Systems Pharmacology Model Development to Provide Physiologically-Based Interpretation and Drug Development Decision Support in Osteoporosis and Other Bone-Related Diseases

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ABSTRACT

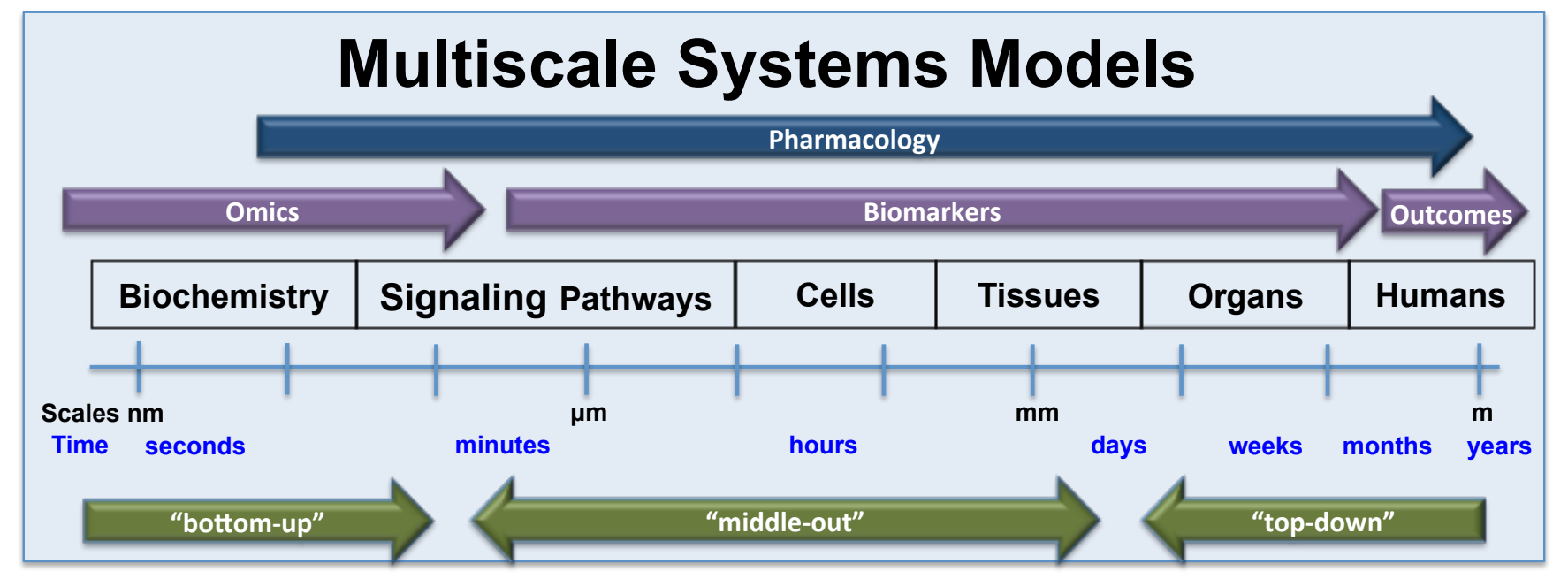
Models describing PK-PD, disease progression, and systems biology provide the components for a **Multiscale Systems Pharmacology Model (MSPM)** with a goal to enable in silico exploration of the ramifications of system perturbations, e.g., those caused by disease, genetic variation, and therapeutic intervention(s). In doing so, the MSPM approach offers a continuum for translating experimental data with clinical biomarkers and outcomes allowing researchers to probe target pathways, understand potential patient-to-patient sensitivities, and ultimately design more efficient and informative clinical trials. Applied broadly, these models instill rapid, seamless knowledge transfer across the research scale by enabling colleagues from multiple disciplines to communicate with a common set of expectations and understanding of these oftentimes complex systems. MSPMs can thereby serve as repositories that contain and connect data, experimentations, overall comprehension, and assumptions of the system.

A MSPM describing bone mineral homeostasis and bone remodeling will be used as an example of how to develop and apply such a model with a focus on MSPM extensibility to evolving and broadening research goals. A brief history of the model construction will be provided with its initial focus on osteoporosis treatment[1] and continued expansion to other natural progressions and diseases involving bone, e.g., natural estrogen loss during menopause transition[2] and during endometriosis treatment,[3] as well as Chronic Kidney Disease-Mineral and Bone Disorder.[4] Additionally, a "middle-out"[5] approach to ongoing research efforts include the translation of bone marker effects to BMD prediction and subsequent fracture risk[8] and inclusion of Vitamin D kinetics. An overview and update on this research, as well as future plans, will be provided.

INTRODUCTION – MODEL BACKGROUND

Multiscale Systems Biology / Pharmacology Models (*Figure 1*)

- Biologic systems expressed as mathematical expressions
- Quantify timecourses, magnitudes of changes (e.g., natural decays, interactions)
- Serve as in silico probes of biologic perturbation (e.g., disease, genetic variation)
- Multiscale systems pharmacology model (**MSPM**): include pharmacologic effects



Multiscale Systems Models

Pharmacology

Omics — Biomarkers — Outcomes

Biochemistry | Signaling Pathways | Cells | Tissues | Organs | Humans

Scales nm, µm, mm, m

Time seconds, minutes, hours, days, weeks, months, years

"bottom-up" — "middle-out" — "top-down"

Figure 1: *Defining multiscale systems models and terminology; reproduced from Riggs 2011*[5]

MSPM of Bone Mineral Homeostasis and Remodeling (*Figures 2, 3*)

- Mathematical (differential equations) construct from experimental and clinical data
- Scales: Cell signaling → organ functions → bone turnover markers (BTMs) → BMD
- Applications:
  - **Denosumab: PTH, serum calcium, BTMs,[1] and lumbar spine BMD[6, 7]**
  - Teriparatide: PTH, serum calcium, and BTMs[1]
  - Disease/Aging [CKD-MBD,[4] **menopause and endometriosis**[3]]: BTMs, BMD and fracture risk[8]
- Software: R (www.R-project.org/)[9]
- Model code available through:
  - Original publication[1] (open-source): www.opendiseasemodels.org
  - GnRH and menopause[3]: See CPT:PSP online supplemental material

Example I: Denosumab (RANK-L Inhibition) (*Figure 4*) [6, 7]

- **MSPM Qualification:** Can the MSPM predict clinical observations that were not included in the original model development? In this case, endpoint data collected from a separate clinical study

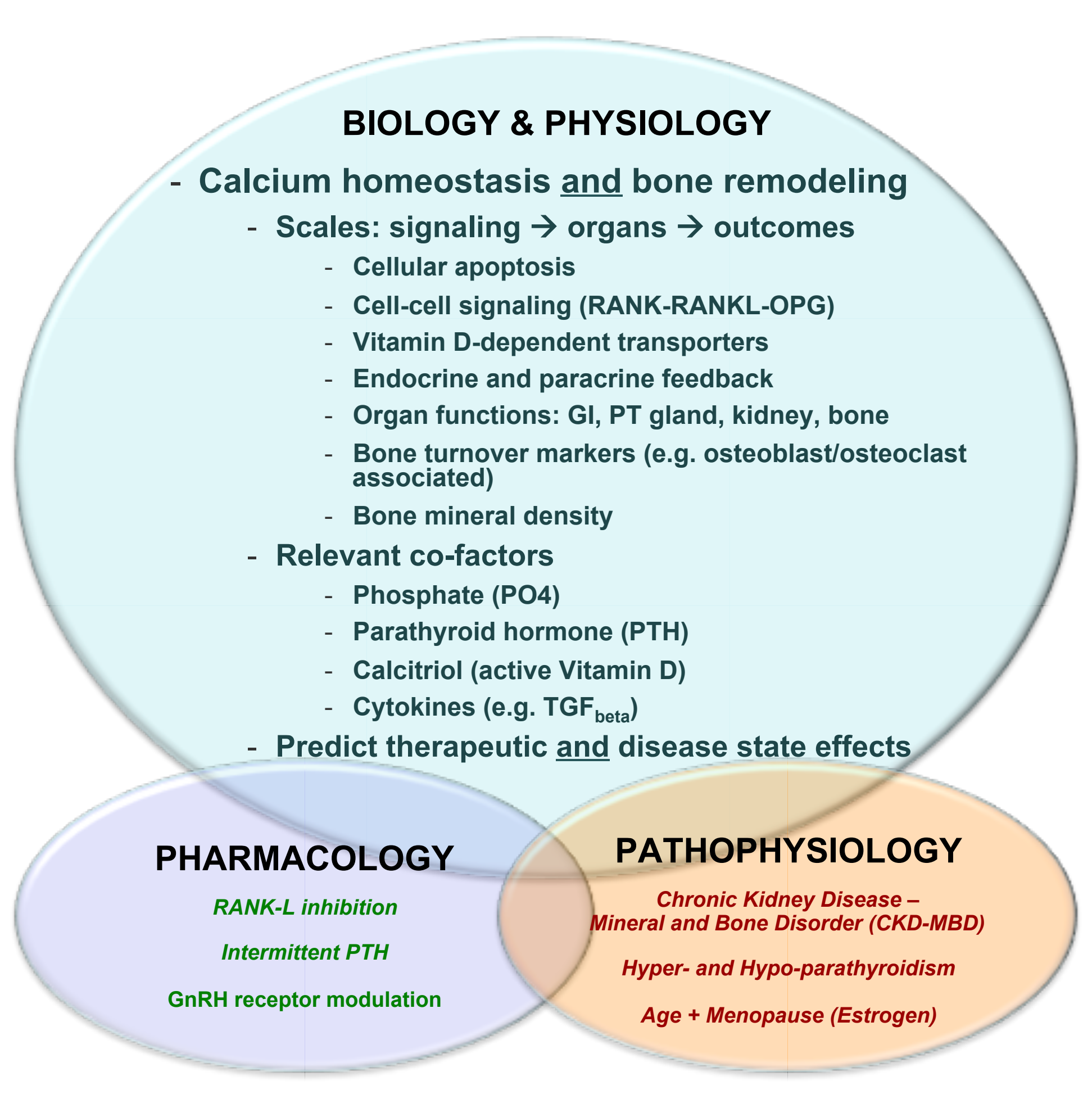
Example II: Menopause and GnRH Modulation (*Figure 5*)

- Provide model-based decision support for gonadotropin releasing hormone (GnRH) modulator programs intended for the management of EM

Example III: Link BMD Change with Fracture Risk (*Figure 9*)

- Develop model simultaneously characterizing BMD and fracture risk

INTRODUCTION – MULTISCALE SYSTEMS PHARMACOLOGY MODEL OVERVIEW



BIOLOGY & PHYSIOLOGY

- Calcium homeostasis and bone remodeling
  - Scales: signaling → organs → outcomes
    - Cellular apoptosis
    - Cell-cell signaling (RANK-RANKL-OPG)
    - Vitamin D-dependent transporters
    - Endocrine and paracrine feedback
    - Organ functions: GI, PT gland, kidney, bone
    - Bone turnover markers (e.g. osteoblast/osteoclast associated)
    - Bone mineral density
  - Relevant co-factors
    - Phosphate (PO4)
    - Parathyroid hormone (PTH)
    - Calcitriol (active Vitamin D)
    - Cytokines (e.g. TGF_{beta})
  - Predict therapeutic and disease state effects

PHARMACOLOGY

RANK-L inhibition

Intermittent PTH

GnRH receptor modulation

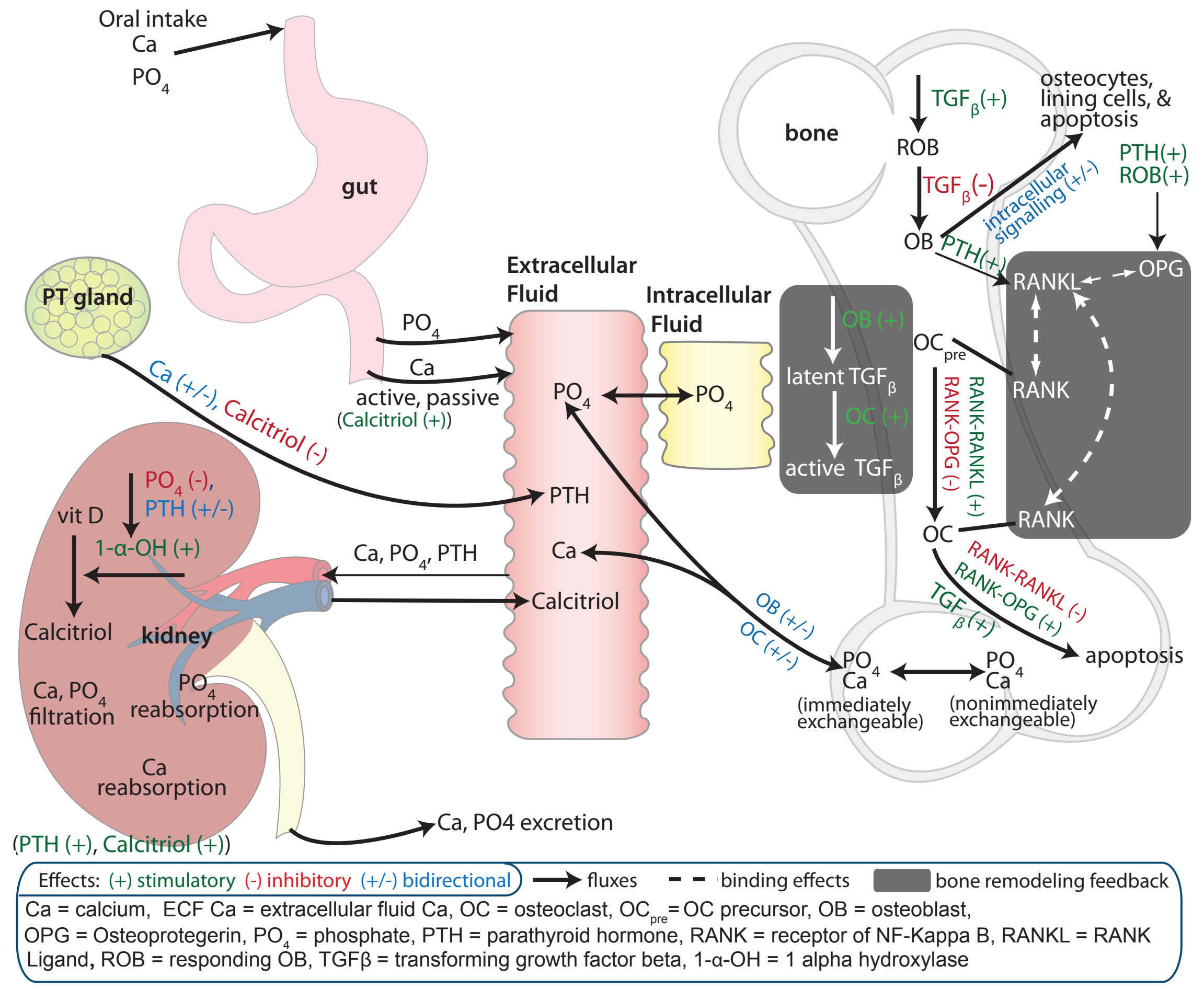
PATHOPHYSIOLOGY

Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD)

Hyper- and Hypo-parathyroidism

Age + Menopause (Estrogen)

Figure 2: *MSPM conceptual framework and content overview.*



Effects: (+) stimulatory (-) inhibitory (+/-) bidirectional → fluxes - - binding effects ▇ bone remodeling feedback

Ca = calcium, ECF Ca = extracellular fluid Ca, OC = osteoclast, OC_{pre} = OC precursor, OB = osteoblast, OPG = Osteoprotegerin, PO_4 = phosphate, PTH = parathyroid hormone, RANK = receptor of NF-Kappa B, RANKL = RANK Ligand, ROB = responding OB, TGFβ = transforming growth factor beta, 1-α-OH = 1 alpha hydroxylase

Figure 3: *Schematic of physiologically-based, multiscale systems pharmacology model; modified from Figure 1 of Peterson and Riggs, 2010.* [1]

METHODS – EXAMPLE I: QUALIFYING PREDICTIONS OF DENOSUMAB EFFICACY

The Receptor Activator of Nuclear Factor-κ B (RANK)-RANK Ligand (RANKL)-Osteoprotegerin (OPG) system

⇑ OC differentiation and ⇑ OC activation: RANK–RANKL

⇓ OC differentiation and ⇑ OC apoptosis: RANKL–OPG, RANKL–denosumab

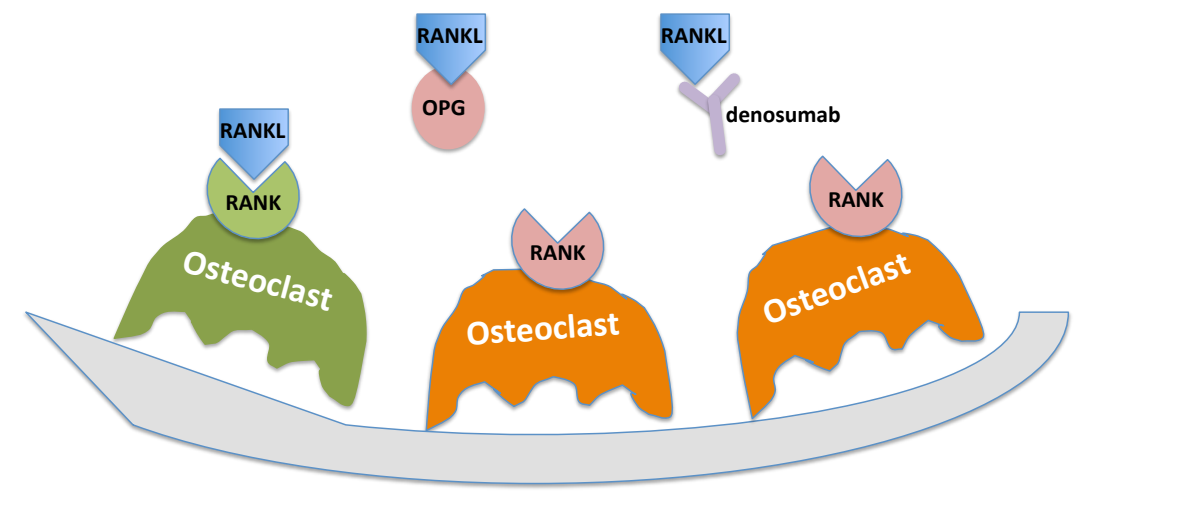


Figure 4: *Depiction of RANK-RANKL-OPG and denosumab interaction.*

Denosumab[10]

- Fully human monoclonal antibody
- Binds to RANKL with high affinity and specificity
- Blocks interaction of RANKL with RANK
- Mimics endogenous effects of OPG

Denosumab–RANKL binding

- ↓ available RANKL
- ↓ RANK–RANKL interaction
- ↓ Osteoclast activity (serum C-telopeptide, CTx)
- ↓ Activation of TGFβ
- ↓ Osteoblast activity (bone-specific alkaline phosphatase, BSAP)
- ↑ bone mineral density (BMD), expressed mathematically[6] as:

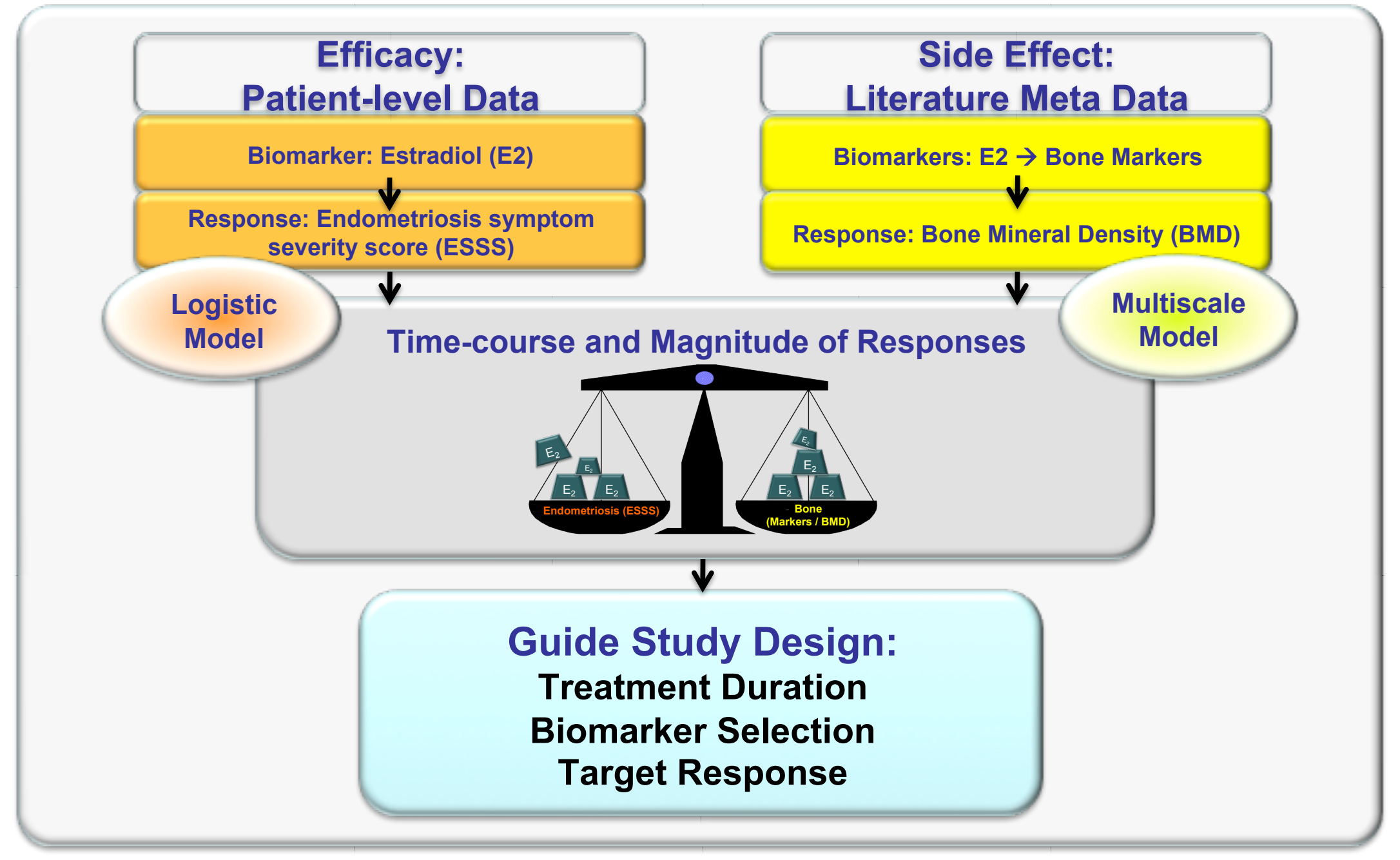
$$\frac{\mathrm{d}(LS\ BMD)}{\mathrm{dt}} = \mathrm{k}_{\mathrm{in},BMD} \cdot \left(\frac{\mathrm{BSAP}}{\mathrm{BSAP}_{\mathrm{baseline}}}\right)^{\gamma_{OB}} - \mathrm{k}_{out,BMD} \cdot \left(\frac{\mathrm{CT_x}}{\mathrm{CT}_{\mathrm{x_{baseline}}}}\right)^{\gamma_{OC}} \cdot LS\ BMD$$

$$\gamma_{OB} = 0.0793 \quad \gamma_{OC} = 0.0679 \quad k_{\mathrm{out,BMD}} = 0.000145\ \mathrm{h}^{-1}$$

EXAMPLE II: A BALANCED SAFETY / EFFICACY TARGET FOR ENDOMETRIOSIS

Gonadotropin Releasing Hormone (GnRH) Modulation[3]

- Estrogen (E2)-mediated effects on bone turnover modeled through actions on TGF-β and RANKL using data from menopause transition[2, 3]



Efficacy: Patient-level Data

Biomarker: Estradiol (E2)

Response: Endometriosis symptom severity score (ESSS)

Side Effect: Literature Meta Data

Biomarkers: E2 → Bone Markers

Response: Bone Mineral Density (BMD)

Logistic Model

Multiscale Model

Time-course and Magnitude of Responses

Guide Study Design:
Treatment Duration
Biomarker Selection
Target Response

Figure 5: *Quantifying the balance between efficacy (endometriosis symptom relief) and safety (loss of BMD) .*

- MSPM describes E2 → bone marker → BMD relationship
- Modeled relationship between GnRH suppression and E2
- Evaluated E2, bone maker, BMD effects sizes and time-courses

METHODS – EXAMPLE III: EXTENTION TO INCLUDE FRACTURE RISK

Subject Level Data: 2005-2008 NHANES[11]

- Demographics, dual energy X-ray absorptiometry, body measures, osteoporosis, and reproductive health datasets
- 1605 postmenopausal ♀ of 63 yr mean age and 45 yr mean final menstrual period (FMP) age; 1 femoral neck BMD measure and 0–5 (204 total) fracture events each

Repeated Time-to-Event Fracture Risk Model[12]

- **Exponential survival (fraction without fracture) time:** $\mathrm{S}(t) = \mathrm{e}^{-(\int_{t_{j-1}}^{t_j} \mathrm{h}(u)du)^{\alpha}}$
- **Hazard: time-dependence through BMD(t):** $\mathrm{h}(t) = \mathrm{e}^{\theta_h \times (1+\theta_{BMD} \times (\mathrm{BMD}(t) - \overline{\mathrm{BMD}}))}$
- BMI, ethnicity, and FMP_{age} included as covariates on BMD model

RESULTS – MSPM QUALIFICATION USING *FREEDOM* DATA (EXAMPLE I)

MSPM Predicted Lumbar Spine BMD and Bone Marker Responses[6, 7]

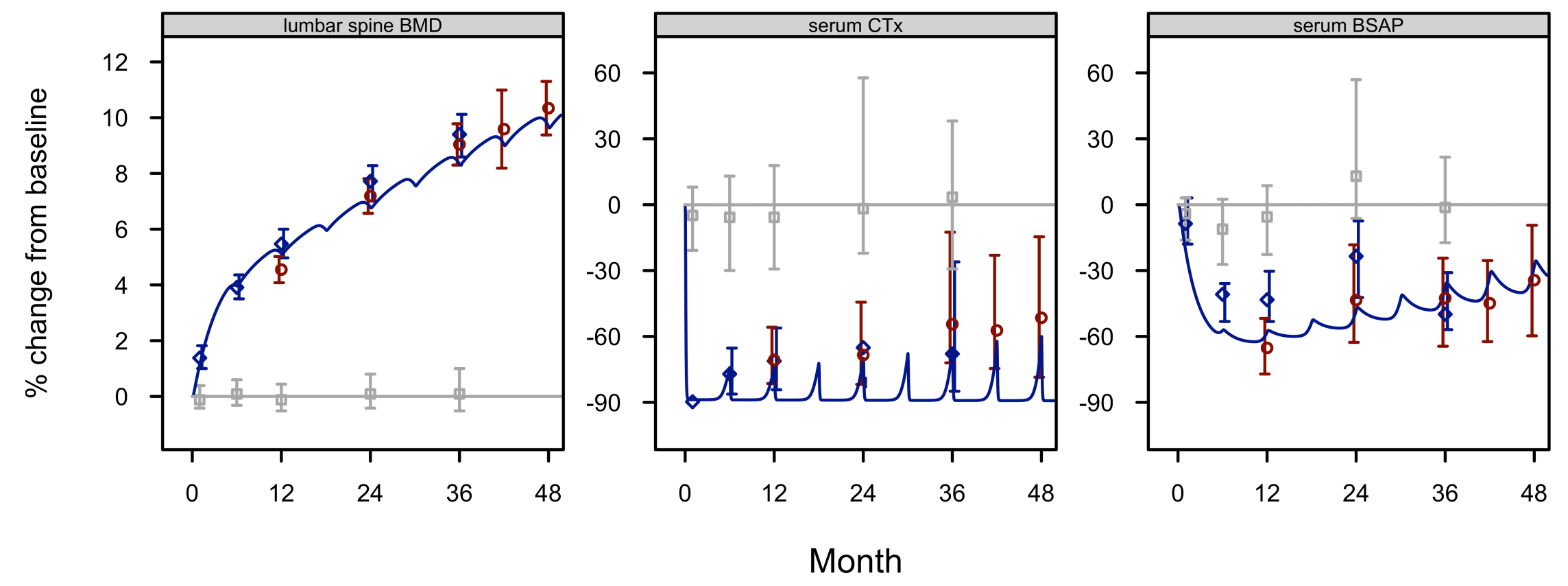


Figure 6: *Observed (symbols) and simulated (lines) BMD, CTx, and BSAP during treatment with 60mg Q6M denosumab. Observed values from denosumab treatment groups: NCT00043186*[10, 15] *(red symbols, for model estimation); NCT00089791 (FREEDOM)*[13, 14] *(blue symbols, for denosumab model qualification) and placebo (grey symbols for reference).*

- MSPM predictions were in close agreement with observed data: Mean absolute percentage error = 9.1%; Mean percentage error = −7.9%
- MSPM predicted near complete decline in osteoclast function with slight increase in pre-dose (q 6 month) bone markers with continued administration

RESULTS – QUANTIFIED EFFICACY / SAFETY TARGET (EXAMPLE II)

ESSS (from logistic regression model); BMD (from MSPM)[3]

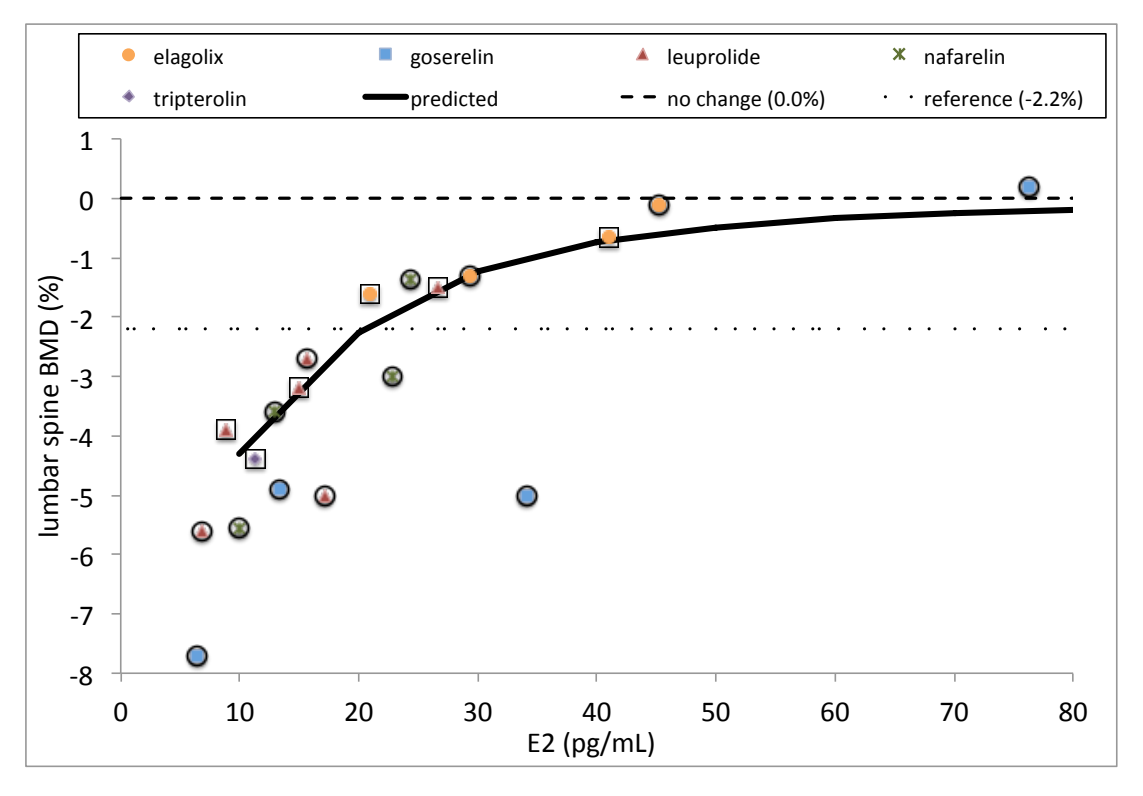


Figure 7: *Observed (evaluation set) and Simulated BMD versus E2*

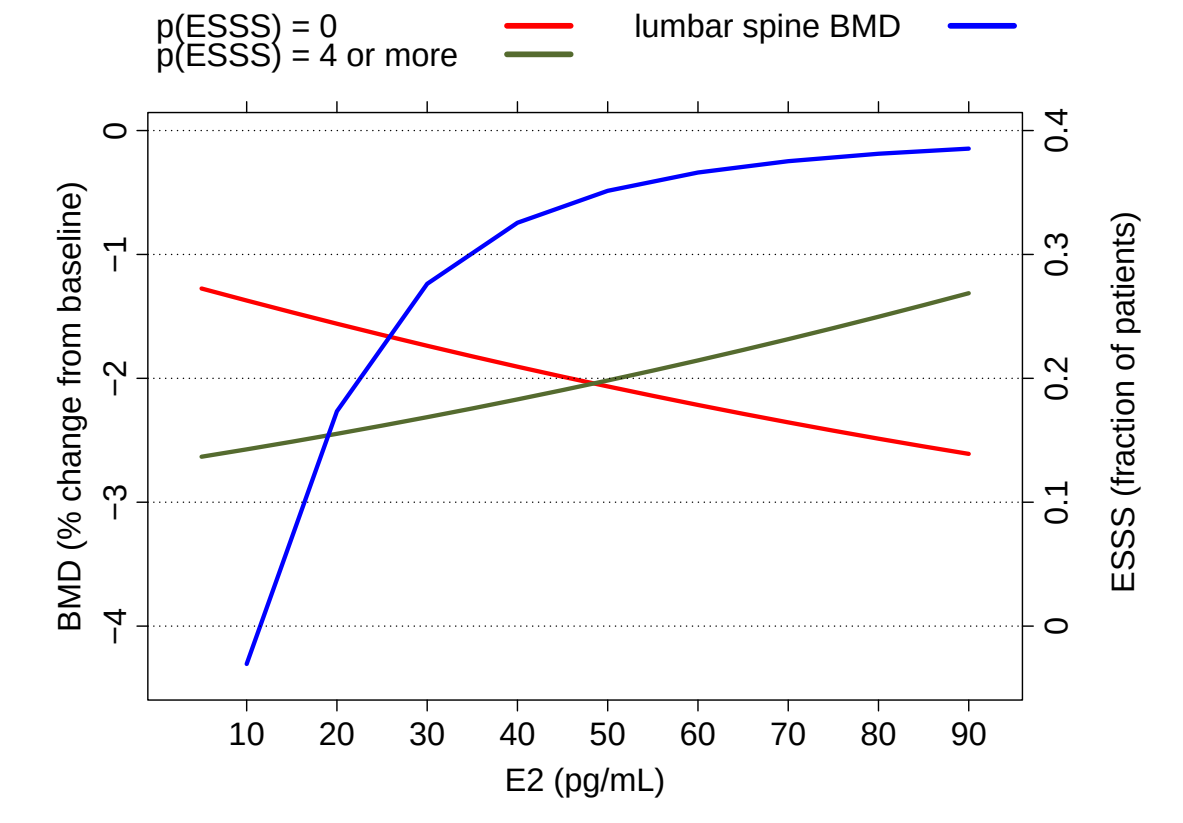


Figure 8: *Comparison of Predicted ESSS and BMD versus E2*

- E2, measured as early as 1–2 months after treatment initiation, a reliable predictor of 6-month BMD change
- GnRH receptor modulation targeting E2 in the range of > 20 to 40 pg/mL expected to provide efficacious EM pain response while minimizing BMD effects (*Figure 8*)

RESULTS – LINKING BMD AND FRACTURE RISK (EXAMPLE III)

"Middle-out" MSPM Expansion to Predict Fracture Risk Clinical Outcome[8]

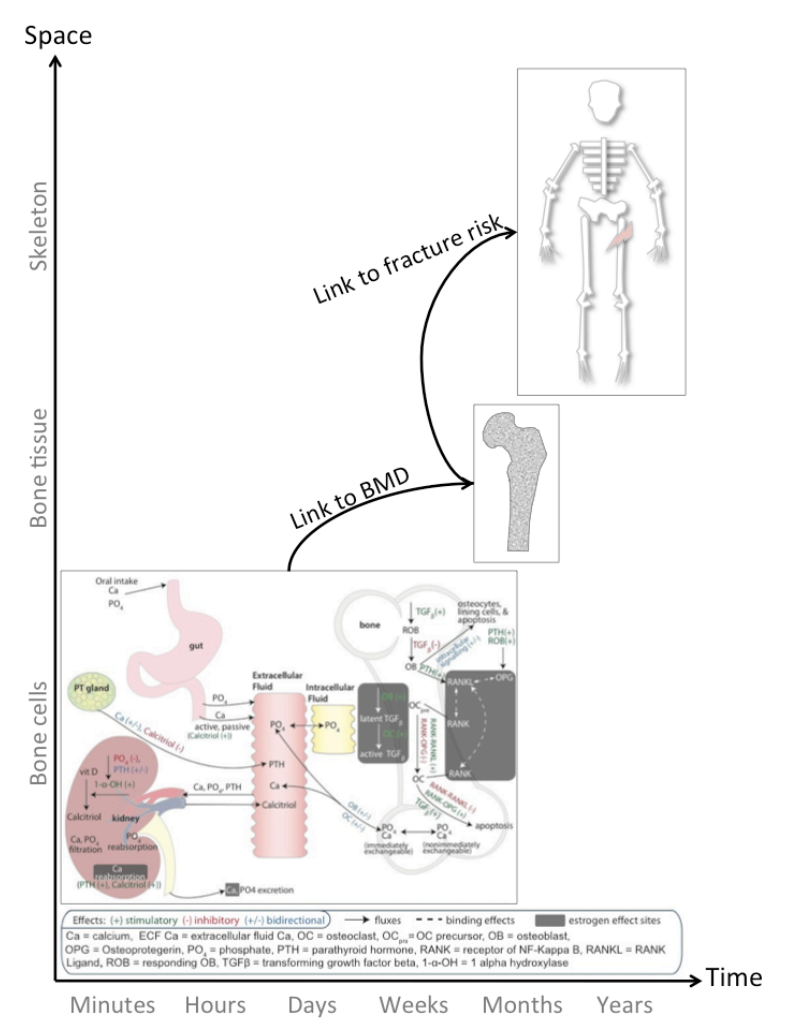


Figure 9: *MSPM extension to fracture risk*

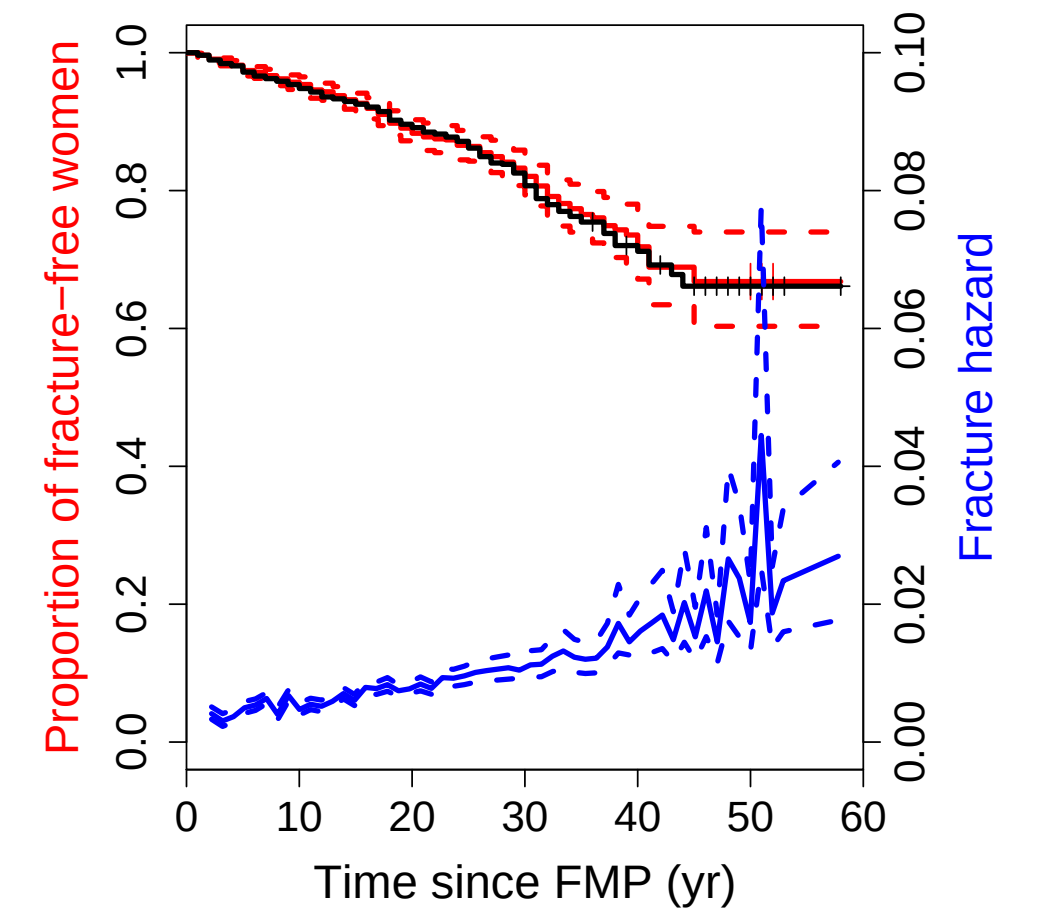
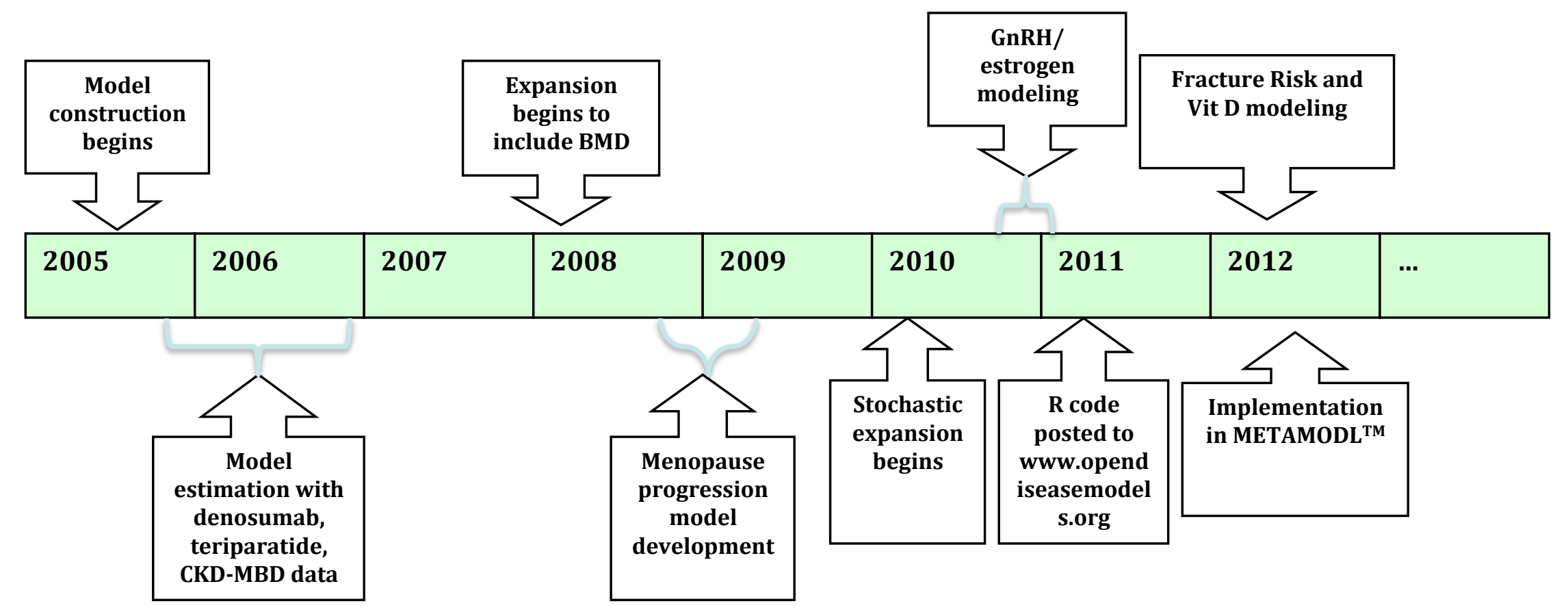


Figure 10: *Simulated fracture hazard and survival*

- FMP_{age} and *time* were indirect covariates with dynamically predicted BMD
- Time-varying hazard reflects increase due to time-dependent BMD decline in final model
- Next steps include development of links with individual drug-relating effects, external evaluations, and consideration of site-specific fracture risks

SUMMARY – MSPM DEVELOPMENT TIMELINE

MSPM as an expandable R&D platform



2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | ...

2005: Model construction begins

2006–2007: Model estimation with denosumab, teriparatide, CKD-MBD data

2008: Expansion begins to include BMD

2008–2009: Menopause progression model development

2010: Stochastic expansion begins

2010–2011: GnRH/ estrogen modeling

2011: R code posted to www.opendiseasemodels.org

2012: Fracture Risk and Vit D modeling

2012: Implementation in METAMODL™

CONCLUSIONS

- An MSPM can be constructed in an adaptable framework to address broad, but systems-related, research questions
- A well-founded MSPM offers efficient, timely extension and application
- MSPMs can serve as a repository of known mechanisms, hypotheses (theory), assumptions, and ongoing R&D goals
- MSPMs' ability to predict multiple therapeutic conditions provides further confidence in model-based predictions for decision-making in drug development and clinical practice

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