Fracture Risk Tool Validation in an Integrated Healthcare Delivery System

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Objective: To evaluate the utility of the Fracture Risk Calculator (FRC, Foundation for Osteoporosis Research and Education) for predicting 10-year hip fracture risk within a "real world" population.

Study Design: Retrospective cohort study.

Methods: We identified female members of Kaiser Permanente Northern California aged ≥50 years with bone mineral density (BMD) measured during 1997-2003. Hospitalization for hip fracture was ascertained up to 10 years following the BMD date, and 10-year observed hip fracture probabilities were calculated. Baseline data for fracture risk calculation were extracted from health plan databases, including age, race/ethnicity, smoking, body mass index, prior fracture, rheumatoid arthritis, glucocorticoid use, disorders associated with bone loss, and femoral neck BMD. Predicted 10-year FRC hip fracture probabilities were compared with observed 10-year hip fracture probabilities.

Results: Among 94,489 women (mean age 62.8 ± 8.6 years, average femoral neck Z-score +0.1), the median duration of follow-up was 6.6 years, during which 1579 (1.7%) hip fractures occurred. Using the FRC, 23% met or exceeded the National Osteoporosis Foundation's 3% hip fracture threshold. The FRC somewhat underestimated observed hip fracture probabilities; across 10-year risk categories <1%, 1% to 2.9%, and 3% to 4.9%, ratios of observed to median predicted probabilities ranged from 1.3 to 1.4.

Conclusions: The FRC tool can be applied to assess fracture risk in large populations using data from administrative databases. Despite some underestimation, this relatively simple tool may assist targeting of at-risk populations for more complete fracture risk assessment.

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To better comply with current osteoporosis Healthcare Effectiveness Data and Information Set (HEDIS) measures,[1] many healthcare delivery systems have developed programs to identify and track women after fracture. Some health plans have also developed quality improvement programs that expand osteoporosis management beyond the HEDIS requirements to include all women and men at increased risk of fracture.[2,3] In large part, the stimulus for such targeting has been evidence that preventive osteoporosis treatment for those at increased risk of fracture is cost-effective[4] and that comprehensive and widespread interventions can substantially reduce hip fracture rates and thereby produce savings for health plans.[2,3] However, adequate information technology resources must be available to capture information on patients, and management systems must be in place to mount large osteoporosis evaluation and treatment initiatives. Many health plans lack the organization for major fracture prevention outreach efforts, and more importantly, lack a simple, convenient system to identify those at increased risk.

Several Web-based fracture risk tools are available,[5-8] but these are designed for entry of individual patient-level information and currently do not function in an easily accessible, large-scale, batch mode where data on thousands of individuals can be instantly uploaded for fracture risk estimation. The most widely used fracture risk tool is FRAX, developed by the World Health Organization Collaborating Centre for Metabolic Bone Disease, University of Sheffield, UK.[6,9] This tool first solicits information on a number of key, independent clinical risk factors and then calculates 10-year probabilities of hip and of any 1 of 4 major osteoporotic fractures. While some of these risk variables are easily obtained from administrative data sets (eg, age, sex), others may be obtained with some effort (eg, race/ethnicity, height and weight, prior fracture, high-dose glucocorticoid exposure, history of rheumatoid arthritis, other conditions known to contribute to osteoporosis, current smoking). Certain variables (eg, family history of osteoporosis, heavy alcohol use) may not be obtained without direct patient questioning. In addition, although many patients have undergone bone mineral density (BMD) testing, numeric results may not be easily accessible; fortunately, fracture risk tools can produce results with or without BMD. Indeed, fracture risk tools can provide accurate probability estimates with less than complete

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input data.[10] Especially for the purpose of population categorization and targeting osteoporosis outreach programs, results based on a limited data input tool would be considered adequate.

In this study, we modified an existing Web-based fracture risk tool (the Fracture Risk Calculator [FRC])[7] to provide batch outputs using input values obtained from administrative data in a large population of women undergoing BMD testing. We evaluated the performance of the FRC batch tool against observed 10-year hip fracture rates. The FRC tool was chosen because it was highly accessible, efficient, and transparent. Furthermore, the FRC batch estimates were provided at no cost, and results were instantly available via a Web interface. We compared observed 10-year fracture rate estimates with average predicted rates in more than 90,000 female members over age 50 years who received a BMD test in Kaiser Permanente Northern California (KPNC) between 1997 and 2003. Our primary goals were to determine what proportion met or exceeded the National Osteoporosis Foundation (NOF) 3% 10-year hip fracture risk threshold[4,11] and to assess whether the tool overestimated or underestimated the true risk of hip fracture.

Take-Away Points

The utility of the Fracture Risk Calculator (FRC) for predicting 10-year hip fracture risk within a "real world" population was evaluated.

- The FRC provided rapid assessment of population fracture risk with some underestimation.
- Bone mineral density as an input parameter appeared to have little overall effect on the tool's discrimination.
- While the FRC underestimated observed 10-year hip fracture probabilities by 30% to 40%, the ability to rapidly assess fracture risk using population data may be useful for osteoporosis programs in the initial identification of high-risk patients.

METHODS

Population Cohort

Kaiser Permanente Northern California is a large integrated healthcare delivery system serving more than 3 million members in Northern California; approximately 0.5 million are women over the age of 50 years. Since 1991, bone densitometry has been available using Hologic dual-energy x-ray absorptiometry (DXA) scanners (Waltham, MA). By 1995, KPNC had a fully integrated, systemwide patient data collection system that included ambulatory visit diagnoses, radiologic records, and prescription drugs that complemented long-standing hospitalization databases. Therefore, we selected as our study cohort all women aged 50 to 85 years who underwent a hip bone density scan on a Hologic scanner (models QDR 2000, 4500, or Delphi), selecting the first scan during 1997-2003. We excluded those who did not have at least 1 year of continuous (<90-day gap) membership both prior to and following the DXA scan date, those for whom DXA data were not electronically accessible, and those with missing race/ethnicity. We also excluded women who had filled a prescription for a bisphosphonate in the year prior to the DXA test. The study was approved by the Institutional Review Board of KPNC.

Fracture Risk Calculator

The fracture model estimate began with population-based 10-year fracture probability for age, sex, and race/ethnicity. Next, specific patient characteristics were compared with those of the base population, and relative risks were applied to factors that differed between the individual patient and the base population. In very simplistic terms, the product of base rate times the risk differences yielded the predicted absolute 10-year risk. The current base US 10-year fracture risks for men and for women used by the FRC are those calculated from the 2006 US National Inpatient Survey by Ettinger et al.[12] The FRC model's relative risks for various clinical risk factors are shown in Table 1. A detailed manual of operations for the Web-based FRC batch tool is available through the Foundation for Research and Education (www.fore.org).

Data Input Variables

Age, race/ethnicity, and body mass index (BMI) were determined at the index BMD scan date. Those with missing BMI were assigned a null value of 25 kg/m^2, which was the median value in our cohort. Using ambulatory care, hospitalization, and pharmacy databases, we obtained each patient's data from the 1 year prior to the DXA measurement to secure the following exposures and diagnoses: glucocorticoid use ≥1825 mg of cumulative prednisone dose equivalent in the prior year (average 5 mg/day), rheumatoid arthritis diagnoses, and secondary causes of bone loss (diabetes mellitus with insulin use, malabsorption syndrome, chronic liver disease, and osteogenesis imperfecta). We determined prior history of fracture after age 45 years (up to 10 years prior to the DXA date) based on hospitalization and outpatient diagnoses of fracture (*International Classification of Diseases, Ninth Revision [ICD-9]* codes 800-829), excluding open fractures, fractures related to severe trauma (*ICD-9* E-codes 800-845), and fractures of the fingers, toes, facial bones, and skull, since these are not generally considered to be osteoporotic. Information on alcohol consumption and parental history of hip fracture was not available, and smoking status was not uniformly available. We assumed that all missing input values were null.

Table 1. Input Characteristics and Relative Risks for Hip Fracture Used by the Fracture Risk Calculator for Women Aged 45 to 85 Years

Characteristic	Relative Risk
Race/ethnicity[a]	
White	1.00
Black	0.43
Asian	0.50
Hispanic	0.53
Body mass index,[b] **kg/m²**	1.6 if age <21 y
Femoral neck BMD Z-score	1.6
Smoking, current	1.7
Alcohol ≥3 units/day	1.7
Glucocorticoid exposure	2.3
Fracture after age 45 y	1.8
Parent with hip fracture	1.8
Rheumatoid arthritis	1.8
Secondary cause of bone loss[b]	1.8

BMD indicates bone mineral density.
[a]Relative to white.
[b]Relative risk applied only if bone mineral density is not included in the model.

Output From Fracture Tools

Under the auspices of institutional agreements for protection of proprietary interests, batch data without patient identifiers were securely uploaded to the Foundation for Osteoporosis Research and Education FRC Web site. Ten-year fracture probabilities were returned, calculated both with and without BMD inputs.

Follow-up and Observed Hip Fracture Outcome

Individual patient data were examined from the index BMD scan date until the earliest of the following: the fourth prescription for a bisphosphonate, likely indicating 1 year of exposure because typical prescriptions provide a 3-month supply (N = 19,440, 20.6%); a principal diagnosis of hip fracture (*ICD-9* code 820.0X, 820.2X, and 820.8X, excluding open fractures and those associated with major trauma, *ICD-9* E-codes 800-845); death; disenrollment (>90-day gap in membership); or when 10 years had elapsed from the index date.

Statistical Analysis

Differences between women with and without subsequent hip fracture were compared using the χ^2 test for categorical variables and the Student *t* test for continuous variables. Incident hip fracture rates and 95% confidence intervals (CIs) were calculated per 1000 person-years up to 10 years follow-up, the censoring date, or December 2009 (whichever occurred first). We used Kaplan Meier product-limit estimates to calculate the 10-year hip fracture probabilities from observed events over time and compared these with the median predicted 10-year hip fracture risk for the subcategories <1%, 1% to 2.9%, and 3% to 4.9%, as well as 5% to 6.9%, 7% to 9.9%, and ≥10%. We also compared the proportions of women in each decade of age meeting or exceeding the NOF's 3% cost-effectiveness hip fracture risk threshold[4,11] both with and without inclusion of BMD as an input parameter. We used the area under the receiver operating characteristic (ROC) curve (C statistic) to compare sensitivity and specificity of the FRC results, with and without BMD.[13] The C statistic ranges from 0.5 (the predictions are no better than chance) to 1.0 (a perfect predictive model). Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and Stata version 9.2 (StataCorp, College Station, TX).

RESULTS

Hologic BMD data were available for 94,489 women between the ages of 50 and 85 years, after excluding those not meeting health plan membership criteria (n = 19,178), those with missing race/ethnicity (n = 318), those with missing BMD data (n = 257), and those who received bisphosphonate drugs in the year prior to the index BMD date (n = 2730).

Table 2 shows the characteristics of the cohort at baseline. The mean femoral neck Z-score was +0.14, suggesting that the study population overall was comparable to the Hologic reference range (National Health and Nutrition Examination Survey III).[14] The median duration of follow-up was 6.6 years (interquartile range 3.6-8.3 years), during which 1579 hip fractures were observed. Those who subsequently suffered a hip fracture were older, more likely to be white, had lower BMI, had other risk factors for osteoporosis, and were less likely to be users of hormone therapy. The mean age at hip fracture was 78 years and hip fracture incidence rates increased markedly with age (Table 3). The incidence of hip fracture in nonwhites (Asians, Blacks, and Hispanics) was approximately half the incidence in whites.

When applying the NOF's 3% 10-year hip fracture probability threshold, the FRC yielded an overall population proportion of 23% with a strong relationship to age (Figure 1). Thus, the proportion of women qualifying under this criterion for osteoporosis management increased from about 1 in 25 at age 50 to 59 years to about 4 in 5 women at 75 years and older. The overall proportion identified as high risk showed no change when BMD was removed from the calculator input; however, when BMD was excluded, the proportion was lower among women aged 60 to 69 years (7.2% vs 17.1%) and higher among women aged 70 to 79 years (81.1% vs 59.4%).

Table 2. Baseline Characteristics of 94,489 Women by Subsequent Hip Fracture Status

Characteristic	Percentage[a]			P[b]
	Overall	No Hip Fracture	Hip Fracture	
Age, y				<.01
50-59	41.4	42.0	7.7	
60-69	34.8	35.0	20.7	
70-79	20.2	19.7	50.0	
80+	3.6	3.3	21.5	
Race/ethnicity				<.01
White	76.1	75.9	90.4	
Black	4.0	4.0	1.7	
Hispanic	6.0	6.1	3.2	
Asian	13.9	14.0	4.7	
Body mass index, kg/m²				<.01
<21	10.3	10.1	18.2	
21-24	27.6	27.6	29.1	
25-29	22.7	22.8	20.1	
≥30	13.1	13.2	7.2	
Missing	26.3	26.3	25.4	
Current smoking	10.0	10.0	13.8	<.01
Glucocorticoid exposure[c]	1.7	1.7	3.6	<.01
Fracture after age 45 y	10.1	9.9	22.0	<.01
Rheumatoid arthritis	1.5	1.5	2.4	<.01
Secondary cause of bone loss	1.7	1.7	4.3	<.01
Hormone therapy at baseline[d]	42.0	42.1	35.5	<.01
Femoral neck BMD T-score				<.01
Above −1.0	39.1	39.6	9.1	
Between −1.0 and −2.5	49.7	49.7	49.2	
−2.5 and below	11.2	10.7	41.7	

BMD indicates bone mineral density.
[a]All values are column percentages.
[b]Comparison of those who had hip fracture with those who did not.
[c]Equivalent to 1825 mg of prednisone based on anti-inflammatory potency.
[d]More than two-thirds of women using hormone therapy at baseline discontinued within 5 years of follow-up.

Table 4 shows the predicted 10-year hip fracture probabilities compared with the observed 10-year hip fracture probabilities. The FRC underestimated the true fracture probabilities by 30% to 40%, particularly in the higher predicted risk categories (Figure 2). Although 40% of our cohort used hormone therapy at baseline, a factor not included in the FRC model, this did not explain the model's tendency to underestimate the observed fracture probability (data not shown). The area under the ROC performances of the FRC tool were similar regardless of whether BMD was included (C statistic = 0.85; 95% CI 0.84, 0.86) or not (C statistic = 0.83; 95% CI 0.82, 0.84).

DISCUSSION

We found that the FRC, a relatively simple, transparent fracture risk tool, provided rapid assessment of population fracture risk with some underestimation. When applied to our large population of women 50 years and older, approximately 1 in 4 were found to potentially qualify for osteoporosis treatment based on the NOF threshold of 3% 10-year hip fracture risk. Although the FRC somewhat underestimated the observed fracture probabilities in our cohort, similar underestimates have been reported by Sornay-Rendu et al when using FRAX

Table 3. Incident Hip Fracture Rate per 1000 Patient-Years by 5-Year Age Ranges for the Study Cohort[a]

Age, y	No. of Observed Hip Fractures	Overall Rate per 1000 Patient-Years (95% CI)	Rate for Whites per 1000 Patient-Years (95% CI)	Rate for Nonwhites per 1000 Patient-Years (95% CI)
50-54	12	0.3 (0.1, 0.5)	0.3 (0.2, 0.6)	0.1 (0.0, 0.5)
55-59	40	0.3 (0.2, 0.5)	0.4 (0.3, 0.6)	0.1 (0.0, 0.3)
60-64	67	0.5 (0.4, 0.7)	0.6 (0.5, 0.8)	0.3 (0.1, 0.6)
65-69	114	1.1 (0.9, 1.3)	1.3 (1.0, 1.5)	0.6 (0.3, 1.0)
70-74	186	2.2 (1.9, 2.6)	2.5 (2.1, 2.9)	1.4 (0.9, 2.0)
75-79	300	5.1 (4.5, 5.7)	5.7 (5.1, 6.4)	2.3 (1.5, 3.4)
80-84	370	11.3 (10.2, 12.5)	12.2 (10.9, 13.5)	6.4 (4.4, 9.0)
85-89	205	19.4 (16.8, 22.3)	20.9 (18.0, 24.1)	9.9 (5.4, 16.6)

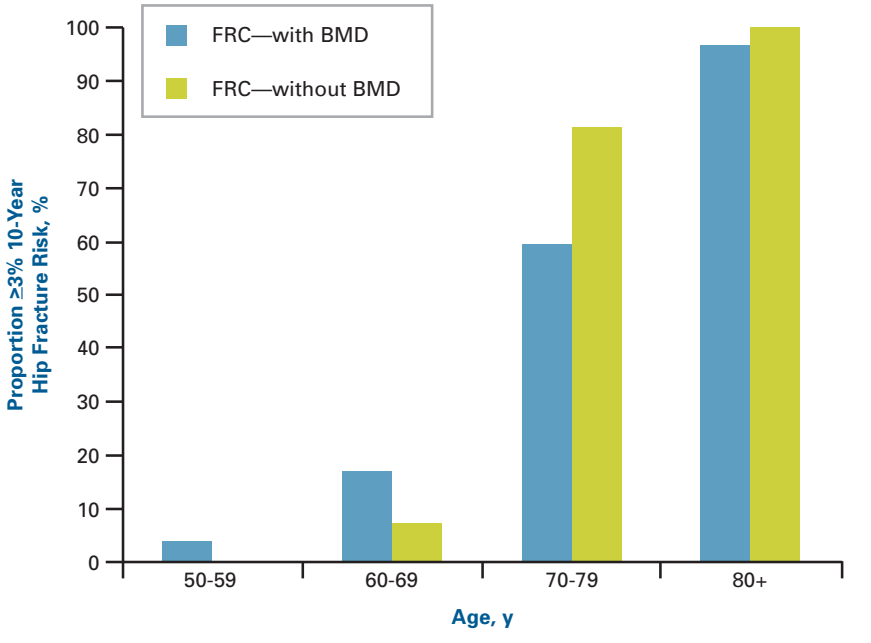
CI indicates confidence interval.
[a]A total of 1579 hip fractures were observed during follow-up for up to 10 years.

to assess the risk of major osteoporotic fracture in a cohort of French women.[15] Both the FRC and FRAX use the same base rate for 10-year fracture risk in women as this rate is provided by the same source[12]; the same risk input variables are also used, although the relative risks differ.[9,16] The FRAX model is also more complex mathematically, because it uses Poisson regressions to accommodate interaction terms and to calculate fracture probability offset by expected mortality.

The inclusion or exclusion of BMD as an input parameter for the FRC batch calculator appeared to have little effect overall on discrimination, as measured by the C statistic (C statistic 0.85 and 0.83 with and without BMD, respectively). Several studies have also shown that FRAX yields similar C statistic estimates in the range of 0.7 to 0.8,[10,15,17,18] including comparison between different models or with different input variables.[10] It should be recognized, however, that there may be limitations to the utility of ROC curves in assessing clinical risk prediction since very large relative risks of included (or removed) variables are necessary to change the statistical outcome.[13]

We believe that both the calibration and discrimination of the FRC tool would be improved with more complete data input, particularly with inclusion of family history data in the model. Epidemiologic studies indicate that parental history of hip fracture increases from about 5% in women in their 50s to about 15% to 20% for women 70 years and older[19]; the model's fracture prediction would nearly double for women with such a history. In addition, our ascertainment of prior fractures, limited to 10 years prior to baseline, yielded a prior fracture prevalence of about half that reported in epidemiologic studies[19,20]; here too, the model predictions would nearly double for women with such a history. Other missing data (eg, alcohol intake missing for all, BMI missing for

Figure 1. Proportion of Women by Age Decade Who Meet or Exceed 3% 10-Year Predicted Hip Fracture Risk Estimated From Fracture Risk Calculator, With or Without Inclusion of Femoral Neck BMD



BMD indicates bone mineral density; FRC, Fracture Risk Calculator.

Table 4. Observed 10-Year Hip Fracture Probabilities Versus Predicted 10-Year Hip Fracture Probabilities, by Fracture Risk Calculator Probability Categories

Predicted Probability Categories (10-Year Hip Fracture Risk)	No. of Women	Median Predicted FRC Probability, %	Observed 10-Year Hip Fracture Probability (Product Limit Estimate), %	Ratio of Observed to Predicted Probability
<1%	47,741	0.3	0.4	1.3
1%-2.9%	24,956	1.6	2.0	1.3
3%-4.9%	8469	3.7	5.0	1.4

FRC indicates Fracture Risk Calculator.

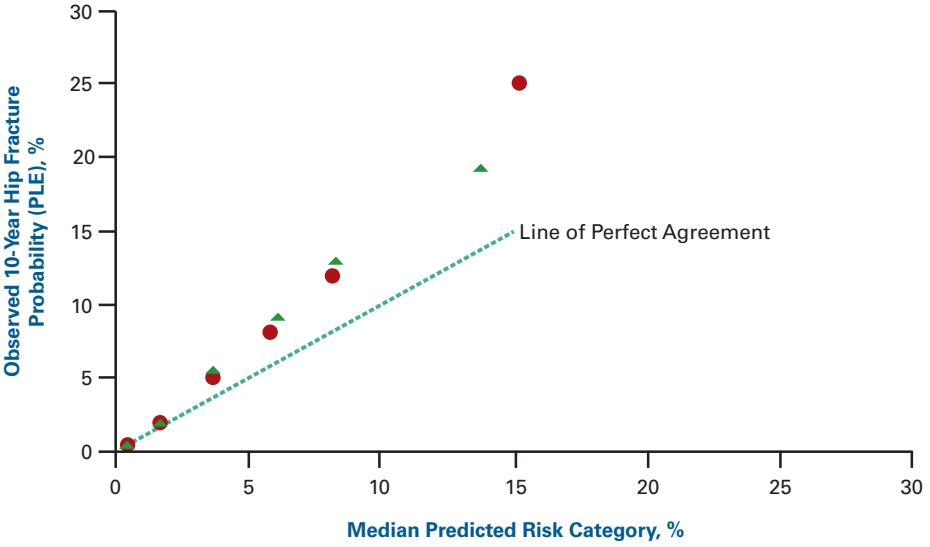
30% of the cohort) are less important in the model's calibration since thinness and heavy alcohol intake are not common in aging women.[15,20] These factors, along with more complete ascertainment of smoking status and other conditions contributing to bone loss, could be important when calculating risk *for an individual*.

Our analyses did not examine thresholds for clinical actions and further did not consider cost-effectiveness of such actions. The threshold for treatment depends on available resources; Kanis et al have suggested for the United Kingdom a changing threshold dependent on age,[21] while in the United States, the NOF thresholds of 3% hip fracture and 20% major osteoporotic fracture probabilities are applied to women irrespective of age.[4] Recently, the US Preventive Services Task Force has suggested thresholds for densitometry screening based on 10-year FRAX fracture risk thresholds of 1.2% for hip fracture and 9.3% for any 1 of 4 major osteoporotic fractures (probabilities equal to the 10-year risks for a 65-year-old white woman without risk factors).[22] We note that FRC is reasonably accurate within this risk range.

The strengths of our study include the large cohort size with more than 1500 hip fracture outcomes and the fact that comprehensive data on both risk factors and outcome were available in the context of an integrated health plan system. Given the high membership retention rates in this population, we had a long follow-up period for hip fracture, accruing more than 570,000 patient-years.

Our study had the following limitations. First, our study population included only women undergoing BMD testing and thus may have included a somewhat higher proportion of younger midlife women. However, our cohort had 34,529 women older than 65 years, and the mean Z-scores of our population suggest our cohort was similar to the National Health and Nutrition Examination Survey III reference populations used by Hologic, Inc.[14] A second limitation was missing or incomplete data for the fracture tool risk factors (discussed above). Others have also shown that less-than-complete risk data input appears to detract only a little from fracture risk prediction models,[10] and a comprehensive assessment of clinical risk factors would be part of the appropriate next step prior to making a clinical treatment decision. Third, we ascertained only hip fracture outcomes and cannot comment on the tool's ability to predict any 1 of 4 major osteoporotic fractures in our population. Determining incident spine fractures from administrative data is extremely difficult without individual

Figure 2. Observed Hip Fracture Incidence by Category of FRC-Estimated Fracture Probability With and Without BMD as an Input Parameter[a]



BMD indicates bone mineral density; FRC, Fracture Risk Calculator; PLE, product-limit estimate from Kaplan Meier curves.
[a]Circles represent predicted FRC risk with BMD, and triangles represent predicted FRC risk without BMD.

chart review. Given the close relationship between hip and any 1 of 4 major osteoporotic fractures,[12] we predicted similar performance of the tool for this outcome. In fact, Leslie and colleagues have shown that one can accurately impute major osteoporotic fracture rates from hip fracture rates.[23] Finally, we did not have complete 10-year follow-up on all patients and thus the observed 10-year fracture rates were estimated.

A major barrier to use of any new clinical tool is its acceptance by providers and support by their institutions. The tool should also be easy to use, require little effort to run, and provide data to patients and providers that are easily grasped and interpreted. After initial targeting of at-risk patients, fracture probability should be assessed at the individual level, whereby decisions regarding aggressive osteoporosis management can be made once patients are properly evaluated and counseled. The FRC batch tool is meant to be used as a population stratification tool and is not intended to replace individual risk assessment. This approach may be helpful not only for systemwide quality improvement efforts but also for assessing potential thresholds for large-scale outreach efforts based on available resources.

In summary, it is now possible to apply a relatively simple risk tool using secure Web-based uploading of batched data in order to acquire aggregate fracture risk information. This population information may be useful for resource planning and integration into osteoporosis quality improvement programs to assist in rapid initial identification of those at risk for fracture.

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