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REVIEW

Personalized fracture risk assessment: where are we at?

Tuan V. Nguyen[a,b,c]

[a]Healthy Ageing Theme, Garvan Institute of Medical Research Darlinghurst Australia; [b]St Vincent's Clinical School, UNSW Sydney, Sydney Australia; [c]School of Biomedical Engineering, University of Technology Sydney Sydney Australia

ABSTRACT

Introduction: Osteoporotic fracture imposes a significant health care burden globally. Personalized assessment of fracture risk can potentially guide treatment decisions. Over the past decade, a number of risk prediction models, including the Garvan Fracture Risk Calculator (Garvan) and FRAX®, have been developed and implemented in clinical practice.

Areas covered: This article reviews recent development and validation results concerning the prognostic performance of the two tools. The main areas of review are the need for personalized fracture risk prediction, purposes of risk prediction, predictive performance in terms of discrimination and calibration, concordance between the Garvan and FRAX tools, genetic profiling for improving predictive performance, and treatment thresholds. In some validation studies, FRAX tended to underestimate fracture by as high as 50%. Studies have shown that the predicted risk from the Garvan tool is highly concordant with clinical decision.

Expert opinion: Although there are some discrepancy in fracture risk prediction between Garvan and FRAX, both tools are valid and can aid patients and doctors communicate about risk and make informed decision. The ideal of personalized risk assessment for osteoporosis patients will be realized through the incorporation of genetic profiling into existing fracture risk assessment tools.

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1. Introduction

Osteoporosis is a skeletal condition characterized by bone fragility that leads to an increased risk of fracture. Bone fragility is primarily assessed by bone mineral density (BMD). Individuals with low BMD are at greater risk of fracture, such that each standard deviation decrease in BMD is associated with about twofold increase in fracture risk [1]. The magnitude of association between BMD and fracture is equivalent to that of between blood pressure and stroke [2]. Just as stroke is an outcome hypertension, fracture is an outcome osteoporosis. Osteoporotic fracture is common in the general population with the residual lifetime risk being 50% in women and 25% in men [3]. In women, the lifetime risk of hip fracture (~12%) is actually equivalent to, or higher than, the lifetime risk of invasive breast cancer [3,4]. Fracture is associated with increased morbidities, deteriorated quality of life and reduced functional level of daily living independence [5–7]. More seriously, an existing fracture signals the risk of further fractures [8,9]. Thus, a single fracture triggers a series of physiological declines leading to interrelated clinical events that increase the risk of mortality.

Indeed, mortality is a serious outcome of osteoporotic fracture, especially hip fracture. Although men have a lower risk of fracture than women, once a fracture has occurred, the risk of mortality in men is higher than women. The relative risk of mortality in men with a fracture (1.8-fold) is significantly greater than that in women (1.4-fold) [10–12]. The increased mortality risk was also observed in younger individuals with fracture [13]. Among osteoporotic fractures, hip fracture is the most serious and costly type. Up to 24% women and 38% men die within the first 3 months after experiencing a hip fracture [14,15]. Taken together, fragility fracture is relatively common in the general population and represents a significant burden to the healthcare system. The burden of fracture is expected to become more pronounced given the ongoing population aging being taken place worldwide.

2. The need for individualized fracture risk assessment

It is therefore important to identify asymptomatic but high-risk individuals for early intervention and prevention. Although it is not possible to predict exactly someone will or will not sustain a fracture, certain risk factors increase an individual's chances of sustaining a fracture. These risk factors can be classified into two broad groups: endogenous and exogenous factors. Endogenous factors include advancing age, genetic factors, hormones, certain diseases (e.g. rheumatoid arthritis, dementia, type 1 diabetes), and a personal history of fracture. Exogenous factors include unhealthy lifestyle (e.g. smoking, excessive alcohol intakes, lack of physical activity, poor nutrition), fall, certain medications (e.g. systemic corticosteroid, antipsychotic drugs, proton pump inhibitors, etc.) that cause bone loss, and low BMD. While it is possible that these factors interact in elevating the risk of fracture for

CONTACT Tuan V. Nguyen t.nguyen@garvan.org.au Garvan Institute of Medical Research384 Victoria Street, Darlinghurst NSW 2010 AUSTRALIA Phone: +612 9295 8277 Fax: +612 9295 8241

Article highlights

- Fragility fracture, especially hip fracture, is associated with increased risk of mortality. Among those who survived a fracture, they suffer an increased risk of refracture.
- Although bone mineral density is the primary indicator of fracture risk, low bone mineral density (e.g. osteoporosis) accounts for 50% or less cases of fracture. Non-BMD factors such as a personal history of fracture and fall contribute to elevated fracture risk.
- Assessment of absolute risk of fracture based on an individual's risk profile is a critical step in the current approach to treatment and prevention. Over the past 10 years, at least 3 models of risk assessment (Garvan, FRAX, and Qfracture) have been developed to estimate an individual's risk of fracture.
- These fracture risk assessment models have acceptable-to-good discriminatory values but modest accuracy. Inclusion of new risk factors such as trabecular bone score and genetic profiling (e.g. polygenic risk score) modestly improved discrimination.
- Future fracture risk assessment models should predict the risk of incident refracture and mortality, and extend to predicting lifetime risk for age-specific groups and ethnicity-specific groups.

an individual, most epidemiologic studies so far suggest that their influences on fracture risk are mostly statistically independent.

The multifactorial nature of osteoporosis and the statistical independence among risk factors for fracture imply that fracture risk assessment must consider all relevant factors rather than focus on any single risk factor. Indeed, while BMD is the most robust predictor of fracture, only two-thirds of fracture cases are attributable to low BMD and advancing age [16]. Thus, two individuals have the same BMD and the same age, but they may well have different levels of fracture risk because their non-BMD risk factors are different. Theoretically, each individual has a unique risk profile, because there exists no 'average individual' in the population. The more risk factors, including environmental and genetic factors, are considered, the greater likelihood of uniqueness of an individual's profile is defined.

It is possible to estimate an individual's absolute risk of fracture by mapping the relationship between an individual's risk profile and fracture incidence. The mapping requires high-quality data that capture the incidence of fracture in a cohort over a period of time, usually more than 10 years. The assignment of weight to each risk factor is commonly done through a statistical model such as the Cox's proportional hazards regression, because clinicians are not able to objectively place appropriate weights on risk factors in the risk profile. Since it is possible to create a unique risk profile for an individual, the statistical model can theoretically generate a unique risk of fracture for the individual.

Determining whether an individual is at high risk of fracture, therefore, requires a multivariable risk assessment model. Since 2007, at least 3 models have been developed and implemented for clinical use: the Garvan Fracture Risk

Table 1. Characteristics of three fracture risk assessment models.

Characteristics	Garvan	FRAX	QFract
Fracture predicted	• Osteoporotic fracture • Hip fracture	• Osteoporotic fracture • Hip fracture	• Hip, wrist, shoulder or spine fracture • Hip fracture (?)
Period of prediction	• 5 years • 10 years	• 10 years	• 5 years • 10 years
Derivation cohort	Dubbo Osteoporosis Epidemiology Study	Multinational cohorts	General practitioners
Age of derivation cohort	50 years and older	40 years and older	30–100 years
Factors included	• Gender • Age • Femoral neck bone mineral density • Number of prior fractures • Number of falls (12 months)	• Gender • Age • Femoral neck bone mineral density • Body mass index • Prior fracture (Y/N) • Parental history of hip fracture (Y/N) • Current tobacco smoking (Y/N) • Ever long-term use of oral glucocorticostroid (Y/N) • Rheumatoid arthritis (Y/N) • Secondary osteoporosis (Y/N) • Daily alcohol consumption of 3 more units daily (Y/N)	• Gender • Age • Ethnicity • Body mass index • Smoking status • Parental history of hip fracture • Living in nursing home • Had a wrist spine hip or shoulder fracture • History of fall • Diabetes • Dementia • Cancer • Asthma or COPD • Heart attack, angina, stroke • Chronic liver disease • Chronic kidney disease • Parkinson's disease • Rheumatoid arthritis • Malabsorption disorders • Endocrine disorders • Epilepsy • Taking antidepressants • Taking steroid tablets • Taking estrogen only HRT

Calculator [17,18], FRAX [19], and Qfracture [20]. The Garvan model was developed using data from the Dubbo Osteoporosis Epidemiology Study, a prospective cohort study that has monitored bone health of more than 3500 men and women, all aged 60 years and older, for more than 20 years. The FRAX model was developed using data obtained from multiple population cohorts around the world, all aged 40 years and older. Qfracture was created from a prospective cohort study that included more than 3 million men and women, all aged 30 years and older, from 420 general practitioners in the United Kingdom.

Each of the above models uses different set of risk profile (Table 1), but all calculators produce 5-year and 10-year probabilities of major fracture and hip fracture. The rationale for 5-year and 10-year risk prediction is that elderly patients can manage their risk more effectively and that they are most likely to benefit from drug therapies.

3. Purposes of fracture risk assessment

It is generally agreed that risk assessment should be individually centered, taking into account the uniqueness of an individual's risk profile. For treatment decision, absolute risk is more relevant than relative risk [21,22]. Thus, the primary purpose of fracture risk calculators is for communication between doctors and patients and shared decision-making. Risk calculators are not designed to replace doctors, but to provide objective risk estimates to assist doctors in risk stratification. An accurate prediction of risk can help avoid the problem of overtreatment of low-risk individuals and undertreatment of high-risk individuals.

Risk prediction also enables doctors to provide personalized counseling on the basis of patient's risk profile, needs and expectation. For instance, a patient with non-osteoporotic BMD but has previously suffered a fracture or a fall is still at high risk of subsequent fracture, and a risk prediction can motivate the patient to improve bone health.

Patients tend to underestimate their fracture risk. Thus, accurate fracture risk estimates can help them gain insight into their bone health as well as empower them to take proactive role in decision-making process. Risk calculators can also motivate patients to take preventive measures (e.g. lifestyle modification) to reduce their long-term risks, and hopefully improve their adherence to therapy.

However, the interpretation of risk estimate should be done appropriately. Risk prediction models provide risk estimates for a group of individuals, not a particular individual. Thus, if an individual has a 10-year risk of 5%, it would be inappropriate to say that the individual's risk is 5%. Rather, a correct interpretation would be to say that, given 100 patients like the patient, we expect that 5 will suffer a fracture in the next 5 years, and 95 will not. It should also be mentioned that for any individual, there is a distribution of risks for a given profile, and the risk we convey to patients is only the *average risk*, but in reality the actual risk could be higher or lower than the average. However, currently recommended medical practice and essentially all evidence-based practices are based on the application of population means to individuals.

4. Predictive performance

Mapping the relationship between a risk profile (or risk factor) and fracture is necessary, but insufficient for its clinical utility. The utility of a prediction model can be evaluated by number of metrics that reflect the information content (e.g. prognostic accuracy) of the model and the ability to discriminate individuals that will fracture from those that will not **(Box 1)**. These metrics are best obtained from independent validation studies.

4.1. Discrimination

Over the past 10 years, there has been a substantial body of literature devoting to validating the predictive performance of the Garvan [23,24], FRAX® [25–30], or both Garvan and FRAX® [23,31–33]. As expected, the discrimination of fracture and hip fracture is highly variable between validation populations. In the Canadian Multicenter Osteoporosis Study [24] which followed 4152 women and 1606 men for over 10 years, the Garvan model had a moderate discrimination of total fracture (with AUC being 0.70), but excellent discrimination of hip fracture (AUC 0.80 for women and 0.85 for men). In the Australian GLOW cohort and New Zealand cohort, the discrimination of fracture by the Garvan model was modest with AUC being 0.63–0.64 for total fracture and 0.67–0.76 for hip fracture. In a recent study using electronic health record of more than 1 million individuals in Israel, Dagan eet al. found that the AUC value for predicting hip fracture by the FRAX, Qfracture and Garvan was 0.83, 0.82, and 0.78, respectively.

In general, the discrimination in hip fracture was better than major fractures. The median AUC value for predicting hip fracture by the Garvan model was 0.80, which was equivalent to that of FRAX® (AUC 0.78). In predicting major fracture risk, the median AUC value for Garvan and FRAX was 0.76 and 0.69, respectively [34].

4.2. Calibration

Most validation studies have focused on the models' discrimination, but few studies have examined their calibration which is practically more important than discrimination. Results of these validation studies suggest that the Garvan model tended to overestimate fracture risk in high-risk groups, but FRAX tended to underestimate fracture risk. In a New Zealand cohort of 1422 postmenopausal women with 229 incident fractures, the Garvan model predicted 276 cases (99% agreement), but over-predicted hip fracture risk by 50%, whole FRAX underestimated fracture risk by 50% [31]. In the Geelong Osteoporosis Study, the Garvan model underestimates fracture risk by approximately 25% in women and 19% in men, and FRAX model underestimates by 55% in women and 66% in men [35]. In the CaMoS cohort, the Garvan model showed a remarkable agreement between predicted 10-year probability of fracture and observed 10-year risk of fracture [24]. In MrOS cohort of 5891 men, with an observed fracture incidence being 3%, but FRAX models predicted only 50% of the cases [30]. In the FRIDEX cohort, FRAX predicted only 41% of hip fracture case and 46% of major fractures [29]. However, in a study by Dagan et al., all three models (FRAX,

Qfracture and Garvan) underestimated total fracture and hip fracture risk [33].

Few studies analyzed the concordance between the predicted risk of fracture and clinical decision of treatment of DXA scan. In a cohort of 531 individuals aged 70 years and older, the Garvan model's predicted risk correctly identified who would be indicated for treatment or required DXA scan 88% of the cases [36]. In a Polish cohort of 218 men with a prior fracture, the Garvan model identified 82% whereas FRAX identified only 8% as 'high risk' for treatment [37]. Moreover, among 251 men with osteoporosis, the Garvan model would recommend 74%, but FRAX would recommend only 9.5% for treatment [37]. The same trend was also observed in women [38].

4.3. Concordance between Garvan and FRAX

A number of studies have compared the predicted risk of fracture between the Garvan and FRAX models, and the concordance is modest, with coefficient of correlation being 0.67 [39]. A study on 2012 postmenopausal women of Polish background found that the concordance in risk classification between the two models was around 80% [32].

The lack of concordance in predicted risks between the two models is expected, because the models use different sets of risk factors and different statistical models. The Garvan model takes into account the number of falls – a key risk factor for hip fractures – in the prediction of risk, FRAX does not as yet take falls into account. The Garvan model treat prior fracture as a quantitative variable (i.e. number of fractures), whereas FRAX considers prior fracture as a binary variable (i.e. yes/no). Thus, for an individual with two (or more) prior fractures, the Garvan model would predict a higher risk of subsequent fracture than for an individual with one prior fracture. By contrast, the FRAX tool treats the two individuals as equal risk.

The estimation of model parameters in the Garvan model was based on the Cox's proportional hazards model in which the outcome variable is the time to fracture. By contrast, FRAX is reported to be based on the Poisson regression model [19] in which the outcome variable is the event of fracture over a duration of follow-up.

More importantly, the Garvan model was developed using data from the Dubbo Osteoporosis Epidemiology Study, where the sequential events of fracture, refracture and death for *every* individual have been directly monitored. Hence, the predicted risk inherently represents the probability of sustaining fracture among those at risk during their specific remaining lifetime. FRAX was developed using multiple cohorts with different durations of follow-up, and not all cohorts had mortality data. FRAX's predicted risk is adjusted for competing risk of mortality, but how the adjustment was made has not been published.

5. Improvement of risk prediction by new markers

The published data to date clearly show that none of the prediction models (Garvan, FRAX and Qfracture) is perfect in terms of discrimination and calibration. Therefore, over the past 10 years, there have been several studies attempting to identify new risk factors for improving the accuracy of fracture risk prediction. These factors included, among others, trabecular bone score and genetic profiling.

5.1. Trabecular bone score

Trabecular bone score (TBS) is a gray-level texture measurement based on a variogram of the 2D BMD projection image [40]. While BMD reflects the 'density' of mineral per area of bone (e.g. the mean), TBS captures the variation (e.g. variance) of mineral distribution on the bone. Thus, two individuals may have the same BMD, but different TBS levels. Previous studies have reported that TBS was correlated with trabecular number, trabecular separation and structure model index [41], but was independent of BMD. More importantly, lower TBS values were associated with increased fracture risk in elderly women [42] and diabetic patients [43] independently of BMD and classical clinical risk factors [44,45].

A recent individual-level meta-analysis of 17,809 men and women from 14 prospective cohort studies found that each standard deviation (SD) decrease in TBS was associated with 1.44-fold (95% CI, 1.35 to 1.53) increase in the risk of osteoporotic fractures. The association between TBS and fracture was independent of FRAX predicted probability. However, it appears that the incremental contribution of TBS in fracture prediction is modest. The AUC for major osteoporotic fracture in a model with clinical risk factors and BMD was 0.64, and adding TBS resulting in an AUC of 0.65. It remains to be shown whether the inclusion of TBS in the existing FRAX model will improve the net reclassification [46].

5.2. Genetic profiling

It has been known for some time that the risk of fracture is partly determined by genetic factors. The first line of evidence is that the risk of hip fracture is increased by twofold among women whose mother had a hip fracture [47]. However, the most important evidence was from twin study. Since monozygotic twins (MZ) share 100% of genotype and dizygotic twins (DZ) share 50% of their genotypes, the higher correlation in MZ twins compared with DZ twins is a strong evidence for heritability. Indeed, analysis of twins showed that the correlation in fracture risk in MZ twins was significantly greater than DZ twins, and that between 35% and 50% of the variance in fracture liability was attributable to hereditary factors [48].

Through llarge-scalecollaborative studies, several genetic variants have been identified. An important study on ~14,000 individuals of Caucasian background discovered 77 genetic variants that were associated with BMD [49]. Some of these variants are located close to or within genes that control bone metabolism (e.g. RANK, RANKL, OPG, ESR1, ZBTB40, VDR and LRP5 genes). Another seminal study based on 81,949 cases and 102,444 controls, also of largely Caucasian background, found 56 loci that were associated with BMD and 13 SNPs associated with fracture [50]. A more recent study using data of UK Biobank identified 518 loci associated with heel ultrasound measurements, of which 301 were new loci [51]. It is expected that future genomewide study will identify more genetic variants that are associated with either BMD or fragility fracture risk.

All of these genetic variants identified so far have modest effect sizes, with odds ratio ranging between 1.01 and 1.50 [52], suggesting that the utility of any single SNP in the prediction fracture risk is very limited. For a population with 5-yr fracture incidence of 10%, a genetic variant with odds ratio being between 1.1 and 1.2 is expected to yield an area under the ROC curve between 0.52 and 0.55, not good enough for predicting fracture risk in an individual [52]. Therefore, it is necessary to combine the individual effects of genetic variants into a single index called 'polygenic risk score' (PRS) for capturing the genetic burden related to a specific phenotype. A simple way to create PRS is to calculate the sum of BMD-associated alleles weighted by the magnitude of association between each SNP and BMD. Thus, PRS can be seen as an estimate of an individual's genetic liability to fracture [53]. PRS can also be used as an index of family history of osteoporosis [54].

We have created such as weighted PRS called '*Osteogenomic Profile*' [53] based on 62 variants that were associated with BMD [49], and found that each unit increase in PRS was associated with a hazard ratio of 1.20 (95%CI, 1.04–1.38) for fracture, independent of age, prior fracture, and falls [53]. More importantly, when PRS was added to the Garvan Fracture Risk Calculator [18], there was a significant improvement in calibration, but not discrimination [53]. A similar genetic profile based on 63 SNPs has been shown to be associated with lower BMD and greater risk of fracture [55]. These data collectively show that BMD-based PRS is a promising predictor that has potential to improve the accuracy of fracture risk prediction.

Quantitative ultrasound measurement (QUS) is associated with fracture [56], and PRS generated from QUS can also help identify individuals at risk of fracture or osteoporosis [57,58]. In a recent study, the investigators generated a PRS based on speed of sound through bone (gSOS), and found that gSOS was associated with a 1.3-fold increase in the odds of osteoporotic fracture. However, when gSOS was incorporated into the existing FRAX model, the improvement in AUC was modest. Specifically, for predicting major fracture, the AUC for the FRAX model was 0.74, and this was increased to 0.74 when gSOS was added to FRAX; for hip fracture, the AUC for the FRAX model was 0.79, and this was increased to 0.80 when gSOS was added to the model. However, the inclusion of gSOS into FRAX improved the proportion of correct classification by 2.4 to 7.2% [59].

It is expected that research into the utility of genetic profiling in the form of PRS will be continued, and several different genetic profiles will be generated. Cost-effectiveness of PRS in fracture risk assessment tools is an issue for future investigation. Experience in other fields such as cancer [60] and cardiovascular disease [61] ssuggeststhat PRS is cost-effective in the improved management of disease. With current technology, it is quite possible to generate PRS with hundreds of thousands or even millions of SNPs for less than 100 USD

The incorporation of PRS into existing prediction models can potentially change the indication of treatment for an individual [54]. Consider a 70-year old woman with femoral neck BMD being 0.72 g/cm^2 (e.g. non-osteoporosis) has no prior fracture, but fell once over the past 12 months. The Garvan Fracture Risk Calculator estimates that her 10-year risk of fracture is 24% which may not be indicated for treatment. However, if the woman has PRS in the top 5% percentile, then her 10-year risk of fracture is now 32% which may be indicated for treatment [54]. The use of PRS for fracture risk assessment will realize the ideal of personalized risk assessment for osteoporosis patients.

6. Thresholds for defining 'high risk'

The risk of fracture is a continuous variable, and there are no obvious natural threshold for distinguish between 'high risk' or 'low risk'. Nevertheless, the National Osteoporosis Foundation recommends that among men and women with femoral neck or lumbar spine BMD T-scores between −1 and −2.5, treatment is recommended when the 10-year probability of any major fracture is at least 20%, or the 10-year probability of hip fracture is at least 3% by FRAX. However, this threshold may change in the future when results of new analysis of clinical benefit and cost-effectiveness is available.

For the Garvan model, by using the decision curve approach, a 10-year probability of any fracture of 20% is a reasonable threshold for recommending treatment [62]. Treating those with a 20% or greater risk of fracture would detect 1 additional case per 324 women or 96 men, and can help to avoid 1 additional unnecessary treatment per 81 women or 24 men.

A major limitation of the existing fracture prediction models is that there has been no controlled-randomized trial to demonstrate that treating those above the recommended threshold (e.g. 10-year risk of 20%) would lead to a reduction in fracture risk. Posthoc analysis of clinical trials found a modest correlation between FRAX-predicted risk and anti-fracture efficacy, such that women in the top 25th percentile of FRAX fracture probability (average probability of 24%), treatment reduced the risk of fracture by 23% over 3 years (hazards ratio [HR] 0.77, 95%CI 0.63–0.95) [63]. Importantly, among those in the top 10% percentile of risk (average fracture probability of 30%), treatment reduced the fracture risk by 31% (HR 0.69, 0.53–0.90) [63]. Analyses of clinical trials concerning the effect of denosumab [64] and bazedoxifene [65] found that in relative risk terms, the magnitude of anti-fracture efficacy was inversely correlated with FRAX-predicted risk of fracture. However, a posthoc analysis of the Fracture Intervention Trial found no appreciable difference in efficacy of alendronate across risk levels [66].

Taken together, these results are consistent with the supposition that the anti-fracture 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.

7. Expert opinion

The development and implementation of fracture risk assessment models represents a significant achievement in translational osteoporosis research. These models, especially FRAX, have played a leading role not just in the dissemination of risk

but also the management of patients affected by osteoporosis. It appears that all models reviewed here do have validity, but their transportability across populations or subpopulations remains to be elucidated.

7.1. Areas needing improvement

The improvement of accuracy and transportability of these models must be pursued in the future. With new risk factors, and advances in quantitative epidemiology, statistical or machine learning, it will be possible to refine the existing models to maximize benefits and preclude potential problems of overmedicalization and false assurance. Moreover, with the addition of large and representative cohorts around the world, especially from Asia, it will be possible to develop ethnic-specific models.

However, new factors are likely to have little effect on changing the discrimination and accuracy of prediction. The modest improvement is expected because given the fact that existing models have AUC in the range of 0.70 to 0.80, it is very difficult mathematically to improve the discrimination. Even if a new factor results in a statistically significant change in AUC, the change is often trivial.

Another area of interest is the development of age group specific models (rather than the existing models based on a wide range of ages). In cardiovascular research [67], age-specific models appear to have better predictive performance because the risk factors included in those models have a stronger magnitude of association. Age-specific models can, theoretically, identify more individuals at risk in the short term rather than a 10-year risk.

Another area for improvement is fracture prediction in type 2 diabetes patients (T2D). Patients with T2D have higher bone mineral density (BMD) [68], but paradoxically, they tend to have a higher risk of fracture, particularly hip fracture [69] and vertebral fracture [70]. However, current fracture risk prediction models were developed on the basis that higher BMD was associated with lower fracture risk, and there is a concern that these models could underestimate the risk of fracture among T2D patients. An analysis of 3518 individuals with T2D and 36,085 individuals without T2D found that T2D was associated with higher risk of fracture, particularly hip fracture. Moreover, the study reported that FRAX underestimated the risk of major osteoporotic and hip fracture risk in T2D patients [71]. This fact raises two possible solutions; one solution is to reduce the measured BMD of T2D patients by 0.5 standard deviation, because it was found that the increased risk of hip fracture in T2D women is equivalent to ~0.5 standard deviation of BMD [72]. Another solution is to incorporate T2D as a risk factor on the existing fracture prediction models. Leslie et al. [73] found that neither approach was optimal in the adjustment for fracture prediction in T2D.

Existing fracture risk calculation tools are designed for the general population, not specific patient groups with specific diseases that compromise bone quality. For instance, patients with hyperparathyroidism, hyperthyroidism, rickets and osteomalacia, type I diabetes, Paget's disease, Cushing's disease, and osteogenesis imperfecta are known to have deteriorated bone quality that increases their risk of fracture [74]. However, there is a lack of data concerning the prognostic performance of existing fracture prediction tools in these patients, and this is another area for future research.

At present, all models produce 10-year risk of fracture, which is necessary for risk management and treatment decision. However, for prevention purpose and disease burden assessment, the lifetime risk is more relevant than short-term risk. With the ongoing development of genetic profiling, it will be possible to predict lifetime risk of fracture for an individual, and this should be an adjunct to the existing 10-year risk prediction.

7.2. Risk communication and *'Skeletal Age'*

It is well established that osteoporotic fracture is associated with increased risks of refracture and mortality [9]. There is hhigh-qualityevidence showing that women with a fracture or osteopenia treated with zoledronic acid have a reduced mortality risk [75, 76]. However, all existing fracture risk assessment models are designed to predict the probability of a first fracture, and the risks of refracture and mortality are not considered by these models.

It would be ideal to consider a *compound risk* of fracture that combines the risk that an individual will sustain a fracture, and the risk that, once a fracture has occurred, they will sustain further fractures and die. Ho-Le et al [9] analyzed the transition between fracture, refracture, and mortality, and advanced the idea of '*Skeletal Age*' which is defined as *the age of an individual's skeleton as a result of the individual's fracture and refracture*. The idea is based on the concept of 'effective age' in engineering which reflects the age of a structure based on its current condition. Thus, for a healthy individual without a fracture, the skeletal age is the same as the individual's chronological age. However, an individual with a preexisting fracture is expected to have older skeletal age. For instance, a 770-year-oldman with a fracture is estimated to have a skeletal age of 75 years, but if the man has suffered another fracture, his skeletal age is increased to 87 years.

At present, mortality risk is not a component in patient-doctor discussion about osteoporosis risk and treatment decision. The skeletal age or the difference between skeletal age and chronological age can be used as a metric for conveying the impact of fracture to patients. We expect that future fracture risk assessment tools will include, in addition to absolute risk, skeletal age as an output.

To reduce the burden of osteoporotic fractures in the general population requires accurate and robust risk assessment models. Current fracture risk assessment models have contributed substantially to the management of osteoporotic patients over the past decade, but much rremainedto be done to enhance the accuracy and robustness of existing models.

8. Box: Metrics for evaluating prediction models

Discrimination: c-statistics or area under the receiver's operating characteristic curve (AUC). A useful model should be able to distinguish individuals who will have a fracture from

those who will not. At any given level of predicted risk, there are two types of classification error: those above the risk level will not suffer a fracture (i.e. false positive), and those below the risk level will have a fracture (i.e. false negative). The complement of false-positive is called 'sensitivity', and the complement of false negative is 'specificity'. Ideally, a risk prediction model should have maximum sensitivity and specificity. However, in reality, sensitivity is inversely proportional to specificity, such that increasing sensitivity is associated with decreasing specificity, and vice-versa. A receiver's operating characteristic (ROC) curve plots the relationship between sensitivity and false-positive rate for every possible risk level. The area under the ROC curve (AUC or c-value) is the measure of discrimination. This AUC value is the probability that given two randomly drawn individuals (one who will have a fracture within 10-year follow-up and one who will not have a fracture), the individual who will sustain a fracture had a higher risk probability than the individual who will not have a fracture. Thus, AUC is really a measure of concordance between predicted risk and the actual occurrence of fracture. As a rule of thumb, a model with an AUC of 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered 'excellent'. Nevertheless, it has been realized that the *AUC* is too insensitive to change [77], and that it may not be the most appropriate method for assessing the contribution of genetic markers.

Calibration. A model with excellent discrimination is not necessarily an accurate model. The accuracy of a prediction model is measured by the degree of agreement between observed outcomes and predicted probabilities. However, in fracture prediction, the outcome has only two possible values (0 for no fracture, and 1 for fracture), and the predicted risk is a continuous variable that ranges between 0 and 1, it is desirable that those with a fracture should have a predicted risk close to 1, and those without a fracture should have a predicted risk close to 0 (e.g. good calibration). For instance, in a subgroup of 100 individuals, among whom 15 individuals sustained a fracture, and if the model predicted 15% fracture risk in the subgroup, then the agreement is 100%. Thus, a plot of observed risk versus predicted risk can indicate the degree of calibration of a model: a slope of 1 indicates a perfectly calibrated model; a slope lower than 1 indicates that the model overestimates the risk among high-risk patients and underestimates the risk among low-risk patients (i.e. overfitting model); a slope higher than 1 indicates that the model was under-fitting [78].

Reclassification. Given the insensitivity of AUC, reclassification has been proposed as a new metric for evaluating the incremental contribution of a new marker to prediction [79]. In this approach, the predicted risk of fracture is estimated for each individual by two models: the base model, and the base model plus the new marker. It is expected that if the marker has incremental predictive value, then the inclusion of the marker in the base model should change the classification. For instance, if genetic profiling is useful for fracture prediction, the probability of fracture estimated by the model with the genetic profiling would be increased for the fracture group and decreased for the nonfracture group. The change in classification can be quantified by two metrics: the *net reclassification improvement* (NRI) and the *integrated discrimination improvement* (IDI). The NRI quantifies how well a new model reclassifies individuals either in the right direction or wrong direction as compared to an old model [80]. The IDI can be interpreted as the proportion of variance explained by a new marker, or an alternative measure of AUC increment.

Decision curve analysis (DCA). In recent years, DCA approach [81, 82] has been proposed as an approach for comparing the prognostic performance between models. Conceptually, for each level of predicted risk, the decision of treatment is a trade-off between benefit and potential harm. The benefit and harm can be quantified in terms of the clinical consequences of true positive and false-positive rates. Consequently, 'net benefit' is defined as a trade-off between different accurately treating high-risk patients (benefit) and unnecessary treatment of low-risk patients (harm). The net benefit is dependent on the threshold probability that defines 'high risk' of fracture. For instance, clinicians may decide to treat patients aged over 50 years with 10-year risk of major osteoporotic fracture at 20% or higher, and would forgo the treatment if the 10-year risk of major osteoporotic fracture is only 19% or lower. The net benefit is evaluated across a range of risk thresholds P_t (where P_t ranges between 0% and 100%) giving a series of net benefits called a *decision curve*. This trade-off evaluation can be performed for competing risk predictive models without the need for external information such as economic and cost-effectiveness.

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Declaration of interest

The author is the developer of the Garvan Fracture Risk Calculator which is freely available to doctors and the public. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

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