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Multiscale VPH models: better predictive accuracy or increased explanatory power? Reflection on the hip fractures problem

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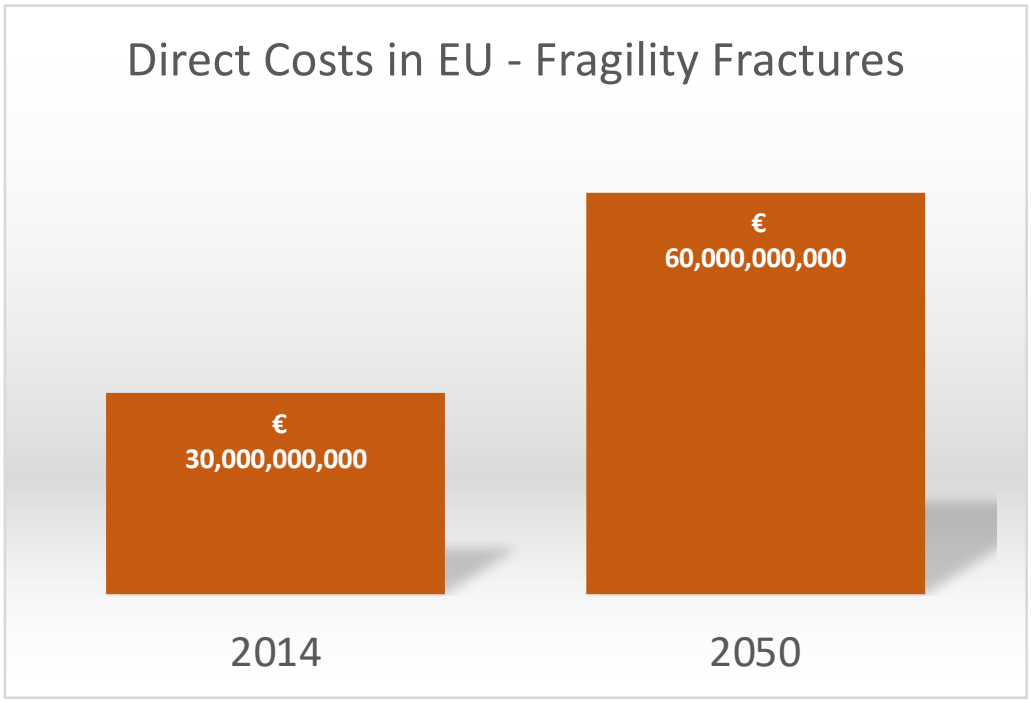
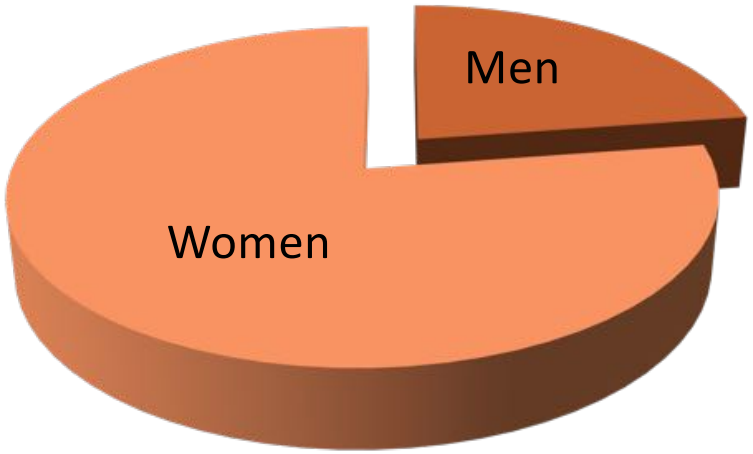
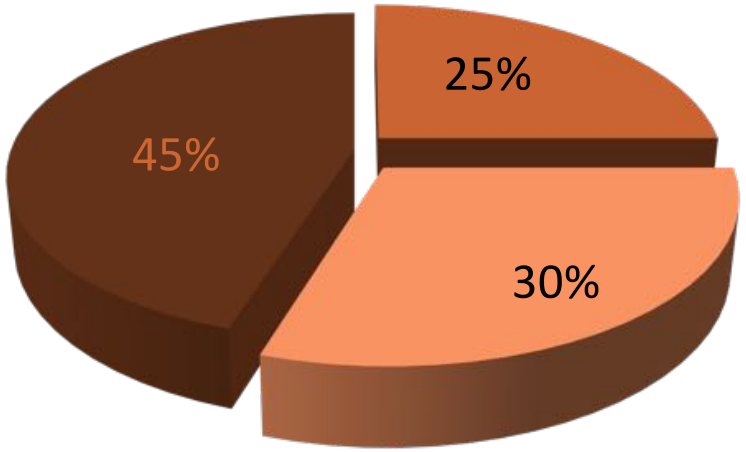


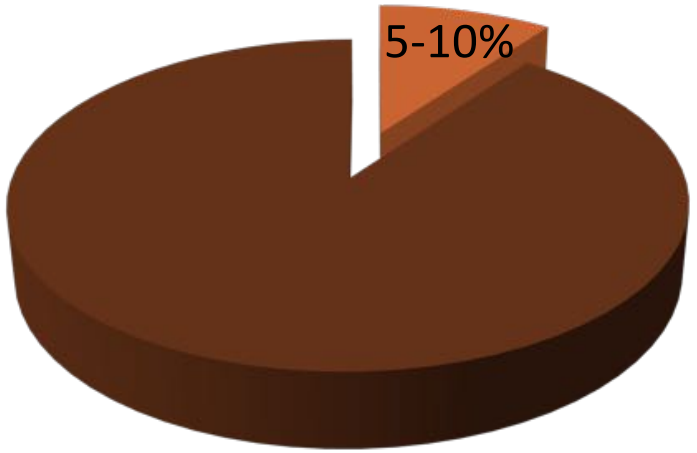
Fragility fractures by gender



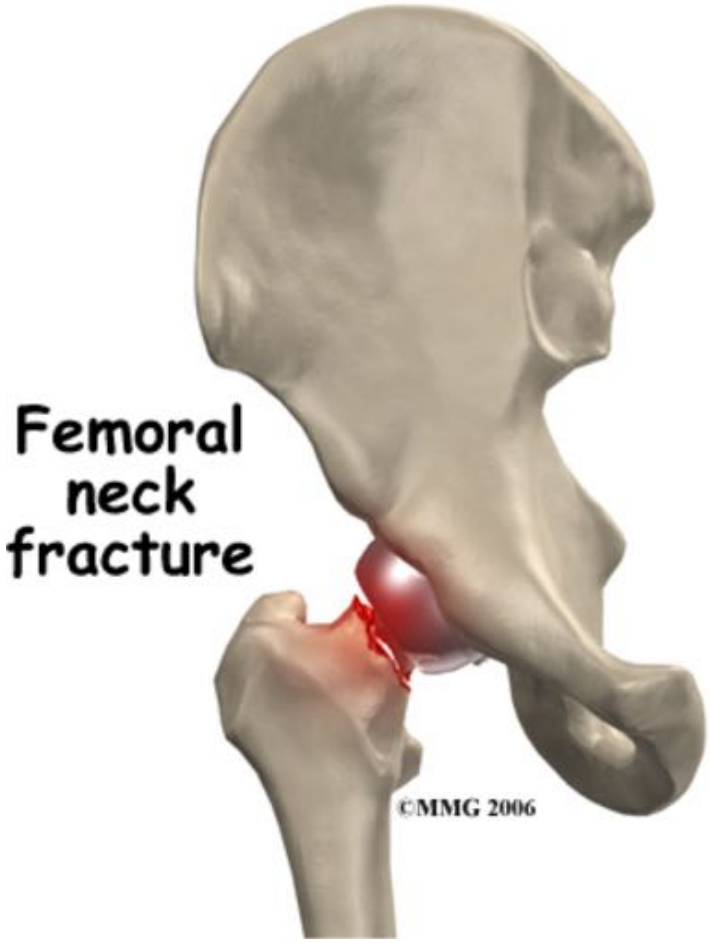
Effect of hip fractures



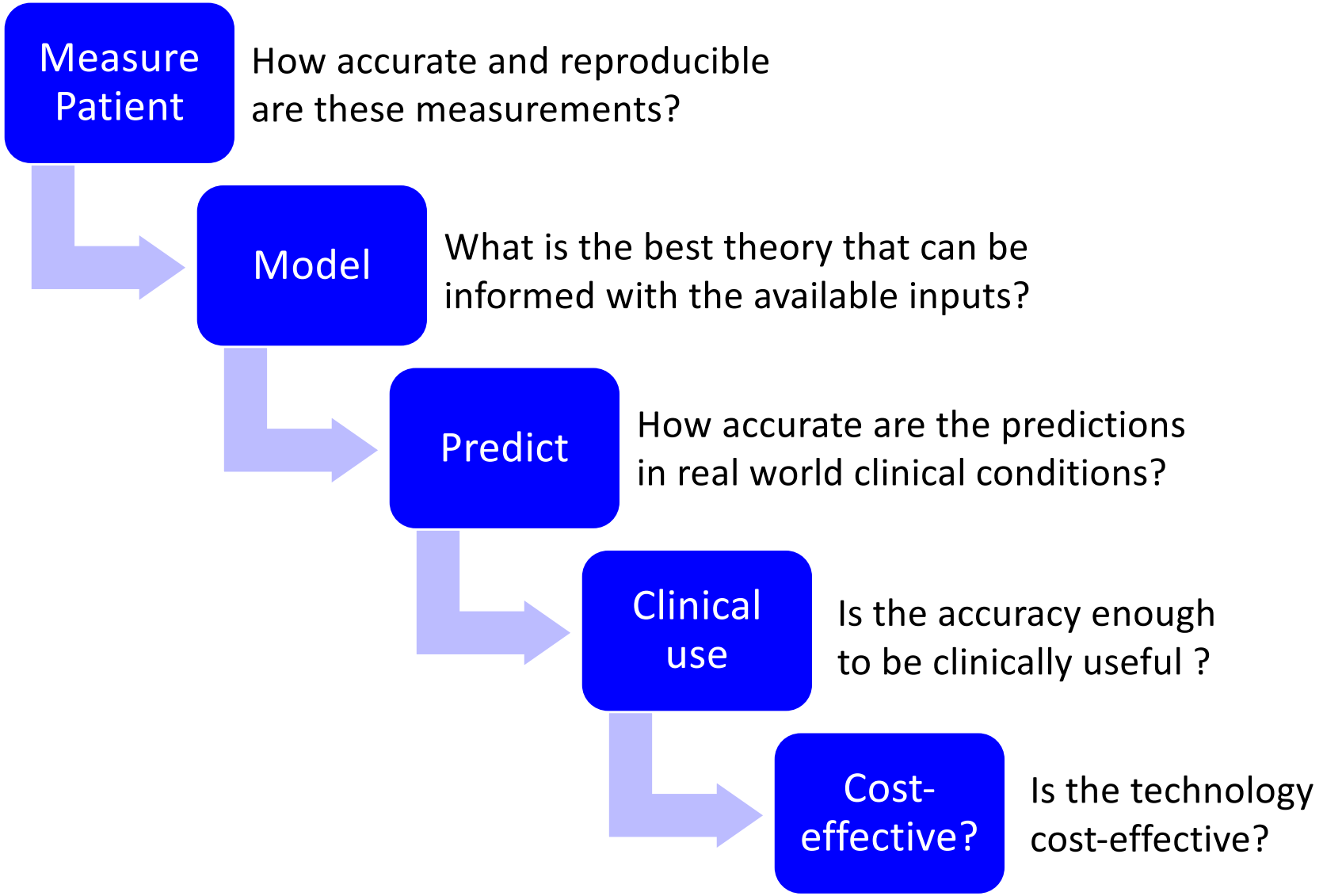
Hip fractures due to falls



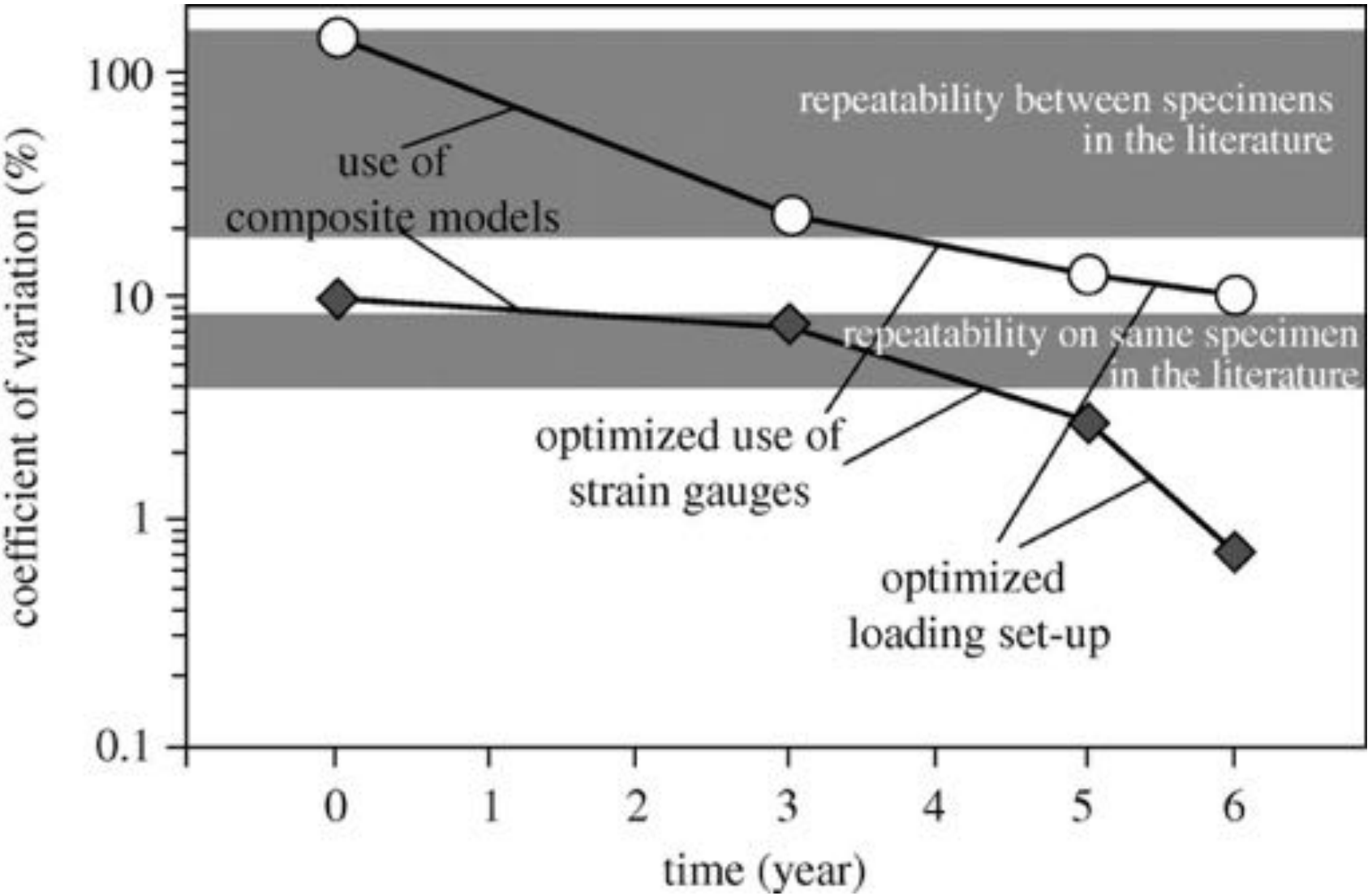
Hip fracture is a mechanic event



ISM: long journey to clinical use

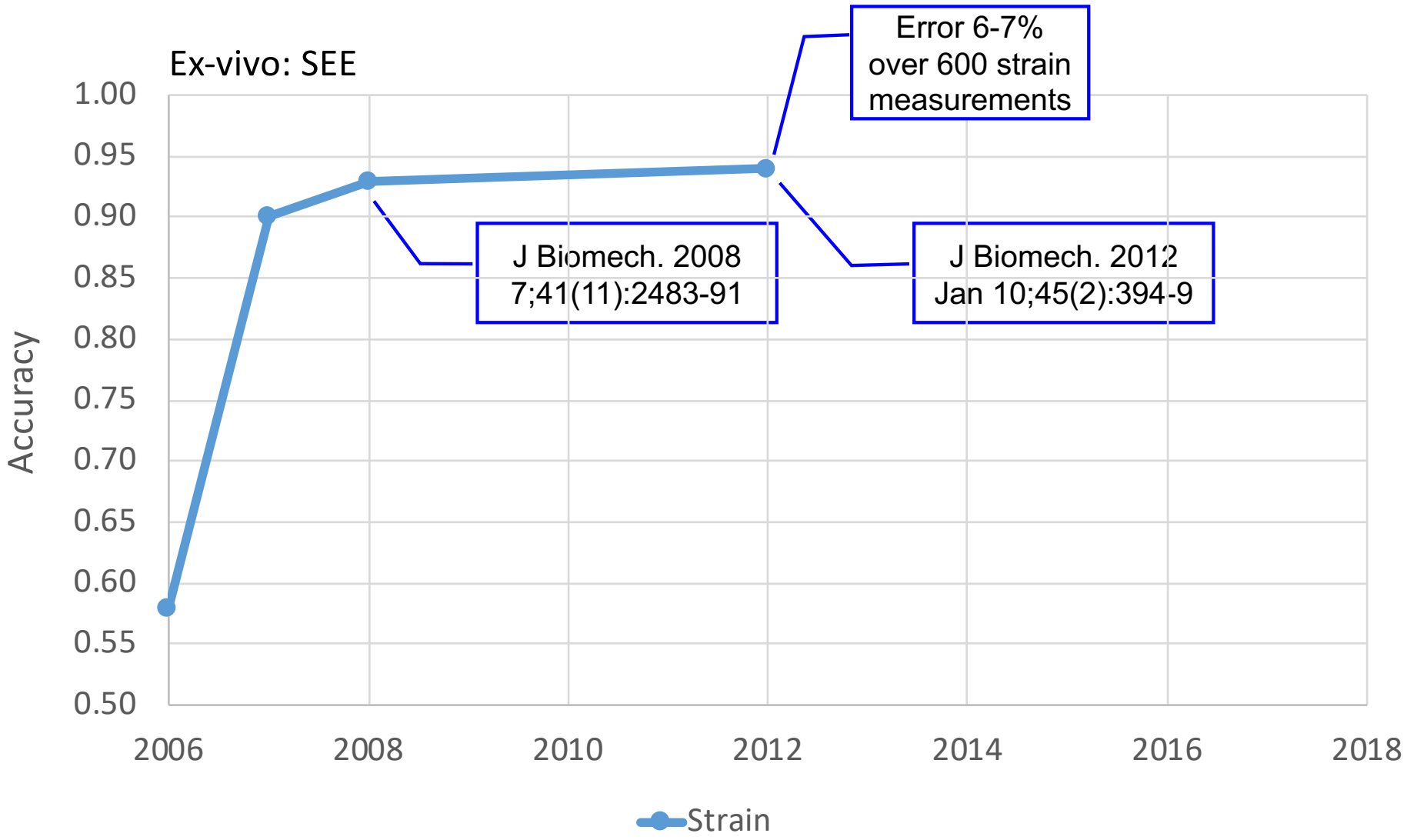


Control the experiment

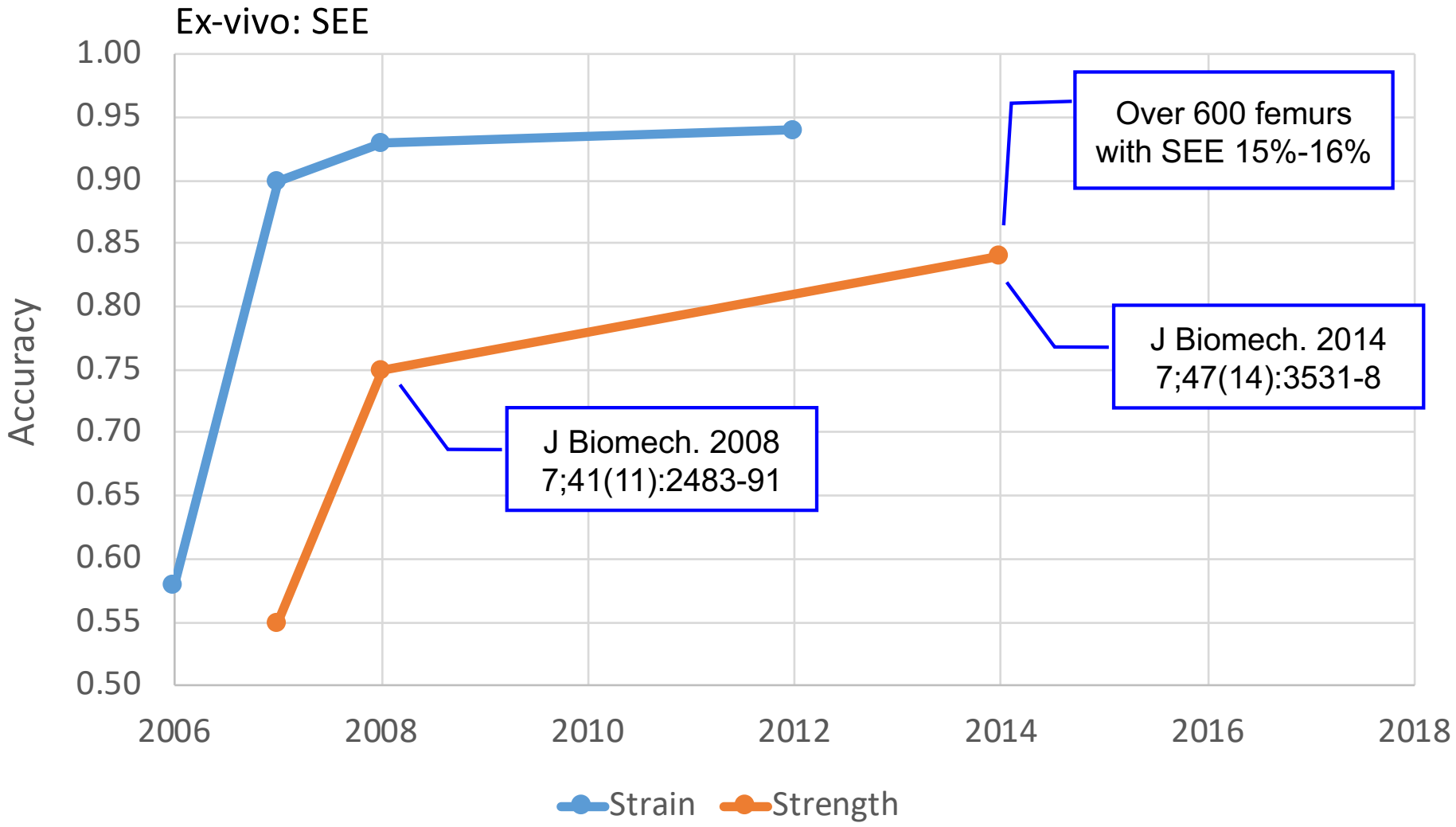


Cristofolini L. et al. Phil. Trans. R. Soc. A 2010;368:2725-2763

Predicting strain



Predicting Strength

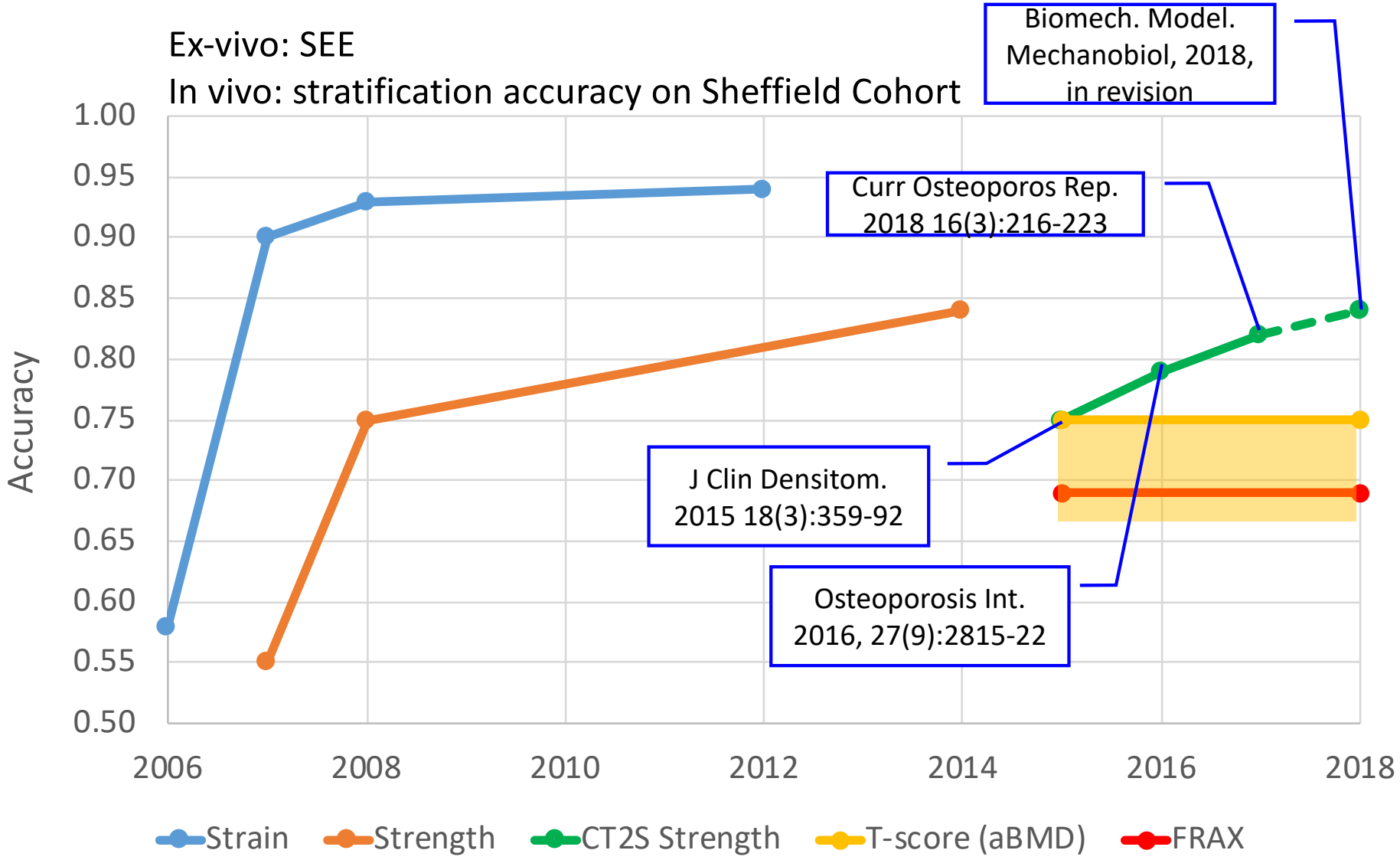


Sheffield cohort

- 50 English women aged over 50 with acute hip fracture
- 50 women pair matched for height, weight, and age
- DXA, CT scan, FRAX risk, etc.

Yang L, Udall WJ, McCloskey EV, Eastell R.
Osteoporos Int. 2014; 25:251-263

Predicting risk of fracture



Dual X-ray Absorptiometry (DXA)

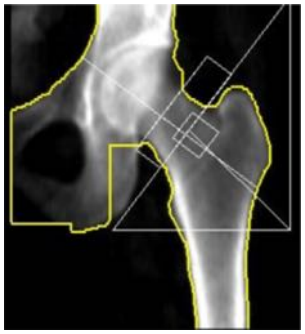
- aBMD: average Areal Bone Mineral Density over selected regions of interest (i.e. femoral neck)
- T-score for standardised ROIs
- Z-score for standardised ROIs

radiation dose

- DXA ➔ 0.001 mSv, Pelvic CT ➔ 6 mSv
- CT2S protocol ➔ < 4.8 mSv (male), < 3.2 mSv (female); greater reductions possible
- Female > 50: death risk for hip fracture 2.8%
- Risk reduction with QCT-SSFE 0.0784%
- Risk increase due to radiation 0.0080%
- Risk-benefit ratio is positive

Viceconti M, *et al.* Are CT-based finite element model predictions of femoral bone strength clinically useful? *Curr Osteoporos Rep*. 2018, 16(3):216-223

Clinical studies: Strength end point



DXA-BMD

Accuracy = 75%

Alpha 0.05; power 80%
Group difference = 20%
Cohort size = 246

CT2S

Accuracy = 82%

Alpha 0.05; power 80%
Group difference = 20%
Cohort size = 128

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SSFE cost-effective for clinical trials

	aBMD	QCT-SSFE
%SEE	75%	82%
Average femoral strength (N)	3265	3265
Standard deviation of predictor (N)	3054	2199
% strength diff. to be detected	20%	20%
α-error	0.05	0.05
b-power	80%	80%
Number of patients per group	123	64
Number of patients in the study	246	128
Fixed costs for trial (£5,000 patient)	£1,230,000.00	£640,000.00
Cost of imaging (£62 DXA; £78 CT)	£15,252.00	£9,984.00
Cost of simulation (£250)	£-	£32,000.00
Total cost	£1,245,252.00	£681,984.00

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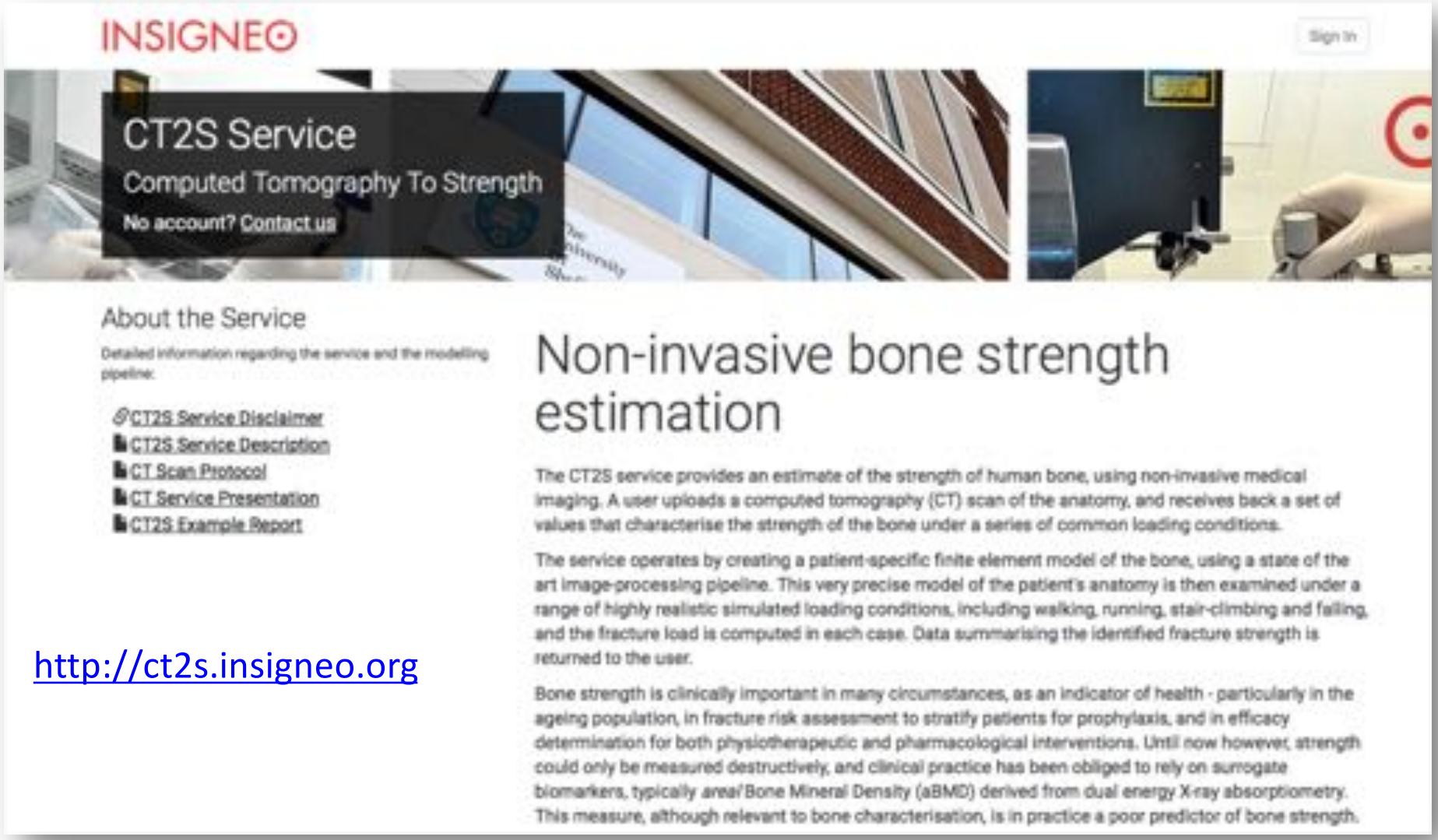
CT2S service



http://ct2s.insigneo.org

Clinical use: cost-effectiveness

	DXA-T-score	QCT-SSFE	Dual pathway
N. of patients referred to secondary care	1,000	1,000	1,000
Patients considered at risk and treated	367	602	633
Patients not treated	633	398	286
Patients who fracture under treatment	147	241	253
Patients who fracture without treatment	316	199	143
Total patients who fracture	463	440	396
Risk assessment costs	£1,255,000	£2,610,000	£1,899,184
Preventive pharma treatment cost	£2,644,898	£4,334,694	£4,555,102
Costs of hip fracture treatment (direct)	£7,552,151	£7,169,553	£6,454,261
Total cost hip fractures (direct costs)	£11,452,049	£14,114,247	£12,908,547
Costs of hip fracture treatment (indirect)	£4,801,282	£4,558,045	£4,103,298
Total cost hip fractures (total cost of care)	£16,253,331	£18,672,292	£17,011,845
Direct costs saved x 1000 patients	£-	**-£2,662,197.96**	**-£1,456,497.96**
Full costs saved x 1000 patients	£-	**-£2,418,961.22**	**-£758,514.29**
Fractures avoided by new pathway	-	**23**	**67**

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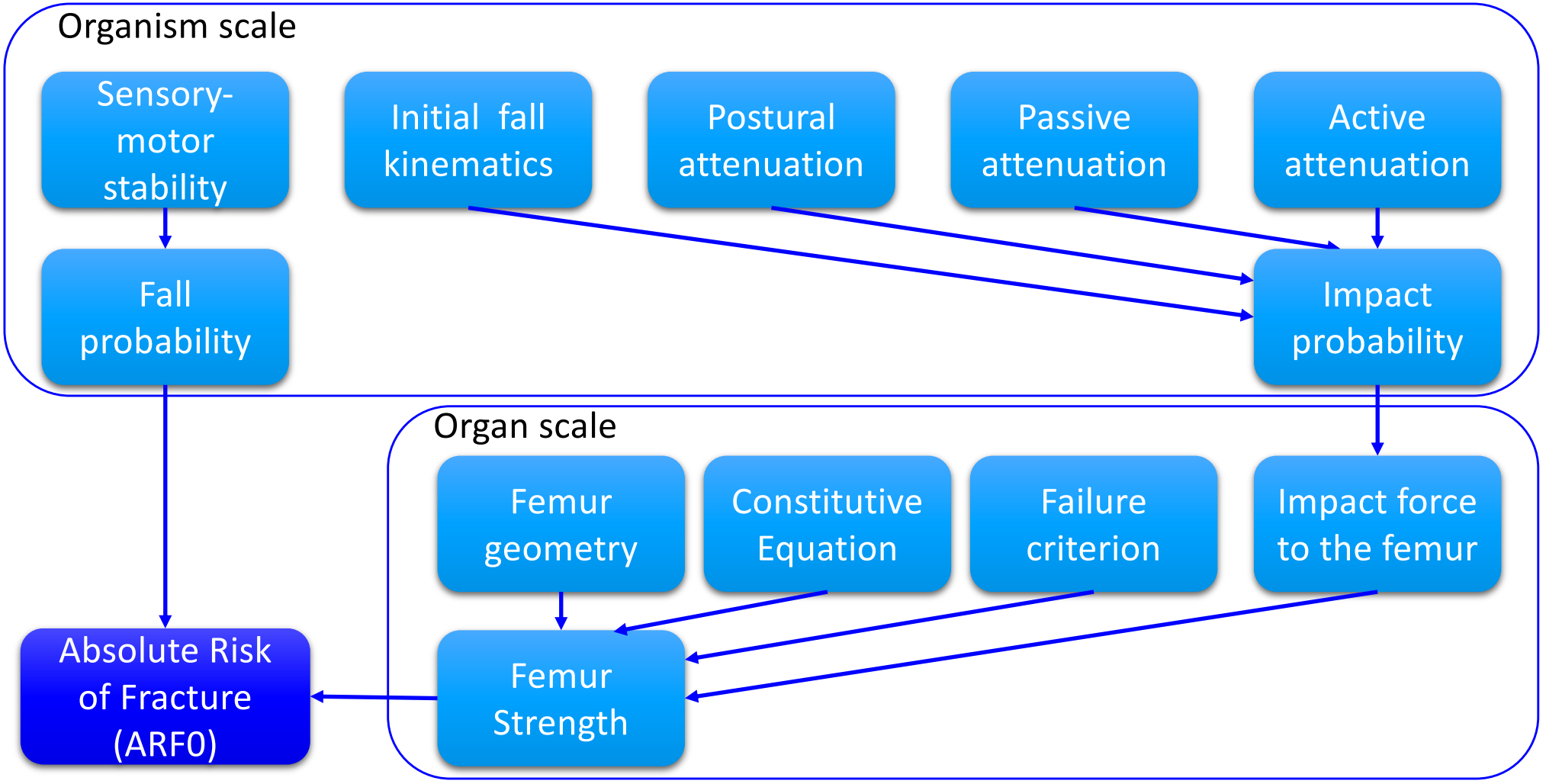
QCT-SSFE: price point?

- Current cost US$ 372
  - Price: CT2S service, not for clinical use; VirtuOs $86 (subsidised)
- Cost-effective ICER < £20,000
  - Criterion NICE – UK NHS; may vary in other countries
- SSFE target US$ 100
  - Increment of cost per Quality-Adjusted Life Year (QALY) achieved £14,656

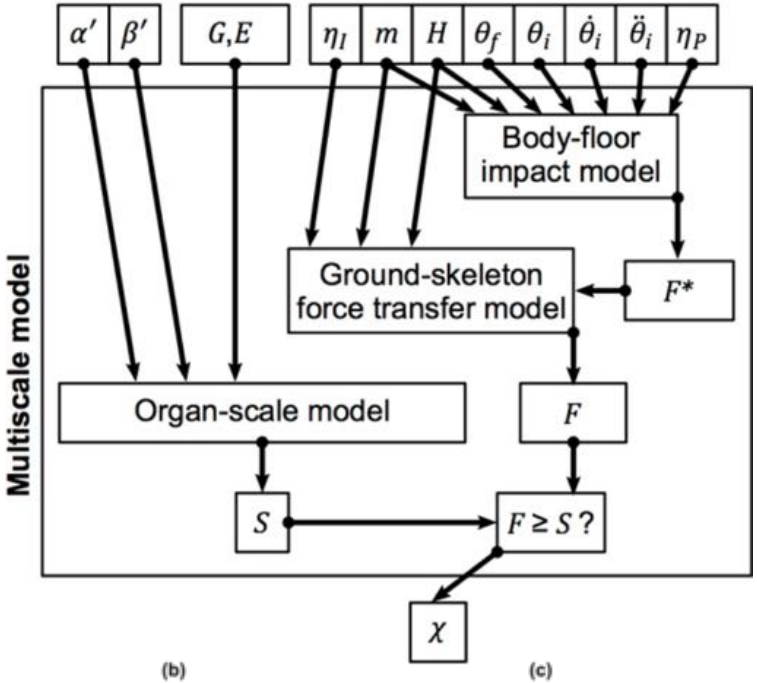
Business might not be viable

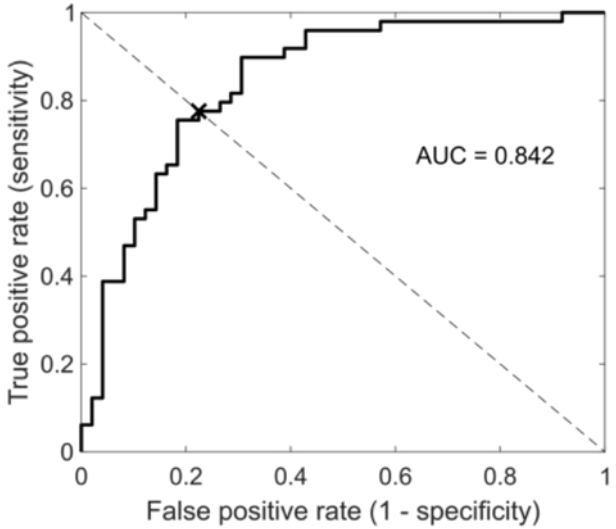
Predicting the risk of hip fracture

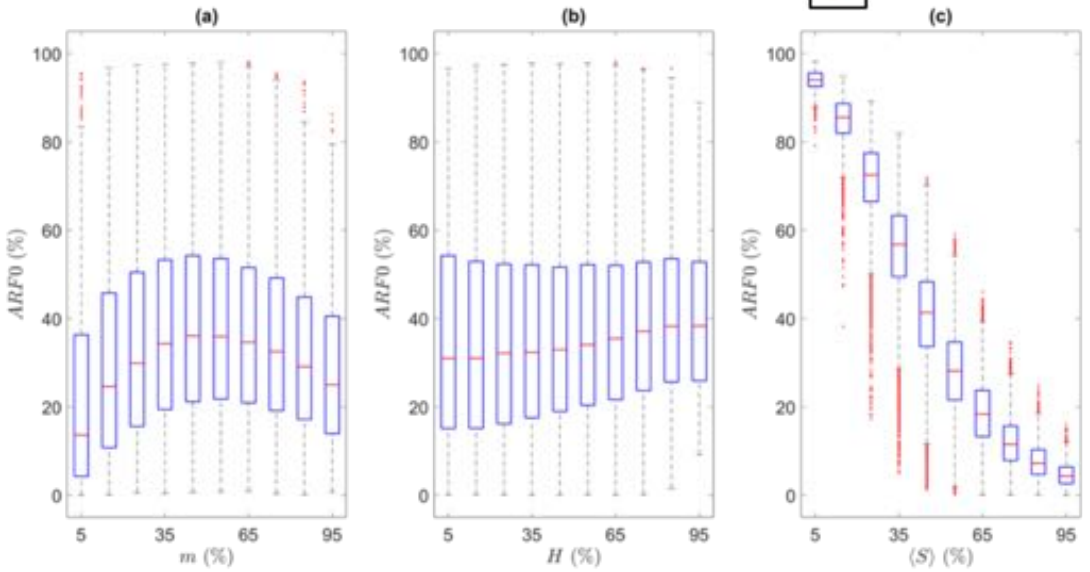


ARF0 fall simulator

- Multiscale model of fall, body-floor dumping, femur deformation
- Full stochastic modelling of fall
- Stochastic modelling of uncertain variables (i.e. soft tissue dumping)
- Accuracy – 0.82 ➔ 0.84







Conclusions

- QCT-SSFE models are now close to 10% more accurate than DXA-aBMD in separating fractured and non fractured patients; further improvement seems difficult
- When used in interventional clinical trials QCT-SSFE is cost-effective
- When used to stratify patients by intervention, cost-effectiveness analyses suggest price-point around $100 per patient; business might not be viable
- Multiscale stochastic models of bone fracture including disease progression can be used for *in silico* clinical trials, but also to provide a differential prognosis for individual patients, which might inform more personalised treatments

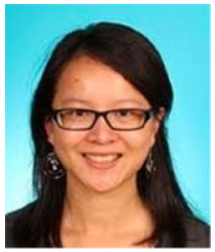
Acknowledgements

Laboratorio di Tecnologia Medica

VPHOP Osteoporotic Virtual Physiological Human

SEVENTH FRAMEWORK PROGRAMME

The University Of Sheffield.



MultiSim EPSRC

CompBioMed

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