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APPENDIX A Decision Tree Parameters

Parameter	Base Value	Distribution*	Source
Proportion of women	0.81	N/A	FSPP data [†]
Proportion of type of index fracture			
Women			
Proportion of women with index proximal femur fractures	0.151	Beta (546, 3073)	FSPP data [†]
Proportion of women with previous fragility fractures	0.180	Beta (651, 2968)	FSPP data [†]
Proportion of women with index proximal humerus fractures	0.199	Beta (722, 2897)	FSPP data [†]
Proportion of women with index distal radius fractures	0.470	Beta (1700, 1919)	FSPP data [†]
Men			
Proportion of men with index proximal femur fractures	0.318	Beta (262, 562)	FSPP data [†]
Proportion of men with previous fragility fractures	0.136	Beta (112, 712)	FSPP data [†]
Proportion of men with index proximal humerus fractures	0.193	Beta (159, 665)	FSPP data [†]
Proportion of men with index distal radius fractures	0.353	Beta (291, 533)	FSPP data [†]
Proportion of people who received pharmacotherapy			
Usual Care			
Index proximal femur fractures	0.163	Beta (48, 245)	22
Previous fragility fractures	0.163	Beta (48, 245)	22
Index proximal humerus fractures	0.094	Beta (42, 403)	21
Index distal radius fractures	0.094	Beta (42, 403)	21
FSPP			
Women with index proximal femur fractures	0.518	Beta (127, 118)	FSPP data [†]
Women with previous fragility fractures	0.497	Beta (154, 156)	FSPP data [†]
Women with index proximal humerus fractures	0.333	Beta (47, 94)	FSPP data [†]
Women with index distal radius fractures	0.327	Beta (102, 210)	FSPP data [†]
Men with index proximal femur fractures	0.485	Beta (49, 52)	FSPP data [†]
Men with previous fragility fractures	0.536	Beta (30, 26)	FSPP data [†]
Men with index proximal humerus fractures	0.200	Beta (7, 28)	FSPP data [†]

Parameter	Base Value	Distribution*	Source
Men with index distal radius fractures	0.229	Beta (16, 54)	FSPP data [†]
Type of pharmacotherapy			
Both arms			
Denosumab	0.42	Fixed	FSPP data [†]
Risedronate	0.58	Fixed	FSPP data [†]

Note. FSPP = Fracture Screening and Prevention Program; N/A = not applicable.

*Beta distributions are specified by parameters alpha and beta.

[†]FSPP data represents all 5,264 patients who met inclusion criteria for the program between July 1, 2017 and May 15, 2018.

APPENDIX B Model Parameters for Markov Model

Parameter	Base Value	Distribution*	Source
Persistence at one-year			
Denosumab	0.819	Beta (766, 169)	24
Risedronate	0.631	Beta (254 161, 148 630)	23
Annual incidence of fracture			
Proximal femur fracture	Varies by age and sex	Fixed	29
Vertebral fracture	Varies by age and sex	Fixed	29
Proximal humerus fracture	Varies by age and sex	Fixed	29
Distal radius fracture	Varies by age and sex	Fixed	29
Proportion of fractures in general population attributable to osteoporosis			
Proximal femur fractures	Varies by age and sex	Fixed	30
Vertebral fracture	Varies by age and sex	Fixed	30
Proximal humerus fracture	Varies by age and sex	Fixed	30
Distal radius fracture	Varies by age and sex	Fixed	30
Relative risk of recurrent fracture by previous fracture site compared to no fracture history			
Relative risk of a proximal femur fracture given a proximal femur fracture	3.7	Lognormal (2.5, 5.3)	6
Relative risk of a proximal femur fracture given a proximal humerus fracture	2.4	Lognormal (1.6, 3.5)	6
Relative risk of a proximal femur fracture given a vertebral fracture	3.7	Lognormal (2.3, 5.9)	6
Relative risk of a proximal femur fracture given a distal radius fracture	2.9	Lognormal (2.0, 4.1)	6

Parameter	Base Value	Distribution*	Source
Relative risk of a proximal humerus fracture given a proximal humerus fracture	2.1	Lognormal (0.3, 17.3)	6
Relative risk of a proximal humerus fracture given a vertebral fracture	3.0	Lognormal (2.0, 4.3)	6
Relative risk of a proximal humerus fracture given a distal radius fracture	2.5	Lognormal (0.6, 10.2)	6
Relative risk of a vertebral fracture given a proximal humerus fracture	3.0	Lognormal (2.2, 4.0)	6
Relative risk of a vertebral fracture given a vertebral fracture	4.9	Lognormal (2.4, 9.8)	6
Relative risk of a vertebral fracture given a distal radius fracture	2.9	Lognormal (1.6, 5.3)	6
Relative risk of a distal radius fracture given a proximal humerus fracture	2.6	Lognormal (1.8, 3.8)	6
Relative risk of a distal radius fracture given a vertebral fracture	1.8	Lognormal (1.1, 3.2)	6
Relative risk of a distal radius fracture given a distal radius fracture	3.2	Lognormal (1.3, 8.1)	6
Treatment efficacy			
Denosumab vs. placebo			
Relative risk of a proximal femur fracture	0.60	Lognormal (0.37, 0.97)	28
Relative risk of a proximal humerus fracture	0.80	Lognormal (0.67, 0.95)	28
Relative risk of a vertebral fracture	0.32	Lognormal (0.26, 0.41)	28
Relative risk of a distal radius fracture	0.80	Lognormal (0.67, 0.95)	28
Risedronate vs. placebo			
Relative risk of a proximal femur fracture	0.74	Lognormal (0.59, 0.93)	27
Relative risk of a proximal humerus fracture	0.46	Lognormal (0.23, 0.93)	27

Parameter	Base Value	Distribution*	Source
Relative risk of a vertebral fracture	0.64	Lognormal (0.52, 0.79)	27
Relative risk of a distal radius fracture	0.68	Lognormal (0.43, 1.07)	27
Relative risk of mortality following first proximal femur fracture, women			
Year 1	2.1	Lognormal (1.7, 2.5)	4
Years 2-5	1.1	Lognormal (1.0, 1.2)	4
Years 6-10	1.0	Lognormal (1.0, 1.1)	4
Relative risk of mortality following first proximal femur fracture, men			
Year 1	2.9	Lognormal (2.5, 3.5)	4
Years 2-5	1.1	Lognormal (1.0, 1.2)	4
Years 6-10	1.0	N/A	4
Relative risk of mortality following second proximal femur fracture, women			
Years 1-10	1.54	Lognormal (1.46, 1.63)	5
Relative risk of mortality following second proximal femur fracture, men			
Years 1-10	1.58	Lognormal (1.42, 1.75)	5
Relative risk of mortality following proximal humerus fracture, women			
Year 1	1.6	Lognormal (1.4, 2.0)	4
Years 2-5	1.0	Lognormal (1.0, 1.2)	4
Years 6-10	1.0	Lognormal (1.0, 1.2)	4
Relative risk of mortality following proximal humerus fracture, men			
Year 1	2.2	Lognormal (1.7, 2.7)	4
Years 2-5	1.3	Lognormal (1.1, 1.5)	4
Years 6-10	1.0	Lognormal (1.0, 1.1)	4

Parameter	Base Value	Distribution*	Source
Relative risk of mortality following vertebral fracture, women			
Year 1	2.0	Lognormal (1.5, 2.6)	4
Years 2-5	1.1	Lognormal (1.0, 1.2)	4
Years 6-10	1.1	Lognormal (1.0, 1.2)	4
Relative risk of mortality following vertebral fracture, men			
Year 1	2.5	Lognormal (1.9, 3.3)	4
Years 2-5	1.3	Lognormal (1.1, 1.5)	4
Years 6-10	1.0	N/A	4
Probability of death	Varies by age and sex	N/A	31

Note. N/A = not applicable.

*Beta distributions were specified by parameters alpha and beta; Lognormal distributions were defined using the 95% confidence interval

APPENDIX C Annual Costs and Utilities

Parameter	Base value	Distribution*	Source
Utility multipliers			
First year following first proximal femur fracture	0.70	Beta (163, 70)	2
Subsequent years following first proximal femur fracture	0.80	Beta (186, 47)	2
First year following second proximal femur fracture	0.56	Beta (130, 103)	Calculated
Subsequent years following second proximal femur fracture	0.64	Beta (149, 84)	Calculated
First year following proximal humerus fracture	0.81	Beta (810, 190)	3
Second year following proximal humerus fracture	0.95	Beta (950, 50)	3, 48
Subsequent years following proximal humerus fracture	0.96	Beta (960, 40)	3, 48
First year following vertebral fracture	0.73	Beta (949, 351)	3
Subsequent years following vertebral fracture	0.87	Beta (1131, 169)	3
First year following distal radius fracture	0.96	Beta (96, 4)	2
Subsequent years following distal radius fracture	1.0	N/A	2
Utility of general population	Varies by age and sex		40
Costs			
FSPP	\$142.76	Fixed	FSPP data†
BMD test with GP visit (A007)	Varies by index		34 FSPP data†

	fracture type		35
Denosumab, 60 mL biannually	\$841.51	Fixed	34, 36
Risedronate, 35 mg weekly	\$151.12	Fixed	34, 36
Women			
First year following first proximal femur fracture	\$50,839	Gamma (16.0, 3177.4)	33
Years 2-8 following first proximal femur fracture	\$18,787	Gamma (16.0, 1174.2)	33
First year following second proximal femur fracture	\$50,839	Gamma (16.0, 3177.4)	Assumption
Years 2-8 following second proximal femur fracture	\$18,787	Gamma (16.0, 1174.2)	Assumption
First year following proximal humerus fracture	\$12,137	Gamma (16.0, 758.6)	33
Years 2-8 following proximal humerus fracture	\$7,046	Gamma (16.0, 440.4)	33
First year following vertebral fracture	\$20,423	Gamma (16.0, 1276.5)	33
Years 2-8 following vertebral fracture	\$9,487	Gamma (16.0, 592.9)	33
First year following distal radius fracture	\$4,595	Gamma (16.0, 287.2)	33
Years 2-8 following distal radius fracture	\$2,911	Gamma (16.0, 182.0)	33
Men			
First year following first proximal femur fracture	\$50,002	Gamma (16.0, 3125.1)	33
Years 2-8 following first proximal femur fracture	\$15,684	Gamma (16.0, 980.2)	33
First year following second proximal femur fracture	\$50,002	Gamma (16.0, 3125.1)	Assumption
Years 2-8 following second proximal femur fracture	\$15,684	Gamma (16.0, 980.2)	Assumption
First year following proximal humerus fracture	\$15,382	Gamma (16.0, 961.4)	33
Years 2-8 following proximal humerus fracture	\$8,777	Gamma (16.0, 548.5)	33

First year following vertebral fracture	\$16,948	Gamma (16.0, 1059.3)	33
Years 2-8 following vertebral fracture	\$5,902	Gamma (16.0, 368.9)	33
First year following distal radius fracture	\$8,709	Gamma (16.0, 544.3)	33
Years 2-8 following distal radius fracture	\$3,077	Gamma (16.0, 192.3)	33

Note. BMD = bone mineral density; FSPP = Fracture Screening and Prevention Program; GP = general practitioner; N/A = not applicable

*Beta distributions were specified by parameters alpha and beta; Lognormal distributions were defined using the 95% confidence interval; Gamma distributions were defined by parameters alpha and beta; if uncertainty estimates for costs were not provided in the source, a coefficient of variation of 25% was assumed (i.e., mean = 0.25 standard deviation). †FSPP data represents all 5,264 patients who met inclusion criteria for the program between July 1, 2017 and May 15, 2018. Costs represent 2018 Canadian dollars.

APPENDIX D List of model and parameter assumptions

Assumption	Reason/Source
Model structure	
Index fragility fractures included proximal femur, distal radius, proximal humerus and excluded all other fracture types	Model simplification
There can be no subsequent non-proximal femur fractures after a proximal femur fracture	Model simplification
An individual can have a maximum of two proximal femur fractures per lifetime	Model simplification
An individual can have a maximum of one fracture per year	Result of cycle length
Patients may stop pharmacotherapy after one year but not reinitiate throughout their lifetime	Model simplification
Patients who persist with pharmacotherapy for one year will remain on pharmacotherapy for five years total	Clinical expert
Patients who did not start pharmacotherapy initially could not throughout their lifetime	Model simplification
The residual treatment effect of risedronate linearly tapers off over the duration it was taken	25
Relative risk of recurrent fractures lasts for 10 years	43
Parameters	
Proportion of treated patients receiving each of denosumab and risedronate	FSPP data*
In usual care, a value for the proportion of people with a previous fragility fracture who receive pharmacotherapy was unavailable so we used the analogous proportion reported for proximal femur fracture patients because current guidelines define both of these populations as being at high-risk ⁴⁶ .	Clinical expert and clinical guidelines ⁴⁶
‘Prior fracture at any site’ was used as a substitute for proximal humerus fractures in relative risk of recurrent fracture ⁶ .	Clinical expert
‘radius/ulna fractures’ was used as a substitute for distal radius fractures in relative risk of recurrent fracture ⁶ .	Clinical expert

Fracture costs after eight years are \$0	33
Eighty percent of people will have a physician visit after receiving a BMD test	Clinical expert
A value for the first year post-second proximal femur fracture was estimated by multiplying the utility value for subsequent years of a first proximal femur fracture by the first year of a proximal femur fracture and a value for subsequent years post-second proximal femur fracture was estimated by squaring the utility value for subsequent years of a first proximal femur fracture	41
Persistence with pharmacotherapy is the same in FSPP and usual care	Assumption
Cost of a first proximal femur fracture is the same as the cost of a second proximal femur fracture	Assumption
The FREEDOM trial did not report the effectiveness of denosumab for proximal humerus and distal radius fractures so we used the estimates for non-vertebral fractures ²⁸	Clinical expert
Proportion of distal radius and proximal humerus fractures attributable to osteoporosis were not included in the study by Melton and colleagues so we used forearm and other fractures, respectively ³⁰	Clinical expert

Note. *FSPP data represents all 5,264 patients who met inclusion criteria for the program between July 1, 2017 and May 15, 2018.

APPENDIX E Values Used for Deterministic Sensitivity Analyses

Parameter	Base value	Low value	High value	Source
Proportion of people received pharmacotherapy				
Usual Care				
Index proximal femur fractures	0.163	0.1214	0.2062	22
Previous fragility fractures	0.163	0.1214	0.2062	22
Index proximal humerus fractures	0.094	0.0672	0.1215	21
Index distal radius fractures	0.094	0.0672	0.1215	21
FSPP				
Women with index proximal femur fractures	0.518	0.4558	0.5809	FSPP data*
Women with previous fragility fractures	0.497	0.4411	0.5524	FSPP data*
Women with index proximal humerus fractures	0.333	0.2555	0.4111	FSPP data*
Women with index distal radius fractures	0.327	0.2749	0.3970	FSPP data*
Men with index proximal femur fractures	0.485	0.3877	0.5826	FSPP data*
Men with previous fragility fractures	0.536	0.4051	0.6663	FSPP data*
Men with index proximal humerus fractures	0.200	0.0675	0.3325	FSPP data*
Men with index distal radius fractures	0.229	0.1302	0.3269	FSPP data*
Persistence at one-year				
Denosumab	0.819	0.559	0.953	24, 49, 50
Risedronate	0.631	0.585	0.750	23, 51, 52
Relative risk of a proximal femur fracture given a proximal femur fracture	3.7	2.5	5.3	6
Relative risk of a proximal femur fracture given a proximal humerus fracture	2.4	1.6	3.5	6

Parameter	Base value	Low value	High value	Source
Relative risk of a proximal femur fracture given a vertebral fracture	3.7	2.3	5.9	6
Relative risk of a proximal femur fracture given a distal radius fracture	2.9	2.0	4.1	6
Relative risk of a proximal humerus fracture given a proximal humerus fracture	2.1	0.3	17.3	6
Relative risk of a proximal humerus fracture given a vertebral fracture	3.0	2.0	4.3	6
Relative risk of a proximal humerus fracture given a distal radius fracture	2.5	0.6	10.2	6
Relative risk of a vertebral fracture given a proximal humerus fracture	3.0	2.2	4.0	6
Relative risk of a vertebral fracture given a vertebral fracture	4.9	2.4	9.8	6
Relative risk of a vertebral fracture given a distal radius fracture	2.9	1.6	5.3	6
Relative risk of a distal radius fracture given a proximal humerus fracture	2.6	1.8	3.8	6
Relative risk of a distal radius fracture given a vertebral fracture	1.8	1.1	3.2	6
Relative risk of a distal radius fracture given a distal radius fracture	3.2	1.3	8.1	6
Treatment efficacy				
Denosumab vs. placebo				

Parameter	Base value	Low value	High value	Source
Relative risk of a proximal femur fracture	0.60	0.37	0.97	28
Relative risk of a proximal humerus fracture	0.80	0.67	0.95	28
Relative risk of a vertebral fracture	0.32	0.26	0.41	28
Relative risk of a distal radius fracture	0.80	0.67	0.95	28
Relative risk of mortality following first proximal femur fracture, women				
Year 1	2.1	1.7	2.5	4
Years 2-5	1.1	1.0	1.2	4
Years 6-10	1.0	1.0	1.1	4
Relative risk of mortality following first proximal femur fracture, men				
Year 1	2.9	2.5	3.5	4
Years 2-5	1.1	1.0	1.2	4
Years 6-10	1.0	1.0	1.0	4
Relative risk of mortality following second proximal femur fracture, women				
Years 1-10	1.54	1.46	1.63	5
Relative risk of mortality following second proximal femur fracture, men				
Years 1-10	1.58	1.42	1.75	5
Relative risk of mortality following proximal humerus fracture, women				
Year 1	1.6	1.4	2.0	4
Years 2-5	1.0	1.0	1.2	4

Parameter	Base value	Low value	High value	Source
Years 6-10	1.0	1.0	1.2	4
Relative risk of mortality following proximal humerus fracture, men				
Year 1	2.2	1.7	2.7	4
Years 2-5	1.3	1.1	1.5	4
Years 6-10	1.0	1.0	1.1	4
Relative risk of mortality following vertebral fracture, women				
Year 1	2.0	1.5	2.6	4
Years 2-5	1.1	1.0	1.2	4
Years 6-10	1.1	1.0	1.2	4
Relative risk of mortality following vertebral fracture, men				
Year 1	2.5	1.9	3.3	4
Years 2-5	1.3	1.1	1.5	4
Years 6-10	1.0	1.0	1.0	4
Costs				
Women				
First year following first proximal femur fracture	\$50,839	\$49,732	\$51,945	33
Years 2-8 following first proximal femur fracture	\$18,787	\$18,623	\$18,951	33
First year following second proximal femur fracture	\$50,839	\$49,732	\$51,945	Assumption
Years 2-8 following second proximal femur fracture	\$18,787	\$18,623	\$18,951	Assumption
First year following proximal humerus fracture	\$12,137	\$11,799	\$12,475	33
Years 2-8 following proximal humerus fracture	\$7,046	\$6,982	\$7,111	33

Parameter	Base value	Low value	High value	Source
First year following vertebral fracture	\$20,423	\$19,601	\$21,246	33
Years 2-8 following vertebral fracture	\$9,487	\$9,385	\$9,589	33
First year following distal radius fracture	\$4,595	\$4,507	\$4,683	33
Years 2-8 following distal radius fracture	\$2,911	\$2,896	\$2,926	33
Men				
First year following first proximal femur fracture	\$50,002	\$48,434	\$51,571	33
Years 2-8 following first proximal femur fracture	\$15,684	\$15,459	\$15,908	33
First year following second proximal femur fracture	\$50,002	\$48,434	\$51,571	Assumption
Years 2-8 following second proximal femur fracture	\$15,684	\$15,459	\$15,908	Assumption
First year following proximal humerus fracture	\$15,382	\$14,632	\$16,132	33
Years 2-8 following proximal humerus fracture	\$8,777	\$8,640	\$8,913	33
First year following vertebral fracture	\$16,948	\$16,205	\$17,691	33
Years 2-8 following vertebral fracture	\$5,902	\$5,818	\$5,985	33
First year following distal radius fracture	\$8,709	\$8,413	\$9,004	33
Years 2-8 following distal radius fracture	\$3,077	\$3,049	\$3,105	33
Costs				
Denosumab	\$841.51	-/+ 25%		34, 36
Risedronate	\$151.12	-/+ 25%		34, 36
Utility multipliers				
First year following first proximal femur fracture	0.70	0.64	0.77	2
Subsequent years following first proximal femur fracture	0.80	0.68	0.96	2
First year following second proximal femur fracture	0.56	0.44	0.74	Calculated
Subsequent years following second proximal femur fracture	0.64	0.46	0.92	Calculated
First year following proximal humerus fracture	0.81	0.73	0.89	3

Parameter	Base value	Low value	High value	Source
Second year following proximal humerus fracture	0.95	0.81	0.96	3, 48
Subsequent years following proximal humerus fracture	0.96	0.81	0.97	3, 48
First year following vertebral fracture	0.73	0.49	0.73	3
Subsequent years following vertebral fracture	0.87	0.66	0.87	3
First year following distal radius fracture	0.96	0.86	1.00	2
Subsequent years following distal radius fracture	1.0	0.96	1.00	2

Note. *FSPP data represents all 5,264 patients who met inclusion criteria for the program between July 1, 2017 and

May 15, 2018. Costs represent 2018 Canadian dollars.

APPENDIX F Lifetime cost-effectiveness comparing FSPP to Usual Care, Results of Scenario Analyses

	Incremental Cost	Incremental QALYs	ICER
Reference case	-\$274	0.018	Dominant*
Discount rate, 0%	-\$331	0.020	Dominant*
Discount rate, 3%	-\$223	0.015	Dominant*
Relative risk of recurrent fracture, 12 years	-\$274	0.018	Dominant*
Persistence with denosumab, 48%	-\$240	0.015	Dominant*
Proportion of treated patients receiving denosumab, 34%	-\$309	0.017	Dominant*

Note. FSPP = Fracture Screening and Prevention Program; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year. *Dominance occurs when an intervention has lower costs and higher effectiveness relative to a comparator (i.e., the intervention is the dominant option). Costs represent 2018 Canadian dollars.

APPENDIX G Lifetime cost-effectiveness comparing FSPP to Usual Care, Results of Subgroup Analyses

	Incremental Cost	Incremental QALYs	ICER (\$/QALY)
Reference case	-\$274	0.018	Dominant*
Women	-\$389	0.020	Dominant*
Start age, 50 years	-\$64	0.005	Dominant*
Start age, 55 years	-\$8	0.005	Dominant*
Start age, 60 years	-\$133	0.008	Dominant*
Start age, 65 years	\$18	0.013	\$1,371
Start age, 75 years	-\$513	0.023	Dominant*
Start age, 80 years	-\$874	0.03	Dominant*
Start age, 85 years	-\$893	0.030	Dominant*

Note. FSPP = Fracture Screening and Prevention Program; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year. *Dominance occurs when an intervention has lower costs and higher effectiveness relative to a comparator (i.e., the intervention is the dominant option). Costs represent 2018 Canadian dollars.

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