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Cost-utility analysis of fracture risk assessment using microRNAs compared with standard tools and no monitoring in the Austrian female population

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ABSTRACT

Background: Osteoporosis poses an immense burden to the society in terms of morbidity, mortality and financial cost. To reduce this burden, it is essential to accurately assess the individual patient's fracture risk and, where indicated, to initiate appropriate treatment that reduces fracture probability. Current screening and monitoring approaches include utilization of FRAX®, a web-based country-specific fracture risk assessment tool, and bone mineral density measurement by Dual Energy X-ray Absorptiometry (DXA). Recently, microRNAs have been recognized as important regulators of bone physiology and potential biomarkers for fracture risk assessment and monitoring. A fracture risk assessment tool based on microRNAs (osteomiR™ test) is currently being developed. The aim of this study was to estimate the cost-effectiveness of fracture risk screening, monitoring, and resulting treatment decisions for the Austrian female population using the osteomiR™ test compared with DXA, with FRAX®, or with no screening/monitoring.

Methods: A cost-utility-model was developed to simulate long-term consequences of Austrian women from age 50 over lifetime or death with respect to osteoporosis. Markov-modelling techniques were used to calculate health state transitions of fracture incidence according to risk groups (high, intermediate, low). High-risk patients receive medical treatment. Probabilities were derived via systematic-literature-review; direct costs (2015, €) from published sources from the payer's perspective. Results evaluate the incremental cost-effectiveness ratios (ICER) for osteomiR™ against the comparators, gains or losses of fractures, life years (LYs), quality-adjusted life years (QALYs), and direct costs. QALYs, life years (LYs) and costs were discounted (3% p.a).

Results: Fracture risk assessment and monitoring using the osteomiR™ test reduces fracture incidence compared with no monitoring, DXA alone, or FRAX® alone. In the per-patient analysis, the ICER/QALY of osteomiR™ vs. no-monitoring was 13,103 €, vs. FRAX® 37,813 €, and vs. DXA -19,605 €, indicating that costs can be saved while gaining QALYs. Considering the total cohort over lifetime, the osteomiR™ test can avoid 57,919 fractures compared with DXA, 31,285 fractures compared with FRAX® and 133,394 fractures compared with no monitoring. Sensitivity analysis confirmed the robustness of these findings.

Conclusion: Fracture risk assessment and monitoring using the osteomiR™ test dominates DXA-strategy and constitutes a cost-effective alternative to FRAX®, and no-monitoring, respectively.

1. Introduction

Osteoporosis is an increasingly important health problem. In 2010, it was estimated that 22 million women and 5.5 million men in the EU had osteoporosis using the diagnostic criterion of the World Health Organization (WHO) [1]. In Austria, the prevalence rate of osteoporosis is 22.2% in women and 6.5% in men aged 50 + years, and 5.5% in the general population [1]. Overall, 393,000 Austrian women aged 50 years and above are affected by osteoporosis, among them 89,200 with a prior hip or vertebral fracture.

Osteoporosis-related fractures are associated with a high degree of morbidity and mortality. Irrespective of the fact that in many countries of the so-called Western World age-standardized hip fracture incidences have been shown to level-off or even decrease, the absolute

Abbreviations: DXA, Dual Energy X-ray Absorptiometry; FRAX, fracture risk assessment tool; ICER, incremental cost-effectiveness ratios; LY, Life year; p.a., per annum; QALY, quality-adjusted life year.

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number of osteoporotic fractures worldwide is expected to increase further, in part due to increased longevity and the increased frailty associated with an aged population [2,27,32]. Approximately 9 million osteoporotic fractures occurred worldwide in 2000, of which 1.9 million were fractures of the hip. The incidence of hip fractures is predicted to increase to 6.3 million in 2050, as the number of individuals at risk increases [2].

In addition to the negative impact on the quality of life of the individual, osteoporosis exerts immense socio-economic burden on health care systems. Costs in the EU are projected to increase from € 37.4 billion in 2010 to € 46.8 in 2025 [1]. A cost-of-illness study calculated that the total annual cost inflicted to the Austrian society due to osteoporosis amount to approximately 707.4 million € for the year 2008. The largest proportion of these costs was incurred by acute hospital treatment, followed by opportunity costs for informal care [3].

If an increased risk of fracture is diagnosed prior to the first fracture, fracture risk can be significantly reduced by preventive pharmacologic treatments and/or lifestyle interventions [4]. At present, however, there is no universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture [5]. Fracture risk assessment tools like FRAX®, and bone mineral density (BMD) measurement by Dual Energy X-ray Absorptiometry (DXA) constitute the standard of care for fracture risk assessment and monitoring osteoporosis, and are frequently recommended in national guidelines for osteoporosis management. The FRAX® questionnaire considers clinical risk factors like body mass index (BMI), smoking, glucocorticoid intake and family history. Some of the FRAX®-specific risk factors have been shown to be partially or wholly independent of BMD, providing information on fracture risk above that of BMD alone. Accordingly, the combined use of such risk factors has been demonstrated to enhance the information provided by BMD alone. Overall, FRAX® has been designed to calculate an individual's 10-year probability of major osteoporotic fractures (MOF), and also of hip fracture alone, based on country-specific fracture incidences and mortality [33]. Decisions on further diagnostic steps are mostly based on the FRAX score, which can be refined by including the BMD value [7].

MicroRNAs are small non-coding RNAs, which regulate gene expression and contribute to the homeostasis of complex biological phenotypes and processes including aging [8]. Therefore, significant changes in microRNA expression are a common feature of pathophysiologic deterioration of cells and tissues [9]. Although microRNAs act intracellularly, they are also actively released and shuttled to other cell types via the circulation [10]. Consequently, it has become possible to monitor important changes in tissue microRNA expression due to onset and progression of disease, based on liquid biopsies, preferably serum or plasma. In the context of musculoskeletal disease, microRNAs are by now well-established regulators of muscle function [11,12] and bone remodeling [13]. On the basis of multi-centric cross-sectional studies in postmenopausal [14,15] as well as idiopathic osteoporosis [16], we and others have recently discovered a panel of microRNA in serum, which could serve as novel biomarkers for fracture risk assessment and monitoring, called “osteomiRs”. On that basis, we have developed a laboratory assay, the osteomiR™ test, which provides reagents and software to quantify 16 microRNAs in 200 μl human serum by quantitative PCR and to calculate a fracture risk score based on the relative abundances of the included miRNAs. Thus, the osteomiR™ test is intended to enable fracture risk assessment based on the standardized analysis of osteomiRs in human serum. The area under the curve (AUC) of the ROC (Receiver Operating Characteristic) curve, a combined measure of sensitivity and specificity, was estimated to achieve 85% for the osteomiR™ test [16], while the projected end-user cost will approximately amount to 50 € per test. The ability of osteomiRs to identify high-risk individuals is largely independent of bone mineral density [16], and could be regarded as a novel independent factor for fracture risk assessment and monitoring to facilitate treatment decisions using anti-osteoporosis medications.

Based on these explanations, the purpose of this study was to estimate the cost-effectiveness of implementing osteomiR™ as a novel tool for screening and monitoring of fracture risk in a cohort of Austrian women aged ≥50 years without prior fractures. The osteomiR™ test was compared with DXA alone, with FRAX® alone, and with no monitoring.

2. Materials and methods

2.1. Markov model design

A cost-utility model was developed to simulate osteoporosis screening and monitoring, as well as its long-term consequences in Austrian females from 50 years of age over lifetime. Markov cohort simulation techniques were used to estimate fracture incidence according to risk group allocation. The four-arm probabilistic Markov model combined a decision tree to categorize patients into three risk categories (Fig. 1A) with the Markov process to assess the long-term clinical and economic outcome (Fig. 1B). According to the decision tree, women were either not subject to fracture risk assessment or monitoring, or they were screened and monitored using either DXA alone, FRAX® alone, or the osteomiR™ test (Fig. 1: Markov Model. A) Decision tree for comparator strategies. B) Markov process with cycle length of 1 year and 7 defined states. Fig. 1A).

In detail, the following fracture risk assessment and monitoring strategies were applied:

- **No assessment**/**monitoring**: In the no-monitoring arm, women receive no regular monitoring. In case of a fracture, patients were monitored with DXA every 2 years.
- **DXA**: Women without prior fractures were monitored by DXA every 2 years from the age of 65 upwards. Women with prior fractures were also monitored with DXA before age 65. Women in the high-risk group were assigned to pharmacological treatment.
- **FRAX®**: In the FRAX® arm, women were monitored with FRAX® every 2 years from the age of 65 upwards. Women in the high-risk group were assigned to preventive pharmacological treatment.
- **osteomiR™**: Women were monitored every 2 years from the age of 65 upwards. Women in the high-risk group were assigned to pharmacologic treatment. After a fracture, women were monitored with DXA every 2 years.

Based on the test result, women were stratified into three risk categories (high, intermediate, low), following the case-finding strategy from the National Osteoporosis Guideline Group 2008 [17]. For either risk assessment method, the classification thresholds vary in dependence of age and number and type of clinical risk factors present, which differ in their predictive strength. High-risk patients receive medical treatment, resulting in risk reduction. The magnitude of risk reduction depends on treatment regimen and fracture type (NICE Guidelines 2008). Every year, a patient has a certain probability of suffering a fracture, remaining healthy, or deceasing. If the patient incurs a fracture, she will move to the health state “fracture”. This health state is subdivided into fracture types: hip, vertebral, wrist/forearm or other osteoporotic fractures. In the following Markov cycle, the patient may experience a recurrent fracture, move to the “post fracture” state or die. The cycle length in the model is one year; therefore, a half-cycle correction was implemented. All patients are followed through the model from 50 years of age over lifetime or an age of 100 years. Unit costs and health outcomes, described as quality-adjusted life years (QALYs), life years and incremental cost-effectiveness, were projected over a life-time horizon. Costs and benefits were discounted by 3% per year. The Markov process is schematically depicted in Fig. 1B.

The analysis was conducted in consideration of the Modeling Good Research Practices published by ISPOR Task Force (Caro et al. [34]) and the Austrian health economic guidelines [35].

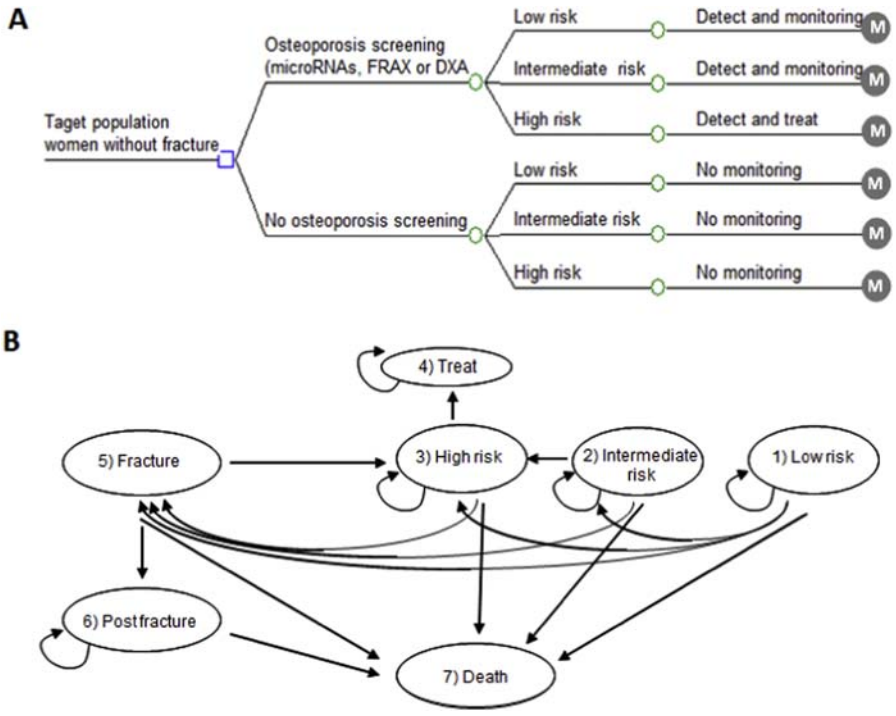

Fig. 1. Markov Model. A) Decision tree for comparator strategies. B) Markov process with cycle length of 1 year and 7 defined states.

2.1.1. Simulated cohort and epidemiological data

The simulated hypothetical cohort included women at the age of 50 years without prior fracture. Women with prior fragility fractures such as those of the hip and/or the vertebrae were not considered because they would be eligible for secondary-preventive pharmacologic treatment without further fracture risk assessment. In 2015, 1,792,652 Austrian women were aged 50 years and above (Statistik Austria, [36]), of whom 5% had already sustained a prior fracture ([1] and Supplementary material Table S1).

2.1.2. Markov model structure

The model assumes that women of the simulated cohort run into the model, and that they could suffer a fracture without having undergone previous risk assessment. These women receive pharmacological treatment. The risk of sustaining a fracture in the model depends on three elements: (i) the risk for an individual in the general population of incurring a fracture, (ii) the increased fracture risk associated with osteoporosis (the relative risk), and (iii) a risk reduction attributed to a treatment. The fracture risk was assessed routinely from the age of 65 years upwards using any of the three comparator strategies (Fig. 1A) according to the case-finding strategies of the National Osteoporosis Guideline Group 2008 to stratify women to risk groups (high, intermediate, low). The individual risk stratification depends on age, BMI and the number of clinical risk factors (CRFs) (Compston et al. [17] and Supplementary material, Table S3A). A high fracture risk denotes that the risk is consistently above the upper assessment threshold, irrespective of the mix of CRFs; a low risk is associated with a risk below the threshold. The intermediate category denotes that fracture probabilities are between these limits and a BMD test should considered (Compston et al. [17] and Supplementary material S3B). Following the risk assessment, the Markov process starts to analyze the long-term effects. Women were distributed to one of the three risk categories referred to as Markov states to model fracture occurrence, associated with fracture dependent risk probabilities and recurrent fractures. Probabilities depended only on the current health state of a person, and not on their previous one (Markov assumption; [18]). The progression from $t = n$ to $t = n + 1$ is called a cycle. All clinically important events were modeled as transitions from one state to another. Probabilities were associated with each transition between two states; these were termed transition probabilities. Each transition probability was a function of the current health state and the treatment.

The following health states were defined: 1) no fracture and low risk, fracture probability according to age, BMI and number of CRFs. 2) no fracture and intermediate risk, fracture probability according to age, BMI and number of CRFs. 3) no fracture and high risk, fracture probability according to age, BMI and number of CRFs. 4) osteoporosis treated – women with high risk and with prior fragility fracture should be considered for treatment. 5) fracture – this health state is subdivided according to the fracture type: hip, vertebral, wrist/forearm or other osteoporotic fractures.6) post fracture – this state encompasses the time after the year in which the fracture occurs. 7) death.

Fig. 1B shows the model design with health states and possible transitions between states. The model was constructed and analyzed using Microsoft Excel 2010. Results were presented per patient and for the total Austrian cohort.

2.1.3. Transition probabilities

Diagnostic accuracy, i.e. the ability of the test to discriminate between fractured and non-fractured individuals, is expressed as area under curve (AUC) of the receiver operator characteristic (ROC) curve. The AUC is calculated after plotting sensitivity against 1-specificity for every individual cut-off. A test with an AUC of 0.9–1 is considered to have excellent diagnostic accuracy, while an AUC of 0.5 gives random results [37]. These values were drawn from literature [7] and were 63% for FRAX alone, 65% for DXA and 66% for FRAX including BMD (Table 1). We have used mean values for the base case analysis, representing the most likely set of assumptions and input values. The AUC of the osteomiR™ test was set to 85%, based on the diagnostic training and validation performances observed in a cohort of postmenopausal women [14,16]. The average fracture risk for the population entering the model was deduced from the average figures for body mass index (BMI) and number of CRFs. The distribution of BMI by age groups was available via official statistics (Statistik Austria, [38]). Regarding the proportion of women facing 1–3 CRFs no information from the literature exists and estimations were the basis for calculations. The estimated

Table 1
Clinical input data.

Incidence of fragility fractures per year

Age groups	Hip	Vertebral	Wrist/Forearm	Other	References
50–54	0,5%	1,2%	3,3%	3,8%	Calculations for Austria based on data from Hernlund et al. [1]
55–59	0,6%	1,4%	3,9%	4,4%	
60–64	0,6%	1,0%	2,3%	2,4%	
65–69	0,9%	1,2%	2,2%	3,4%	
70–74	1,2%	1,5%	2,0%	3,4%	
75–79	1,7%	1,4%	1,6%	3,9%	
80–84	3,0%	1,6%	1,8%	5,5%	
85–90	4,4%	1,9%	1,8%	8,5%	
90–95	4,2%	1,7%	1,3%	8,1%	
95–100	10,8%	4,1%	2,8%	21,8%	

RR of mortality compared with the normal population

Age groups	Hip 1st year	Vertebral 1st year	Hip 2+ years	Vertebral 2+ years	References
50–54	9,79	12,07	3,62	7,94	Johnell et al. [30], Swedish National Patient Register
55–59	8,64	10,15	3,34	6,67	
60–64	7,69	9,04	3,11	5,94	
65–69	6,39	7,43	2,7	4,88	
70–74	5,54	5,93	2,44	3,93	
75–79	4,16	4,39	1,91	2,88	
80–84	2,92	2,75	1,39	1,81	
85–90	2,15	1,98	1,06	1,3	
90–95	1,63	1,36	1	1	
95–100	1,63	1,36	1	1	

AUC of ROC curve for discrimination between fractured and non-fractured individuals.

Strategy	Mean	Minimum	Maximum	95% CI	References
FRAX without BMD	63%	61%	72%	61–65%	[7,14,16,31]
FRAX with BMD	66%	62%	74%	64–68%	
BMD	65%	61%	71%	62–67%	
osteomiR	85%	80%	90%		

number of CRFs (1–3) among age groups was calibrated in a way that corresponds to the number of total fractures observed. The combined relative risk is estimated as:

$$RR_{fracture}(age)^{(year1\ldots n)} = RR_{BMI}(age)^{(year1\ldots n)} \times RR_{CRF}{}^{(1-3)}(age)^{(year1\ldots n)} \quad (1)$$

$$RRCRF^{(1-3)}(age)^{(year1\ldots n)} = \frac{RR_{fracture}\ (age)^{(year1\ldots n)}}{RR_{BMI}\ (age)^{(year1\ldots n)}} \quad (2)$$

Based on these criteria, women were assigned to one of the three risk groups (Supplementary material Table S3A).

Data on fracture incidences were derived from Hernlund and colleagues [1]. Sub-classification of fractures into hip, vertebral, wrist/forearm and other fractures was performed. Age-specific incidence was obtained by linear interpolation between the age intervals, and the value shown was a set for the age in the middle of the interval (e.g., the incidence rate for women 70–74 was used for 72-year old women) (Table 1).

Hip fractures are associated with an increased risk of death, particularly during the immediate post-fracture years [19]. Age-differentiated mortality during the first and following years after a hip fracture has been described in Swedish National Inpatient Register. A clinical vertebral fracture, i.e. not defined morphometrically but based on acute clinical symptoms, is also associated with increased mortality. Age-differentiated mortality risks (first and following years) after clinical vertebral fractures were derived from Johnell and colleagues [20]. Wrist/forearm fractures are not associated with increased mortality. Mortality rates without prior fracture were extracted from the Austrian mortality table [Statistics Austria].

Efficacy data of osteoporosis treatment for the different active substances, comprising alendronate, ibandronate, risedronate, strontium ranelate, zoledronate, raloxifene and denosumab, were obtained from meta-analyses conducted for a NICE appraisal (National Institute for Health and Care Excellence, [39]) and the FREEDOM trial for denosumab (Cummings et al., [40]) (Supplementary Table S1).

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2.2. Cost assessment

The cost assessment was based on the assignment of costs to the health states. The costs of each health state were determined by the resource utilization (RU) associated with a health state. Resource use (i.e. the type and frequency of medical goods and services rendered to the patient) and monetary value (prices, tariffs and/or opportunity costs) for each unit of medical goods and services were used to calculate the total direct costs in the Austrian setting. In order to estimate the disease costs of osteoporosis including osteoporotic fractures in Austria, only direct costs were included in the analysis. Direct medical costs were collected from the payer's perspective for the year 2015.

Resource use due to fractures was derived from a retrospective chart review, which was conducted at the Institute for Pharmaeconomic Research, Vienna, in 2010. The study protocol was approved by Ethical Committee of the Medical University of Graz. A sample ($n = 166$) of female osteoporosis patients with low energy hip, vertebral and wrist fractures (mean age 76 years) was assessed by random sampling (according to defined inclusion and exclusion criteria) in seven Austrian centers. Direct medical costs of osteoporotic fractures comprise the following costs: inpatient stays, co-medication, general practitioner (GP) consultation, medical specialist consultation, and hospital outpatient department consultations. The resource consumption based on medical records was collected for a follow-up period of 1 year. Resource use data were linked with current cost data to calculate recent fracture costs. Costs for other fractures were estimated as an average value of hip, vertebral and wrist/forearm fractures. The percentage of patients in Austria assigned to preventive pharmacologic treatment was estimated based on published data ([3]; QuintilesIMS DPMOE 2015, data on file). The market share of medication prescribed was derived from QuintilesIMS sales data. The model assumes a slight upward treatment rate (e.g. 20.2% with high risk, without fracture in 2015).

Outpatient costs for osteoporosis screening (screening intervals as quoted in the comparator description) and medical consultation costs were derived from the tariff catalogs of the nine Austrian regional health insurance funds. Outpatient costs represent weighted average values. We assessed inpatient costs using the Austrian Diagnosis-related group DRG-System, a patient classification system that provides a clinically meaningful way of relating the types of patients treated in a hospital to the resources required by the hospital. We used the 2015 version of the Austrian DRG-System, which is based on ICD-10, the internationally valid International Statistical Classification of Diseases and Related Health Problems of the WHO, version 2016.

Medication costs represent reimbursement prices and were extracted from the official Austrian classified index of goods ("Warenverzeichnis"). Supplementary Table S2 gives an overview on costs for resources used. Supplementary Table S4 shows costs incurred by specific types of fracture.

2.3. Health state utilities

Utilities are a measure of preference between health states, where preference can be equated with value or desirability. Utilities for health states included in the model were obtained from international literature, and, if necessary, re-expressed on a utility scale from 0 to 1 (where 0 represents death and 1 represents full health) by using weighting factors. The QALY (Quality-adjusted life year) concept allows combining the effects of health interventions on quantity and quality of the remaining life years into a single index. QALYs are calculated by multiplying the length of time spent in a certain health state by the utility score associated with it [21].

Further, we use age-dependent utilities derived from [22]. The impact on quality of life during the first year after a fracture (hip, vertebral and wrist/forearm) as well as during subsequent years after a hip fracture was based on a meta-analysis [23]. Empirical data on the disutility after other fractures were derived from Kanis and colleagues [24] and Borgström and colleagues [25]. Our analysis assumed that these utilities can be applied to the Austrian population. All utilities are presented in Supplementary Table S5.

2.4. Sensitivity analysis

A deterministic one-way sensitivity analysis was performed to assess how variations of individual input parameter values affects the model outputs, specifically, the resulting incremental cost-effectiveness ratio (ICER), and thus to judge the robustness of our findings. Input ranges for sensitivity analysis were obtained from 95% confidence intervals (CI) when available. Otherwise, input ranges were derived by adding or subtracting percentage values to or from the baseline estimates. In addition, a probabilistic sensitivity analysis was performed. This global probabilistic sensitivity analysis allows the contribution of each parameter to model outcomes to be investigated while also taking into account the uncertainty of other model parameters. For this purpose, we incorporated a probability distribution of the input variables by means of a second order Monte Carlo simulation. Each simulation was based on a different value drawn randomly from the distribution of each variable. Second order Monte Carlo simulations of 500 hypothetical patients were performed based on the distributions of all input variables; gamma distribution was assumed for cost and beta distribution for probabilities and utilities.

3. Results

3.1. Base case results per woman

The potential long-term impact of using a new fracture risk assessment and monitoring tool that is based on serum microRNA profiles ("osteomiR™") was appraised in comparison with DXA alone, with FRAX® alone, or with no monitoring, using a four-arm probabilistic Markov model. The target group was the female Austrian population aged 50 years or older without previous fractures.

Table 2 gives a complete overview over the lifetime cost and health, which was measured as quality-adjusted life years, life years, and fractures per women for each of the four scenarios.

The main cost driver was found to be fractures. These were lowest for osteomiR™ (7794 €) followed by FRAX® (7848 €), DXA (8215 €) and no monitoring (8493 €). The cost for monitoring were highest for the FRAX® scenario (423 €), followed by osteomiR™ (€ 333), DXA (290 €), and no monitoring (170 €). Costs for medication were highest for the osteomiR™ scenario (1352 €) followed by FRAX (1105 €), DXA (1054 €), and no monitoring (665 €). In total, the no monitoring scenario was found to result in lowest discounted cost (9327 €) followed by FRAX® (9377 €), osteomiR™ (9479 €) and DXA (9557 €). The highest number of quality-adjusted-life-years was observed for osteomiR™

Table 2
Results of cost effectiveness analysis per woman.

Calculation components	No monitoring	DXA	FRAX	osteomiR
COSTS [EUR]				
Monitoring costs	169,54	289,82	423,44	333,20
Osteoporosis medication costs	664,91	1.053,64	1.105,29	1.352,13
~Hip fracture costs	3.315,56	3.178,62	3.023,37	2.995,83
~Vertebral fracture costs	478,99	449,97	430,84	422,15
~Wrist/forearm fracture costs	575,41	566,01	552,92	551,01
~Other fracture costs	3.806,77	3.711,82	3.546,73	3.531,17
~Post fracture costs	316,03	308,76	294,21	293,69
Total fracture costs	8.492,75	8.215,18	7.848,07	7.793,85
Total costs	9.327,20	9.558,64	9.376,80	9.479,18
Cost difference	151,98	−79,46	102,39	
QALYs				
QALYs	19,3758	19,3834	19,3847	19,3874
QALY difference	0,0116	0,0041	0,0027	
ICER/QALY	13.102,82	−19.604,80	37.812,98	
LYs				
LYs	35,2347	35,2455	35,2470	35,2508
LY difference	0,0161	0,0053	0,0038	
ICER/LY	9.428,22	−15.019,26	27.266,85	
Fractures avoided				
Hip fractures	0,598	0,584	0,580	0,574
Vertebral fractures	0,272	0,254	0,253	0,247
Wrist/forearm fractures	0,313	0,311	0,309	0,308
Other fractures	1290	1279	1270	1264
Total fractures	2,47	2,43	2,41	2,39
Fractures avoided	−0.08	−0.03	−0.02	

(19.388), followed by FRAX (19.385), DXA (19.384) and no monitoring (19.376). The same trend was observed for life years and in reversed order for total fractures (Table 2).

To interpret the cost effectiveness of osteomiR™, the difference in total cost per women were divided by the difference in QALY expressing the incremental cost effectiveness ratio (ICER). Additional cost of € 13,103 per QALY gained compared with no monitoring and € 37,813 per QALY gained compared with FRAX were observed for osteomiR™. Compared with DXA, osteomiR™ resulted in lower life time cost and higher QALYs per women, resulting in a negative ICER of −19,605 €.

3.2. Base case results for the entire cohort

The extended analysis based on the total Austrian female population aged ≥50 years without prior fracture was carried out to transfer per patient results, which relate exclusively to women from age 50 over lifetime, to the age distribution of the total population which was then followed over lifetime. The results are summarized in Table 3.

The ICER of an osteomiR™-based strategy vs. a FRAX®-based strategy is associated with 28,490 €, vs. DXA of 33,388 € and vs. no treatment of 36,427 €. The ICER for the entire cohort vs. no treatment and DXA is higher than the ICER calculated per woman. The entire cohort consists of a mixture of different risk and age groups, while the results per woman assume the ideal situation of an individual complying perfectly with the recommended monitoring scheme. Consequently, the increase of fracture costs and associated disutilities account for a higher magnitude in case of osteomiR™ than for no treatment and for DXA. Compared with FRAX®, utility decrease is slightly higher than cost increase; results remain nearly equal. In a younger population, screening strategies based on osteomiR™, but also FRAX, are more cost-effective. In addition, it is possible to avoid fractures using an effective risk-assessment and monitoring strategy. Compared with a FRAX-based strategy, use of osteomiR™ can avoid 31,285 fractures over the lifetime of the entire cohort, 249 already in the first year. Compared with DXA, the number of avoided fractures increases to 57,919; 418 of which within the first year. The difference compared with no fracture risk assessment/monitoring is significant, because the number of avoidable fractures rises to 133,394, 1.066 of which in the first year.

3.3. Deterministic sensitivity analysis

The one-way deterministic sensitivity analysis was performed to assess the impact of variations in single parameters like fracture risk, number of CRFs, sensitivity of the different monitoring strategies, mortality, costs, utilities and the discount rate on the ICER of osteomiR™-based screening compared with FRAX® alone, with DXA alone, and with no monitoring. Tornado diagrams (Fig. 2) where chosen to display the results.

The comparison of the osteomiR™ test with the FRAX strategy (Fig. 2A) shows that among input values considered, the risk reduction of fractures due to treatment, the osteoporosis medication costs, utility values and the discount rate exhibit the greatest influence. Overall, the ICER was observed to range between 75,066 € and being dominant (ICER <0 €), which means that the intervention costs less and is at least as effective as the comparator. Results compared with DXA show that cost savings persisted for the osteomiR™ test in all variations, except for the discount rate. The ICER was observed to range between 16,130 € and being dominant. Variables with the greatest influence on model output are the discount rate, fracture costs, utility values and osteoporosis medication costs. When the osteomiR™ test was compared with no monitoring, the strongest influence was identified by varying the discount rate, fracture costs, the risk reduction of fractures due to treatment, and osteoporosis medication costs. The ICER ranges between 33,987 € and a dominant situation. The factors of influence show a common picture across the different comparators. Analyses performed from the Austrian statutory health insurances or payer's perspective demonstrated benefits similar to those seen in the base-case analysis.

3.4. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed using a Monte Carlo simulation of 500 hypothetical patients. The incremental costs and health effects due to osteomiR™ were plotted against alternative fracture risk assessment and monitoring strategy, i.e. FRAX, DXA or no monitoring. The resulting scatter plots (Fig. 3A–C) revealed that increasing the sensitivity of screening and monitoring using the osteomiR™ test is cost-effective or dominant compared with highly specific tests such as DXA or FRAX. It was observed that in case of a willingness-to-pay (WTP) of 25,000 €, >97.5% of the simulations show a cost-effective result; in case of a WTP of 30,000 €, >98% of simulations are cost-effective.

4. Discussion

The aim of this study was to assess the ramifications of a more accurate fracture risk assessment and -monitoring on cost and health, based on the female Austrian population aged 50 years and above. A Markov model was built using data from current literature as well as in-house chart reviews. The model evaluated four scenarios: i) no monitoring, or screening and monitoring ii) by bone mineral density assessment (DXA) alone, iii) by clinical risk factor score (FRAX®) alone or iv) by a novel molecular diagnostic (MDx) test - the osteomiR™ test. The cost for the novel MDx test was approximately twice as high as the standard-of-care.

In the base case analysis, that is, the analysis based on the most likely set of assumptions and input values, no monitoring resulted in the lowest value of QALYs per women and the highest number of incident fractures. The implementation of either DXA or FRAX® improves health per women as well as for the entire cohort, compared with no monitoring. The increase in AUC for identification of individuals who will subsequently sustain a fracture from 65% to 85% through implementation of the osteomiR™ test, which features a high true positive rate and low false positive rate, leads to cost increases for medication and diagnosis per woman. Compared with FRAX®, the concomitant increase in health (QALYs, number of fractures) is cost-effective, because the incremental cost per QALY gained amounts to 37,813 € per woman and 28,490 € for the entire cohort over lifetime. The osteomiR™ test was further observed to be dominant compared with DXA, considering the lifetime

Table 3
Cost-effectiveness results for the total cohort over lifetime.

Calculation components	No monitoring	DXA	FRAX	osteomiR
Costs	21,871,009,547.84	22,626,027,524.27	22,775,791,407.89	22,978,147,380.52
QALYs	24,748,211.66	24,768,058.43	24,771,501.84	24,778,604.64
ICER/QALY	36,427.42	33,388.29	28,489.61	
LYs	33,655,808.90	33,670,323.67	33,672,249.86	33,677,244.40
ICER/LY	51,649.74	50,879.05	40,515.44	
Fractures	4,002,382.52	3,926,907.81	3,900,273.24	3,868,988.34
Fractures avoided	−133,394	−57,919	−31,285	

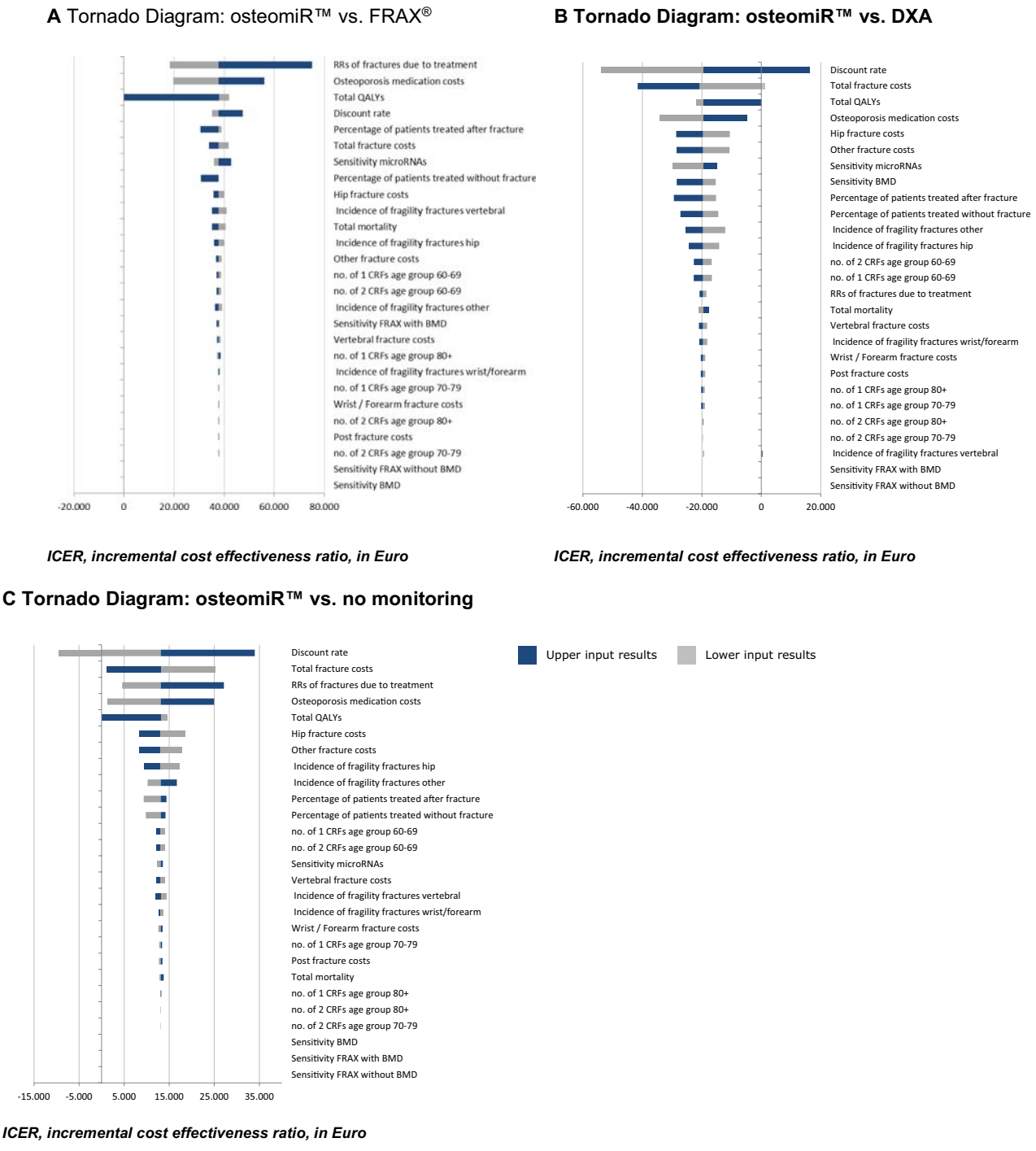

Fig. 2. Deterministic Sensitivity Analysis visualized as Tornado plots. Deterministic sensitivity analysis was used to identify the critical variables affecting risk analysis. Results are displayed as Tornado diagrams, where each bar represents a one-way sensitivity analysis, and width of bars represents impact on model results. The ICER per women is plotted on the x-axis.

cost per woman (ICER = −19,605 €). For the entire cohort, osteomiR™ is cost-effective compared with DXA alone, considering additional costs of 33,388 € per QALY gained. In sum, osteomiR™ dominates DXA as a tool for screening and monitoring fracture risk in Austria, and can be considered as a cost-effective improvement compared with no monitoring and with FRAX®.

Our model distinguishes between a per-patient view to demonstrate the ideal world with the earliest possible usage of risk assessment/monitoring, and a full cohort view to capture the total number of patients screened within a health care program. The higher the percentage of elderly women facing a worse risk profile, the higher is the ICER of the osteomiR™ test versus other risk assessment and monitoring strategies (except FRAX®). This is due to the fact that risk factors for fracture and fracture locations differ between early postmenopausal and elderly women. With increasing age of an individual, the number of fractures that can be avoided within the remaining life years decreases, and in consequence, the economic benefit of accurate fracture risk assessment/monitoring is reduced. However, results regarding risk assessment/monitoring in older women over 80 years should be generally interpreted with caution, because in this age group the predicted 10-year fracture risk may underestimate the short-term fracture risk.

The robustness of these results was examined using a deterministic and probabilistic sensitivity analysis, where one or all input parameters were varied within defined ranges or selected distributions. Both

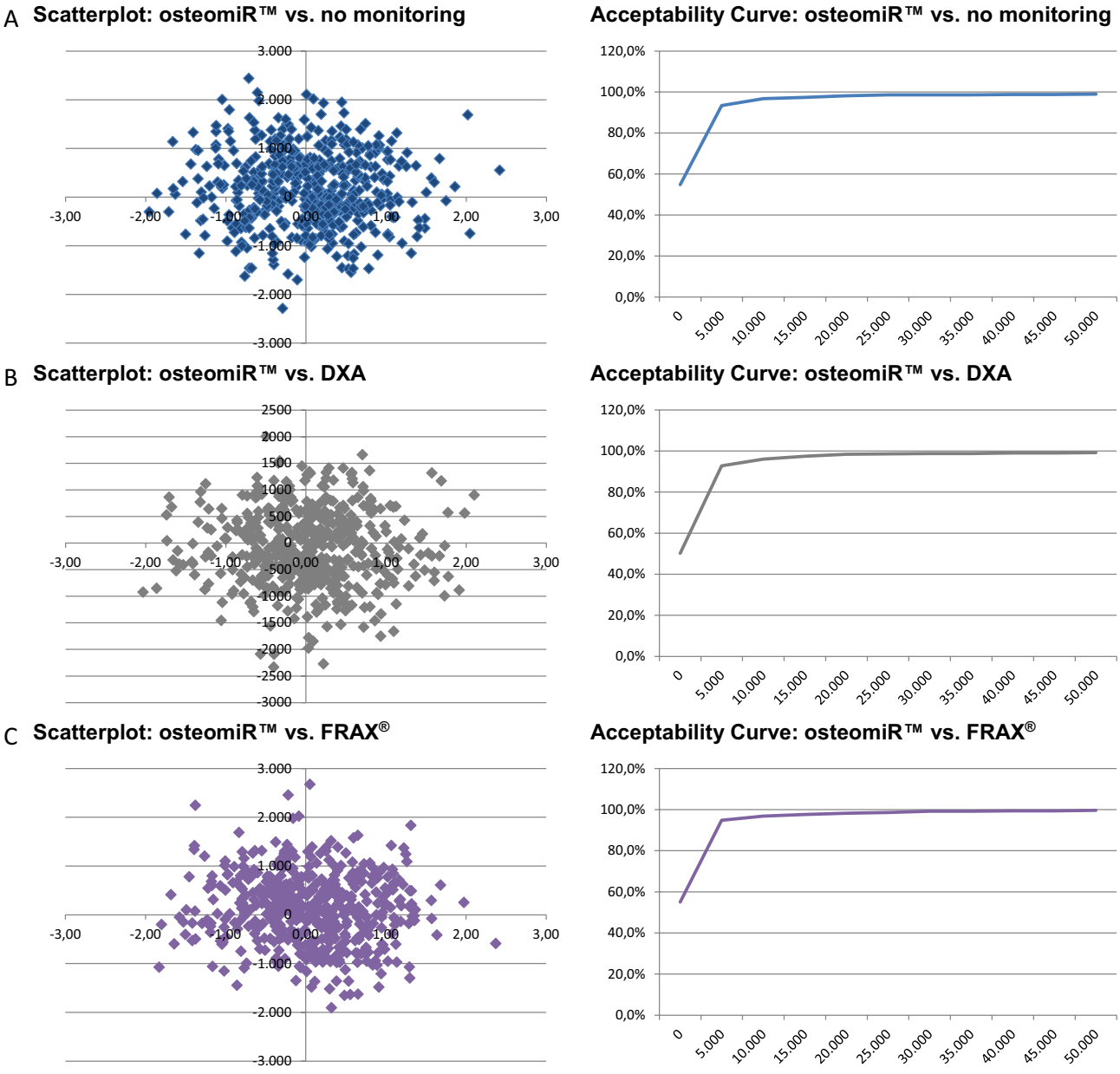

Fig. 3. Probabilistic Sensitivity Analysis. Left panels: The Scatterplot shows results of the Monte Carlo probabilistic sensitivity analysis for 500 patients. Incremental cost is plotted on the Y-axis, incremental effectiveness is plotted on the X-axis. Location of majority of points around the origin shows that majority of simulations yields similar results as the base case scenario, attesting the model low levels of uncertainty. Right panels: Cost-effectiveness acceptability curves display the percentage of iterations that favor microRNAs in comparison with other strategies, over a range of willingness-to-pay. The X-axis displays reported values as € per QALY.

approaches clearly demonstrated robust cost-effectiveness of osteomiR™ compared with comparator scenarios. The parameters with the highest impact on cost-effectiveness were identified to be the risk reduction rates due to anti-osteoporotic treatment, as well as the cost for medication and fracture costs. This means that effective diagnostic tools in conjunction with the availability of effective drugs significantly reduce fracture risk and corresponding costs.

This study has several strengths and limitations. Strengths include, first, the extensive amount of data that has been collected regarding the capacity of the osteomiR™ test to discriminate between individuals with and without fractures. Thus, the assumed AUC of the osteomiR™ test is well grounded. Second, our analysis includes a large array of variables that are often not considered in health economic analyses, for example specific costs and effects for 11 different osteoporosis medications, and the costs of case-finding. Third, the model precisely depicts the Austrian clinical practice. Resource utilization data were derived only from local sources and patient groups to represents the Austrian health care system. Unit cost inputs represent prices and tariffs of the year 2015, no estimation and data transferability among counties were necessary.

Among the limitations is the fact that the model assumes that fracture risk is assessed routinely only from the age of 65 years upwards. Can it deduce any recommendations on fracture prevention in younger postmenopausal women between 50 and 64 years of age? For identification of women with incident major osteoporotic fractures, the AUC value for FRAX® is only 0,56 in woman aged 50–64 years [26]. In our model, changes in sensitivity influence medication costs; more precisely, osteoporosis medication costs of women distributed to the high risk category, without fracture. Hence, a change of sensitivity rates for FRAX® would reduce osteoporosis medication costs from 1105.29 € to 1064.40 € per woman. The number of fractures avoided would decrease from 0.020 to 0.019. Therefore, as pictured in the deterministic

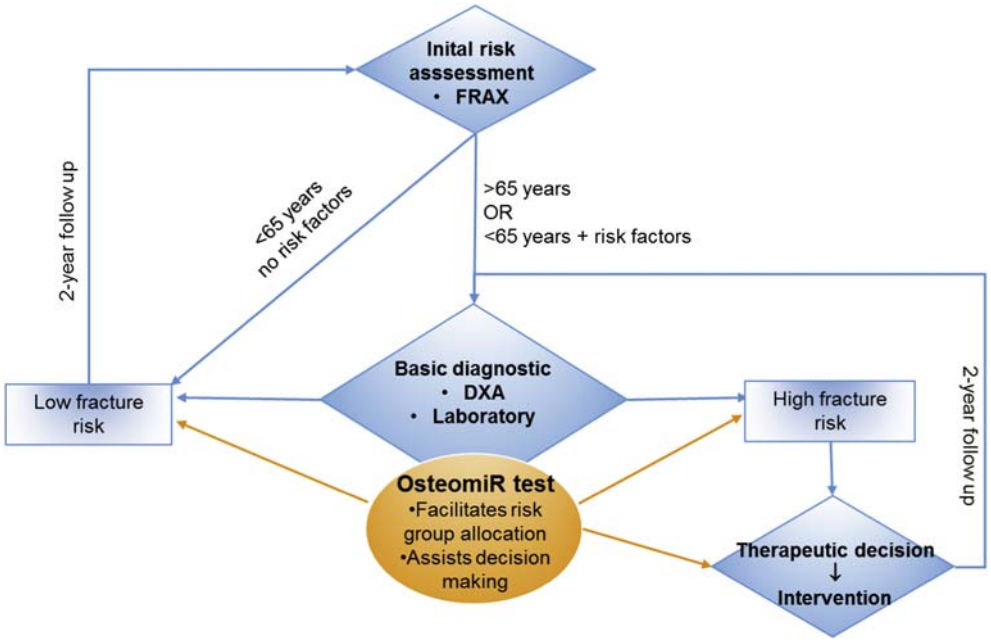

Fig. 4. Proposed positioning of the osteomiR™ test in the standard diagnostic procedure of osteoporosis.

sensitivity analysis, slight changes in the sensitivity of FRAX® have almost no effect on results. However, more data need to be collected in order to determine the AUC of osteomiR™ and compare risk assessment strategies in this age group.

Another possible limitation is that the model is based on simplifications as it cannot reproduce all aspects of osteoporotic fracture risk assessment/monitoring and treatment. For example, treatment complications, which have been observed to be a challenge in chronic diseases like osteoporosis, were only included in terms of resource use reported via the retrospective chart review. Complication-associated disunities were not considered in addition to the fracture utility decrements. The model uses sales data obtained from the healthcare information provider QuintilesIMS. That entails the assumption that all filled prescriptions were consumed and ensure an anti-fracture effect. Non-adherence in terms of patients using more or less than the prescribed treatment, using their medication at the wrong time or discontinuing treatment prematurely, is therefore not captured.

In addition, it should be noted that the model lacks the possibility to track multiple fractures in individual patients. The probability of sustaining multiple fractures is low, and the impact of having sustained multiple, different fractures on mortality and quality of life have been poorly investigated. Therefore, the conservative approach of only looking at the isolated effects of the most severe fracture type is used.

The estimated number of CRFs among age groups was calibrated so that total fractures corresponded to the total number of fractures observed. The used estimations were subject to the deterministic sensitivity analysis. Sensitivity analysis demonstrated that the distribution of the number of CRFs among females has only a marginal influence on the results. Changes from base case amount to 1000 €; results that are dominant in the base case analysis remain superior.

European fracture incidence rates in the EU27 in 2010 were used [1]. The set of data include age-specific hip, vertebral, forearm and other fragility fractures investigated in one population. In our attempt to validate the model, a comparison with specific Austrian epidemiological data indicates that hip and distal forearm fractures correspond to EU27 data [27,28]. For vertebral fractures, only European data were available. The model also includes "other fractures", which represent the majority of sustained fractures, in order to avoid underestimation.

We do not yet know if our findings would be transferable to other countries. For the estimation of costs and epidemiological data in the present study, mainly Austrian sources have been utilized, and hence, respective figures might be different for other countries. In the rare case where no Austrian-specific data were available, we relied on data published for other European countries, for example regarding mortality following hip fractures. Efficacy data of various anti-osteoporotic medications and utility data are transferable between countries.

This analysis has been carried out from the health care payer's perspective. If carried out from a societal perspective, results might vary as 78% of the Austrian women between 50 and 54, and 54% between 55 and 59 belong to the working population, and hence also the loss of productivity caused by the occurrence of osteoporotic fractures would need to be taken into account. However, prevalence of osteoporosis, defined as a T-score of −2.5 SD or less at the femoral neck, is below 10% in the age group between 50 and 59 years [1]. In the more highly affected female population above 60 years of age, only 16% of the women between 60 and 64 and only <4% of women aged 65 years and over belong to the working population [29].

5. Conclusions

This study presents the first comprehensive attempt to model the cost-effectiveness of two widely used strategies for bone fracture risk assessment and monitoring in a female post-menopausal population – the FRAX® tool and BMD measurement by DXA. In addition, this study provides evidence for cost-effectiveness of the osteomiR™ test, a novel molecular diagnostic method to assess fracture risk in postmenopausal women. Results of the cost-utility analysis have shown that comprehensive application of the osteomiR™ test for fracture risk monitoring in postmenopausal women in Austria will not generate any further cost in comparison with DXA, but would in fact lower health expenditures, as the ICER/QALY of osteomiR™ versus DXA has a negative value of −26,368.99 €. Therefore, the introduction of the osteomiR™ test is highly cost-effective and is therefore in the interest of the public health and a willingness of the health care payers to reimburse the cost for testing can be assumed.

As DXA is widely used and safely established in clinical practice, and as it provides the criterion required for osteoporosis diagnosis according to the WHO, the osteomiR™ test is not intended to replace DXA. Instead, since BMD is not a suitable method for identifying high-risk patients with sufficient accuracy, the osteomiR™ test is intended to complement

the standard of care and to provide doctors seeing osteoporosis patients with a solid basis for treatment decisions, as depicted in Fig. 4. For initial screenings, we envision that all patients above 65 years or carrying risk factors implicating intermediate or high risk according to FRAX should undergo thorough examination by DXA and osteomiR™, in order to achieve a reliable diagnosis and fracture risk assessment. For patients classified as "low risk" in the initial screening, we recommend osteomiR™ to be carried out within the scope of routine monitoring once their age exceeds 65 years or once additional risk factors come up. For patients classified as intermediate or high risk in the initial screening, we envisage osteomiR™ to be part of all routine monitoring examinations, in order to track alterations of fracture risk. As the monitoring costs make up only a small part of the total costs (289.36 € per woman for DXA and 333.55 € per woman for osteomiR™) considered for each monitoring strategy, even a combination of DXA and the osteomiR™ test would still be cost-effective and would lead to an immense gain of life quality at virtually identical costs.

What can be generally concluded from this study is that an increase in diagnostic performance of fracture-risk assessment tools will have a positive impact on both the state of health of postmenopausal women at risk of osteoporotic fractures, as well as on health care budgets.

Disclosures

MH and JG are co-founders and HD is employee of TAmiRNA GmbH, developer of the osteomiR™ test.

Contribution statement

E.W. has substantially contributed to the concept of the study, to the analysis and modelling and interpretation of the data, drafted the article, revised the article and finally approved the version to be published. M.H. designed the study, drafted the article, revised the article and finally approved the version to be published. H.D. drafted and revised the article and contributed to figures. J.G. and H.P.D. acquired the data, drafted the article and finally approved the version to be published.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2017.12.017.

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