will be used in a variety of ways and thus created two models for each wound/

ulcer type. Clinicians have long desired a method of identifying patients most in need of advanced therapeutics early in their treatment course, thus avoiding weeks of wasted conservative care. Therefore, we created a model for each wound type based on the factors known at the time of the *initial* visit. This model can identify hard-to-heal patients in clinical practice, but can also be used to stratify patients enrolled in prospective trials to ensure appropriate allocation of study and control groups. During and at the conclusion of a patient's course of care, additional information is available that we found can further improve outcome prediction (e.g., whether the patient required hospitalization at any time). These slightly more predictive "end of treatment course" models can be used in retrospective data analysis to determine those treatments that are associated with the fastest healing.

## LIMITATIONS

These data may be affected by the quality and consistency of clinical documentation. As clinicians must do their medical charting anyway, data needed for the registry are collected at the same time the medical record is created. This provides access to a broad cross-section of clinical care, without regard to individual physician or facility motivation for research. Both physicians and nurses performed point of care EHR charting. Data for the registry were not obtained by secondary data entry. Importantly, as the EHR automatically and internally abstracts the chart to calculate charges, and those charges determine both facility (clinic) and physician revenue, all clinicians were highly incentivized to perform thorough documentation.

The inability of the ICD-9-CM coding system to specifically identify many wound or ulcer types is a potentially serious limitation. For example, "arterial ulcers" can only be identified when a chronic ulcer is linked to the secondary diagnosis of atherosclerosis, since no ICD-9-CM code specific to "arterial ulcer" exists. In addition, even the most experienced clinician may be challenged to correctly classify a wound/ulcer when multiple etiologies may apply (e.g., a heel ulcer in a patient with severe arterial disease and diabetes). Furthermore, which ICD-9-CM code is chosen has profound implications regarding whether certain diagnostic studies and clinical treatments will be covered, thus incentivizing clinicians to use those codes that have more favorable coverage policies whenever possible. For example, the Centers for Medicare and Medicaid Services does not cover arterial vascular testing for pressure ulcers ("decubitus ulcers") of the lower extremities even though vascular evaluation may be critical to determine their likelihood of healing and whether revascularization is needed. In addition, diagnoses such as pressure ulcers have medico-legal implications. For example, the National Quality Forum includes pressure ulcers in the list of events that should never happen to hospitalized patients and that their development is evidence of poor care. Even though data do not support this assertion, litigation over the formation of pressure ulcers is common and may decrease the willingness to use pressure ulcer ICD-9-CM codes. It is likely that, particularly on the lower extremity, many pressure-related ulcers were classified as other wound types. The multifactorial nature of lower extremity ulcers and the extreme lack of functionality of the ICD-9-CM coding system may account in part for conflicting data on the importance of certain comorbid conditions among various wound/ulcer types.

Although the WHI was validated with a particular wound care-specific EHR, the variables can be translated to other platforms so that providers using other methods of wound care data collection can utilize it. Despite the limitations of these data, registries created from pooled, de-identified EHRs represent a way to determine the real-world *effectiveness* of wound care treatments once efficacy has been established in RCTs. True "comparative effectiveness" studies of expensive modalities used among chronic wound patients have been limited by the absence of a method to stratify patients by severity of illness and the WHI may now help to overcome this obstacle.

In conclusion, this study is among the largest wound-healing studies ever performed, and represents a significant advance both in terms of the volume of data analyzed and the completeness of the dataset. Our data confirm that certain patient and wound factors affect the likelihood of healing in a predictable way. Furthermore, the prevalence of significant comorbid conditions (e.g., diabetes among patients with non-diabetic ulcers, malnutrition, renal transplant) confirms previous observations that the majority of patients typically seen in outpatient wound centers would have been excluded from virtually all randomized controlled trials thus far performed in the field of wound healing. The next phase of research for the U.S. Wound Registry is to use these WHI predictive models to stratify patients/wounds and analyze the effectiveness of various treatments on outcomes.

## ACKNOWLEDGMENTS

*Source of Funding*: The authors would like to thank Kinetic Concepts, Inc for their financial support of this study.

*Conflict of Interest*: Dr. Fife is the Chief Medical Officer of Intellicure and Mr. Thomson is the Chief Information Officer of Intellicure. Dr. Horn, Mr. Smout, and Mr. Barrett have no potential conflicts of interest to disclose.

## REFERENCES

1. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol* 2009; 62: 499–505.
2. Carter MJ, Fife CE, Thomson B, Walker D. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. *Adv Skin Wound Care* 2009; 22: 316–24.
3. Kent D, Hayward R. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. *JAMA* 2007; 298: 1209–12.
4. Centers for Medicare and Medicaid Services. *Medicare Coverage Advisory Committee Meeting [transcript]*. March 29, 2005. Available at http://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/downloads/id28a.pdf (accessed March 29, 2013).
5. Institute of Medicine. *Key capabilities of an Electronic Health Record System (Electric Health Record Functional Model: Letter Report)*. Washington, DC: Institute of Medicine National Academies Press, 2003.
6. Federal Coordinating Council for Comparative Effectiveness Research. *Report to the President and Congress*. June 30,

2009. Available at http://www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf (accessed March 22, 2010).
7. Fife CE, Buyukcakir C, Otto G, Sheffield P, Love T, Warriner III R. Factors influencing the outcome of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy. *Wound Repair Regen* 2007; 15: 322–31.
8. Cukjati D, Robnik-Sikonja M, Rebersek S, Kononenko I, Miklavicic D. Prognostic factors in the prediction of chronic wound healing by electrical stimulation. *Med Biol Eng Comput* 2001; 39: 542–50.
9. Birke JA, Novick A, Patout C, Colenan WC. Healing rates of plantar ulcers in leprosy and diabetes. *Lepr Rev* 1992; 63: 365–74.
10. Johnson M. Using cluster analysis to develop a healing typology in vascular ulcers. *Vasc Nurs* 1997; 15: 45–50.
11. Lavery LA, Barnes SA, Keith MS, Seaman JW, Armstrong DG. Prediction of healing for post operative diabetic foot wounds based on early wound area progression. *Diabetes Care* 2008; 31: 26–9.
12. Sheehan P, Jones P, Caselli A, Givrin JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003; 26: 1879–82.
13. Christman AL, Selvin E, Margolis D, Lazarus GS, Garza LA. Hemoglobin A1c predicts healing rate in diabetic wounds. *J Invest Dermatol* 2011; 131: 2121–7.
14. Prince S, Dodds SR. Use of ulcer size and initial responses to treatment to predict the healing time of leg ulcers. *J Wound Care* 2006; 15: 299–303.
15. Claesson K, Kolbel T, Acosta S. Role of endovascular intervention in patients with diabetic foot ulcer and concomitant peripheral arterial disease. *Int Angiol* 2011; 30: 349–58.
16. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcomes in individuals with diabetic foot ulcers without peripheral arterial disease. The EURODIALE Study. *Diabetologia* 2008; 51: 747–55.
17. Barberan J, Granizo JJ, Aguilar L, Alguacil R, Sainz F, Menendez MA, et al. Predictive model of short-term amputation during hospitalization of patients due to acute diabetic foot infections. *Enferm Infecc Microbiol Clin* 2010; 28: 680–4.
18. Lyman IR, Tenery JH, Basson RP. Correlation between decrease in bacterial load and rate of wound healing. *Surg Gynecol Obstet* 1970; 130: 616–22.
19. Lipsky BA, Weigelt JA, Xiaowu S, Johannes RS, Derby KG, Tabak YP. Developing and validating a risk score for lower-extremity amputation in patients hospitalized for a diabetic foot infection. *Diabetes Care* 2011; 34: 1695–700.
20. Morback S, Fuchert H, Groblinghoff U, Hoffmeier H, Kersten K, Klauke GT, et al. Long-term prognosis of diabetic foot patients and their limbs. Amputation and death over the course of a decade. *Diabetes Care* 2012; 35: 2021–7.
21. Sherratt JA, Dallon JC. Theoretical models of wound healing: past success and future challenges. *C R Biol* 2002; 325: 557–64.
22. Zimny S, Schatz H, Pfohl M. The effects of ulcer size on the wound radius reductions and healing times in neuropathic diabetic foot ulcers. *Exp Clin Endocrinol Diabetes* 2004; 112: 191–4.
23. Zimny S, Schatz H, Pfohl M. Determinants and estimation of healing times in diabetic foot ulcers. *J Diabetes Complications* 2002; 16: 327–32.
24. Mayrovitz HN, Smith J, Ingram C. Geometric, shape, and area measurement considerations for diabetic neuropathic plantar ulcers. *Ostomy Wound Manage* 1997; 43: 58–65.
25. Cukjati D, Rebersek S, Miklavcic D. A reliable method of determining wound healing rate. *Med Biol Eng Comput* 2001; 39: 263–71.
26. Cukjati D, Rebersek S, Karba R, Micklavcic D. Mathematical modeling of chronic wound healing. *Electo-Magnet Biol* 1998; 17: 235–40.
27. Cukjati D, Karba R, Rebersek S, Miklavcic D. Modeling of chronic wound healing dynamics. *Med Biol Eng Comput* 2000; 38: 339–47.
28. Olsen LM, Maini PK, Dallon JC, Sherratt JA. Mathematical modeling of anisotropy in fibrous connective tissue. *Math Biosci* 1998; 158: 145–70.
29. Geris L, Gerish A, Schugar RC. Mathematical modeling in wound healing, bone regeneration, and tissue engineering. *Acta Biotheor* 2010; 58: 355–67.
30. Stark P. Congressional intent for the HITECH Act. *Am J Manag Care* 2010; 16 (12 Suppl. HIT): SP24–8.
31. Fife CE, Wall V, Carter MJ, Walker D, Thomson B. Examining the relationship between physician and facility level-of-service coding in outpatient wound centers: results of a multicenter study. *Ostomy Wound Manage* 2012; 58: 20–2, 24, 26–8.
32. Horn SD, Torres A Jr, Willson D, Dean JM, Gassaway J, Smout R. Development of a pediatric age- and disease-specific severity measure. *J Pediatr* 2002; 141: 496–503.