

# A MODEL TO ESTIMATE COST-SAVINGS IN DIABETIC FOOT ULCER PREVENTION EFFORTS

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**ABBREVIATIONS**

DFU, diabetic foot ulcer

ICER, incremental cost-effectiveness ratio

IQR, interquartile range

RR, relative risk

QALY, quality-adjusted life-year

## ABSTRACT

**Background:** Sustained efforts at preventing diabetic foot ulcers (DFUs) and subsequent leg amputations are sporadic in most health care systems despite the high costs associated with such complications. We sought to estimate effectiveness targets at which cost-savings (i.e. improved health outcomes at decreased total costs) might occur.

**Methods:** A Markov model with probabilistic sensitivity analyses was used to simulate the five-year survival, incidence of foot complications, and total health care costs in a hypothetical population of 100,000 people with diabetes. Clinical event and cost estimates were obtained from previously-published trials and studies. A population without previous DFU but with 17% neuropathy and 11% peripheral artery disease (PAD) prevalence was assumed. Primary prevention (PP) was defined as reducing initial DFU incidence.

**Results:** PP was more than 90% likely to provide cost-savings when annual prevention costs are less than \$50/person and/or annual DFU incidence is reduced by at least 25%. Efforts directed at patients with diabetes who were at moderate or high risk for DFUs were very likely to provide cost-savings if DFU incidence was decreased by at least 10% and/or the cost was less than \$150 per person per year.

**Conclusions:** Low-cost DFU primary prevention efforts producing even small decreases in DFU incidence may provide the best opportunity for cost-savings, especially if focused on patients with neuropathy and/or PAD. Mobile phone-based reminders, self-identification of risk factors (ex. Ipswich touch test), and written brochures may be among such low-cost interventions that should be investigated for cost-savings potential.

## INTRODUCTION

The management of diabetes-associated foot complications— including the treatment of diabetic foot ulcers (DFUs) and infections, leg amputations, and lower extremity revascularization procedures – comprise a considerable amount of the huge total costs diabetes care<sup>1–3</sup>. Despite these large costs, very few studies describe the effectiveness of efforts directed *primary prevention* (avoiding the development of DFUs) or *secondary/tertiary prevention efforts* (providing timely, adequate treatment for those with DFUs who are not /are aware of its presence, respectively<sup>4</sup>; hereafter considered together and abbreviated as “secondary prevention”).

The implementation of primary prevention efforts for diabetic foot complications is sporadic in most health care systems, and delays in initiating secondary prevention (timely, adequate treatment) are common among patients with DFUs.<sup>4</sup> Uncertain return on investment may be one of many reasons for such meager efforts to prevent leg amputations. The current study was therefore undertaken to determine whether an argument for more extensive prevention/treatment efforts could be made on an economic basis. Specifically, the goal of the current study was to identify effectiveness thresholds at which primary and/or secondary prevention efforts had a high probability of producing *cost-savings*: improved health benefits at a cost lower than that of standard care. Herein we describe findings from our cost-effectiveness analysis in which the costs and benefits of varying levels of primary and secondary prevention efforts were assessed to identify the potential for cost-savings.

## METHODOLOGY

### Model Structure

A cost-effectiveness analysis was performed using a Markov cohort model with probabilistic sensitivity analyses that simulated the DFU-related clinical events and associated health care costs for a hypothetical population with diabetes over a five year period. For each baseline set of assumptions, an analysis consisted of 1,000 repeated simulations of 100,000 hypothetical patients with diabetes but no current DFU and no prior history of DFU who were followed over a five year period.

Six main clinical states were modelled: (1) no DFU; (2) uninfected DFU; (3) infected DFU; (4) limb loss, i.e. major (above-ankle) amputation; (5) healed DFU; and (6) death from any cause (see Figure 1). All hypothetical patients were in one clinical state at any given time. The model simulated transitions between these various clinical states occurring at monthly cycles over a period of five years. The probability of moving from one clinical state to another during any given cycle of the simulation was described by the transition probability (see below). Each clinical state had an associated monthly cost estimate. Hypothetical patients accumulated the costs associated with time spent in each clinical state during the simulated five-year period.

### Transition Probabilities between Clinical States

A three-level array of transition probabilities were then used to simulate baseline risk level and probability of developing various DFU-related complications. These three levels correlated with the levels in a modified version of the foot risk score from the International Working Group of the Diabetic Foot<sup>5</sup> and the foot risk score used within the Veterans Healthcare Administration<sup>6</sup>. Specifically, transition probabilities for the low risk stratum was based on the reported clinical outcomes of diabetic patients without peripheral neuropathy or peripheral arterial disease. The moderate risk stratum was based on reported clinical outcomes of diabetic patients with peripheral neuropathy but without peripheral arterial disease, and the transition probabilities of the high risk stratum was based on outcomes of diabetic patients with peripheral arterial disease, with or without peripheral neuropathy. Based on 2011 national Veterans Healthcare Administration data, 71.6% of the hypothetical population

with diabetes was assumed to be low risk, 17.5% moderate risk, and 11.0% high risk. Transition probabilities were obtained from two extensive literature searches, each of which summarized in a separate review article<sup>4,7</sup>. One review focused on the incidence of DFUs, the effectiveness of prevention efforts, and incidence of delays in diagnosis and treatment<sup>4</sup>, while the second focused on the natural history of foot wounds associated with significant peripheral arterial disease (PAD) with or without diabetes and the clinical outcomes associated with various management strategies for this, including revascularization and major amputation<sup>7</sup>. Selected probabilities are shown in Table 1. Of note, the monthly probabilities for initial DFU occurrence were based on work by Lavery and colleagues<sup>5</sup>. The monthly rates listed in Table 1 for these initial DFU occurrence corresponded to annual incidence rates of 1.3% (25-75% interquartile range of 1.0 to 1.6%) for low risk patients, 3.7% (range 3.0 to 4.7%) for moderate risk patients, and 13.8% (12.7 to 15.0%) for high risk patients. Probabilistic sensitivity analyses were achieved through the use of beta and triangular distributions for all state transition probabilities.

#### *Costs and Health Utilities Associated with Clinical States*

The societal cost perspective over a five-year time horizon was used for this study. The costs associated with the management of DFUs in the low and moderate risk strata were obtained from previously-published estimates (see Table 2). The costs associated with management of the high risk stratum were obtained from a previous study focusing on this patient population<sup>8</sup>. Specifically, total (direct and indirect) inpatient costs associated with revascularization, wound care, and major and minor amputations were estimated for patients with PAD and foot ulcers undergoing these procedures at a single institution. Detailed cost estimates were derived from an activity-based cost accounting system from that institution. All outpatient costs, including those associated with outpatient nursing care, wound care and any needed limb prostheses were obtained from a thorough literature review.<sup>7</sup> All cost values are reported in 2011 U.S. dollars (USD) and represent a median value unless otherwise noted. All currency conversions were performed using the United States Department of Labor Consumer Price Index. The standard discounting rate of 3.5% was applied to all cost values<sup>9</sup>. Gamma distributions were used for all cost parameter estimates. Estimates of the health utilities associated with each of the six

aforementioned clinical states were obtained from a previous literature review.<sup>7,8</sup> As with costs, the standard discounting rate of 3.5% was applied to utility estimates.

#### Cost-Effectiveness Analysis & Sensitivity Analyses

The effectiveness and costs of efforts to prevent DFUs and/or limb loss are uncertain<sup>4</sup>. As such, estimates of the clinical effectiveness of prevention efforts were varied in a deterministic (i.e. controlled) fashion. Prevention efforts that reduced the incidence of initial DFU occurrence were considered *primary* limb loss prevention efforts (*primary prevention*). The relative risk (RR) of developing a DFU when primary prevention efforts were provided was varied deterministically from 0.95 to 0.75 (i.e. a 5% to 25% relative decrease in the incidence of an initial DFU). Primary prevention efforts were assumed to reach 90% of the intended population. At any given level of primary prevention effectiveness the cost of prevention efforts was varied deterministically between \$25 and \$300. The objective of these deterministic sensitivity analyses were to identify cost thresholds which had a 90% or higher probability of providing cost-savings – that is, avoiding subsequent (downstream) costs that equal or exceed the costs of the initial prevention efforts – when compared to no primary prevention efforts (0% of the intended population).

Similarly, the impact of secondary prevention efforts was investigated. Consistent with our previous definitions of prevention efforts<sup>4</sup>, we considered secondary limb loss prevention efforts to be the initiation of adequate DFU treatment after the development of an initial or recurrent DFU. Adequate treatment for DFUs in the low and moderate risk groups was assumed to consist of offloading and wound care therapy provided within a month of DFU occurrence. Adequate treatment for DFUs in the high risk group was assumed to consist of revascularization, offloading and wound care therapy within a month of DFU occurrence. The transition probabilities from the DFU state to the healed DFU state or the limb loss state were based on outcome data described for these treatment combinations for patients receiving adequate treatment, while the corresponding transition probabilities for those not receiving adequate treatment were based on studies describing natural history (esp. for the high risk group) or placebo/comparator groups in DFU treatment trials (ex. non-removable cast-walker trials for moderate risk patients). Selected transitional probabilities for the three strata are shown in Table 1. As

for the simulations investigating the effects of varying levels of primary prevention effectiveness, the objective of the deterministic sensitivity analyses of secondary prevention effectiveness and costs was to identify levels at which a 90% or higher probability of providing cost-savings would be achieved.

Although some literature suggest that adequate treatment is initiated for only 30% of patients with new DFUs during any given month<sup>10,11</sup>, the more conservative 50% point estimate for secondary prevention was used for scenarios in which the primary prevention effectiveness was deterministically varied. A range of 30-100% was used in for the deterministic sensitivity analyses of scenarios focused on improving secondary prevention rates. The cost of accurately stratifying patients with DFUs (especially, distinguishing between moderate and high risk patients) and thereby providing adequate treatment as estimated at \$100 per person and was applied to the proportion of the population that received adequate secondary prevention. No primary prevention efforts were assumed to occur during simulations in which secondary prevention effectiveness and cost was deterministically varied.

Cost-effectiveness evaluations in this study are presented in incremental cost-effectiveness ratios (ICERs) as measured by 2011 U.S. dollars per quality-adjusted life-year (QALY) gained.



## RESULTS

### *Results of Primary Prevention Efforts for the General Diabetes Population*

Simulations of primary prevention efforts with effectiveness ranging from a relative risk of 0.95 to 0.75 were modelled in comparison to simulations with no prevention efforts. As would be expected, the number of amputations declined as the effectiveness of primary prevention efforts increased (i.e. as the relative risk decreased). With these prevention efforts directed at all persons with diabetes, there was median of 58 fewer major amputations over the five year period at a RR of 0.95, 116 fewer at a RR of 0.90, 171 fewer at a RR of 0.85, 227 fewer at a RR of 0.80, and 290 fewer at a RR of 0.75 (see Table 3). Without prevention efforts, the median incidence rate of major amputation ranged from 166 to 168 per 100,000 per year in the simulations. In comparison, the incidence rates per 100,000 per year decreased to 162 (3.4% decrease) at a RR of 0.95, 154 (8.3% decrease) at a RR of 0.90, 145 (12.7% decrease) at a RR of 0.85, 139 (16.2% decrease) at a RR of 0.80, and 133 (20.3% decrease) at a RR of 0.75.

The primary prevention effort cost thresholds at which  $\geq 90\%$  of simulations demonstrated cost savings were \$13 for primary prevention efforts with a 0.95 RR of DFU incidence, \$50 for a 0.90 RR, \$84 for a 0.85 RR, \$117 for a 0.80 RR, and \$148 for a 0.75 RR. In other words, a primary prevention effort that decreased the incidence of DFU occurrence by 10% (0.90 RR) at a cost of  $< \$50$  per person, for example, would have a  $> 90\%$  probability of reducing the number of leg amputations among a population with diabetes at costs that are equal to or lower than standard care (Table 4, Figure 2).

### *Results of Primary Prevention Efforts for the Moderate- and High-Risk Diabetes Populations*

Simulations were repeated with primary prevention efforts directed only to moderate and high risk patients. As with the base case scenario, effectiveness ranged from a relative risk of 0.95 to 0.75 compared to no prevention efforts. Simulations suggested such efforts would decrease the total number of amputations somewhat less than primary prevention efforts aimed the entire population with diabetes (Table 3). For example, there was median of 37 fewer major amputations over the five year

period at a RR of 0.95, 78 fewer at a RR of 0.90, 117 fewer at a RR of 0.85, 159 fewer at a RR of 0.80, and 199 fewer at a RR of 0.75 (see Table 2). Primary prevention efforts directed at moderate and high risk patients decreased the amputation incidence rates per 100,000 per year to about the same degree as efforts directed at the entire population with diabetes, however: 160 major amputations per 100K per year (4.1% decrease) at a RR of 0.95, 153 per year (7.8% decrease) at a RR of 0.90, 147 (12.5% decrease) at a RR of 0.85, 139 (16.3% decrease) at a RR of 0.80, and 133 (20.4% decrease) at a RR of 0.75 (Table 2).

As expected, the primary prevention effort cost thresholds at which  $\geq 90\%$  of simulations demonstrated cost savings were higher when directed specifically at moderate and high risk patients than when directed to the entire population with diabetes. Specifically, the cost thresholds were \$25 for primary prevention efforts with a 0.95 RR of DFU incidence, \$125 for a 0.90 RR, and \$250 for a 0.85 RR. Primary prevention efforts  $> \$400$  were  $> 90\%$  likely to produce cost-savings if associated with a RR of  $\leq 0.80$  (Table 4, Figure 2).

#### Results of Secondary Prevention Efforts

Multiple scenarios were simulated to identify cost-thresholds at which an increase in the rate of secondary prevention efforts (i.e. the proportion of patients with a DFU for whom adequate treatment is initiated during any given month) would be likely to produce cost-savings. No scenario was identified in which the probability of cost-savings was high. Increasing the proportion of patients receiving secondary prevention efforts did appear to improve outcomes at acceptable levels of cost-effectiveness (Table 5). Specifically, leg amputation rates decreased from 165 per 100,000 persons per year at a 50% rate of secondary prevention to 140 per year at a secondary prevention rate of 90%. Costs and QALYs both increased with increasing rates of secondary prevention. Compared to a 50% rate of secondary prevention, increasing secondary prevention rates up to 100% has ICERs that were near or below 3,500 USD per QALY (Table 5; see also Figure 3).

*The Effect of Secondary Prevention Rates on the Cost-Savings Potential of Primary Prevention*

Deterministic sensitivity analyses in which the rate of initiating adequate, timely care to patients with DFU (i.e. secondary prevention) was varied from the baseline rate of 50% were performed to evaluate the impact of this rate on the effectiveness of primary prevention efforts. This was done to evaluate the potential impact of primary prevention efforts in settings where access to adequate DFU care may be sporadic or is often delayed. In the scenarios evaluated, the probability of achieving cost-savings at any given primary prevention RR and cost directed at all patients with diabetes were sensitive to the rates of secondary prevention, with increased rates of secondary prevention increased the likelihood of achieving cost-savings. For example, at a primary prevention RR of 0.90 and annual cost of \$50, the probability of achieving cost-savings was 48.7% with a 40% rate of secondary prevention, 89.3% with a 50% rate of secondary prevention, and 99.7% with a 60% rate of secondary prevention.

Similar deterministic sensitivity analyses were performed for scenarios in which primary prevention efforts were directed at moderate and high-risk patients (that is, those with sensory neuropathy, peripheral artery disease, or other risk factors). A similar relationship was seen, with increased rates of initiating adequate, timely care to patients with DFU (i.e. secondary prevention) decreasing the likelihood of achieving cost-savings. For example, at a primary prevention RR of 0.90 and annual cost of \$125, the probability of achieving cost-savings was 100% with a 40% rate of secondary prevention, 92.9% with a 50% rate of secondary prevention, and 40% with a 60% rate of secondary prevention. These results suggest that the ability of various prevention efforts to provide cost savings is very dependent on patients who develop DFUs receiving adequate, timely foot care. In other words, health care systems in which DFU care is sporadic or often delayed would be unlikely to realize the cost savings potential of primary prevention efforts.

## DISCUSSION

Despite the impact DFUs have on limb loss, health care costs, and quality-of-life, only a small number of trials or prospective studies have examined the effectiveness of prevention efforts (see review)<sup>4</sup>. Few health care systems have robust DFU or limb loss prevention efforts in place, and the rates of secondary/tertiary prevention (providing adequate, timely DFU treatment) are often low even within academic referral centers. The reasons for this are not entirely clear, but a perceived lack of economic benefit may be one of several contributing factors.

Other investigators have performed cost-effectiveness analyses that have previously also found prevention efforts to be cost-effective and possibly cost-savings. In a 2001 Markov model-based analysis, Ragnarson Tennvall and Apelqvist found “optimal management” (defined as preventative podiatric care, therapeutic footwear, and patient education ) would provide cost-savings for patients with neuropathy and for patients with a previous history of foot ulcers but not for patients with peripheral artery disease.<sup>12</sup> Ortegón, Redekop and Niessen found the potential for cost-effectiveness (though not cost-saving) in a 2004 Markov model-based analysis of both prevention and treatment efforts.<sup>13</sup> Other authors reviewing clinical outcomes (without cost-effectiveness analyses) and those informally evaluating cost-effectiveness have argued that primary prevention and/or treatment efforts may have utility when applied to high risk populations.<sup>14–17</sup>

The current study differs from these previous studies. The primary difference is that this analysis made no assumptions about the effectiveness of primary prevention efforts; instead, levels of effectiveness were varied in a deterministic fashion to identify cost thresholds at which prevention efforts would be likely to provide cost-savings (equal or improved health benefits at a reduction in total costs). This approach was taken because there is very little good-quality evidence that firmly demonstrates the effectiveness of primary prevention efforts.<sup>18–20</sup> The cost-savings threshold estimated by the current analysis may hopefully provide a framework for the economic justification of implementing primary prevention programs as the clinical effectiveness of such efforts becomes more firmly established. Our main focus was on cost-savings rather than any arbitrary thresholds of cost-

effectiveness, as the potential for improved outcomes at lower cost should be very appealing to all health care systems.

Three additional differences between the current study and previous analyses also exist. First, analyses separately examined the cost-effectiveness of primary prevention (preventing the development of an initial DFU) and secondary prevention (initiation of adequate, timely treatment of a foot ulcer) to better inform resource allocation in cost-restricted health care environments. Unlike other analyses, the current analysis did not assume that all patients received treatment, as previous studies demonstrate that only 30-50% of patients receive adequate, timely care after the development of a DFU (see review<sup>4</sup>). The modeling of health benefits, costs, and utilities for high-risk patients (those with peripheral artery disease ) in this study was based on recent analyses that have focused exclusively on this subgroup not available for use in previous DFU models<sup>7,8</sup>. Finally, the stratification of limb loss risk among patients with diabetes requires evaluation, possibly with non-invasive testing for peripheral artery disease. Unlike previous studies, the current study did not assume that this assessment and risk stratification is done routinely or accurately without evaluations that may incur monetary costs.<sup>21-</sup>

23,23

We found that primary prevention efforts directed at patients with diabetes who are at moderate or high risk for DFUs would be very likely to provide cost-savings if DFU incidence was decreased by at least 10% and/or the cost was less than \$150 per person per year (Figure 2). Daily foot thermometry is one such prevention effort that may meet these criteria. Previous trials and studies of thermography done among moderate risk patients with healed DFUs have shown recurrence rates of 2% in comparison to 20% with standard therapy alone.<sup>24-27</sup> The cost of these devices appears to be well within the \$150 threshold for cost-savings as well. Other interventions that could achieve these modest cost and effectiveness goals may include the podiatric care at regular intervals or direct education in a group or one-on-one setting.

Our model also suggests that cost-savings would be likely with low-cost prevention efforts directed at people with diabetes in general. Specifically, interventions that provide a 10% reduction in DFU incidence at a cost of <\$50 per person per year would be very likely to provide cost-savings (Figure 2). Such efforts might include distribution of written brochures explaining the Ipswich touch test or health behaviors for maintaining foot health; mobile phone-based reminder or education programs; or mailed reminders about scheduling foot exams or providing advice on the selection of appropriate footwear in the setting of sensory neuropathy or structural foot abnormalities. While it may seem apparent that directing efforts toward moderate and high risk individuals would be preferable, this is not always feasible as it assumes risk levels are known (or can be determined accurately without cost). Thus it is worthwhile noting that health care systems that have not done such risk stratification may still obtain cost-savings from primary prevention directed at all patients with diabetes.

The model did not identify scenarios in which secondary/tertiary prevention efforts would be likely to produce cost-savings. This is not to say such efforts would not be worthwhile; indeed, these efforts may have a lower probability of producing cost-savings or may be cost-effective (providing improved health outcomes at an additional cost that is within an accepted/agreeable range). For the purposes of our study, we used very strict thresholds to identify only scenarios that would provide a very compelling economic argument.

We would hope that this analysis might strengthen the argument for primary prevention efforts or research studies. We used a very restrictive setting – a 90% probability of providing cost-savings – to identify scenarios in which even the most conservative, risk-averse health care system might still consider allocating some money toward primary prevention efforts. Cost-effective analyses like these might also give more support for smaller trials designed to test whether various primary prevention efforts might achieve certain levels of clinical effectiveness without the additional yoke of needing to also demonstrated cost-effectiveness or cost-savings at an early stage of evaluation.

There are several limitations to this study. First, we assumed that the ability to direct primary prevention efforts toward the moderate and high risk populations (rather than the general population) was without additional cost. In reality, the ability to identify moderate- and high-risk patients from among a general population with diabetes requires time and effort – and therefore additional costs, and additional testing may be required. Finally, this analysis was based on clinical event and cost parameters that are estimated from currently available data derived from a variety of sources. We would hope that investigators undertaking a prospective economic analysis of some primary or secondary prevention efforts being implemented into a health care system would help validate the cost savings projected by this cost-effectiveness analysis.

In summary, primary prevention efforts directed at populations with diabetes that are at moderate or high risk for DFU are very likely to produce cost-savings when the prevention efforts have modest levels of cost and effectiveness. Low cost primary prevention efforts of modest effectiveness may provide cost-savings when directed at a general population with diabetes. Improving rates of secondary/tertiary prevention (adequate, timely treatment among those with DFUs) may be cost-effective but did not appear likely to produce cost-savings.

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## TABLES

**Table 1:** Monthly probabilities of transitioning to various clinical states in the model..

<b>event</b>	<b>low risk</b>	<b>moderate risk</b>	<b>high risk</b>
<b>initial DFU occurrence</b>	0.1% (0.5-0.2%)	0.3% (1.5-6.0%)	1.2% (0.9-1.6%)
<b>infection risk for yet-uninfected DFU</b>	7.4% (6.6-7.9%)	11.5% (10.0-13.0%)	12.5% (10.0-13.0%)
<b>DFU healing <i>without</i> adequate treatment*</b>	15.0% (10.0-20.0%)	10.0% (5.0-15.0%)	4.3% (2.4-6.8%)
<b>DFU healing <i>with</i> adequate treatment*</b>	20.0% (15.0-25.0%)	15.0% (10.0-20.0%)	10.9% (5.9-15.9%)
<b>limb loss for DFU <i>without</i> adequate treatment*</b>	1.0% (0.5-1.5%)	2.0% (1.5-2.5%)	3.1% (2.4-6.8%)
<b>limb loss for DFU <i>with</i> adequate treatment*</b>	0.2% (0.1-0.6%)	0.9% (0.7-1.1%)	1.2% (1.0-1.4%)
<b>DFU recurrence</b>	1.0% (0.5-1.5%)	2.0% (1.5-2.5%)	3.1% (2.4-6.8%)
<b>mortality</b>	0.5% (0.3-0.8%)	0.8% (0.6-1.0%)	1.0% (0.8-1.2%)

\* "adequate treatment" assumes offloading and local wound care for all patients and revascularization for PACT 3 patients.

**Table 2:** Cost estimates used in the model.

<b>event</b>	<b>median</b>	<b>25% centile</b>	<b>75% centile</b>
monthly DFU cost for low and moderate risk patients	1,029	868	1,174
monthly DFU cost for high risk	1,381	1,221	1,547
monthly cost for healed DFU	45	38	54
cost of a DFU infection	12,955	10,189	15,565
cost of a revascularization	35,340	33,005	38,070
cost of major lower extremity amputation	38,934	33,684	44,830
monthly post-amp cost	1,241	1,148	1,340
mortality	1	1	1

**Table 3:** The number and incidence rate of major amputations at various levels of primary prevention effectiveness.

RR	total 5-year major amputations			Σ	incidence of major amputation during year 2, per 100K			Σ
	without prevention efforts	primary	with prevention efforts		primary	without prevention efforts	with prevention efforts	
all patients								
0.95	1,448 (1,325-1,585)		1,388 (1,269-1,527)	-58 (-37 to -78)	168 (153-184)		162 (146-177)	-7 (-3 to -10)
0.90	1,467 (1,343-1,595)		1,352 (1,234-1,466)	-116 (-94 to -138)	168 (153-184)		154 (140-149)	-13 (-9 to -17)
0.85	1,433 (1,310-1,568)		1,262 (1,150-1,387)	-171 (-148 to -198)	166 (152-180)		145 (132-159)	-20 (-16 to -24)
0.80	1,441 (1,303-1,581)		1,212 (1,093-1,329)	-227 (-199 to -254)	166 (151-182)		139 (126-153)	-26 (-22 to 31)
0.75	1,448 (1,320-1,581)		1,157 (1,052-1,268)	-290 (-256 to -324)	167 (151-182)		133 (119-145)	-34 (-29 to -39)
moderate and high risk patients only								
0.95	1,444 (1,315-1,578)		1,404 (1,280-1,538)	-37 (-20 to -55)	167 (152-182)		160 (146-176)	-6 (-2 to -10)
0.90	1,444 (1,322-1,597)		1,365 (1,246-1,511)	-78 (-61 to -96)	166 (152-181)		153 (139-166)	-13 (-9 to -17)
0.85	1,427 (1,315-1,572)		1,309 (1,203-1,450)	-117 (-98 to -137)	168 (152-180)		147 (134-161)	-20 (-16 to -25)
0.80	1,440 (1,313-1,582)		1,274 (1,159-1,415)	-159 (-137 to -180)	166 (152-182)		139 (126-153)	-27 (-22 to 31)
0.75	1,441 (1,313-1,580)		1,244 (1,119-1,366)	-199 (-173 to -224)	167 (152-182)		133 (120-145)	-33 (-29 to -39)

**Table 4:** Percentage of simulations demonstrating cost-savings from primary prevention efforts directed at *all* patients with diabetes at various levels of effectiveness (as measured by relative rate, or RR) and cost (in USD). Results in bold denote scenarios in which at least 90% of scenarios produced cost-savings.

Annual cost	RR=0.95	0.90	0.85	0.80	0.75
<i>for primary prevention efforts directed at <u>all</u> patients</i>					
\$25	75.4	<b>99.7</b>	<b>100</b>	<b>100</b>	<b>100</b>
\$50	34.7	89.3	<b>99.8</b>	<b>100</b>	<b>100</b>
\$75	6.7	58.2	<b>94.0</b>	<b>100</b>	<b>100</b>
\$100		26.3	74.2	<b>95.7</b>	<b>99.9</b>
\$125	0	9.0	43.6	83.3	97.3
\$150	0	2.4	25.4	61.9	88.2
\$175	0	0.3	9.7	42.7	73.8
\$200	0		5.2	22.4	55.6
\$225	0	0	1.5	13.6	37.0
\$250	0	0	0.7	6.6	24.0
\$275	0	0	0.3	3.0	14.1
\$300	0	0	0.2	1.1	7.9
Annual cost	RR=0.95	0.90	0.85	0.80	0.75
<i>efforts directed at <u>moderate and high risk</u> patients only</i>					
\$25	<b>90.0</b>	<b>100</b>	<b>100</b>	<b>100</b>	<b>100</b>
\$50	81.7	<b>99.2</b>	<b>100</b>	<b>100</b>	<b>100</b>
\$75	73.2	<b>98.6</b>	<b>100</b>	<b>100</b>	<b>100</b>
\$100		<b>95.6</b>	<b>100</b>	<b>100</b>	<b>100</b>
\$125		<b>92.9</b>	<b>100</b>	<b>100</b>	<b>100</b>
\$150		88.6	<b>100</b>	<b>100</b>	<b>100</b>
\$175		78.1	<b>99.1</b>	<b>100</b>	<b>100</b>
\$200			<b>97.0</b>	<b>100</b>	<b>100</b>
\$225			<b>93.8</b>	<b>99.9</b>	<b>100</b>
\$250			<b>90.0</b>	<b>99.0</b>	<b>100</b>
\$275			83.9	<b>95.3</b>	<b>99.9</b>
\$300			75.1	<b>95.3</b>	<b>99.8</b>

**Table 5:** Costs, health benefits, and incremental cost-effectiveness ratios (ICERs) associated with increasing the rate of secondary prevention (initiation of adequate, timely treatment) from the baseline rate of 50%.

proportion receiving secondary prevention	leg amputation incidence (per 100K/year)	median 5-year cumulative leg amputations	median 5-year cumulative costs, millions of 2011 USD	median $\Delta$ cost	median 5-year cumulative quality-adjusted life-years (QALYs)	median $\Delta$ QALYs	ICERs, USD/QALY
50% (comparator)	165	1,451	558.403	---	5,075,932	---	---
60%	160	1,437	629.406	70.614	5,096,187	20,255	3,486
70%	155	1,417	647.275	87.493	5,132,429	40,172	2,178
80%	150	1,412	665.788	104.423	5,151,124	61,363	1,702
90%	145	1,400	679.080	120.379	5,131,667	88,684	1,492
100%	140	1,376	698.978	137.572	5,125,682	101,415	1,357

## FIGURE LEGEND

**Figure 1:** A schematic diagram demonstrating the clinical states modeled and transitions between these states.

**Figure 2:** Graph showing the cost-thresholds at which primary prevention efforts of varying levels of effectiveness (as measured in relative risk, or RR) at which cost-savings were demonstrated in at least 90% of simulated scenarios. The upper (green) area denotes the cost-threshold for efforts directed specifically at patients with diabetes at moderate and high risk for DFU; the lower (yellow) area denotes the cost-threshold for efforts directed at all patients with diabetes.

**Figure 3:** Cost-effectiveness acceptability curves demonstrating the probability (*vertical axis*) of increasing the proportion of patients receiving adequate, timely treatment ("secondary prevention") having an incremental cost-effectiveness ratio (ICER) at or below various ceiling ratios (*horizontal axis*). Separate curves shown for increasing monthly proportion receiving secondary prevention from 50% (the base-case scenario) to 60% (violet line), 70% (blue line), 80% (green line), 90% (orange line), or 100% (red line).



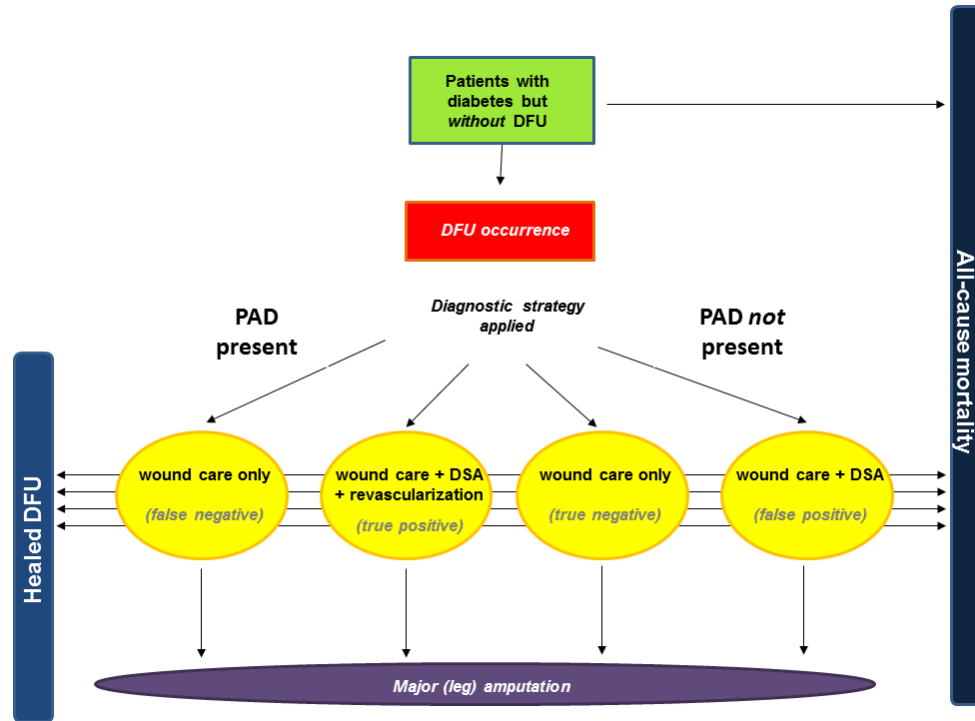


Figure 1

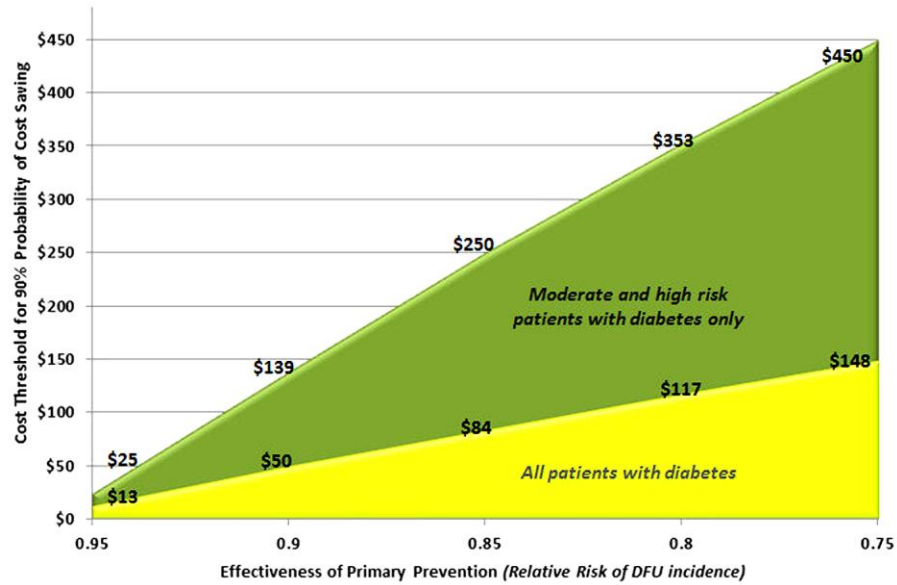


Figure 2

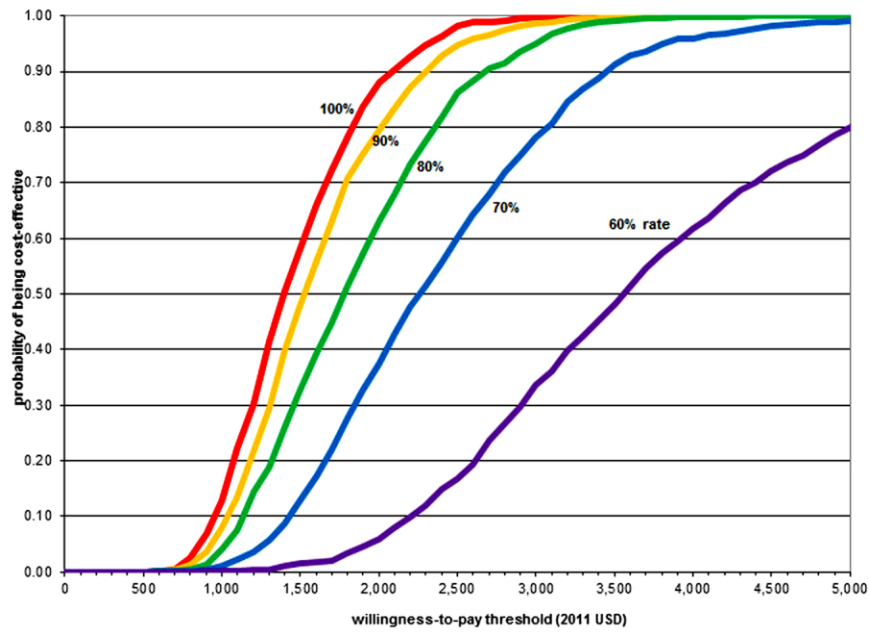


Figure 3