Individualized fracture risk assessment: progresses and challenges

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Purpose of review
Fragility fracture is a major public health burden, because it is associated with a substantial morbidity and mortality. Risk prediction models, including the Fracture Risk Assessment Tool (FRAX) and Garvan Fracture Risk Calculator (GFRC), have been developed to provide a useful clinical framework for communicating the risk of fracture. The present review examines the validation of risk prediction models in osteoporosis and identifies some major challenges.

Recent findings
Recent validation studies suggested that the area under the ROC curve in fracture discrimination ranged from 0.61 to 0.83 for FRAX, and from 0.63 to 0.88 for GFRC, with hip fracture having a better discrimination than fragility fractures as a group. FRAX substantially underestimated the risk of fracture, whereas the predicted risk by GFRC was close to or slightly higher than the actual risk. Results of post-hoc analyses of clinical trials indicated the antifracture efficacy of alendronate, coronate, bazedoxifene, and denosumab was greater in patients with higher predicted risk of fracture. However, there was no correlation between antifracture efficacy and predicted fracture risk among patients on raloxifene and strontium ranelate.

Summary
The prognostic performance of FRAX and GFRC for fracture prediction is not perfect, but these predictive models can aid patients and doctors to communicate about fracture risk in the medium term and to make rational decisions. However, the application of these predictive models in making decisions for an individual should take into account the individual's perception of the importance of the risk of fracture and its severity outcomes.

Keywords
fracture, Fracture Risk Assessment Tool, garvan fracture risk calculator, osteoporosis

INTRODUCTION

Osteoporosis and its consequence of fracture impose significant healthcare burden on society. From the age of 50, the residual lifetime risk of fracture is approximately 50% in women and approximately 30% in men [1]. In women, the lifetime risk of hip fracture is equivalent to or higher than the risk of invasive breast cancer [1,2]. In men, the lifetime risk of hip and clinical vertebral fractures (17%) is comparable to the lifetime risk of being diagnosed with prostate cancer [2,3]. In Australia alone, direct costs attributable to osteoporotic fractures were estimated to be US$ 700 million in 1994 [4]. More recent estimates, including indirect costs, are US$ 7 billion annually [5]. This figure, relatively similar across countries, translates to US$ 1 every day for every person. Osteoporotic fractures and their adverse outcomes are projected to increase in parallel with the ageing of the population [6].

Osteoporosis [or low Bone mineral density (BMD)], fragility fracture, recurrent fracture, and premature mortality are highly clustered. Individuals with osteoporosis have an increased risk of an initial fracture, and the presence of a fracture signals increased risk of subsequent fractures for the next 5–10 years [7,8]. Individuals with osteoporosis,

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KEY POINTS

- Fragility fracture is associated with an increased risk of adverse outcomes, including disability and mortality.
- FRAX and GFRC are models for predicting the absolute risk of fracture. The models have been developed and implemented based on a set of risk factors for fracture.
- The discrimination of fracture versus nonfracture by FRAX and GFRC is imperfect, with area under the ROC curve ranging between 0.6 and 0.85.
- FRAX substantially underestimated the risk of fracture in men and women.
- The prognostic performance of these predictive models can be improved by incorporating genetic information and time-related changes in clinical risk factors within individuals.

fracture and recurrent fracture have a greater risk of mortality than those with an initial fracture or without a fracture. Indeed, numerous studies [7,9,10], including our own, have consistently shown that the relative risk of death in men with fracture (1.8-fold) is significantly greater than that in women (1.4-fold). The increased mortality risk was also observed in younger individuals with fracture [3].

Bisphosphonates are considered first-line treatment of osteoporosis, and recent evidence suggest that this group of drugs could also reduce the risk of mortality among men and women with a fracture [11,12]. In a large randomized controlled trial, zoledronic acid treatment was shown to reduce the risk of posthip-fracture mortality by 28%, when given within 90-days posthip surgery [13]. Interestingly, only a small part of the benefit of reducing death postfracture was attributable to preventing refracture. More recent studies [11,12,14] have also suggested that individuals on oral bisphosphonates have lower risk of mortality. Collectively, the evidence from clinical trials suggests that the first 5 years, particularly the first year, after fracture is perhaps the ideal time for intervention to reduce the risk of mortality among hipfracture patients. Yet, less than 30% of women and less than 10% of men, who have already had an osteoporotic fracture, receive treatment to reduce their risk of subsequent fractures [15].

TRANSLATION OF RISK FACTORS INTO PREDICTIVE MODELS

Low BMD is the most robust predictor of fracture risk. Each SD difference in BMD is associated with about a two-fold change in the risk of fracture [16,17]. However, BMD alone cannot reliably predict an individual who is (or is not) going to sustain a fracture. It has been estimated that less than 40% of fracture cases occur in people with BMD in the osteoporotic range [18]. Among women aged 60 years or older with low BMD (high-risk group) only 40% sustained an osteoporotic fracture within a 13-year of follow-up [18]. On the contrary, among those who sustained a fracture, almost 60% had BMD above the osteoporotic cut-point (T-score <-2.5). In other words, more than half of individuals with low BMD were 'resistant to fracture'. The situation in elderly men is similar: 70% of men with low BMD did not sustain a fracture; and among fracture cases, 77% occurred in those with non-osteoporotic BMD levels.

The modest predictive value of BMD in terms of fracture prediction is not unexpected. It is well known that fracture, as well as other important health events, is the end result of multiple risk factors. During the past three decades, several non-BMD risk factors have been identified to be associated with fracture risk. These risk factors can be broadly classified into two groups: modifiable and nonmodifiable, each with modest strengths of association. The risk factors not amenable to modification include the personal history of a prior fracture after the age of 40; history of fracture in a close relative; advancing age; being a woman; and genetic factors that are yet to be identified. Risk factors that are potentially modifiable include current cigarette smoking; low body weight; estrogen deficiency or early menopause (in women) or hypogonadism (in men) (without sex hormone therapy or replacement); long-term low calcium intake; excessive alcohol intake; limited physical activity; poor health or frailty (including rheumatoid arthritis, hyperthyroidism, impaired eyesight, and dementia); long-term exposure to anticonvulsant drugs; and a history of falls or recurrent falls. Among these risk factors, four key risk factors are identified: advancing age, personal history of a fragility fracture, falls, and low BMD [19–21].

At any given level of BMD, fracture risk varies widely in relation to the burden of other risk factors, including advancing age, prior fracture, and falls. Thus, for any one individual, the likelihood of fracture depends on a combination of these and other risk factors [22]. This means that two individuals, both with 'osteoporosis', can have different risks of fracture because they have different risk profiles. Similarly, an osteoporotic individual can have the same risk of fracture as a nonosteoporotic individual due to the difference in constellation of risk factors between the two individuals. In other words, the prognosis for fracture risk can and should be

individualized by using an individual's unique risk profile.

In an attempt to translate multivariable risk factors into individualized risk prediction, a number of algorithms have been developed. Among these algorithms, the Garvan Fracture Risk Calculator (GFRC) [21,23], Fracture Risk Assessment Tool (FRAX) [24], and Qfracture [25] are widely available and used. FRAX uses 12 risk factors, including femoral neck BMD, anthropometric factors, lifestyle factors, and comorbidities. The GFRC uses five risk factors, namely, age, sex, femoral neck BMD, prior fracture, and history of falls. Although FRAX provides 10-year risk of hip fracture and major osteoporotic fractures, the GFRC provides 5-year and 10-year risks of hip fracture and major osteoporotic fractures (Table 1). The development and implementation of these models represents an important advance in osteoporosis assessment and treatment, because they provide clinicians with tools that can estimate short-term estimates of risk of fracture for an individual. This individualized assessment overcomes the problem of population risk stratification that is applicable to groups of individuals (rather than to an individual).

PROGNOSTIC PERFORMANCE

The usefulness of a predictive model is usually quantified in terms of its discrimination and reclassification. Discrimination is the ability to separate individuals who will sustain a fracture along a continuum from those who will not. The primary metric of discrimination is the area under the ROC curve (AUC), which was developed during the Second World War for the detection of radar signals. In the medical context, the AUC evaluates the compromise between sensitivity and specificity, and is thus a global estimate of prognostic accuracy [26]. However, AUC is a rather insensitive measure [27]. Hence, a clinically meaningful difference in prognostic value between two predictive models is not necessarily reflected by the AUC.

Another feature of usefulness of a predictive model is risk reclassification [28]. For a given threshold of risk (e.g. 10-year risk of 20%), an individual can be classified as 'high-risk' or 'low-risk'. With additional risk factors the individual may change risk category from one to another. If a new risk factor or marker is materially useful, then the addition of the risk factor should result in more individuals who will subsequently fracture being classified into the high-risk group than to the low-risk group; conversely, among those who will not subsequently fracture, more would be classified into the low-risk group than the high-risk group. The net difference between the two proportions of reclassification is referred to as net reclassification improvement (NRI) [29]. Thus, when treatment decisions are

Table 1. Risk factors included in FRAX and garvan fracture risk calculator

	FRAX	GFRC
Risk factors (inputs)	Age	Age
	Sex	Sex
	Femoral neck BMD	Femoral neck BMD (or body weight)
	Body weight	Number of prior fractures
	Height	Number of falls during the past 12 months
	History of prior fracture	
	Parental history of hip fracture	
	Current smoking	
	Chronic glucocorticoid use	
	Rheumatoid arthritis	
	Secondary osteoporosis	
	Alcohol (3 or more units per day)	
Output	10-year risk of hip fracture	5-year risk of hip fracture
	10-year risk of major fractures	5-year risk of any fragility fracture
		10-year risk of hip fracture
		10-year risk of any fragility fracture
Website	http://www.shef.ac.uk/FRAX	www.fracturerisk calculator.com

GFRC, garvan fracture risk calculator.

based on risk threshold, the NRI can be helpful for making a clinical decision concerning an individual.

The usefulness of any predictive model is considered preliminary until it has been tested in multiple independent populations. In the past 5 years or so, several independent validation studies have been carried out to examine the prognostic performance of GFRC [30,31], FRAX [32–35,36▪,37▪▪], or both GFRC and FRAX [30,38,39]. In general, the discrimination in hip fracture was better than all fractures. In predicting hip fracture risk, the median AUC value for FRAX and GFRC was 0.78 and 0.80, respectively. In predicting major fracture risk, the median AUC value for FRAX (0.69) was lower than that for GFRC (0.76) (Table 2) [30–32,34,35,36▪, 37▪▪,38–40]. The concordance in the predicted probabilities of fracture between GFRC and FRAX was modest, with the coefficient of correlation being 0.67 [41].

Given the modest correlation, it is perhaps not surprising that the two models have different discrimination values. The discriminatory value of FRAX and GFRC was examined in a case–control study [30], where the average 10-year probability of fracture in the fracture group was consistently higher than in the nonfracture group: GFRC model (0.33 versus 0.15) and FRAX-US (0.30 versus 0.19). In men, the GFRC model yielded higher average probability of fracture in the fracture group than the nonfracture group (0.32 versus 0.14); however, fracture probability estimated by the FRAX-US model (0.17 versus 0.19) or FRAX-UK model (0.09 versus 0.12) were not different between fracture and nonfracture group. The AUC for the GFRC, FRAX-US, and FRAX-UK algorithms was 0.84, 0.78 and 0.77, respectively. In men, the respective AUC value for the three algorithms was 0.76, 0.54, and 0.57 [30]. Another validation study [39] in 2012 postmenopausal women of Polish background found that there was a considerable discrepancy in risk estimates between GFRC and FRAX models with the GFRC model predicting fracture more accurately than FRAX.

The GFRC model has been validated in the Canadian Multicenter Osteoporosis Study [31] that

Table 2. Area under the receiver operating characteristic curve for FRAX and garvan fracture risk calculator models in predicting hip fracture and major osteoporotic fractures

Study	Fracture (sex)	FRAX (with BMD)	GFRC
Sandhu *et al.* [30]	Major fractures (women)	0.78	0.84
	Major fractures (men)	0.54	0.76
Pluskiewicz *et al.* [39]	Hip fracture (women)	0.73	0.85
	Major fractures (women)	0.83	0.88
Langsetmo *et al.* [31]	Hip fracture (women)		0.80
	Major fractures (women)		0.70
	Hip fracture (men)		0.85
	Major fractures (men)		0.69
Bolland *et al.* [38]	Hip fracture (women)	0.70	0.67
	Major fractures (women)	0.62	0.63
Sambrook *et al.* [40]	Hip fracture (women)	0.78	0.76
	Major fractures (women)	0.61	0.64
Leslie *et al.* [32]	Hip fracture (women)	0.82	
	Hip fracture (men)	0.79	
	Major fracture (women)	0.70	
	Major fracture (men)	0.66	
Ensrud *et al.* [34]	Hip fracture (women)	0.76	
	Major fractures (women)	0.69	
Tamaki *et al.* [35]	Hip fracture (women)	0.88	
	Major fractures (women)	0.69	
Azagra *et al.* [36▪]	Hip fracture (men and women)	0.85	
	Major fractures (men and women)	0.72	
Ettinger *et al.* [37▪▪]	Hip fracture (men)	0.77	
	Major fractures (men)	0.67	

GFRC, garvan fracture risk calculator.

followed 4152 women and 1606 men for over 10 years, and observed 123 hip fractures (93 women) and 672 fragility fractures (579 women). Application of GFRC models to predict fracture yielded good discrimination results, particularly for hip fracture (AUC 0.80 for women and 0.85 for men). The study also shows a remarkable agreement between GFRC predicted 10-year probability of fracture and observed 10-year risk of fracture.

Most validation studies [35,36▪,37▪▪,38] suggest that the FRAX model underestimates the risk of fracture (Table 3). A validation study [38] on 1422 postmenopausal women living in New Zealand found that FRAX consistently underestimated the risk of fracture for every risk level. The study observed 229 fracture cases, but FRAX predicted only 121 cases (53% accuracy), and GFRC predicted 276 cases (99%). The study also found that GFRC overestimated the risk of fracture among individuals in the top quartile of fracture risk [38], which is also noted in the initial development study [21,23]. In the FRIDEX cohort [36▪], FRAX predicted only 41% of actual hip fracture cases and 46% of major fractures. In contrast, FRAX tended to overestimate the risk of fracture in a Japanese cohort [35].

In white men, FRAX also underestimated the risk of fracture. In the Canadian Multicentre Osteoporosis Study cohort, results of validation suggest that FRAX underestimated the risk of fracture in men: predicted 5.4% versus observed 6.4% [33]. In a validation study in 5891 men of the Osteoporotic Fracture in Men (MrOS) cohort [37▪▪], the FRAX 10-year predicted probability of hip fracture was 1.4%, whereas the actual risk was 3% (Table 3). For major osteoporotic fractures, the discrepancy between 10-year predicted risk (6.5%) and observed risk (6.9%) was not significant. This study also found that the AUC value for discriminating fracture versus nonfracture was modest (0.76 for hip fracture and 0.69 for major osteoporotic fracture).

The study also reveals a remarkably poor sensitivity of FRAX in the prediction of major fractures. Among 373 men who sustained a fracture during the follow-up period, only 15 (or 4%) had FRAX predicted 10-year risk of at least 20%; among 5517 men without a fracture, 5410 or 98% were classified as low-risk (FRAX predicted 10-year risk of less than 20%). Similarly, using the predicted 10-year risk of 20% as a cut-off value to define high versus low risk, the sensitivity and specificity for predicting hip fracture were 39 and 79%, respectively [37▪▪]. Another study [42▪] observed that 50% of patients with fracture were not classified as 'high-risk' based on the FRAX predicted risk just before the fracture event occurred.

Whether including BMD into a predictive model can result in an improvement in the discrimination or not is a contentious issue. In the MrOS cohort [37▪▪], a FRAX and BMD model produced a lower risk of fracture than a FRAX without BMD model. However, other studies [32,35,36▪] found that a FRAX with BMD model produced greater AUC value than the model without BMD. Nevertheless, a complicated model with multiple risk factors does not necessarily improve the prognostic performance of a predictive model. Indeed, a simple model with age and femoral neck BMD or a model with age and fracture history was as good as a more complicated model such as FRAX in terms of fracture prediction [34,41,40].

Table 3. Comparison between predicted (FRAX and garvan fracture risk calculator) and actual fracture risks in some validation cohorts

Study	Fracture (sex)	FRAXpredicted/observed fractures	GFRC predicted/observed fractures
Bolland *et al.* [38]	Hip fracture (women)	43/57	85/57
	Major fractures (women)	121/229	276/279
	Hip fracture (men)		41/39
	Hip fracture (women)		232/116
	Osteoporotic fractures (men)		180/140
	Osteoporotic fractures (women)		756/673
Tamaki *et al.* [35]	Hip fracture (women)	8/4	
	Major fractures (women)	50/43	
Azagra *et al.* [36▪]	Hip fracture (men and women)	7/17	
	Major fractures (men and women)	30/65	
Ettinger *et al.* [37▪▪]	Hip fracture (men)	1.4%/3.0%	
	Major fractures (men)	6.5%/6.9%	

GFRC, garvan fracture risk calculator. Note: data are actual number of fractures.

THRESHOLD FOR INTERVENTION

One application of fracture prediction models is for selecting patients suitable for intervention. However, this application raises serious challenges, because the predicted risk of fracture is a continuous probabilistic variable ranging from 0 to 1, and selecting a predicted probability to classify an individual as 'high-risk' or 'low-risk' requires a thorough research. Nevertheless, the National Osteoporosis Foundation guidelines recommend treatment in the following clinical situations in postmenopausal women and men aged 50 years or older [43]: with a hip or clinical vertebral fracture or a morphometric vertebral fracture; with femoral neck or lumbar spine BMD T-scores being equal to or less than −2.5 after excluding secondary cause of osteoporosis; with femoral neck or lumbar spine BMD T-scores between −1 and −2.5 and a 10-year risk of hip fracture at least 3% or a 10-year risk of major osteoporotic fracture at least 20%. The clinical benefit and cost-effectiveness of these recommendations should be subject to more systematic research.

The individualization of fracture risk assessment can be applied to optimize the number needed to treat (NNT). In several randomized clinical trials [44] the number of patients needed to be treated (NNT) to reduce one vertebral fracture compared with the untreated group ranged between 8 and 83. For hip fracture, the NNT ranged between 91 and 250 [44]. The NNT varies inversely with the background risk, such that treatment of high-risk individuals inherently yields lower NNT (Fig. 1). The large variability in the NNTs among trials is assumed to be due to the variability in fracture rates among the study samples. However, the variability is expected given the multiple risk factors that affect the incidence of fractures. In the presence of such variability, selecting patients based on their absolute risk of fracture (rather than based on a BMD threshold value) may improve the consistency of therapeutic efficacy and efficiency of trials. Trials specifically testing the efficacy of multivariable risk based therapy have not been done. However, such approaches could be expected to prove more cost-effective and yield a more consistent NNT, particularly if the duration, typically 3 years, is standardized.

Recent analyses of correlation between FRAX-predicted fracture risks and antifracture efficacy yielded mixed results. One clinical trial [45] randomized 5212 women aged 75 years and older into two groups: placebo receiving calcium and vitamin D with placebo or clodronate (800 mg daily po). Ten-year probability of fracture was computed for each woman using baseline clinical risk factors including BMI, prior fracture, glucocorticoid use, parental hip fracture, smoking, alcohol and secondary osteoporosis. In women in the top 25th percentile of fracture probability (average probability of 24%), treatment reduced the risk of fracture by 23% over 3 years (hazards ratio 0.77, 95% CI 0.63–0.95). Importantly, among those in the top 10% percentile of risk (average fracture probability of 30%), treatment reduced the fracture risk by 31% (hazards ratio 0.69, 0.53–0.90) [45]. Thus, treatment of individuals at high risk or moderate risk could reasonably be expected to have similar benefit in relative but greater effect in absolute risk reduction for the higher-risk group.

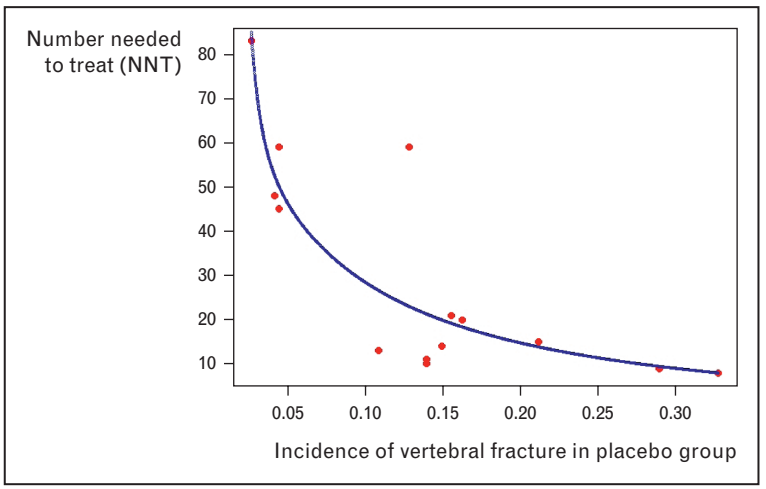

FIGURE 1. Relationship between background risk (rate of fracture in the placebo group) and number of patients needed to treat to reduce one case of fracture. Each dot in the figure represents the result of a randomized controlled trial. Adapted from [44].

In a post-hoc analysis of the fracture intervention trial, the investigators used FRAX to estimate each patient's 10-year risk of fracture, and then correlated the risk with antifracture efficacy. The investigators conclude that the magnitude of effect of alendronate was constant across FRAX-predicted risks [46▪▪]. However, a close examination of the data reveals that the absolute risk reduction increased with absolute risk levels, and as a result, the number needed to treat decreased as absolute risk increased. For example, among those in the first tertile of risk (4.8–22.1%) the NNT was 76, but among those in the highest tertile (34.2–85.4%) the NNT was 40.

Results of post-hoc analyses of clinical trials appear to suggest that in relative risk terms, the magnitude of antifracture efficacy of denosumab [47▪▪] and bazedoxifene [48] was dependent on absolute risks of fracture, such that those at high risk had better relative efficacy than those at low risk of fracture. However, the antifracture of strontium ranelate [49] and raloxifene [50] seemed to be independent of the fracture risk assessed by FRAX. However, it is not clear whether absolute risk reduction or the number needed to treat was independent of patients' absolute risk levels. Nevertheless, taken together, these results are consistent with the supposition that the antifracture effect size of pharmacologic therapies are inversely associated with patients' absolute risks, supporting the use of predictive models for selecting patients to include in future randomized controlled trials of osteoporosis.

ISSUES FOR FURTHER RESEARCH

Although the development and implementation of fracture prediction models represent a significant advance in osteoporosis research, several issues need to be addressed in the future. Current prognostic models have been developed based on the 'one size-fits-all' approach. For example, each model uses a set of risk factors for predicting 5-year or 10-year risk of all types of fracture, because it is assumed that the set of risk factors is associated with any type of fracture in any ethnic population in both men and women. This assumption is strong and likely untenable, because a risk factor may be uniquely associated with a type of fracture. For instance, fall is a major risk factor for hip fracture; it is not a risk factor for vertebral fracture.

An important weakness of current fracture prediction models is that they are based on a single measurement of risk factors, with the underlying but not stated assumption that the risk factors do not change with time. Obviously, this assumption is not true in many risk factors such as BMD and body weight that are known to decline or change with time. Moreover, the rates of decline in BMD varied substantially among individuals. Similarly, the risk of a second fracture is greater closer in time to the initial fracture with risks declining substantially after 10 years. Therefore, one important aspect of future model development should take the time-varying nature of risk factors into account to achieve a better estimate of risk for an individual.

Osteoporosis has traditionally been viewed in terms of hip fracture, or more recently, morphometric vertebral fracture. As a result, most previous studies have focused on the search for risk factors of hip and vertebral fractures. There is a serious lack of literature of the risk factors for nonhip and nonvertebral fractures. However, emerging evidence has shown that virtually all types of fracture are associated with increased risk of other fractures and even more importantly of premature mortality. Therefore, it is important to gain insight into common and specific risk factors for specific types of fracture, refracture, and mortality.

The assessment of fracture risk should be individualized, and genetic factors can improve the reliability of fracture prediction in an individual [51,52]. Genome-wide association studies [53–65] over the past 5 years have identified many novel genes involved in determination of bone density, some of which have been also associated with fracture risk. At present, these common variants explain only a small proportion of the apparent heritability and they have yet to be incorporated into fracture prediction models.

Risk communication in osteoporosis needs much more research attention. 'Risk' is an elusive concept that is not easily understood by patients and doctors. Although in medical parlance, risk is commonly seen as the probability of getting a disease over a certain period, it is formally defined as the product of probability and consequence of an adverse event [66]. The probability component measures the uncertainty, whereas consequence measures the impact of an event. Virtually all predictive models in medicine, including FRAX and GFRC, provide only the uncertainty, not impact, of a health event. From a probabilistic viewpoint, it can be argued that probability does not exist [67]. Probability is derived from statistical modeling of factors that are assumed to occur an infinite number of times under similar conditions. In osteoporosis, fracture risk is predicted from multiple factors that were measured in the past, and this information is used to estimate the fraction of

individuals with a similar risk profile who will have a fracture in the future. However, the risk factors change with time. Thus, although risk exists as an objective identity, its measure – probability – does not exist objectively. This explains why risk perception is widely different among individuals. For some, a 20% probability of fracture is a significant concern, but for others the probability does not warrant any preventive action. Some fractures will be of limited concern to some people but of great concern to others, who have a more personal and perhaps more accurate view of their impact on quality of life and even survival. An individual's absolute risk over a meaningful time period, arguably 5 rather than 10 years [68▪], has to be considered alongside that individual's concern about the outcome of interest.

The above consideration leads to the issue of mode of risk communication. The effect and consequence of risk factors are commonly expressed in terms of relative risk, which is not an optimal way in risk communication [69] because it can be misleading. Natural frequency [70] and absolute probability [71] are better ways to communicate risk to patients. In recent years, NNT [72], an absolute risk based metric, is increasingly used to convey the benefit of treatment. In hip fracture prevention, NNT has been shown to be an effective tool for improving patients' acceptance of treatment [73]. However, NNT can be limited for most members of the public, especially when the duration is ignored.

CONCLUSION

Evidence from validation studies so far indicates that the prognostic performance of FRAX and the Garvan Fracture Risk Calculator for fracture prediction is not perfect, but is still as good as, if not better than, models for other chronic health conditions. The area under the ROC curve for FRAX is largely under 0.8, and somewhat better for the Garvan Fracture Risk Calculator. This level (0.8) is considered to be 'good' discrimination and is certainly clinically useful.

Despite their imperfect discrimination, both FRAX and Garvan Fracture Risk Calculator can aid patients and doctors to communicate about fracture risk in the medium term. In the era of evidence-based medicine, patients and non-patients alike need to be given reliable and easy-to-understand information about health risk and benefit of intervention. The risk information from these models can help patients and their doctors to reach a rational decision. However, for communication purposes, it is important to note that FRAX tends to underestimate the risk of fracture in both men and women, and the reason for this is not clear.

Certainly, FRAX and GFRC used different risk factors and different weights for each risk factor in the estimation of fracture risk. Moreover, there is some debate about how the potential effect of mortality on the predicted risk of fracture is applied in the two models. However, the use of these predictive models in making decisions for an individual does not take into account the individual's perception of the importance of the risk. Improvement of these predictive models to include the effects of genetic variants on the one hand and severity of outcomes on the other will enhance their clinical utility.

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None.

Conflicts of interest

The authors are developers of the Garvan Fracture Risk Calculator.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 559–560).

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