Preparing for the coming tsunami: telemonitoring can be a cost-effective way to screen for diabetic foot complications

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Running title: Economic evaluation of telemonitoring in DFU

Key Words: telemonitoring, diabetic foot ulcer, health economics, cost-effectiveness analysis, early health technology assessment

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Abstract

Background:
Diabetes rates are increasing worldwide, and the associated increasing cost of healthcare are undeniable. One of the most common (and costly) complications of diabetes are diabetic foot ulcers (DFUs), which often result in lower extremity amputation. While regular foot care can reduce complications, half of Canadians with diabetes do not participate in screening. In this work, we sought to evaluate the health and economic effects of using telemonitoring for DFU prevention.

Methods:
We used Markov modeling to compare current screening standards to population-wide and targeted telemonitoring programs in a hypothetical cohort of Canadian patients aged 60 years. Intervention effectiveness, defined as rate of DFU prevention, was varied to explore cost-effectiveness using model parameters from published literature and clinical experts.

Results:
At 20%-40% effectiveness, population-based prevention resulted in 0.01196 – 0.02369 quality-adjusted life years (QALYs) gained per person over 5 years and an incremental cost of $479 - $402, respectively, compared to current screening standards (incremental cost-effectiveness ratios of $40,034 - $16,971). At 15%-40% effectiveness, high-risk prevention resulted in a cost decrease per person over 5 years ($1.26 - $25.55, respectively) with health benefits of 0.00062 – 0.00174 QALYs gained.

Interpretation:
The use of telemonitoring in the diabetic lower extremity can offer patients better quality of life and be cost effective compared to current Canadian screening practices. Future work should focus on developing and validating technologies based on objective outcome measures for remote monitoring of diabetic feet.

INTRODUCTION

The management and care of diabetic foot ulcers (DFUs) imposes a tremendous burden on patients with diabetes, and decreases their quality of life (1). Moreover, rates of lower extremity amputation (LEA) are 22x higher in people with a DFU than in the general population (2). Up to 85% of DFU-related LEAs are preventable with frequent monitoring and prompt treatment (3–5). However, only 51% of Canadians with diabetes had a foot screen in 2009 (6), and foot care services essential to DFU prevention like chiropody and orthotic foot care are not funded in Ontario's healthcare system (7). This gap in care has led to sporadic prevention efforts and delayed care for DFUs (8).

Some barriers to frequent screening and monitoring (travel distance, time limitations, and unorganized referrals to foot specialists) can be overcome by using technology to make medical services more accessible (known as telemedicine, TM). Telemedicine is an increasingly popular mechanism for remote monitoring of chronic conditions, and has been used successfully in diabetic populations to monitor (and improve) HbA1c levels, increase inpatient understanding of diabetes, and improve cohesion among members of health-care teams (9–12). Currently, there is mixed evidence on the effectiveness of telemedicine for monitoring DFUs, largely due to a lack of controlled studies in large cohorts (13–24). Also, no studies have examined the use of TM for the prevention of DFUs. Several technologies designed to diagnose DFUs have recently been developed, and could potentially compliment a telemedicine-based program (25–27) given enough evidence of effectiveness.

The global prevalence of diabetes is currently 8.5% (up from 4.8% in 1980) and is expected to increase (28). In 2011, total DFU-related cost in Canada was $540M, or $21,371 per prevalent case (29). Healthcare systems, which have traditionally been treatment-oriented and less focused on prevention, must adapt to meet increased demands and costs. While multidisciplinary efforts were found to improve patient outcomes (30), the success of these initiatives is dependent on scale of resource allocation, additional personnel, and coordination of diverse clinical teams including podiatrists, infectious disease specialists, and plastic surgeons (7,31). The lack of efficacy evidence of these specialized early-intervention programs makes funding them difficult from a policymaking perspective (32,33). The current study explored the preliminary cost-effectiveness of a TM intervention for the prevention of DFUs. Specifically, the goal was to identify effectiveness thresholds at which telemedicine prevention efforts using a device could be cost-effective in Canada.

METHODS
The analysis and reporting were done according to Canadian Agency for Drugs and Technologies in Health guidelines and Consolidated Health Economic Evaluation Reporting Standards (34,35).

Comparators
Intervention
The intervention was a TM device used to monitor the feet of people with diabetes remotely. TM efforts were based on number of visits to physicians annually recommended by the International Working Group on the Diabetic Foot (IWGDF) (Supplementary Information (SI) Table 1) (4, 36). We defined two approaches: 1) a high-risk intervention (a TM device given to an individual after their first DFU); and 2) population-based intervention (a TM device given before the formation of a DFU).

Current Prevention Efforts in Canada (Control)
The current prevention efforts (CPE) model was defined as in-person visits to a physician according to the number of visits annually recommended by IWGDF. The number of visits per patient were adjusted to the 51% proportion of Canadians that received foot screens as reported by the Canadian Institute for Health Information (CIHI) (6).

Cohort and Time Horizon
The cohort were Canadians aged 60 years with diabetes and no history of DFUs. Cycle length was four months (the average time for a DFU to completely heal (37)) and the time horizon was 5 years.

Model
A Markov model simulated the history of DFUs in Canada using Microsoft Excel version 15.41. The model (Figure 1) included 10 states: (1) person with diabetes; (2) low risk for DFU; (3) moderate risk for DFU; (4) low risk DFU; (5) moderate risk DFU; (6) healed DFU; (7) DFU recurrence; (8) amputation; (9) healed amputation; (10) death due to any cause. Cohort members started in state (1) and moved into pre-defined health states in 4-month cycles for five years. Each state had a 4-month cost estimate, and costs accumulated per time patients spent in each state. Model validation is outlined in more detail the Supplementary Information. .

Effectiveness
To determine effectiveness thresholds (32), we varied the effectiveness of primary prevention efforts at three possible states: low risk for DFU, moderate risk for DFU, and healed DFU. Effectiveness was varied between 5%-40% based on clinical expert opinions, which is defined as the decrease in the number of DFUs. Specifically, the transition from a healed DFU state to a recurrent DFU state was decreased by 5%-40% (high-risk) and the transition from a low risk, moderate risk and healed DFU state to a DFU state was decreased by 5%-40% (population-based).

Model Parameters and outcomes

Model parameters are listed in Table 1 and SI Table 2, including DFU incidence, amputation rates, healing rates, and mortality rates. Outcomes were expressed in quality-adjusted life years (QALYs) (38). Values were based on a review of utility values for type 2 diabetes by Beaudet, et al. 2014 (39) (see Supplementary Information). Beta distributions were used for all utility values with 1.5% discount rate (34,38).

Resource Use and Costs

We used a public payer perspective of cost using sources including CIHI's Patient Cost Estimator and Ontario's Schedule of Benefits: Physician Services Under the Health Insurance Act (40,41). Costs associated with each state are listed in Table 1. Gamma distributions were used for all cost parameters with 1.5% discount rate reported in 2015 Canadian dollars (34,38). Please see the Supplementary Information for details regarding how costs were derived, such as screening, DFU treatment, and amputation.

Analysis

Cost-effectiveness was explored by varying TM effectiveness and comparing results to the CPE model. Separate analyses were conducted for population-based and high-risk approaches. Results were presented as the difference in cost, difference in QALY, and incremental cost-effectiveness ratios compared to the CPE model.

Sensitivity analysis

Probabilistic Sensitivity Analysis (PSA)

To explore uncertainty, Monte-Carlo simulations of 1,000 trials were conducted for population-based and CPE, and high-risk and CPE. All input parameters in the models were considered as random quantities from an associated probability distribution (38). At 30% effectiveness, the PSA results for the high-risk and population-based approaches were compared on a cost-effectiveness plane. We constructed cost-effectiveness acceptability curves (CEAC), with willingness-to-pay (WTP) thresholds of $0-$100,000. A variation of the CEAC was also used. Proportions of simulations resulting in cost-effectiveness at varying effectiveness levels were identified for specific WTP thresholds.

One-way analysis

One-way analyses were conducted to explore the effect on ICERs when key parameters were varied based on data in literature and expert opinion.

RESULTS

We set out to evaluate the cost-effectiveness of a telemedicine (TM) intervention in a hypothetical cohort of Canadian patients aged 60 years with diabetes. A Markov cohort model was constructed including 10 states (Figure 1) and de-bugged to validate the model's functionality (see Supplementary Information for details). Outcomes from our analysis were expressed as Quality-Adjusted Life Years (QALYs) and as incremental cost-effectiveness ratio (ICERs; a value that incorporates both the difference in costs between comparators in the

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numerator, and the difference in QALY in the denominator). We compared the cost-effectiveness of a using a TM device to monitor the feet of diabetics to prevent DFUs in two scenarios: 1) a population-based approach, where all diabetics are monitored, and 2) a high-risk approach, in which diabetics are monitored by TM after their first DFU is diagnosed and has healed.

Population-based Approach
We conducted a search of the literature to assign cost and effectiveness values to each transition state in our Markov model (Table 1) and ran the scenarios described above. We found that a population-based approach was both costlier and more effective than current DFU prevention efforts (Table 2). When effectiveness of the TM intervention increased, QALYs gained increased while incremental costs decreased. If adopting population-based TM approach decreased DFU incidence by 20%-40%, the resulting health benefit was 0.01196 – 0.02369 QALYs per person, respectively. A population-based approach using TM was a more widespread screening strategy than is currently in place in Canada, which translated into incremental costs of $479 - $402 per person and ICERs of $40,034 - $16,971, respectively.

High-risk Approach
People with diabetes who have had a DFU are more likely to develop subsequent ulcers. Our second approach analyzed DFU recurrence and evaluated the cost and effectiveness of TM prevention after a patient healed from their first DFU. We found that screening a high-risk population was slightly less costly and more effective compared to current DFU prevention efforts at 15% effectiveness (Table 1). As expected, when effectiveness of DFU prevention increased, there was also an increase in cost-savings and QALYs gained. Over 5 years with effectiveness of 15%-40%, people in this cohort had a health benefit of 0.00062 – 0.00174 QALYs per person while costs decreased by $1.26 - $25.55 per person, respectively.

Sensitivity analysis
We next compared the Monte-Carlo simulation of 1,000 trials at 30% effectiveness for the population-based and the high-risk approach (Figure 2). The majority of simulations for the population-based approach resulted in more QALYs and higher costs, since more people were screened. We also found that some simulations from both approaches resulted in less QALYs than the CPE model, which is attributed to uncertainty in utility values. The costs in these cases were consistent with simulations that resulted in QALYs gained. We also conducted Monte Carlo simulations for all models (please see Supplementary Information for details).

Identifying Highest Probability of Cost-effectiveness
Although the population-based approach was more effective at preventing DFUs, the cost of such an approach was intuitively higher. To determine the WTP threshold at which a population-based approach was more likely to have a lower ICER than the high-risk approach, we calculated the probability of cost-effectiveness for both population-based and high-risk approaches at 30% effectiveness. The results showed that a high-risk screening strategy had a higher probability than the population-based approach of being cost-effective up to a WTP

threshold of $66,500/QALY gained (Figure 3). Beyond that threshold, the population-based approach had a higher probability than the high-risk approach. We next varied effectiveness levels at defined WTPs (Figure 4). Not surprisingly, increasing the effectiveness of the intervention increased the probability of cost-effectiveness for both the high-risk and population-based approaches. At a WTP of $100,000 and effectiveness above 15%, the population-based approach had a higher probability of cost-effectiveness than the high-risk approach.

Further analyses summarizing the effects of varying parameters related to cost of TM, DFU utility state values, and DFU incidence rates can be found in Supplementary Information Figure SI1 and SI2. Influential parameters were utility values for healed DFU, active DFU, no history of DFU, and incidence rates for low risk, moderate risk, and recurrent DFUs.

INTERPRETATION

As the Canadian population ages, the strategic allocation of resources in our healthcare system becomes increasingly important. By 2020, an estimated 3.7 million Canadians will have diabetes, with an associated cost of nearly $17 billion (42). Diabetes accounted for 3.5% of Canadian healthcare spending in 2005 (42), including an estimated $547 million dollars on DFU care (29). Cost of a single DFU case was $52,360, including costs of admissions, ER and clinic visits, drugs and dressings, home and long-term care (29).

TM is an increasingly popular mechanism for remote monitoring of chronic conditions, and has been applied successfully in diabetics (9–12). In this work, we sought to evaluate the health and economic effects of using TM to prevent DFUs. Given that a history of DFUs is associated with an increased risk for future ulcers, we stratified our analysis into 1) population-wide or 2) targeted screening approaches. Although the absolute effect of TM-based screening on DFU incidence is unknown without clinical data, the potential health benefit associated with population-based screening was appreciable, ranging from 0.01196 – 0.02369 QALYs per person at a conservative effectiveness of 20%-40%. For context, screening for hepatitis C in Canada reported QALY increase of 0.0032 - 0.0095 per person (43). However, population-based screening is a more widespread strategy than is currently in place in Canada, and would result in incremental costs of $479 - $402 per person over 5 years. In contrast, we found that implementing a TM strategy following a patient's first DFU had a high probability of being cost-effective while also slightly increasing quality of life (health benefit of 0.00062 – 0.00174 QALYs per person; decreasing costs of $1.26 - $25.55 per person at 15%-40% effectiveness, respectively). Cost savings were attributed to a reduction DFU recurrences and complications, which is enhanced when screening is more effective at preventing recurrence. As fewer screening devices are required in the high-risk approach, the up-front cost to the healthcare system are lower, and targeting a group of patients with higher chances of DFU formation eliminates waste.

Limitations

Our analysis was based on data from various sources, but there is a lack of data on DFU prevalence and associated costs in Canada. We used conservative parameter estimates for DFU

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incidence to avoid inflated results, and therefore our models may underestimate the impact TM has on the preventing DFUs (44). Moreover, costing data available for this study does not encompass all costs associated with DFUs. For example, costs of the 'DFU state' in our model only included the cost of physician services and treatment in hospital-based acute care. However, not all DFUs are treated on an inpatient-basis. An analysis using outpatient clinic and homecare costs would likely result in greater cost-effectiveness as cost-savings from prevention would increase, but data in these realms of patient care is not available. Furthermore, indirect cost from a societal perspective was not included, such as productivity loss (45) and travel costs incurred to the patients.

Also, the models constructed were simplified representations of DFUs. DFUs require personalized care since wounds can progress through various stages during the healing process, including potential for infection and surgical debridement (3). It is unknown how this would change our results. Furthermore, the age of the cohort simulated was 60 because model parameters were sourced from observational studies on patients with this average age. However, DFUs occur in patients with diabetes across all age groups (46). Lower rates of DFU incidence would increase ICERs and while higher rates would improve ICERs. Subgroup analyses should be explored in future studies. This analysis should be considered an early health technology assessment given the lack of important data on various parameters. The findings, however, represent the first piece of evidence on this important solution to a growing problem.

Conclusion and future directions
Rising rates of diabetes have been likened to an impending global tsunami. Healthcare systems must find a way to re-focus care away from the reactionary and turn to prevention. The use of TM in the diabetic lower extremity can be an economically attractive alternative to current screening practices in Canada. Future work should focus on developing and validating technologies based on objective outcome measures for remote TM of diabetic feet.

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Tables and Figures

Table 1. Summary of key model parameters over a 4-month period

Variable/State	Value (Range)	Reference
Transition Probabilities		
Rate of developing low risk DFU, %	0.3% (0.3 - 0.41)	(44)
Rate of developing moderate risk DFU, %	0.45% (0.45 - 2.18)	(44)
Rate of developing recurrent DFU, %	11.21% (7.17 - 15.66)	(47), (48)
Healing rate for low risk DFU, %	45.71%	(49)
Healing rate for moderate risk DFU, %	32.32%	(49)
Healing rate for recurrent DFU, %	11.51%	(50)
Amputation rate for low risk DFU, %	0.67% (0.3 - 0.77)	(44), (49), (51)
Amputation rate for moderate risk DFU, %	2.74% (0.063 - 8.54)	(44), (49), (52), (53)
Amputation rate for recurrent DFU, %	3.45% (0.68 - 3.45)	(44), (50)
Mortality rate for low risk DFU, %	1.17% (1.01 - 2.73)	(49), (52)
Mortality rate for moderate risk DFU, %	3.26% (3.26 - 8.07)	(49), (52)
Mortality rate for recurrent DFU, %	3.26% (3.26 - 8.07)	(49), (50) , (52),
Mortality rate for amputation	See Supplementary Figure 3, Kaplan-Meier curve	(54)
Utilities or Cost*		
No Ulcer	0.7850 (0.681 - 0.889)	(39)
Active DFU	0.615 (0.578 - 0.652)	(39)
Healed DFU	0.680	(55)
Amputation	0.505 (0.396 - 0.615)	(39)
Initial Screen	$60	(41)
At low risk for DFU	$67.80	(41)
At moderate risk for DFU	$85.87	(41)
DFU	$2,395.75	(41), (40)
Amputation	$16,752.15	(41), (40)
Healed Amputation	$78.40	(41), (40)
Healed DFU	$135.60	(41)
TM device	$20.00	(56)
TM service	$14.65	(57)

*All cost in 2015 Canadian Dollars.

Table 2. Estimated cost-effectiveness for population-based and high-risk approach DFU prevention using TM at varying levels of effectiveness.

| RR for DFUs	Effectiveness (%)	Quality-Adjusted Life Years (QALY)	Cost, 2015 Can$	Incremental Cost ($)	Incremental Effect (QALY)	Incremental Cost-Effectiveness Ratio (QALY)
High-risk Approach						
0	0	10.95213	732.42	-	-	-
0.95	5	10.95233	740.12	7.70	0.00020	38,005.72
0.9	10	10.95254	735.69	3.27	0.00041	7,995.00
0.85	15	10.95275	731.16	-1.26	0.00062	Dominant
0.8	20	10.95296	726.53	-5.89	0.00083	Dominant
0.75	25	10.95318	721.78	-10.63	0.00105	Dominant
0.7	30	10.95341	716.93	-15.49	0.00128	Dominant
0.65	35	10.95363	711.96	-20.46	0.00151	Dominant
0.6	40	10.95387	706.87	-25.55	0.00174	Dominant
Population-based Approach						
0.95	5	10.95514	1,272.41	539.99	0.00301	179,475.12
0.9	10	10.95813	1,252.67	519.25	0.00601	86,468.75
0.85	15	10.96112	1,231.25	498.83	0.00899	55,496.76
0.8	20	10.96409	1,211.17	478.75	0.01196	40,034.44
0.75	25	10.96704	1,191.43	459.01	0.01491	30,776.87
0.7	30	10.97000	1,172.06	439.64	0.01786	24,622.45
0.65	35	10.97291	1,153.07	420.65	0.02078	20,241.98
0.6	40	10.97582	1,134.48	402.06	0.02369	16,970.87

Dominant = less costly and more effective
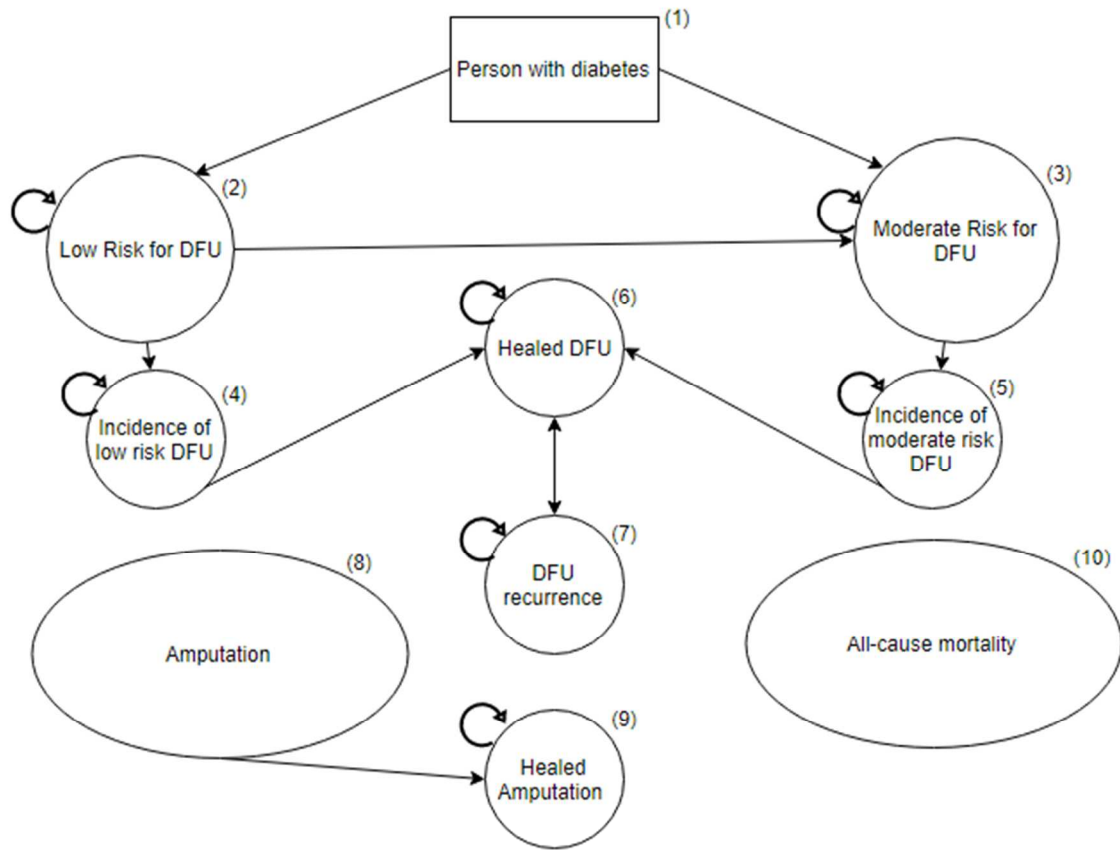
Figure 1. Markov model of DFU incidence and progression. All states can also transition to the amputation state, and all states can be absorbed by the death state (not shown). For details on each health state, see Supplementary Information~~ Methods 2~~.
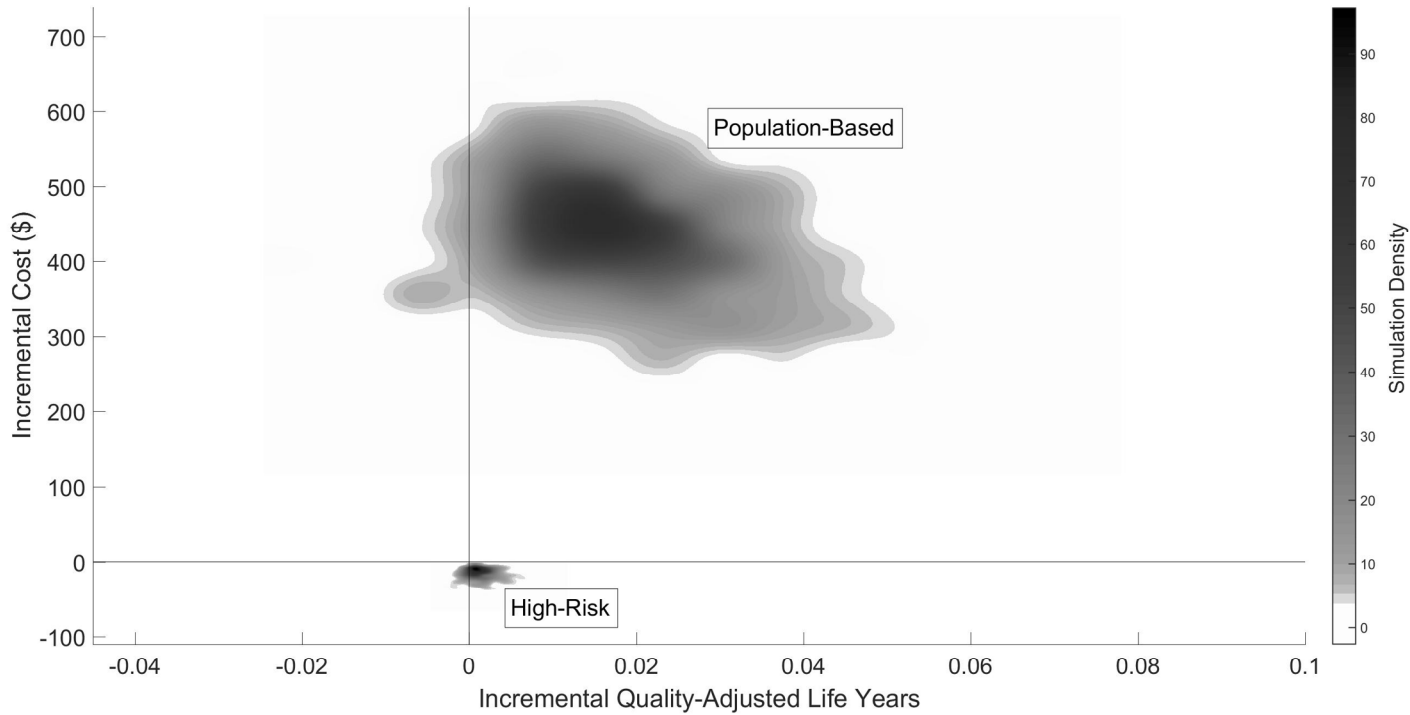
Figure 2. Cost-effectiveness plane of 1,000 Markov simulations in both a high-risk approach and population-based approach assuming a DFU prevention effectiveness of 30%. The majority of simulations conclude that screening by TM results in a gain of QALYs, while only the high-risk screening strategy results in cost savings to the health care system.

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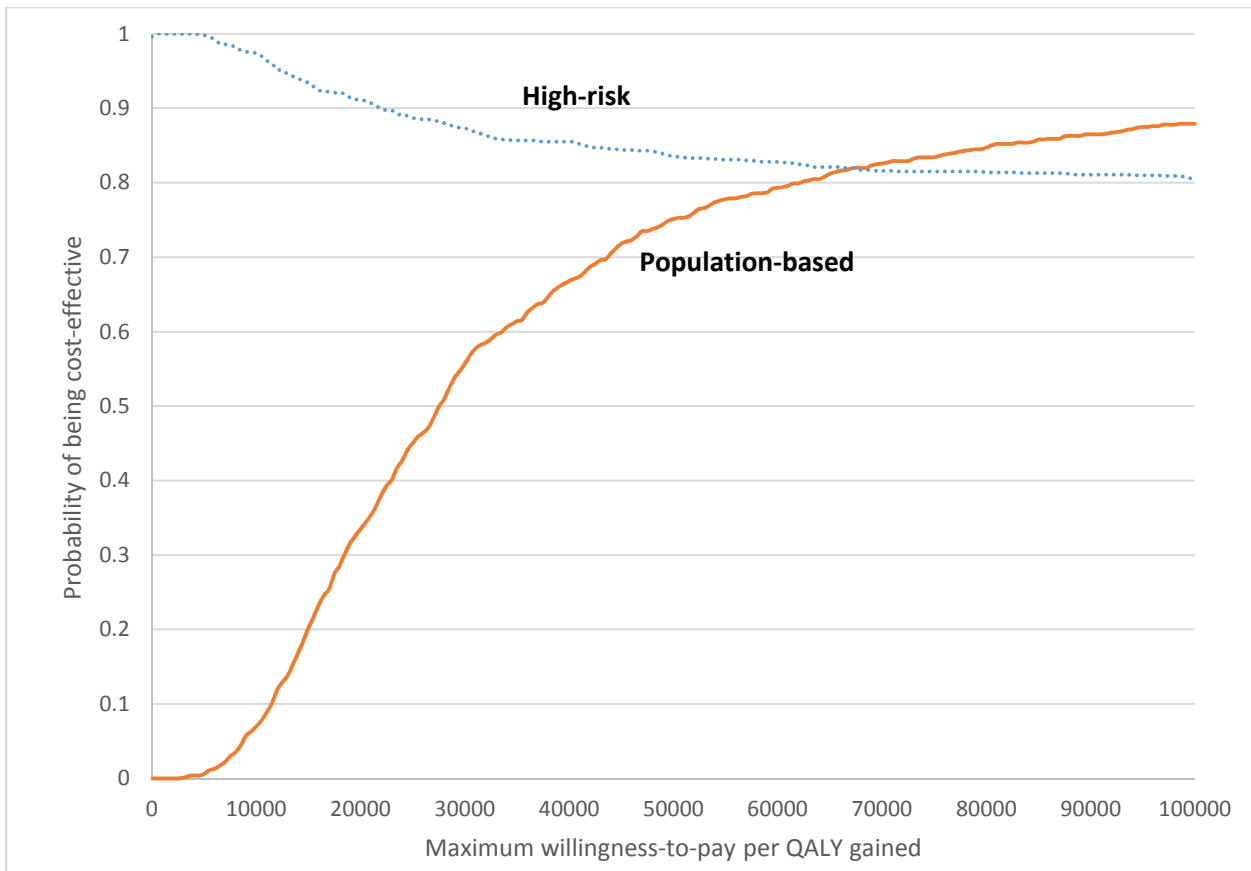42
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Figure 3: Cost-effectiveness acceptability curve, which summarizes the impact of uncertainty on the results, showing the proportion of simulations that resulted in an ICER less than a WTP threshold (x-axis) for the high-risk and population-based approaches at 30% effectiveness. These proportions can be interpreted as probability of cost-effectiveness, based on 1000 simulations.
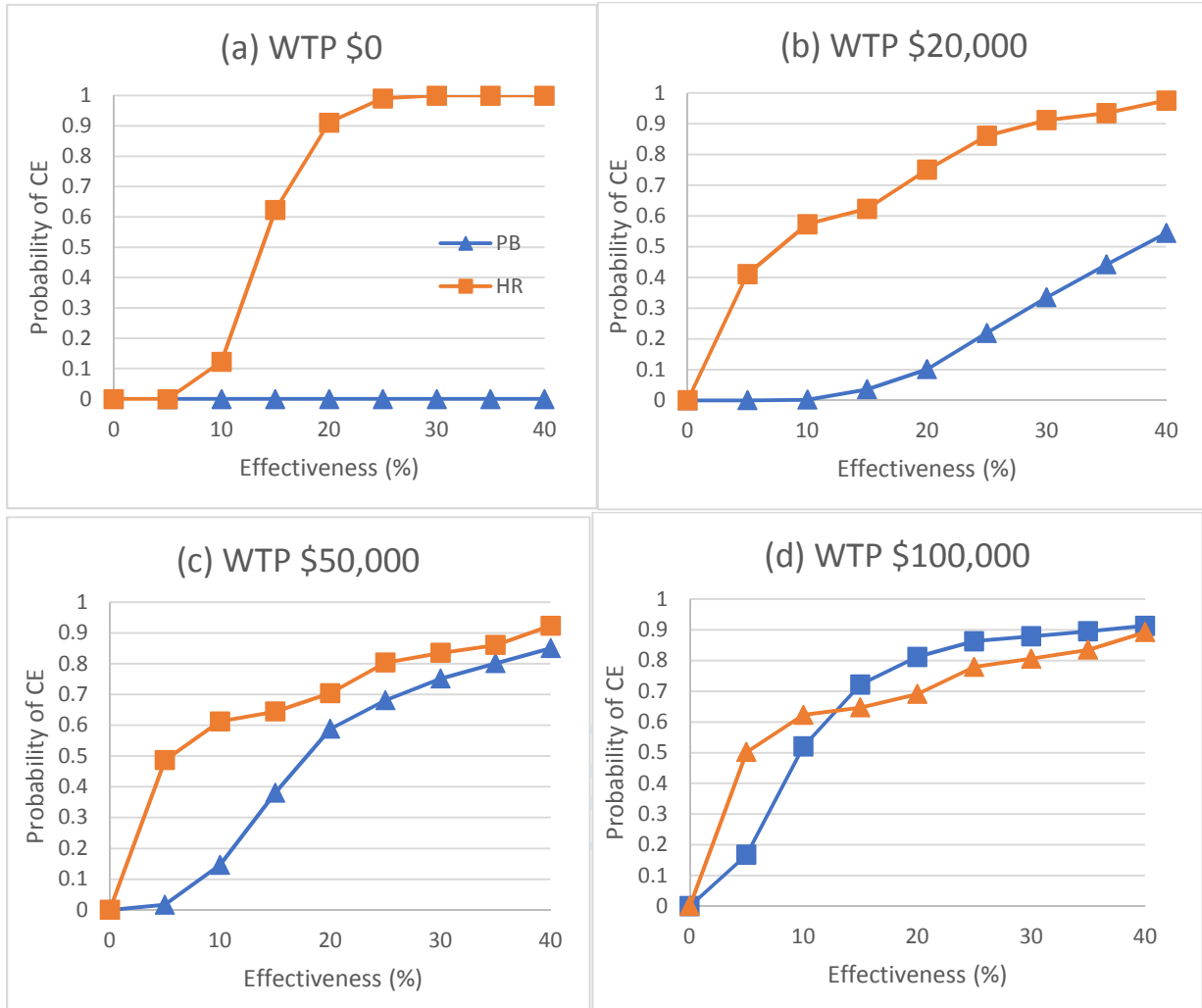
Figure 4. Varying the effectiveness of the TM intervention influences the probability of cost-effectiveness at given willingness-to-pay (WTP) thresholds. At a WTP of $0 (A), $20,000 (B), and $50,000 (C), the high-risk approach has a higher probability of cost-effectiveness. At a WTP of $100,000 (D) and effectiveness above 15%, the population-based approach had a higher probability of cost-effectiveness than the high-risk approach.

Supplementary Information

Methods
Model validation
The following validation techniques are based on ISPOR-SMDM recommended practices for model transparency and validation(1). As the prevention of DFUs is not well studied in literature(2), it is important to note that this model serves as a framework for future research in this area.

Face validity
Multiple steps were taken to ensure face validity. The problem formulation process determined a focus on a Canadian context, identified a population with diabetes who are low to high risk of DFUs, defined a TM intervention that aims to prevent DFUs, and selected a time horizon that reflects the natural history of DFUs.

The model structure was constructed and rigorously adjusted by experts in modelling (WI) and diabetic foot care (KC) to emulate recommended practices in DFU prevention according to the International Working Group for the Diabetic Foot. Since the modelling of DFU prevention is in its early stages in literature, data applicable to this model was limited. With this in mind, the data sources consulted for the construction of the model were verified for appropriate study design and applicability of results. Decisions were made to include certain DFU states and to exclude others, such as not distinguishing between minor and major amputations. Also, the complexity of DFU progression was not modelled, due lack of applicable data for this progression and that representing it as a number of discrete states is clinically impractical.

Verification
To ensure the correct mathematical equations were used in the model, a structured walk-through of the code was conducted by CB to WI. To ensure that the model performed according to its specification, extreme-value analysis was conducted by predicting the behaviour of the model when a certain parameter is adjusted.

Cross Validity
Since no other studies have explored the cost-effectiveness of TM, we identified other studies with models that evaluate the cost-effectiveness of DFU prevention.

The first study identified was by Tennvall and Apelqvist, 2001 where a cost-utility analysis was conducted to evaluate the prevention of DFUs and amputations(3). The prevention strategy defined was patient education, foot care, and footwear. It was found that DFU and amputation incidence needs to be reduced by 25% to be cost-effective, which was identified as ICER < €100,000/QALY. This is similar to the results our model produced as there is an increase in cost per QALY gained. However model structures are different. For example, the model did not include the stratification of risk groups, but instead the model was simulated individually for each group at risk for DFUs. Also, the healing rates of DFUs were assumed to be same, regardless of which risk group the DFU originated from. This assumption can influence the

results, as DFUs with and without peripheral arterial disease can heal at different rates(4). Similarly, Ortegon et al., 2004 also varied the effectiveness (between 10%-90%) of the interventions to identify thresholds of cost-effectiveness (5). Also, the model included states for risk groups before DFU development. However, the cohort was assumed to be all in the lowest risk group and transitioned into the others over time, which is not representative of a diabetic population. Similar to Tennvall and Apelqvist 2001, this model also assumed DFUs healed at the same rates regardless of risk group. As expected, the outcomes (ICERs) between this model and ours were different. However, both models showed that, depending on prevention effectiveness, there is an increase in cost per QALY gained. Lastly, Barshes et al. 2017, estimated cost-savings in diabetic foot ulcer prevention efforts(6). Specifically, this study explored the effects of improved prevention (primary) and treatment (secondary) by varying its effectiveness. A major distinction is that this model identifies annual prevention cost thresholds for cost-savings, rather than the traditional ICER. This makes it's difficult to compare outcomes of the models. In addition, the model did not include a cost for stratifying a person into a risk group, which can significantly change the results presented. However, similar methodologies were used in both models, such as varying effectiveness thresholds and incorporating the stratification of the cohort into risk groups in order to determine appropriate screening strategies. Also, this model used a one-month cycle length, which may not reflect how DFUs progress in current available research, as follow-up visits are 1 year on average.

Definitions of study parameters
Pre-DFU

The risk groups defined in this paper were based on the guidelines from *Best Practice Recommendations for the Prevention and Management of Diabetic Foot Ulcers* published by Wounds Canada (See Table 1). These recommendations were used to define 3 risk groups for our model: low risk, moderate risk, and high risk (recurrent DFU). The high-risk group assumed that recurrent DFUs either recurred at the same spot as the prior DFU, or in a new spot, as many studies do not distinguish between the types. The transition probability into the moderate risk group was derived from the estimate of 1/3 people with diabetes having peripheral artery disease (PAD) by the American Diabetes Association and Barshes et al. 2013. The mortality rate for the moderate risk group was based on a study by Mueller et al. 2014 that reported mortality rates in patients with diabetes and PAD. The mortality rate for the low risk group was based on Statistics Canada 2008 data on the number of deaths per 100,000 population with diabetes. Amputation rates prior to DFU formation was based on a study that observed lower limb amputation rates among diabetes patients without foot ulcer in Medicare and private insurance (12).

DFU

The transition probability from a low risk group to a moderate risk group was obtained from a previous cost-effectiveness study by Ortegon et al. 2004 (5). The transition probabilities for the development of low-risk and moderate-risk DFUs were derived from Lavery et al. 2008, where the incidence of DFUs were observed in people with diabetes stratified by risk factors with preference for conservative estimates (13). Amputation rates from low risk, moderate risk and

recurrent DFUs were compared between five studies to derive the probabilities used in this model (16-21) . Since little data exists on mortality rates for recurrent DFUs, and Orneholm et al. 2017 (17) reports a significantly lower mortality rate than rates reported for DFUs with PAD, it was assumed that the mortality rate is the same as having a moderate risk DFU.

Amputation

The amputation state was assumed to include both major and minor amputations and does not distinguish the cost difference between the two. The effects of this is further explored in the sensitivity analysis. When in the amputated state, a person can transition into either the healed amputation state or death. Mortality rates are adjusted as time increases via Markov tunnel states. As time increases, mortality rates increase. This increase is derived from Kaplan Meier survival estimates in Aulivola et al. 2004 and Fortington et al. 2013 (20, 21) (Figure 2).

Probability sensitivity analyses were achieved using Dirichlet and beta distributions for all state transition probabilities (22).

Cost and utilities values

Measurement and Valuation of Outcomes

Estimates of health utilities associated with each state was obtained from an extensive review of utility values in type 2 diabetes specific for economic modelling (23). This review did not include a utility value for healed DFUs, which was derived from Redekop, 2000 (24).

Resource Use and Costs

The costs of treatment were based on annual estimates of hospital costs from the Canadian Institute for Health Information's Patient Cost Estimator (25). This report included the cost of Diabetes with Foot Ulcer, Amputation of Hand/Foot, Biopsy of Bone and Orthopedic Aftercare (SI Table 3). Hopkins et al. 2015 reported that the average number of admissions per prevalent case was 0.66, so this was used to adjust the cost proportion in the DFU state (26).

The physician fees were based on the Schedule of Benefits: Physician Services under the Health Insurance Act (5) (SI Table 4). Validated by KC, billing codes descriptions used for DFUs are Wound and ulcer debridement and Wound and ulcer debridement extending into any of the following structures: tendon, ligament, bursa and/or bone. The average of these costs was used in this model. Physician fees for amputations are the average costs of Amputation-Bone Code-Musculoskeletal System for Metatarsal/phalanx disarticulation, Ray(single), Symes, Transmetatarsal/transtarsal, Terminal Symes, and the average costs of Biopsies for Need-Punch, Needle – under general anasethetic, Needle – open, and Joint – open. Physician fees for screening and prevention visits prior to a DFU (for both in-person and telemedicine) and follow-up visits with a healed DFU were based the average costs for Diabetic screening with a family physician, and endocrinologist visits. Table 3 lists all of the billing codes used to derive costs in the model.

The cost of a TM solution was derived from the operating costs of the Ontario Telemedicine Network (OTN) in a financial statement from 2016 (27). The services provided by the OTN leverages similar technology required for a hypothetical telemonitoring intervention for DFUs

and was used as our baseline cost. The cost of the TM device was derived from Fasterholdt et al. 2016 using www.xe.com, where a similar device was used to monitor DFUs (28). Since this cost is sourced from a different jurisdiction and represents a small portion of total costs, laborious cost conversion is irrelevant. The physician fees associated with the use of the device for screening was assumed to be the combined cost of telemedicine billing codes defined in the OHIP Billing Information for Telemedicine Services September 2011 and the cost of a regular in-person screening visit. This assumption was made as the type of interaction via the TM device is not defined within the Schedule of Benefits.

Tables and Figures

SI Table 1. Risk groups for developing DFUs used in models based on International Working Group on the Diabetic Foot (IWGDF) guidelines reported by Wounds Canada.

| Clinical state in model	IWGDF(7)	Recommended Professional Follow-up(7)	Characteristics
Low Risk for DFU	0	Every 12 months	No loss of protective sensation No peripheral arterial disease (PAD)
	1	Every 4-6 months	No loss of protective sensation ± non-changing foot deformity
Moderate Risk for DFU	2a&b	Every 3 months	PAD and/or deformity ± loss of protective sensation
DFU Recurrence	3a&b	Every 1-3 months	Presence of diabetes with previous history of ulceration/amputation
Active DFU states	Urgent	Immediate referral	Open ulcer ± infections Charcot foot

SI Table 2. All transition probability parameter estimates, and sources used in Markov Model for current screening efforts in Canada. All telemonitoring Markov Models used same parameter estimates, except DFU incidence rates. Specifically, the transition from a healed DFU state to a recurrent DFU state was decreased by 5%-40% (high-risk) and the transition from a low risk, moderate risk and healed DFU state to a DFU state was decreased by 5%-40% (population-based).

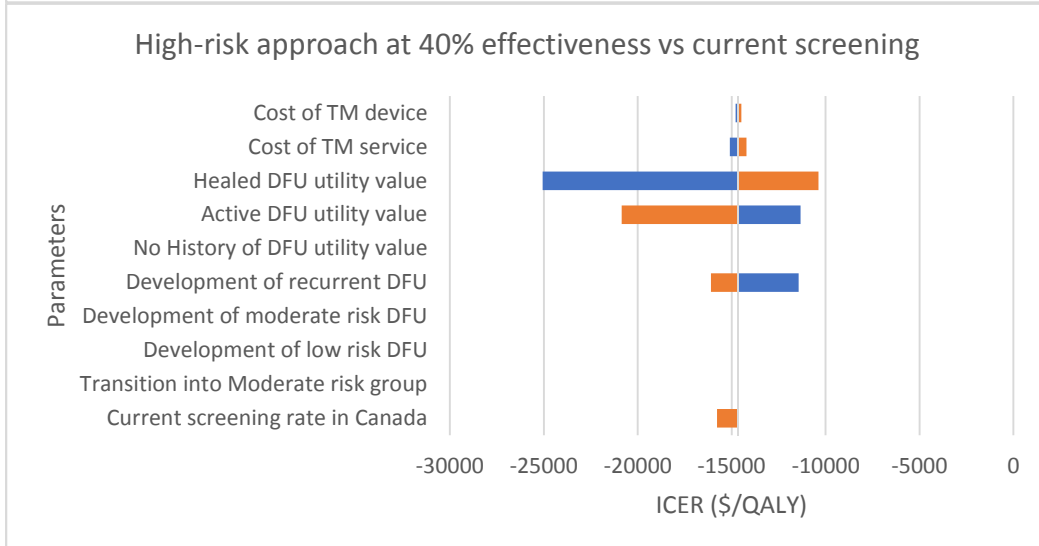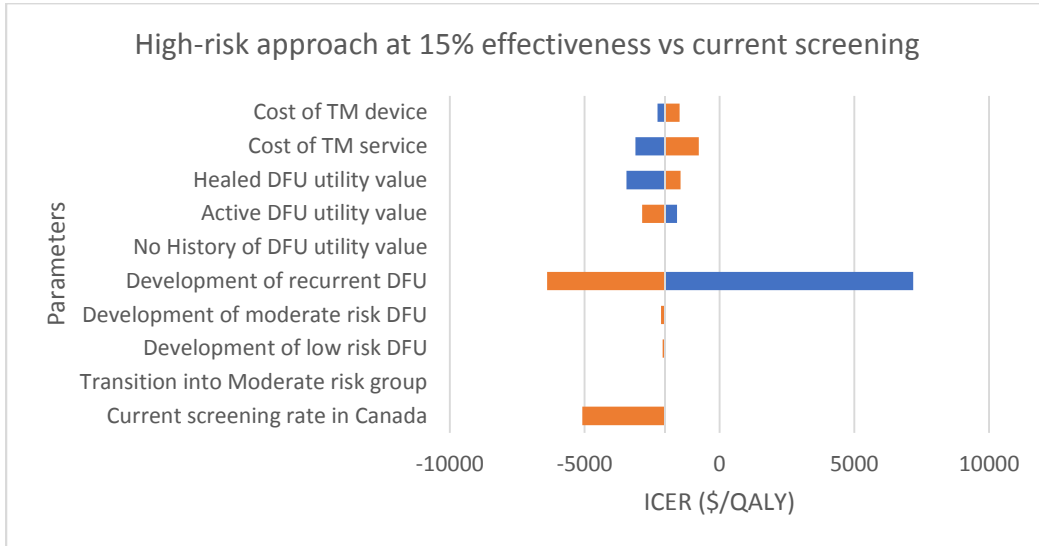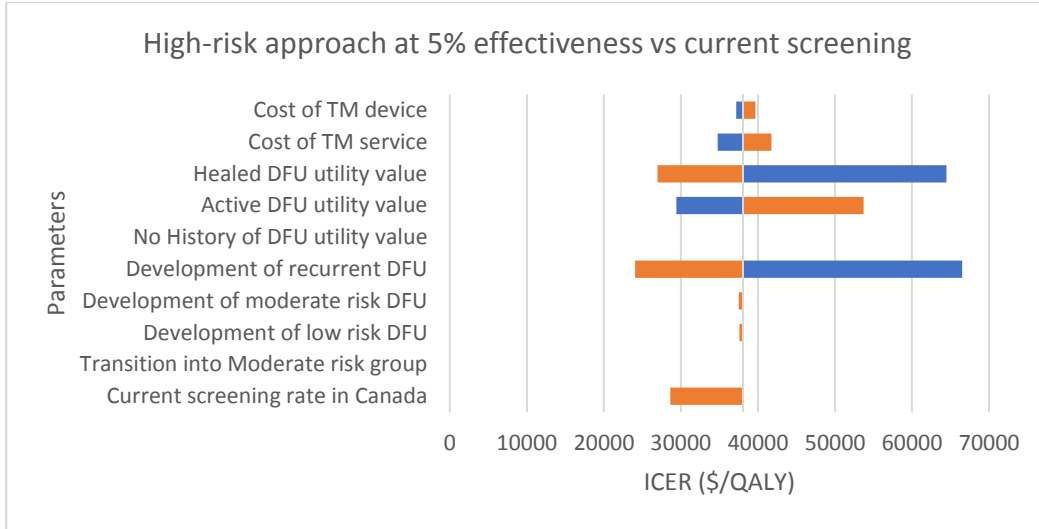| Transitions		Value(Range)	Source
Person with Diabetes	At low risk of DFU	66.83%	
	At moderate risk of DFU	33.0%	American Diabetes Association, 2014(8)
	Amputation	0.01%	Rice et al., 2014(12)
	Death	0.16%	Statistics Canada, 2014(11)
Amputation	Healed amputation	See figure 2	
	Death	See figure 2	Aulivola et al., 2004(20)
At low risk of DFU	At low risk of DFU	99.46%	
	Amputation	0.01% (0.00667 - 0.01334)	Rice et al., 2014(12)
	Develop low risk DFU	0.3% (0.18 - 0.41)	Lavery et al., 2008(13)
	Death	0.16%	Statistics Canada, 2014(11)
	At moderate risk of DFU	0.07%	Ortegon et al., 2004(5)
Develop low risk DFU	Develop low risk DFU	52.45%	
	Healed DFU	45.71%	Prompers et al., 2008(4)
	Amputation	0.67% (0.3 - 0.77)	Lavery et al., 2008(13), Moulik et al., 2003(8), Prompers et al., 2008(4)
	Death	1.17% (1.01 - 2.57)	Prompers et al., 2008(4), Morbach et al., 2012(16)
At moderate risk of DFU	At moderate risk of DFU	99.38%	

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	Amputation	0.01%	Rice et al., 2014(12)
	Develop high risk DFU	0.45% (0.27 - 1.31)	Lavery et al., 2008(13)
	Death	0.67%	Mueller et al., 2014(10)
Develop moderate risk DFU	Develop high risk DFU	61.68%	
	Healed DFU	32.32%	Prompers et al., 2008(4)
	Amputation	2.74% (0.063 - 8.54)	Lavery et al., 2008(13), Morbach et al., 2012(16), Oyibo et al., 2001(15), Prompers et al., 2008(4)
	Death	3.26% (3.26 - 8.07)	Prompers et al., 2008(4), Morbach et al., 2012(16)
Healed DFU	Healed DFU	87.06%	
	Develop recurrent DFU	11.21% (7.17 - 15.66)	Armstrong et al., 2017(18), Dubsky et al., 2013(13)
	Amputation	0.01%	Rice et al., 2014(12)
	Death	1.01% (0.57 - 1.56)	Orneholm et al., 2017(17)
Recurrent DFU	Recurrent DFU	81.78%	
	Healed DFU	11.51%	Orneholm et al., 2017(17)
	Amputation	3.45% (0.68 - 3.45)	Lavery et al., 2008(5), Orneholm et al., 2017(17)
	Death	3.26%	Prompers et al., 2008(4), Morbach et al., 2012(9), Orneholm et al., 2017(17)

SI Table 3. Canadian Institute for Health Information Patient Cost Estimator (25) data used for costing DFUs and amputations.

Case Mix Group	Age Group	Estimated Average Cost	Estimated Average Cost (all age groups)	Average Acute LOS days
402 Diabetes with Foot Ulcer	18-59 Years (Adult)	$ 9,984.36	$ 10,250.73	7.8377483
	60-79 Years (Adult)	$ 10,647.33	$ 10,250.73	9.4900459
	80+ Years (Adult)	$ 9,822.41	$ 10,250.73	9.8122271
183 Amputation of Hand/Foot	18-59 Years (Adult)	$ 9,864.15	$ 10,071.53	8.6962963
	60-79 Years (Adult)	$ 10,153.88	$ 10,071.53	9.4888889
	80+ Years (Adult)	$ 10,138.53	$ 10,071.53	12
342 Biopsy/Invasive Inspection of Bone	1-7 Years (Paediatric)	$ 5,406.19	$ 5,145.99	5.0833333
	8-17 Years (Paediatric)	$ 4,069.78	$ 5,145.99	1.8627451
	18-59 Years (Adult)	$ 4,758.34	$ 5,145.99	2.6986301
	60-79 Years (Adult)	$ 5,387.70	$ 5,145.99	3.6666667
	80+ Years (Adult)	$ 9,163.79	$ 5,145.99	12.434783
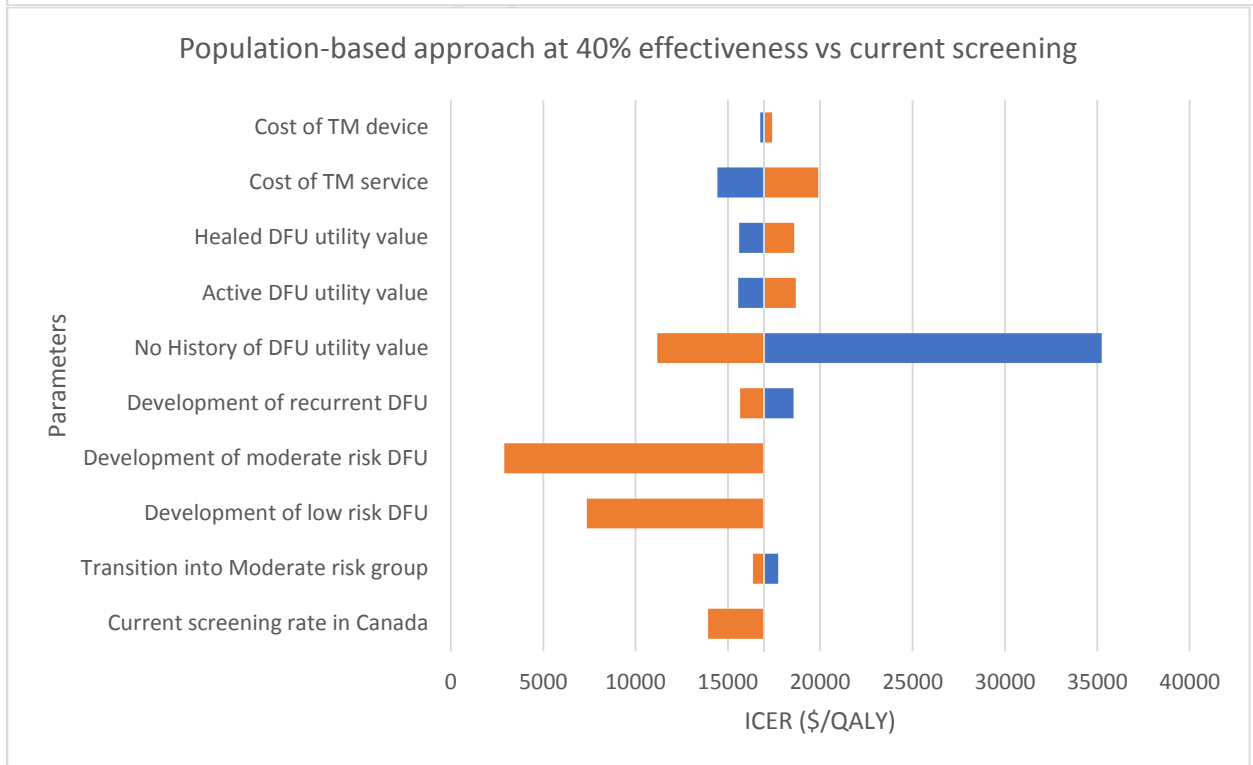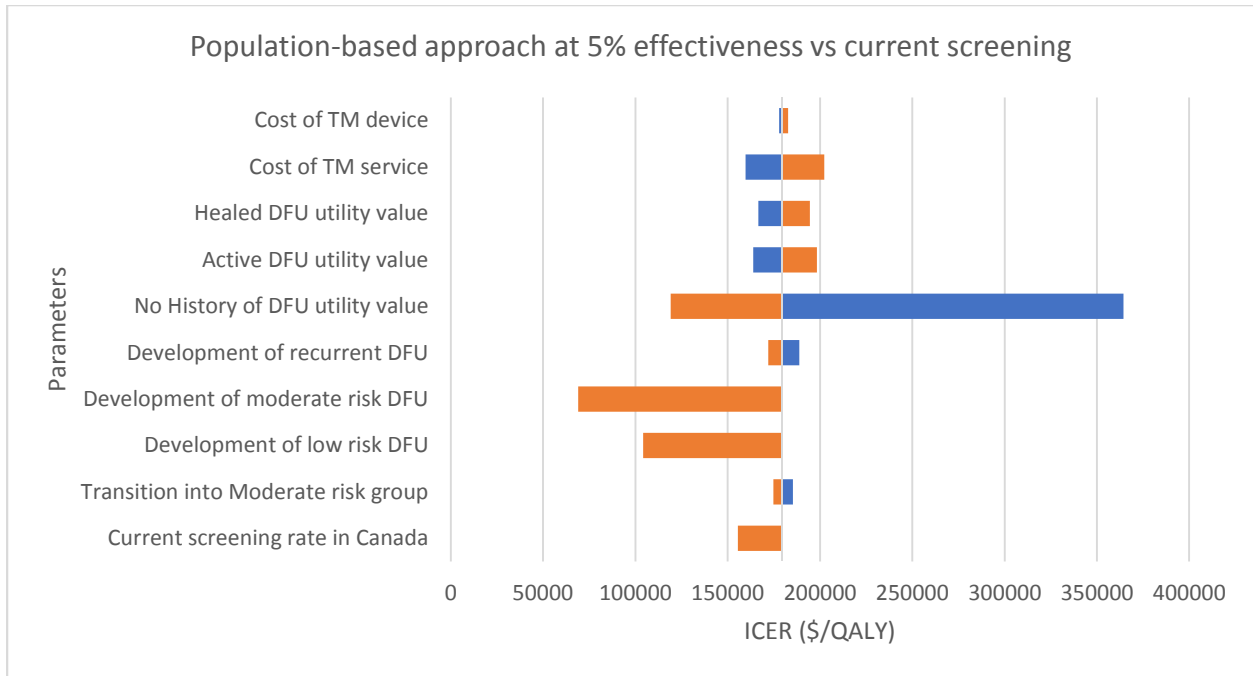
SI Figure 1: Population-based approach one-way sensitivity analyses. Analyses were run for effectiveness values ranging from 5% to 40% in increments of 5%, but since trends changed very little only the highest and lowest effectiveness values are shown.

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SI Figure 2: High-risk approach one-way sensitivity analyses. Analyses were run from 5% effectiveness to 40% effectiveness in increments of 5%. Trends changed more dramatically than the population-based analysis, and representative tornado diagrams are shown.
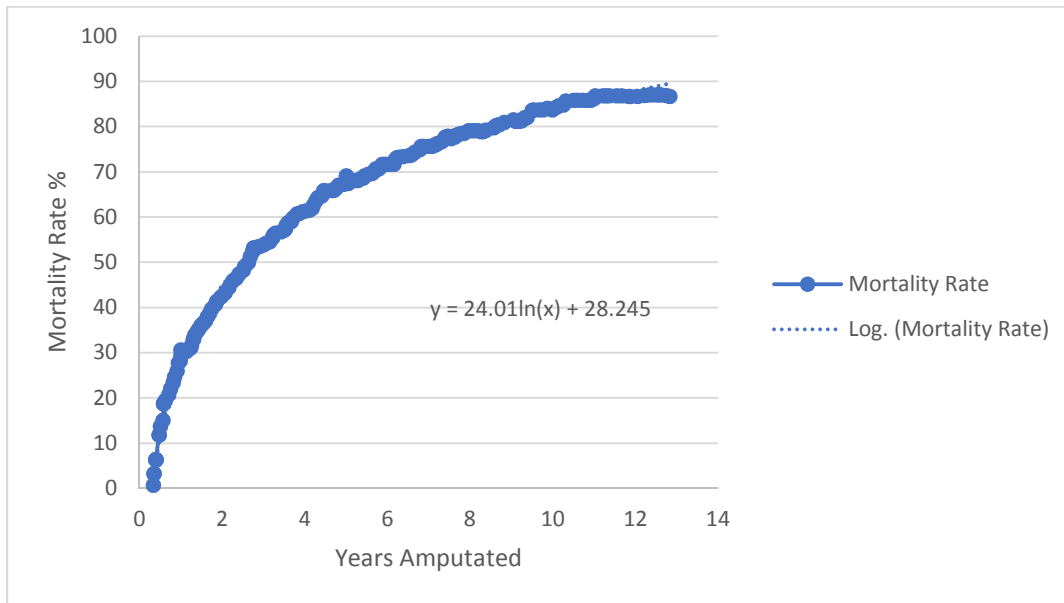
SI Figure 3: Kaplan Meier curve derived from Aulivola et al. 2004 (20) and Fortington et al. 2013 (21) mortality rates for diabetics with lower extremity amputations.

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