

Cost utility analysis of monitoring osteoporosis fracture risk by a circulating microRNA based strategy compared to standard measure and no monitoring

Evelyn Walter^a, Johannes Grillari^b, Otto Kanzler^c, Matthias Hackl^c

^a IPF Institute for Pharmaeconomic Research, Vienna, Austria ^b Christian-Doppler Laboratory of Biotechnology of Skin Aging, Department of Biotechnology, University of Natural Resources and Life Sciences Vienna, Austria ^c TAmiRNA GmbH, Vienna, Austria

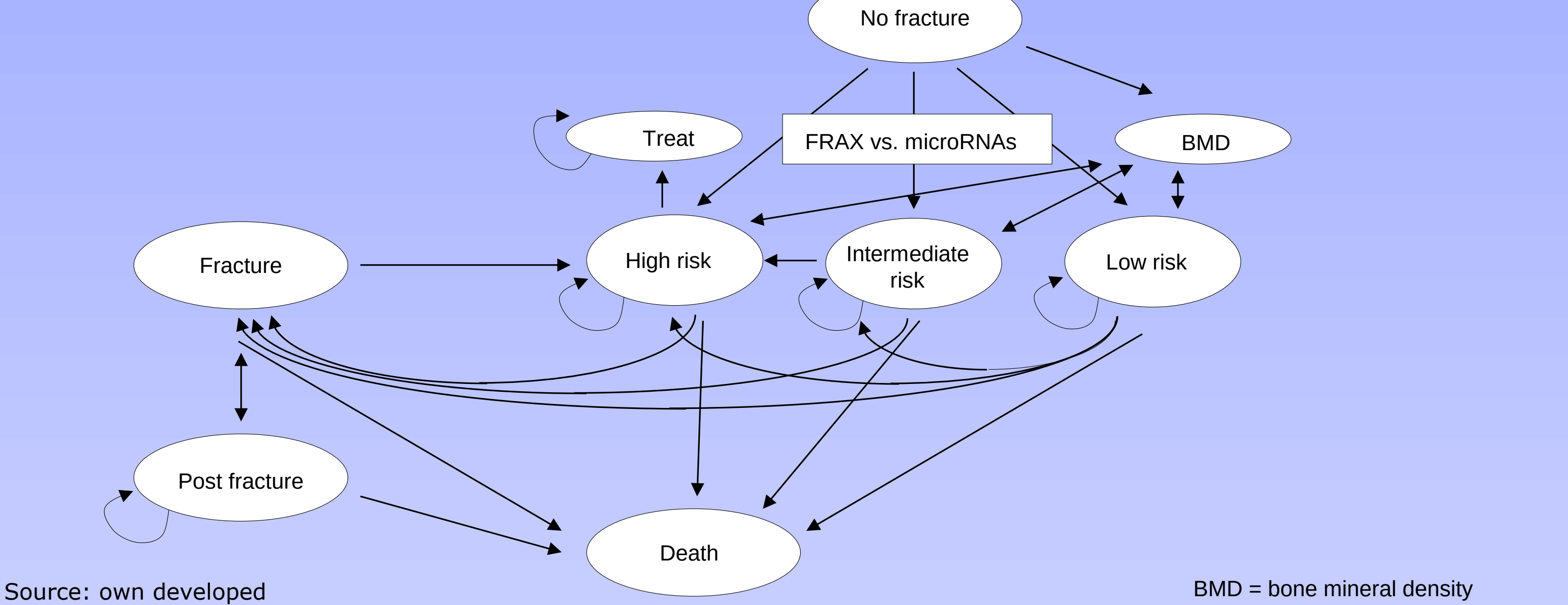
Objectives

Due to its prevalence worldwide, osteoporosis is considered a serious public health concern with over 200 million patients worldwide, not limited to, but most prevalent in postmenopausal women. In Austria 393,000 women are affected, 89.200 with a prior fracture. Bone-mineral-density (DXA) and the Fracture-Risk-Assessment-Tool (FRAX) are considered to be the standard measure for fracture risk assessment. MicroRNAs have recently emerged as important factors in bone physiology and specific blood-circulating microRNAs have been suggested as biomarkers for osteoporosis. The osteomiR™ test is a novel diagnostic device for prognosis of fracture-risk. The purpose of this analysis was to estimate the cost-effectiveness of osteoporosis fracture-risk monitoring for treatment decisions using either microRNAs, DXA, FRAX or no-monitoring in women without prior fracture.

Methods

A Cost-Utility-Model was developed to simulate long-term consequences of osteoporosis in females from age 50 over lifetime. Markov-modeling techniques were used to estimate fracture-incidence according to risk-groups. If women were monitored they follow the case finding strategy from the National Osteoporosis Guideline Group 2008 and were split in 3 risk-categories (high, intermediate, low). High-risk patients receive medical treatment, with the consequence of risk reduction. Each year a patient has a 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 on fracture type: hip, vertebral, wrist/forearm or other osteoporotic fractures. In the next Markov cycle the patient may experience a recurrent fracture or move to the “post fracture” state or die. The cycle length is 1 year (cycle correction was implemented) and all patients are followed through the model from age 50 over lifetime. QALYs (utilities from the literature), life-years (LYs) and costs were discounted (3% p.a)

Fig. 1: Model Design



Clinical Data

Distribution of the number of clinical risk factors (CRF) among age groups were estimated based on Austrian BMI data. The fracture risk according age and number of CRF is documented by Compston et al. (2009). Based on the number of total fractures the distribution of the number of CRFs were calculated. The sensitivity of the different monitoring strategies were derived from literature. Risk Reduction due to osteoporosis drug treatment was obtained from a NICE publication, which includes sixteen reviews of individual pharmacological interventions.

Resource Use (RU) and Costs

Monitoring is considered as described:

- no 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 fractures were monitored from age 65, every 2 years. Women with a fracture were also monitored with DXA before age 65.
- FRAX:** In the FRAX arm women were monitored with FRAX yearly from age 50 according the case finding strategy from the National Osteoporosis Guideline Group 2008. Women in the high risk group were treated.
- microRNAs:** Women were monitored yearly from age 50. Women with high risk were treated. After a fracture women were monitored with DXA.

RU due to fractures were derived from a retrospective chart review which IPF has conducted in the year 2010. A sample (n=166) of female osteoporosis patients with a low energy fracture (mean age 76 years) was assessed by random sampling (according to defined in- and exclusion criteria) in seven Austrian centers. Direct medical costs comprise all treatment costs due to osteoporosis after fracture (**table 1**). The RU based on medical records were collected for a follow up of 1 year..

The percentage of pharmacologically treated patients were estimated based on an Austrian publication (Dimai et al. 2012) and the market share of medication was derived from IMS data.

Outpatient costs were derived from the tariff catalogues from all 9 regional health insurance companies. Inpatient costs were calculated based on the Austrian diagnosis related groups (DRGs) refunding (=LKF System) and medication costs were excreted from the Austrian official price list. All costs represent data from 2015 and were dis-counted with 3%.

Tab. 1: Fracture costs 2015 € (without osteoporosis medication) 1 year follow-up				
Cost components	Hip fracture	Vertebral fracture	Wrist fracture	Other fracture
Inpatient	16.146,65	4.225,69	3.776,46	8.049,60
Co-Medication	559,68	430,68	553,19	514,52
General Practitioner (consultations, treatment)	63,94	80,74	74,18	72,95
Medical Specialist (radiological examinations; consultations Gynaecologist, Internist, orthopaedist, ambulatory)	19,29	29,84	32,80	27,31
Hospital outpatient department consultations	8,72	4,70	10,32	7,91
Hospital outpatient department examinations	18,47	10,56	25,85	18,29
Hospital outpatient department lab tests	86,31	41,94	18,09	48,78
Corsage	0,00	50,09	0,00	
TOTAL	16.903,07	4.874,24	4.490,89	8.739,37

Source: own calculations

CONTACT:
Dr. Evelyn Walter
IPF Institute for Pharmaeconomic Research
Wolfengasse 4/7
1010 Vienna, Austria
Tel +43-1-5132007-13
Fax +43-1-5132007-15
Email: e.walter@ipf-ac.at
Web: www.ipf-ac.at



Results

Life-time costs in the microRNA biomarker-arm amount to 9,409€ and 19.389 QALYs (35.252 LYs). Costs associated with the DXA-strategy are 9,353 € and 19.384 QALYs (35.245 LYs). The incremental-cost per QALY gained (ICER) vs. DXA was 10,404 €. Costs associated with the FRAX-strategy are 9,501 € and 19.385 QALYs (35.25 LYs). MicroRNAs dominate FRAX. Life-time cost without monitoring amount to 9,189 € and 19,376 QALYs (35,235 LYs). The ICER vs. no-monitoring was 17,038 €.

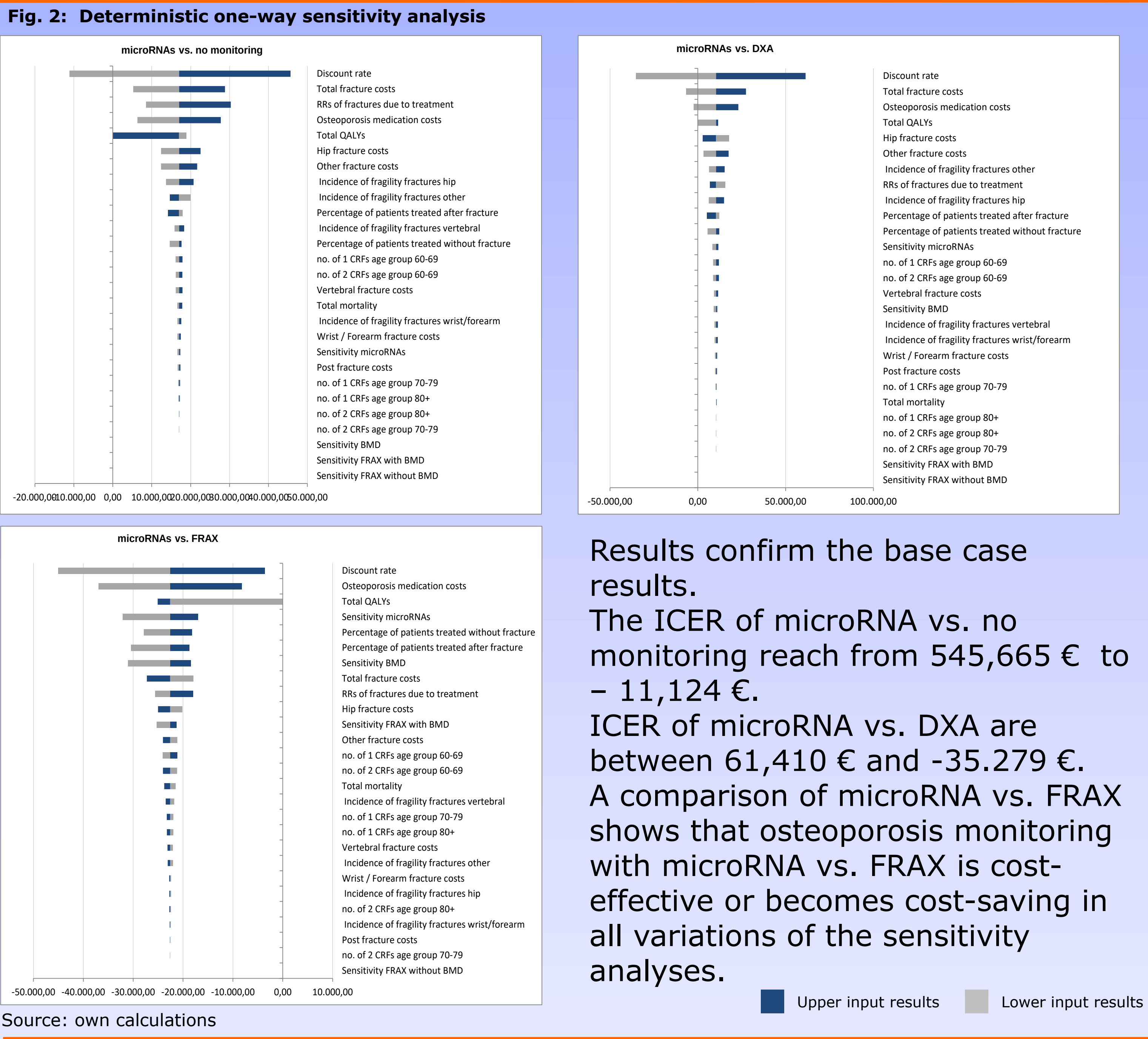
Tab. 1: Results, 2015				
Calculation components	No monitoring	DXA	FRAX	microRNAs
COSTS				
Monitoring costs	169,04	289,36	748,91	460,28
Osteoporosis medication costs	605,59	958,32	1.005,18	1.296,77
~ Hip fracture costs	3.266,03	3.109,95	2.959,75	2.910,11
~ Vertebral fracture costs	489,02	464,74	444,52	433,48
~ Wrist / Forearm fracture costs	571,36	559,96	547,12	543,33
~ Other fracture costs	3.771,90	3.663,18	3.501,57	3.472,23
~ Post fracture costs	315,60	307,73	293,48	292,57
Total fracture costs	8.413,91	8.105,57	7.746,45	7.651,72
TOTAL costs	9.188,54	9.353,25	9.500,53	9.408,77
Cost difference	220,23	55,52	-91,76	
QALYs				
QALYs	19,376	19,384	19,385	19,389
QALY difference	0,013	0,005	0,004	
ICUR /QALY	17.037,87	10.403,82	-22.581,75	
LYs				
LYs	35,234	35,245	35,246	35,252
LY difference	0,017	0,007	0,005	
ICER /LY	12.692,19	8.082,01	-16.845,50	

Source: own calculations

ICER = incremental cost effectiveness ratio
ICUR = incremental cost utility ratio

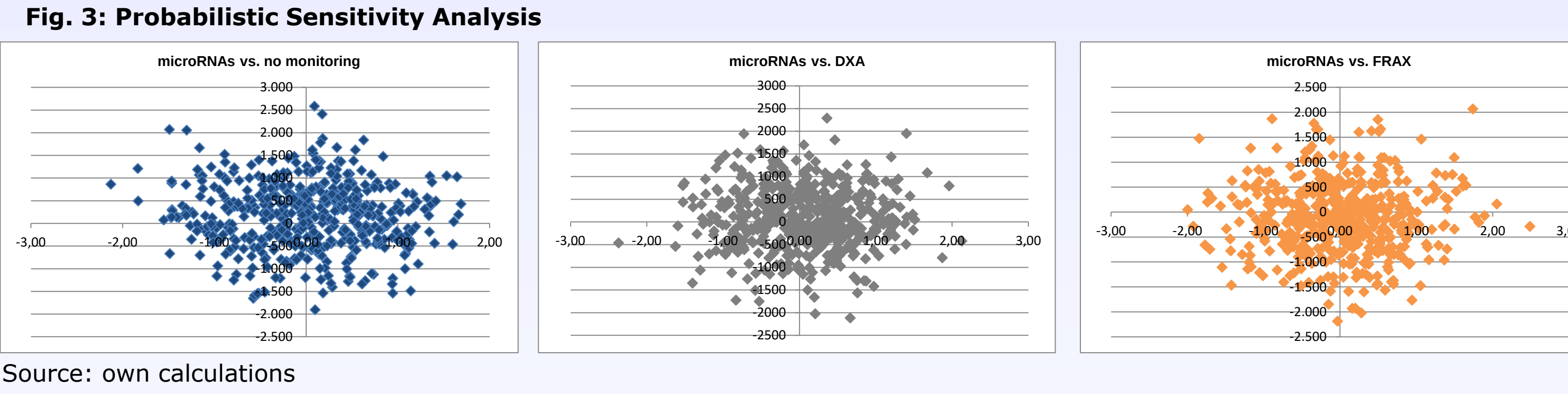
Sensitivity Analysis

Deterministic and probabilistic sensitivity analysis was carried out. **Fig. 2** displays the deterministic sensitivity analysis.



Results confirm the base case results. The ICER of microRNA vs. no monitoring reach from 545,665 € to – 11,124 €. ICER of microRNA vs. DXA are between 61,410 € and -35.279 €. A comparison of microRNA vs. FRAX shows that osteoporosis monitoring with microRNA vs. FRAX is cost-effective or becomes cost-saving in all variations of the sensitivity analyses.

Monte Carlo probabilistic sensitivity analysis, results of 500 trials plotting incremental cost versus incremental effects, demonstrated that osteoporosis monitoring with microRNAs was cost effective compared to comparator strategies.



MicroRNAs is cost-effective against no monitoring in more than 95% of simulations with a willingness-to-pay-value up to 10,000 €; in 97% compared to DXA and more than 98% compared to FRAX (**Fig. 3**).

Conclusion

Fracture-risk assessment using microRNAs dominates FRAX-strategy and is a cost-effective alternative vs. DXA and no-monitoring.

References

Borgström F, Zethraeus N, Johnell O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int*. 2006; 17(5): p. 637-50.
Burström M, Johannesson K, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. *Qual Life Res*. 2001; 10(7): p. 621-35.
Compston J, Cooper A, Cooper C, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* 62 (2009), 105-108
Dimai HP, Redlich K, Peretz M, et al. Economic burden of osteoporotic fractures in Austria. *Health Economics Review* 2012, 2:12
Johnell O, Kanis JA, Odén A, et al. Mortality after osteoporotic fractures. *Osteoporos Int*. 2004, 15(1): p. 38-42.
Hackl M., Heilmeier, U., Wellner, S., & Grillari, J. (2016). Circulating microRNAs as novel biomarkers for bone diseases – Complex signatures for multifactorial diseases? *Molecular and Cellular Endocrinology*, 432, 83–95.
Kanis JA, Johnell O, De Laet C et al., A meta-analysis of previous fracture and subsequent fracture risk. *Bone*. 2004, 35(2): p. 375-82.
Kocjan, R., Muschitz, C., Geiger, E., Skalkicky, S., Baierl, A., Dormann, R., ... Hackl, M. (2016). Circulating microRNA signatures in patients with idiopathic and postmenopausal osteoporosis and fragility fractures. *The Journal of Clinical Endocrinology & Metabolism*, (September), jc.2016-2365
National Clinical Guideline Centre at The Royal College of Physicians. Osteoporosis: fragility fracture Risk Osteoporosis: assessing the risk of fragility fracture, 2012
NICE National Institute for Health and Clinical Excellence: Systematic reviews of clinical effectiveness prepared for the guideline Osteoporosis: "Assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk", 2008
Peasgood T, Herrmann K, Kanis JA, et al. An updated systematic review of Health State Utility Values for osteoporosis related conditions. *steoporos Int*. 2009 Jun;20(6):853-68
Trémolieres FA, Poullès JM, Drewniak N, et al. Fracture Risk Prediction Using BMD and Clinical Risk Factors in Early Postmenopausal Women: Sensitivity of the WHO FRAX Tool. *J Bone Miner Res*. 2010 May;25(5):1002-9.
Additional Literature with the author