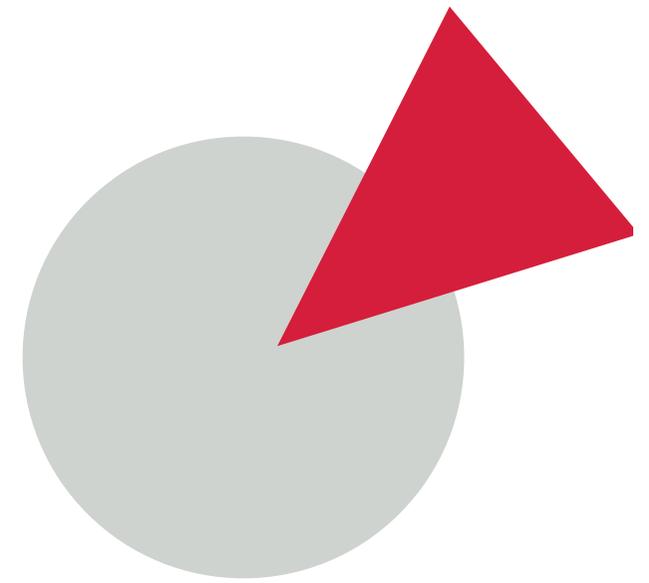


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Institute for *in silico* Medicine



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

Marco Viceconti, Pinaki
Bhattacharya and Xinshan Li

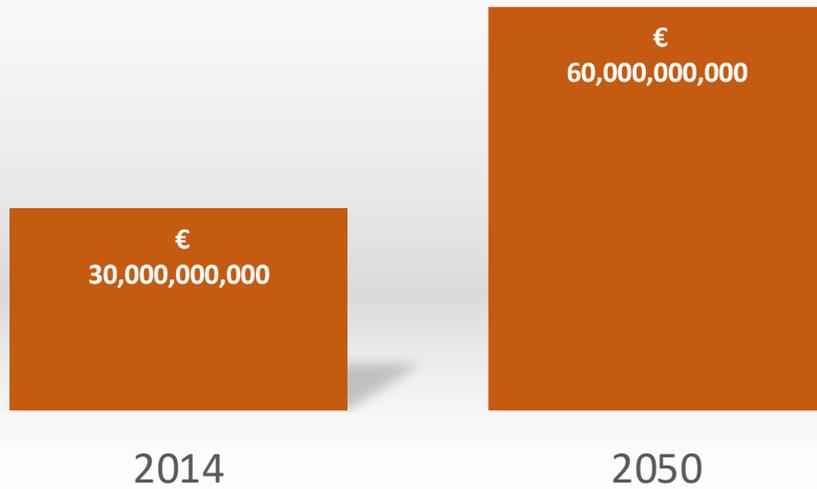


The
University
Of
Sheffield.

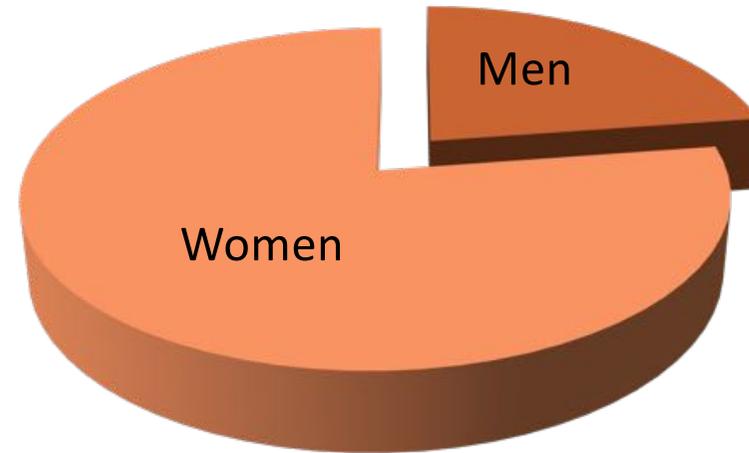
Sheffield Teaching Hospitals
NHS Foundation Trust



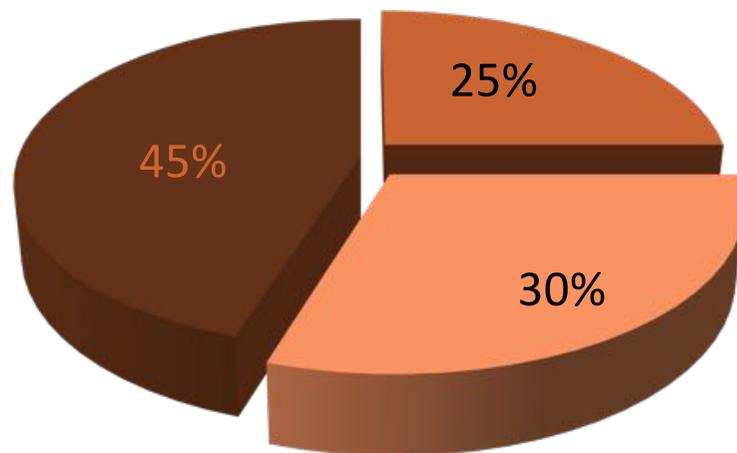
Direct Costs in EU - Fragility Fractures



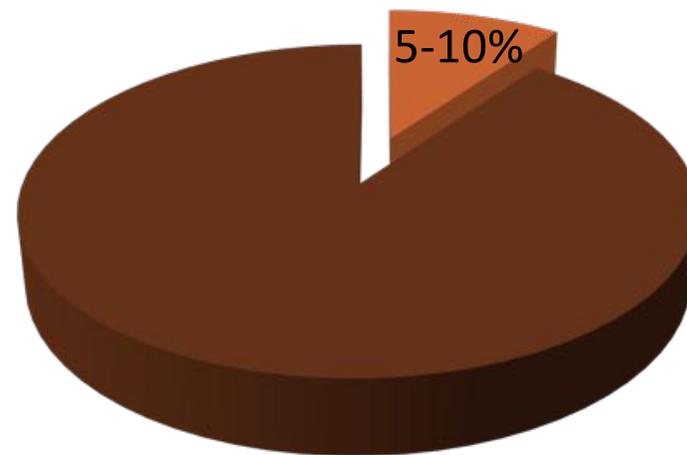
Fragility fractures by gender



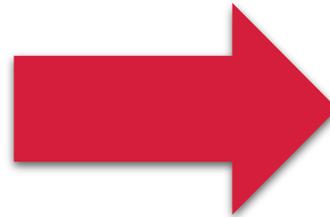
Effect of hip fractures



Hip fractures due to falls



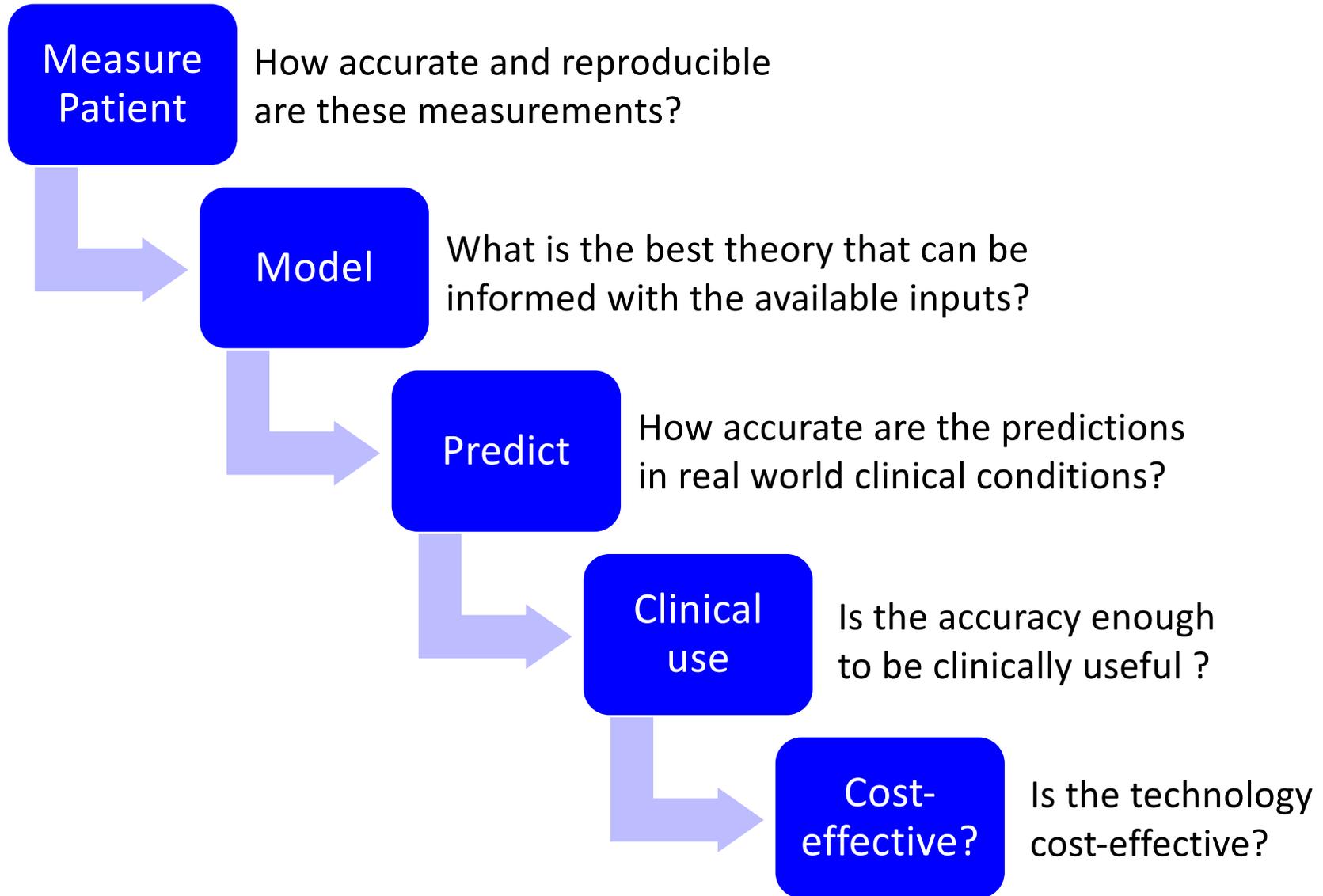
Hip fracture is a mechanic event



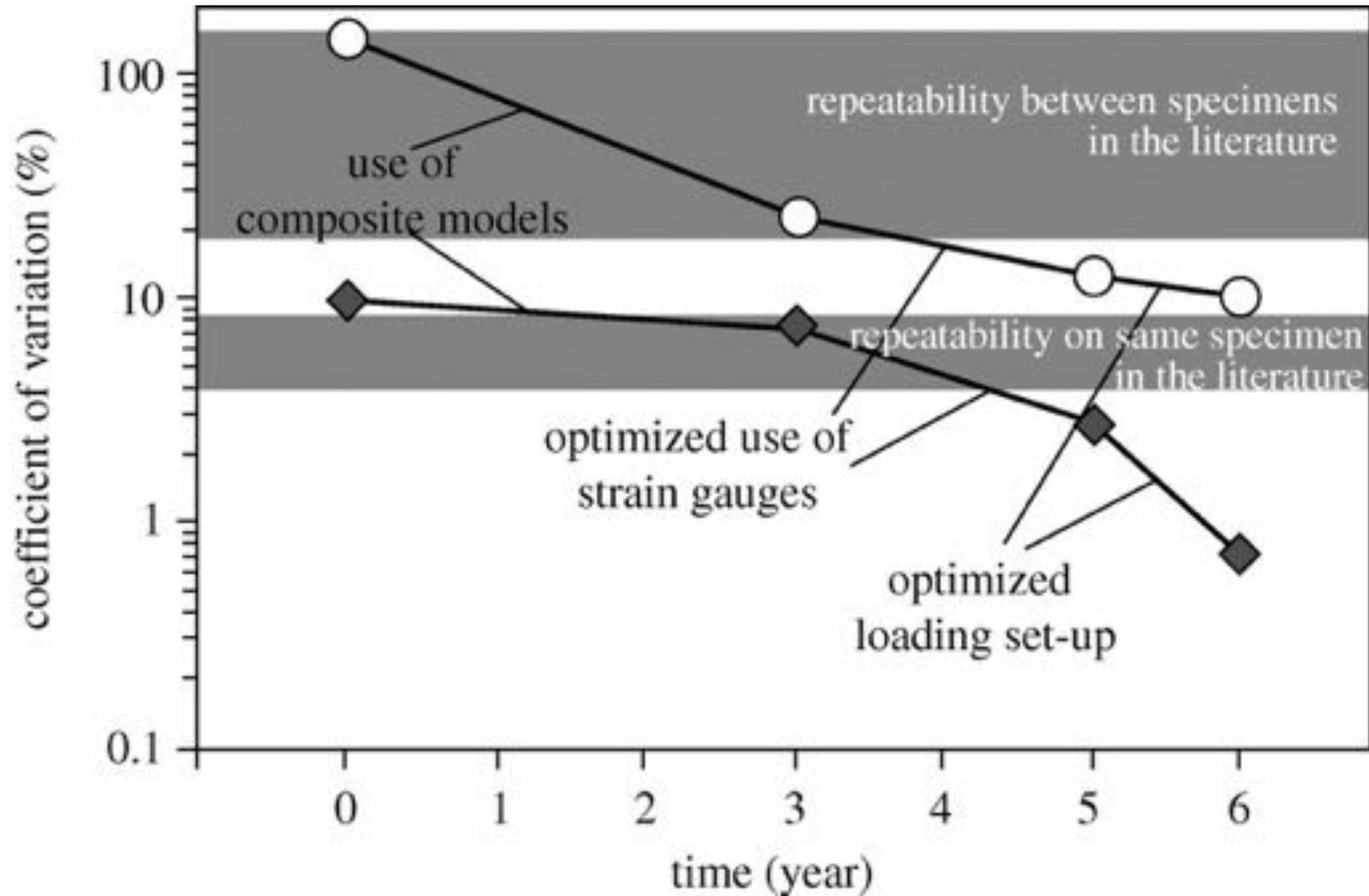
Femoral neck fracture



ISM: long journey to clinical use

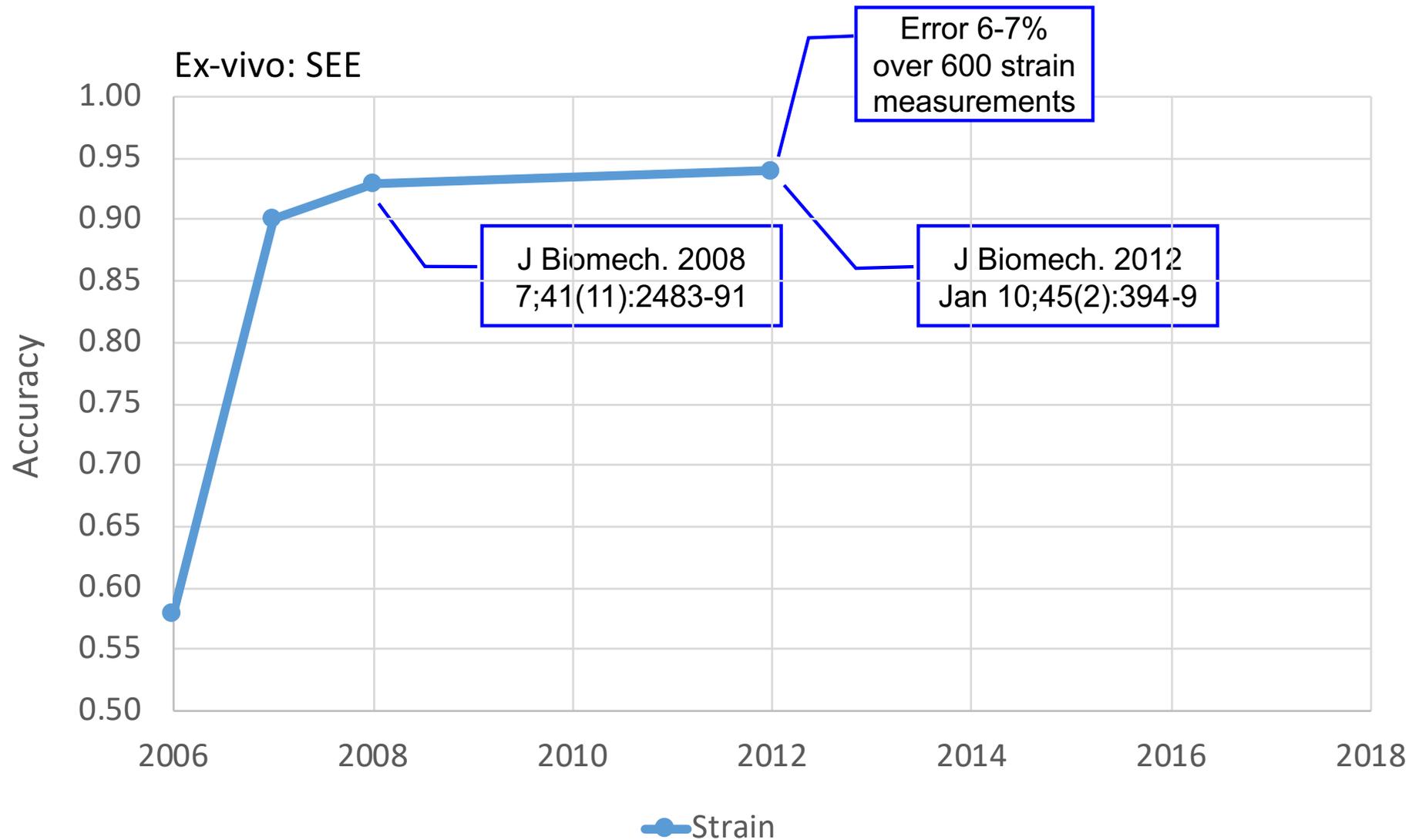


Control the experiment

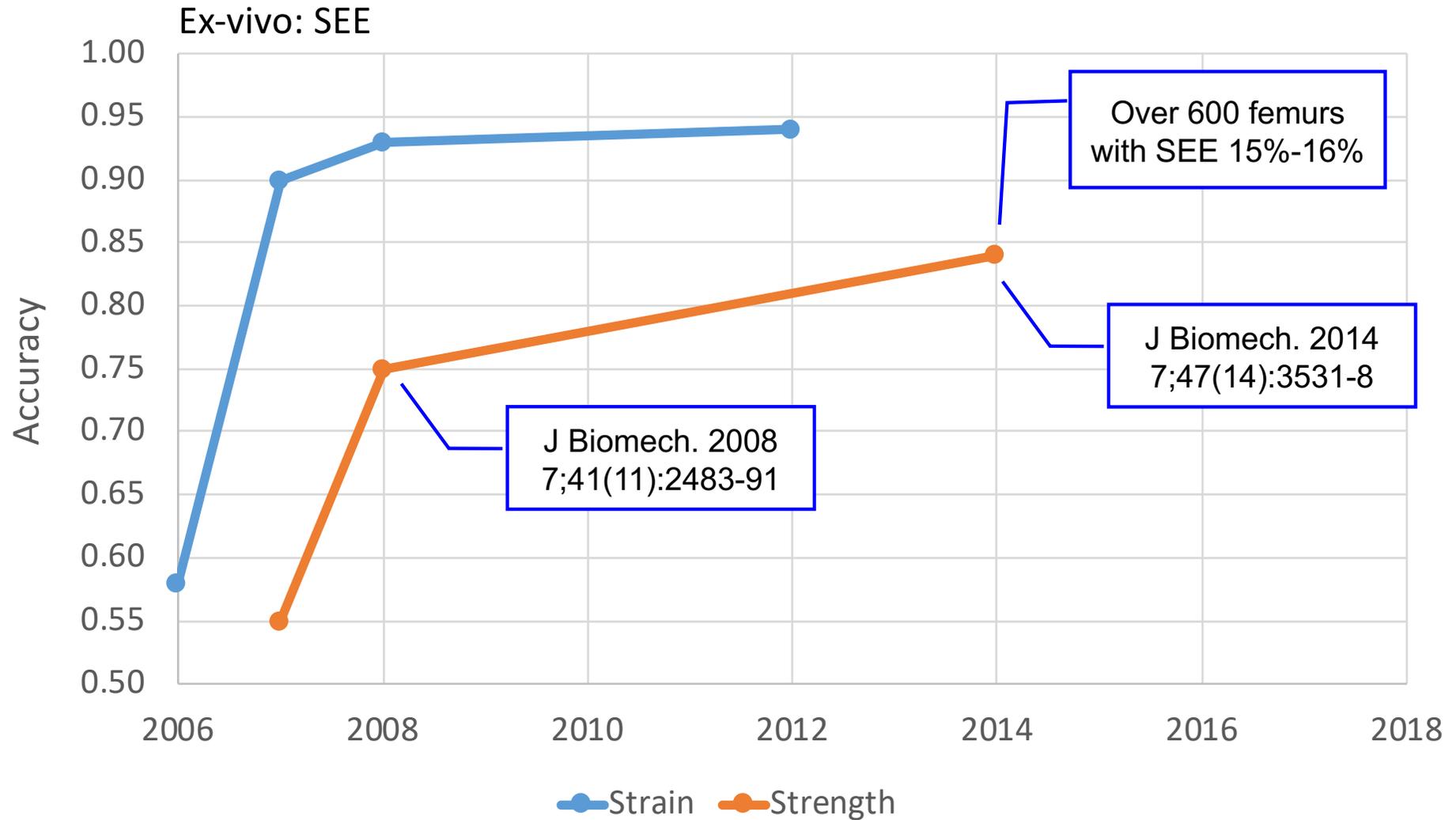


Cristofolini L. et al. Phil. Trans. R. Soc. A 2010;368:2725-2763

Predicting strain



Predicting Strength

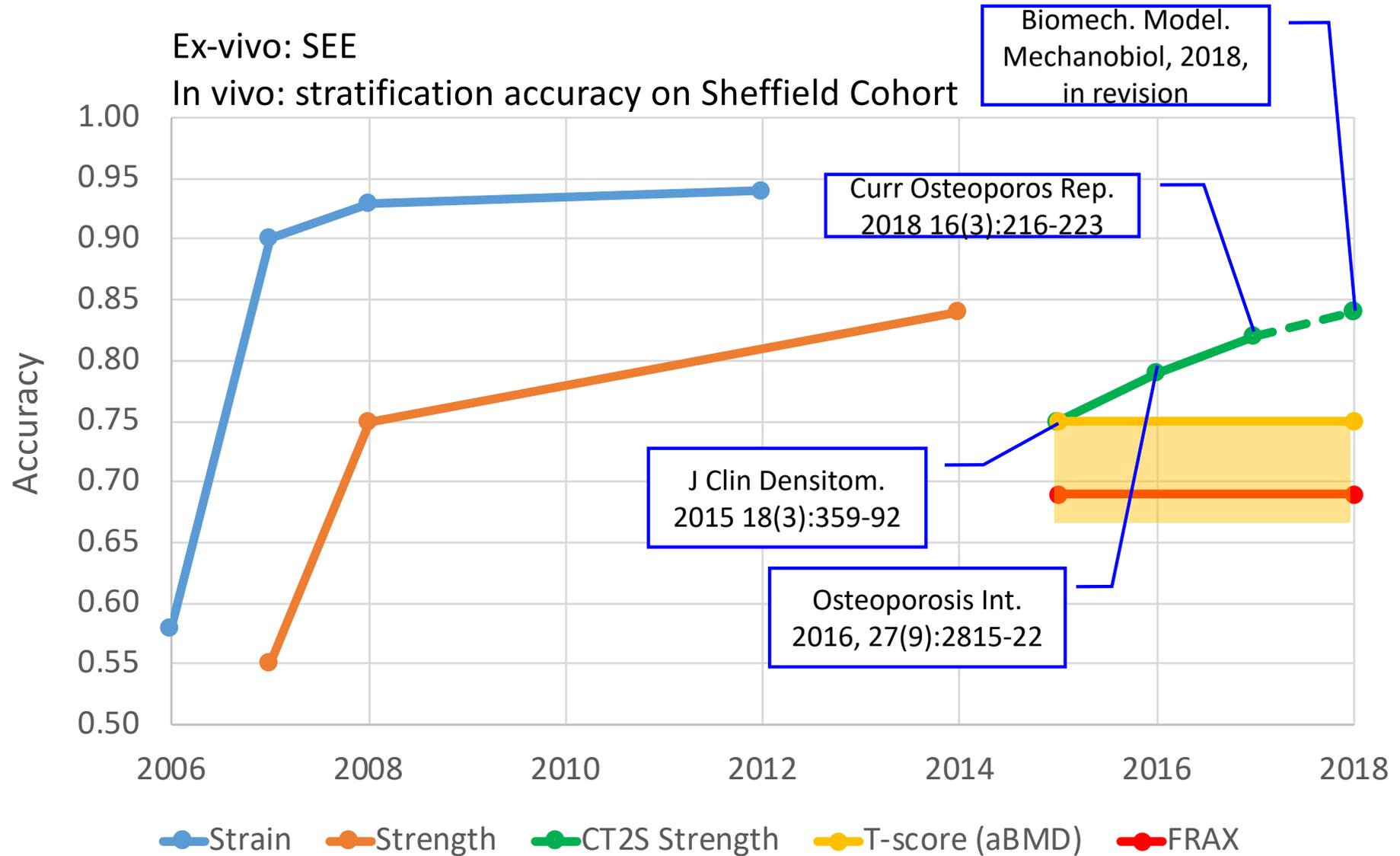


Sheffield cohort

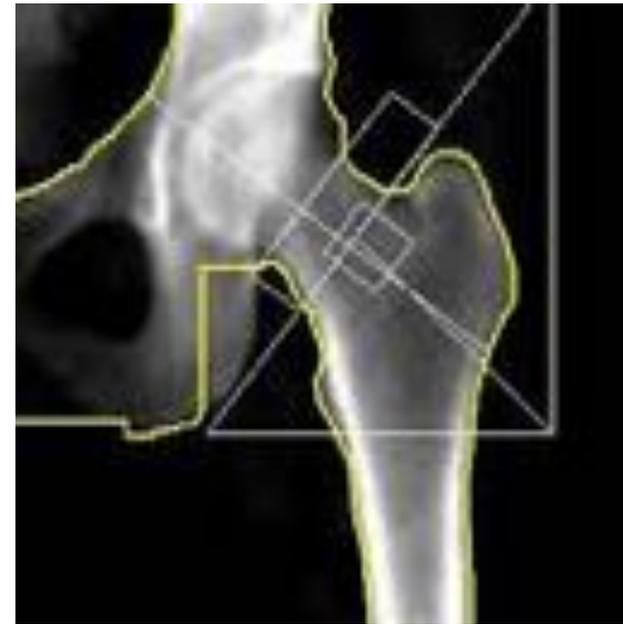
- 50 English women aged over 50 with acute hip fracture
- 50 women pair matched for height, weight, and age
- DXA, CT scan, FRAX risk, etc.

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

Predicting risk of fracture



Dual X-ray Absorptiometry (DXA)



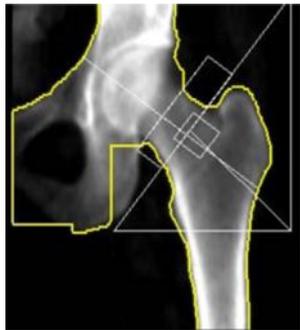
- aBMD: average Areal Bone Mineral Density over selected regions of interest (i.e. femoral neck)
- T-score for standardised ROIs
- Z-score for standardised ROIs

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

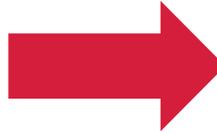
Clinical studies: Strength end point



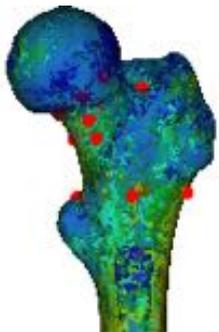
DXA-BMD



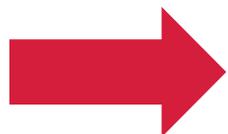
Accuracy = 75%



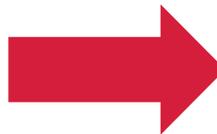
Alpha 0.05; power 80%
Group difference = 20%
Cohort size = 246



CT2S



Accuracy = 82%



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

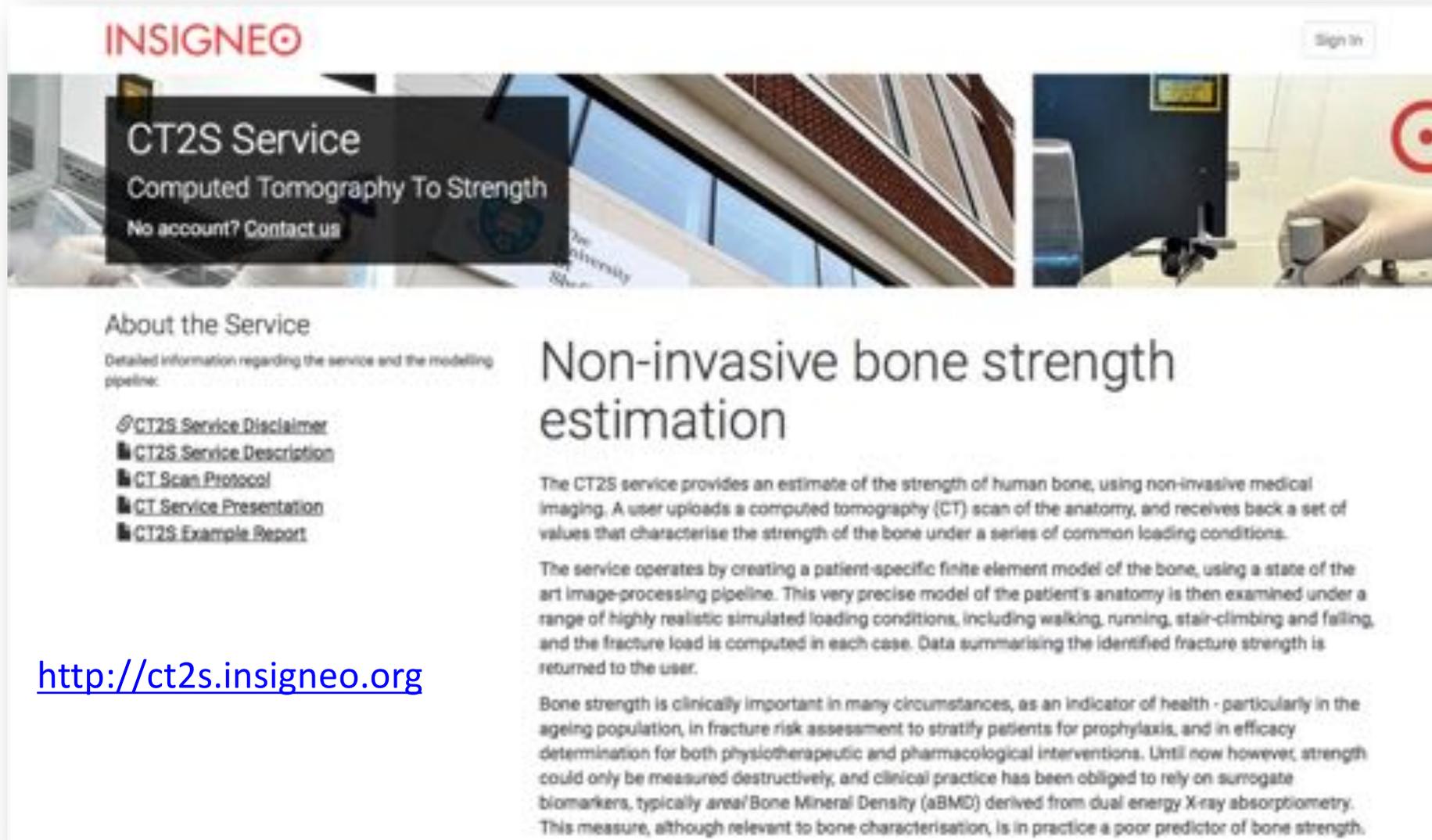
Viceconti M, *et al.* Are CT-based finite element model predictions of femoral bone strength clinically useful? *Curr Osteoporos Rep.* 2018, 16(3):216-223

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

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

CT2S service



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CT2S Service

Computed Tomography To Strength

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About the Service

Detailed information regarding the service and the modelling pipeline:

- [CT2S Service Disclaimer](#)
- [CT2S Service Description](#)
- [CT Scan Protocol](#)
- [CT Service Presentation](#)
- [CT2S Example Report](#)

Non-invasive bone strength estimation

The CT2S service provides an estimate of the strength of human bone, using non-invasive medical imaging. A user uploads a computed tomography (CT) scan of the anatomy, and receives back a set of values that characterise the strength of the bone under a series of common loading conditions.

The service operates by creating a patient-specific finite element model of the bone, using a state of the art image-processing pipeline. This very precise model of the patient's anatomy is then examined under a range of highly realistic simulated loading conditions, including walking, running, stair-climbing and falling, and the fracture load is computed in each case. Data summarising the identified fracture strength is returned to the user.

Bone strength is clinically important in many circumstances, as an indicator of health - particularly in the ageing population, in fracture risk assessment to stratify patients for prophylaxis, and in efficacy determination for both physiotherapeutic and pharmacological interventions. Until now however, strength could only be measured destructively, and clinical practice has been obliged to rely on surrogate biomarkers, typically areal Bone Mineral Density (aBMD) derived from dual energy X-ray absorptiometry. This measure, although relevant to bone characterisation, is in practice a poor predictor of bone strength.

<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

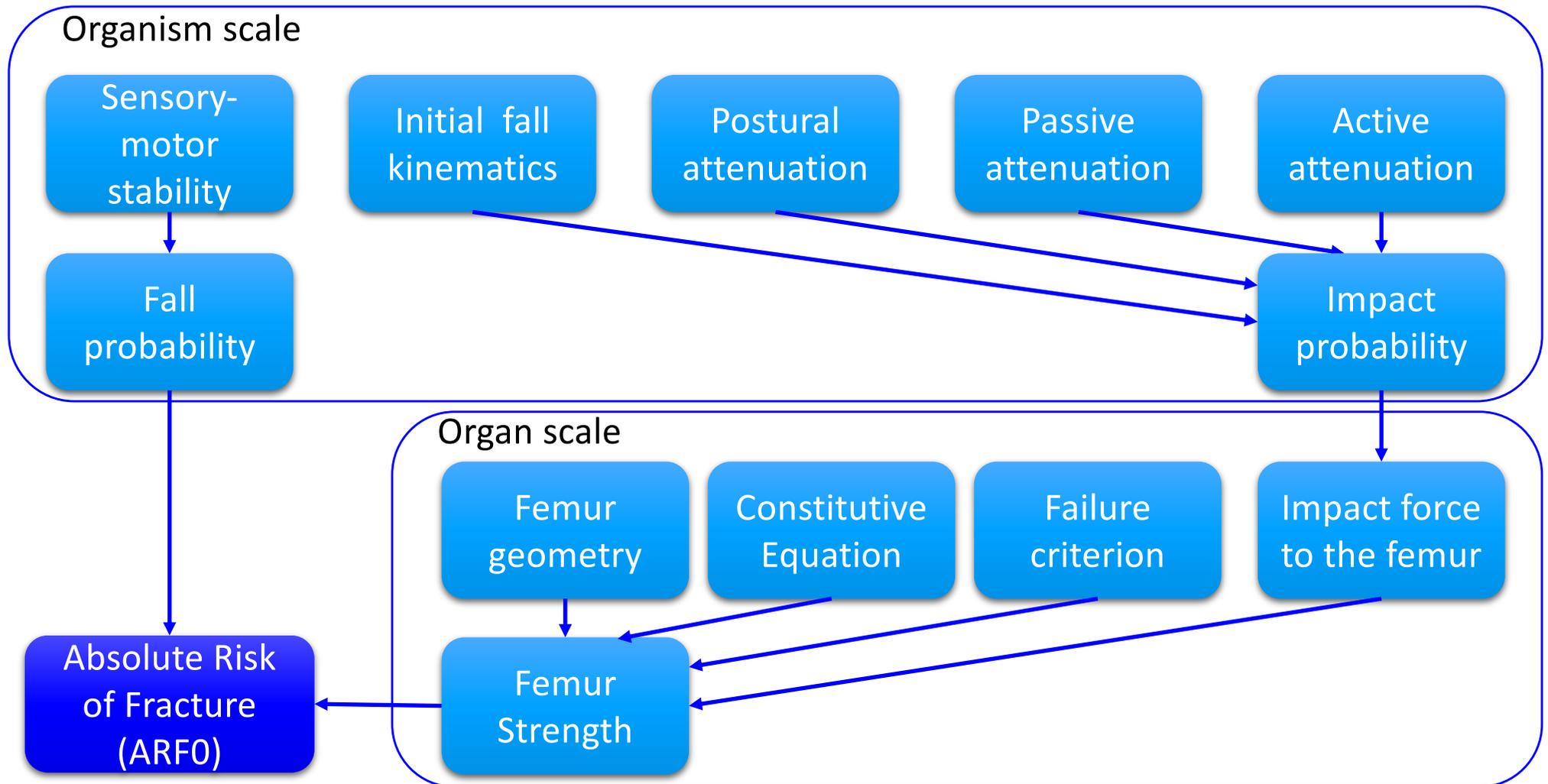
Viceconti M, *et al.* Are CT-based finite element model predictions of femoral bone strength clinically useful? *Curr Osteoporos Rep.* 2018, 16(3):216-223

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

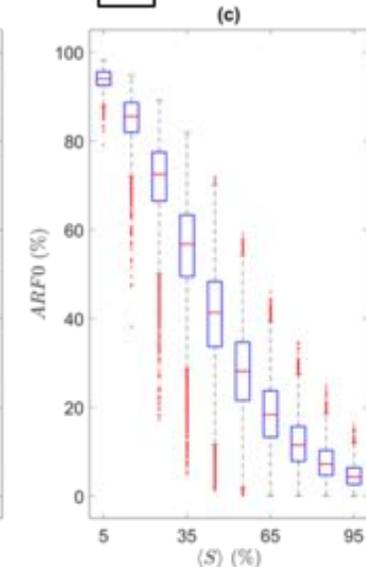
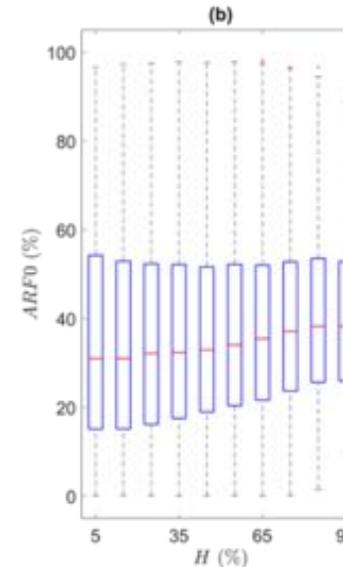
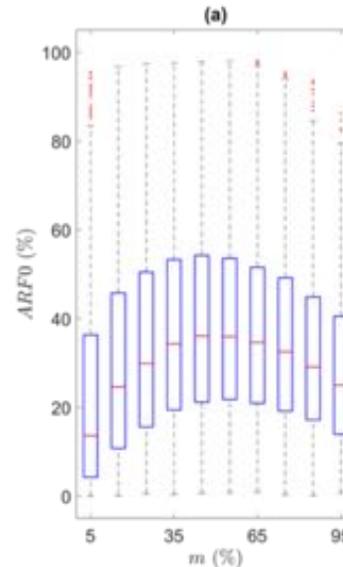
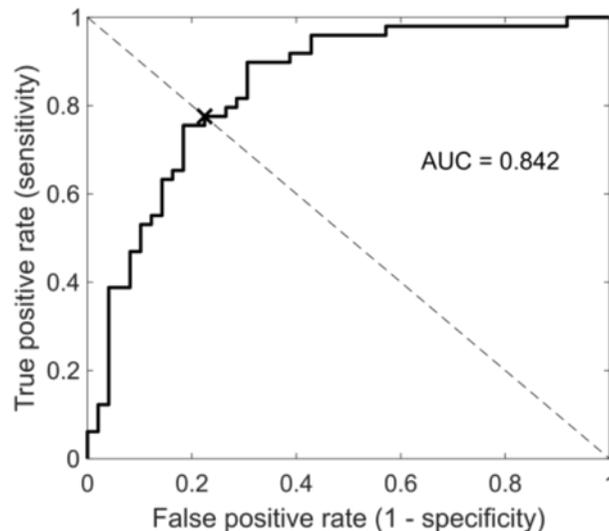
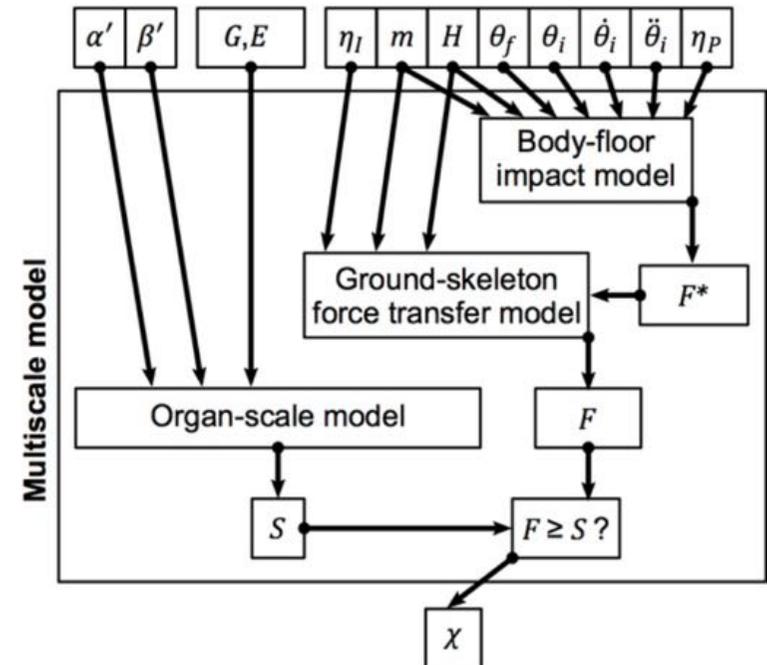
Business might not be viable

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

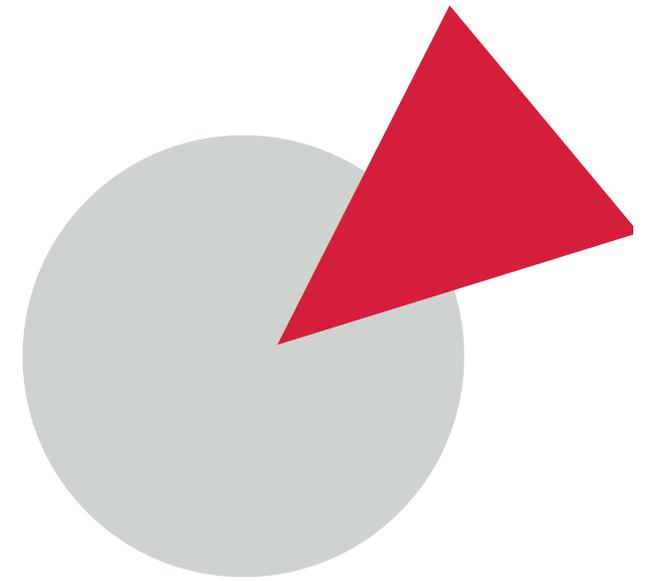


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