Extensions of a Multiscale Systems Pharmacology Model of Bone Mineral Balance and its Regulation of Bone Health

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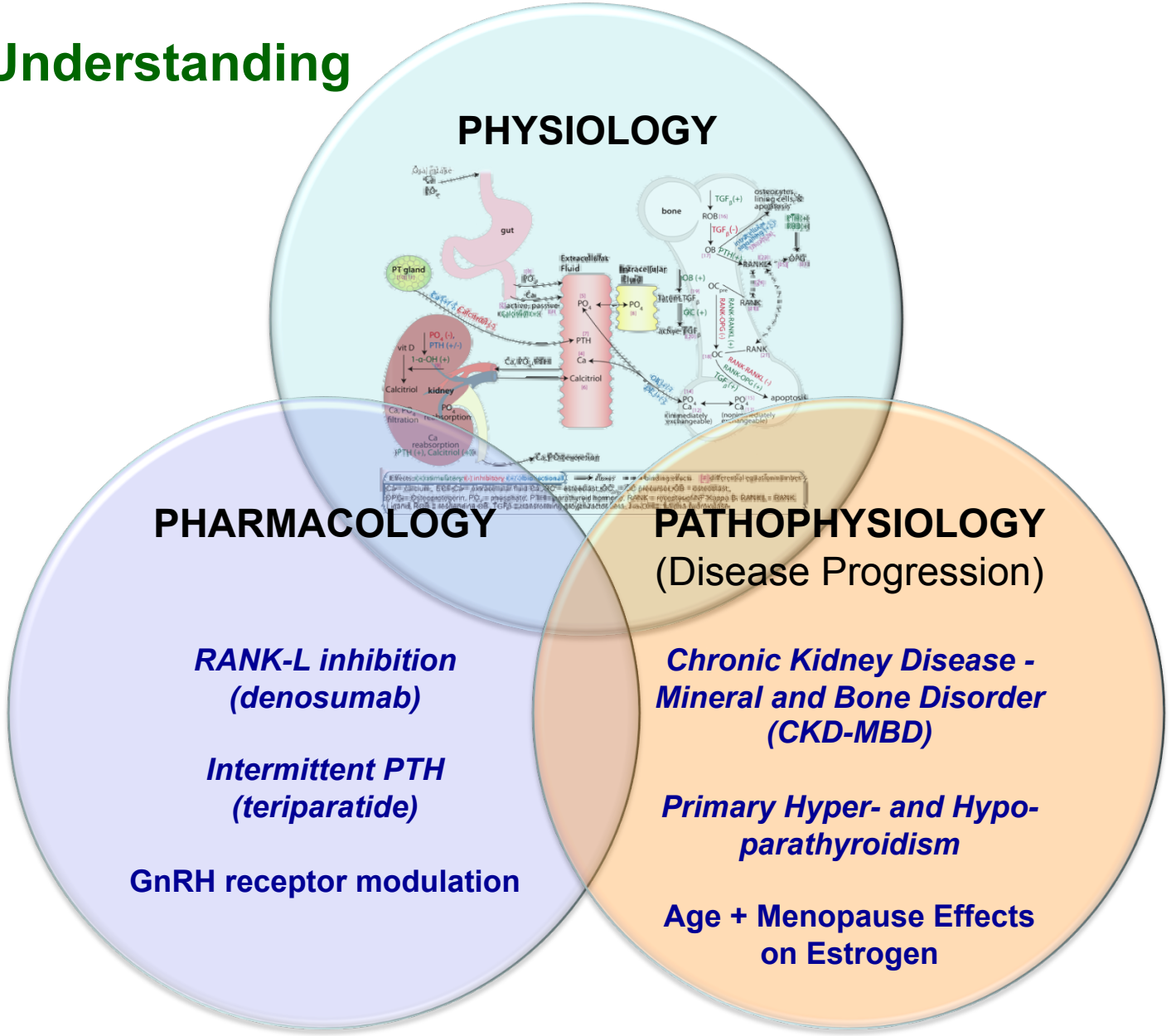
METRUM
RESEARCH GROUP

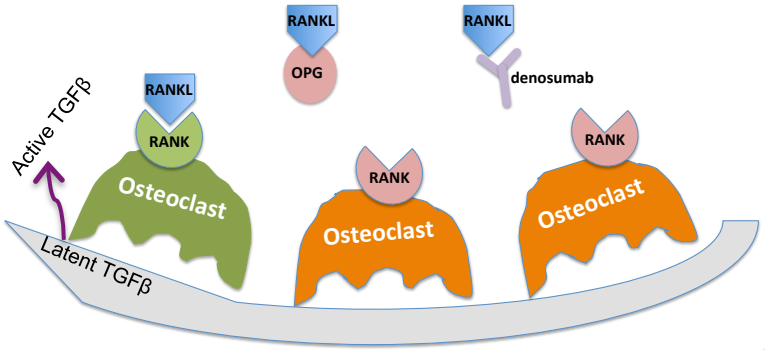
Multiscale Systems Pharmacology Modeling (MSPM)

- Introduction
  - MSPM to Integrate Physiology, Pharmacology and Disease
  - Motivation
  - Getting Started
- MSPM of Bone-Related Effects
  - Osteoporosis: Efficacy Response to Denosumab
  - Endometriosis: Balancing Symptom Relief with BMD loss
  - Ongoing R&D
- In Summary
  - Concept: A Research Platform
  - Parting Thoughts

- Integrated Understanding



Denosumab: RANKL inhibition



- ↓ available RANKL
- ↓ RANK--RANKL interaction
- ↓ Osteoclast activity (sCTx)
- ↓ Activation of TGF-β
- ↓ Osteoblast activity (BSAP)
- ↑ bone mineral density (BMD)

- ↓ Calcium release from bone
- ↓ Serum calcium
- ↓ Ca sensing in PT gland
- ↑ PTH release (calcium-sparing)

- Observed 12 Month Data:
  - ↓ Bone resorption markers (near immediate)
  - ↓ Bone formation markers (delayed, less pronounced)
  - ↓ Serum Ca (transient)
  - ↑ PTH (transient)
- Can these effects be described using a single, physiologically representative model?

Multiscale Model of Calcium and Bone

- Intentions
  - Represent physiology
    - Include multiscale mechanisms (signaling → organs → outcomes)
    - Incorporate relevant co-factors
      - Phosphate (PO4)
      - Parathyroid hormone (PTH)
      - Calcitriol
      - Cytokines (e.g. TGFβ)
      - Cell Signaling
      - Bone turnover markers (e.g. osteoblast/osteoclast associated)
  - Predict Ca homeostasis and bone remodeling
  - Provide a platform for evaluating longitudinal therapeutic and disease state effects

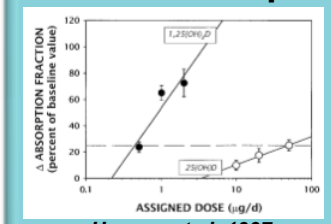
Multiscale Model of Calcium and Bone

- Existing Research / Data
  - 200+ references
  - From 70+ sources (journals, texts, regulatory documents, etc.)
  - Publications: 1959 – present (5+ decades)

- But How to Bring It All Together?

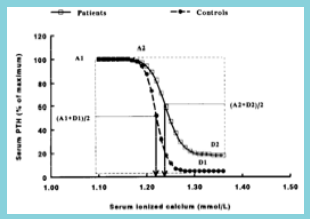
Integrating Existing Data and Models

Calcium Absorption



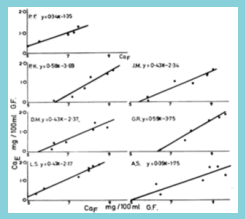
e.g., *Heaney et al. 1997*

PTH Secretion



e.g., *Ramirez et al. 1993*

Calcium Excretion



e.g., *Peacock and Nordin 1968*

Bone Therapeutics

Anabolic (*teriparatide, 2004*)

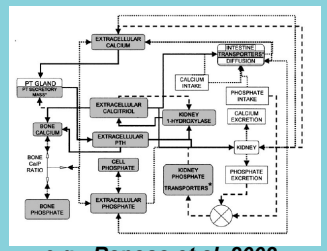
Catabolic (*denosumab, 2006*)

Disease States

Hyper- and hypo-PTH

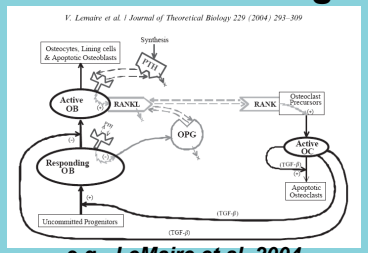
CKD-MBD (*Rix et al. 1999*)

Calcium Homeostasis



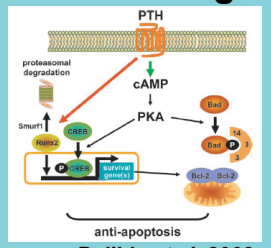
e.g., *Raposo et al. 2002*

Bone Remodeling



e.g., *LeMaire et al. 2004*

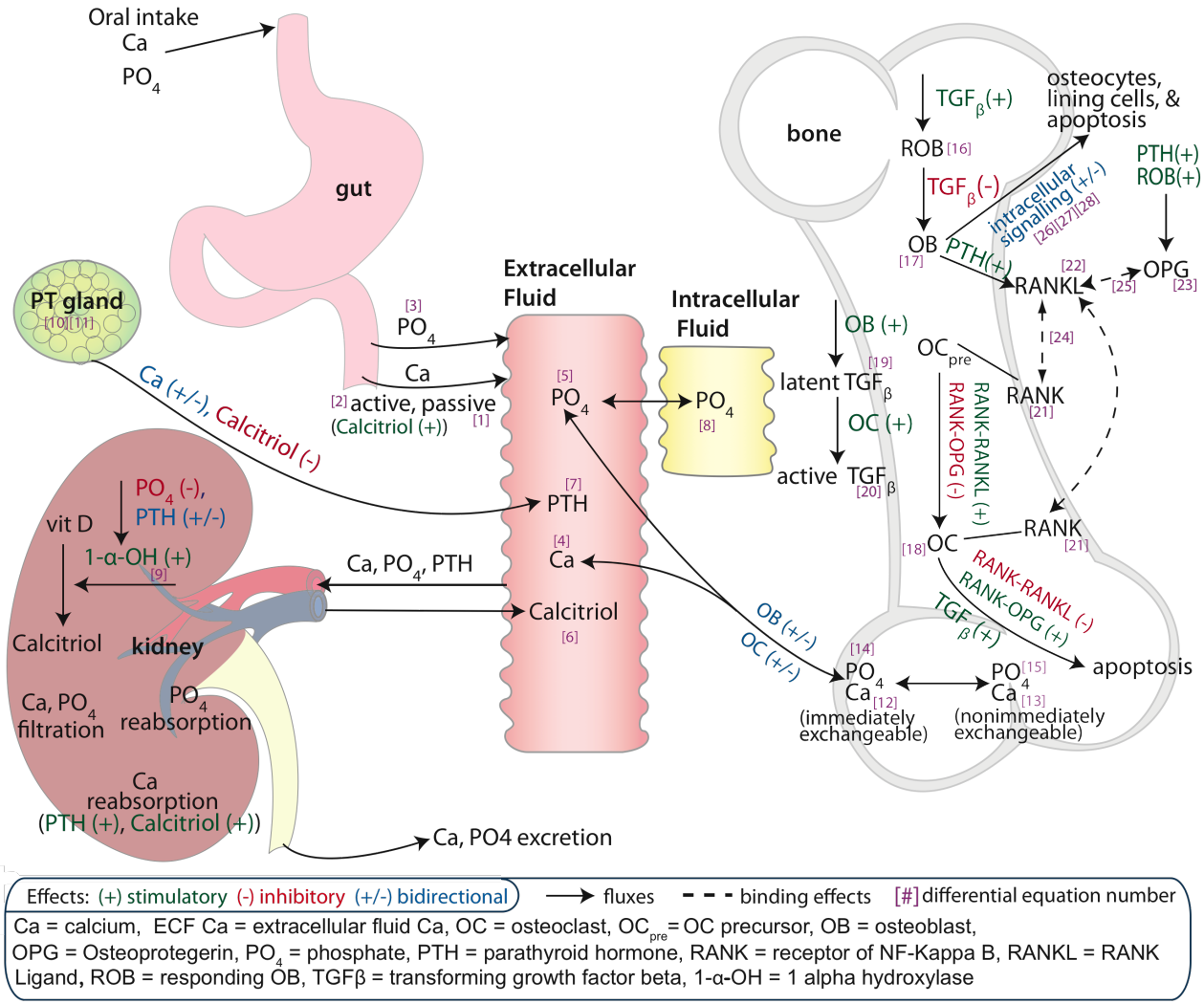
Intracellular Signaling



e.g., *Bellido et al. 2003*

- Multiscale Model:
  - *Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.*

Multiscale Model of Calcium and Bone



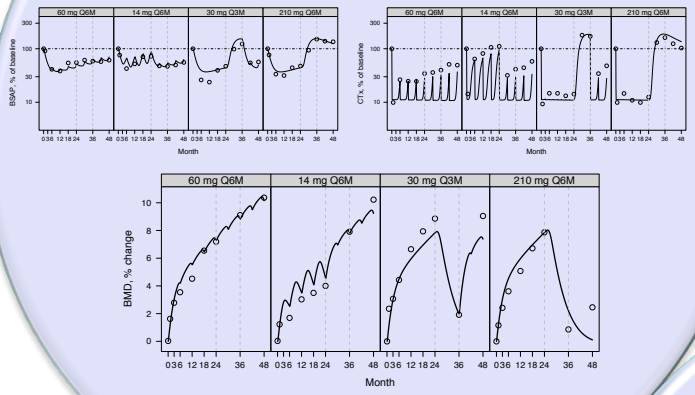
Schematic of physiologic system model to describe calcium homeostasis and bone remodeling (reprinted from Figure 1 of *(Peterson and Riggs, 2010)*)

Applications: Therapeutic Response

PHARMACOLOGY

DENOSUMAB

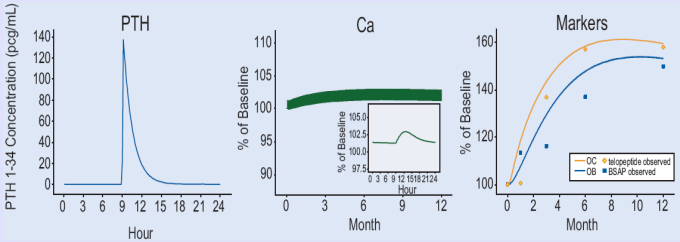
Rebound in bone metabolism is predictable.
BMD can be modeled as a function of bone markers



CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

TERIPARATIDE

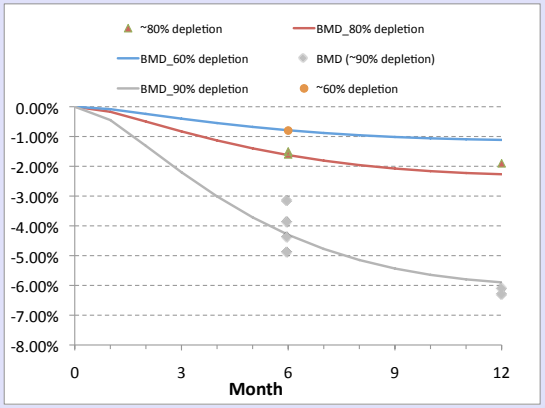
Bone anabolics are predictable.
Effects on Ca / other physiology can be evaluated



Peterson MC and Riggs MM. Bone 46:49-63; 2010

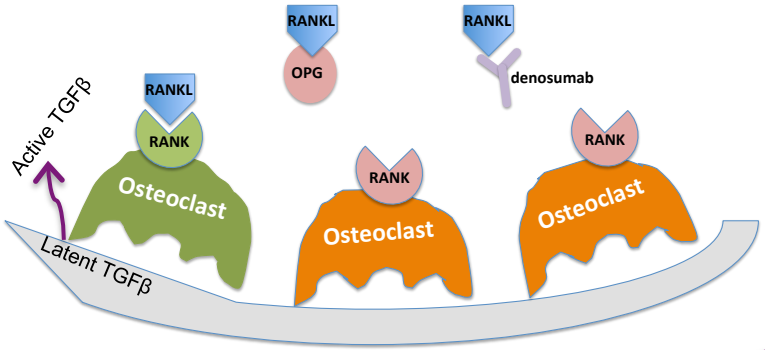
GnRH RECEPTOR

Estrogen-BMD relationship is predictable.
Degree of GnRH modulation targeted



CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

Denosumab: RANKL inhibition



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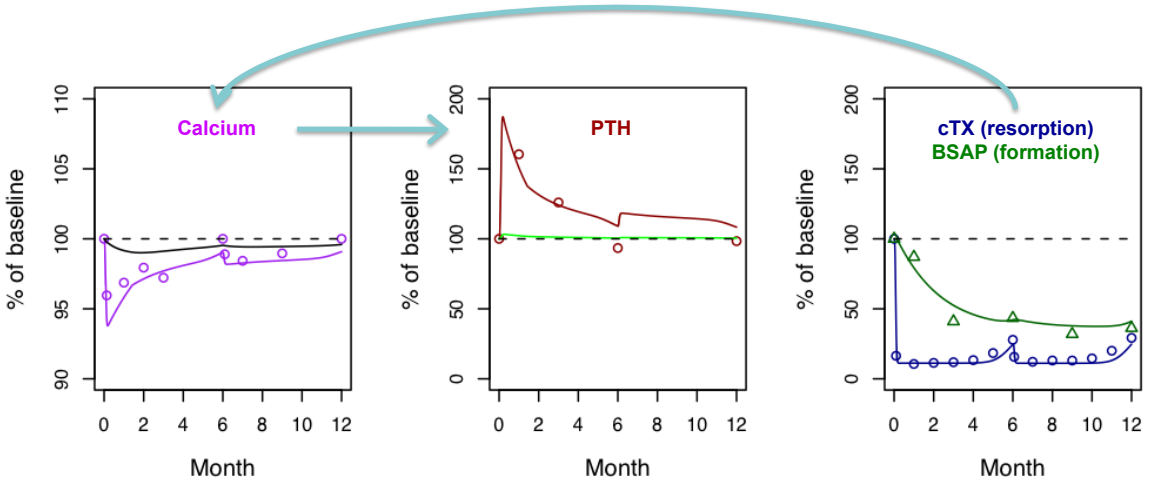
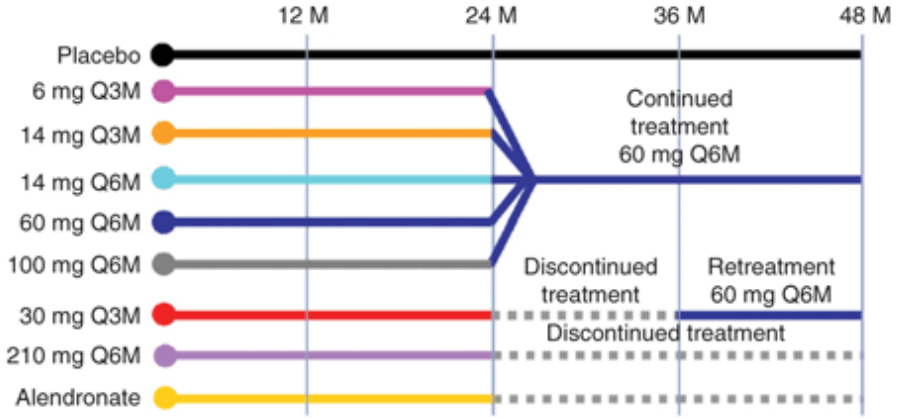
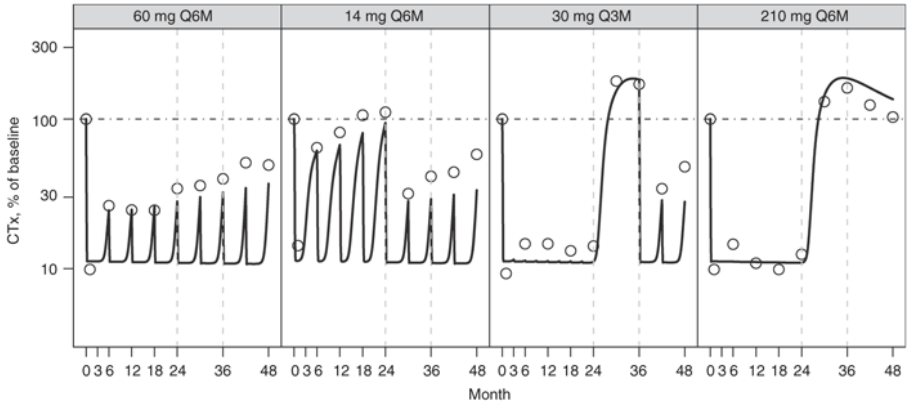


As reported in: M. R. McClung, E. M. Lewiecki, S. B. Cohen, M. A. Bolognese, G. C. Woodson, A. H. Moffett, M. Peacock, P. D. Miller, S. N. Lederman, C. H. Chesnut, D. Lain, A. J. Kivitz, D. L. Holloway, C. Zhang, M. C. Peterson, P. J. Bekker, and AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med, 354(8):821–31, Feb 2006.*

Denosumab: RANKL inhibition → Bone Markers

Dose-Ranging Bone Marker Responses





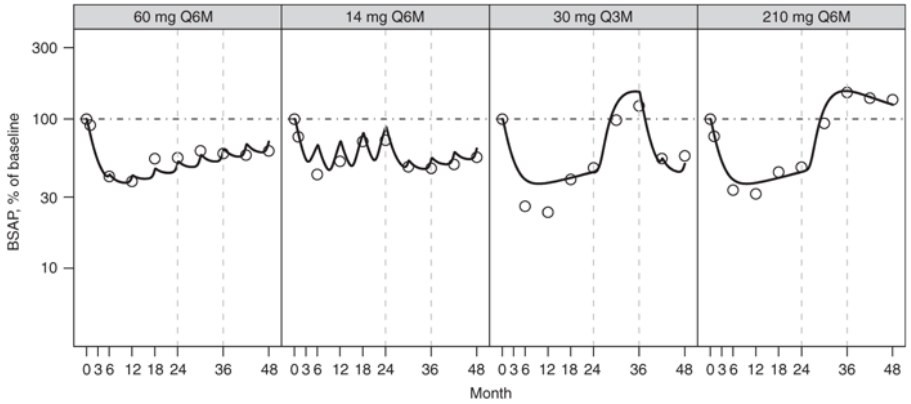


Fig.3 and 4; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

Denosumab: RANKL inhibition→Bone Marker→BMD

Dose-Ranging BMD Responses

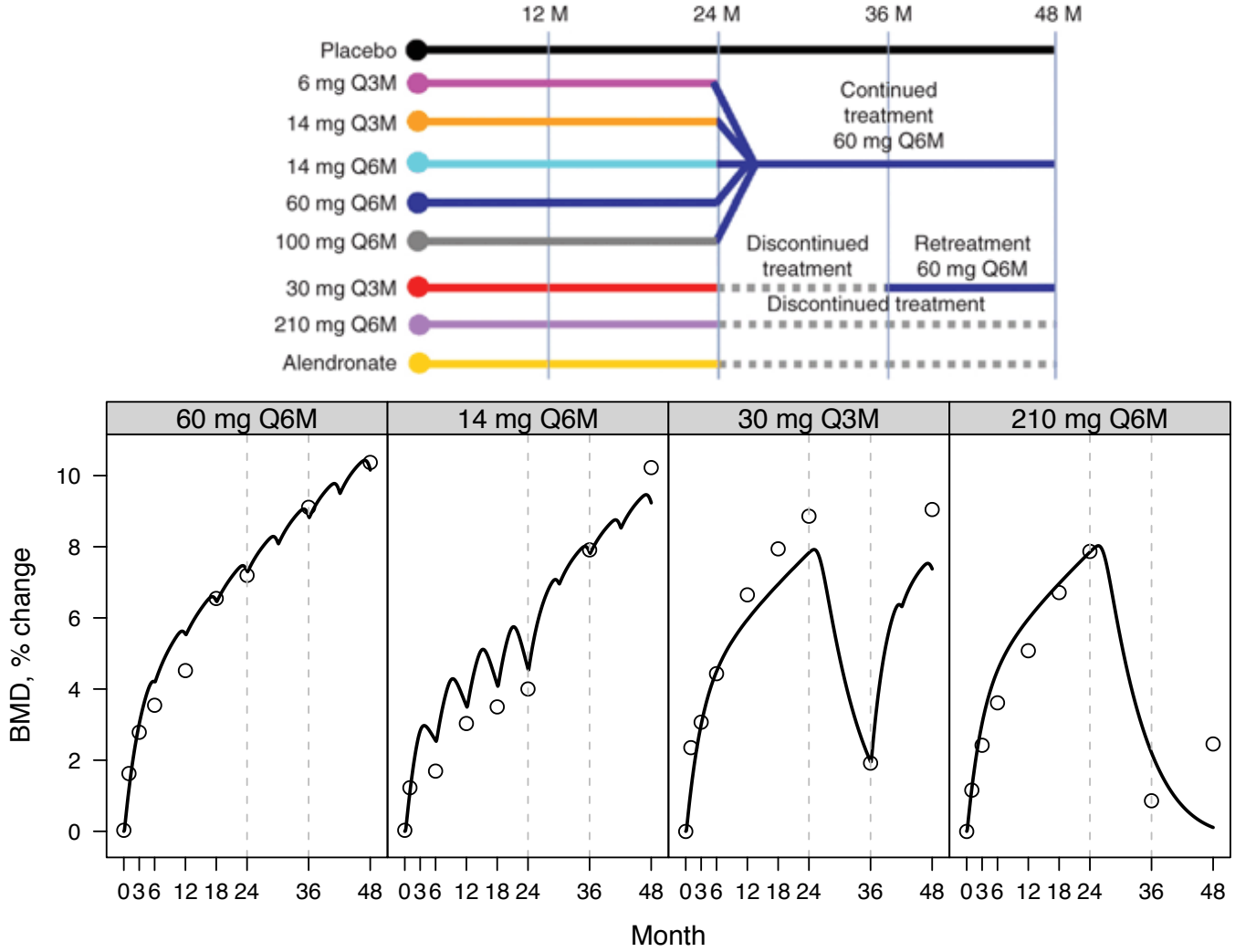
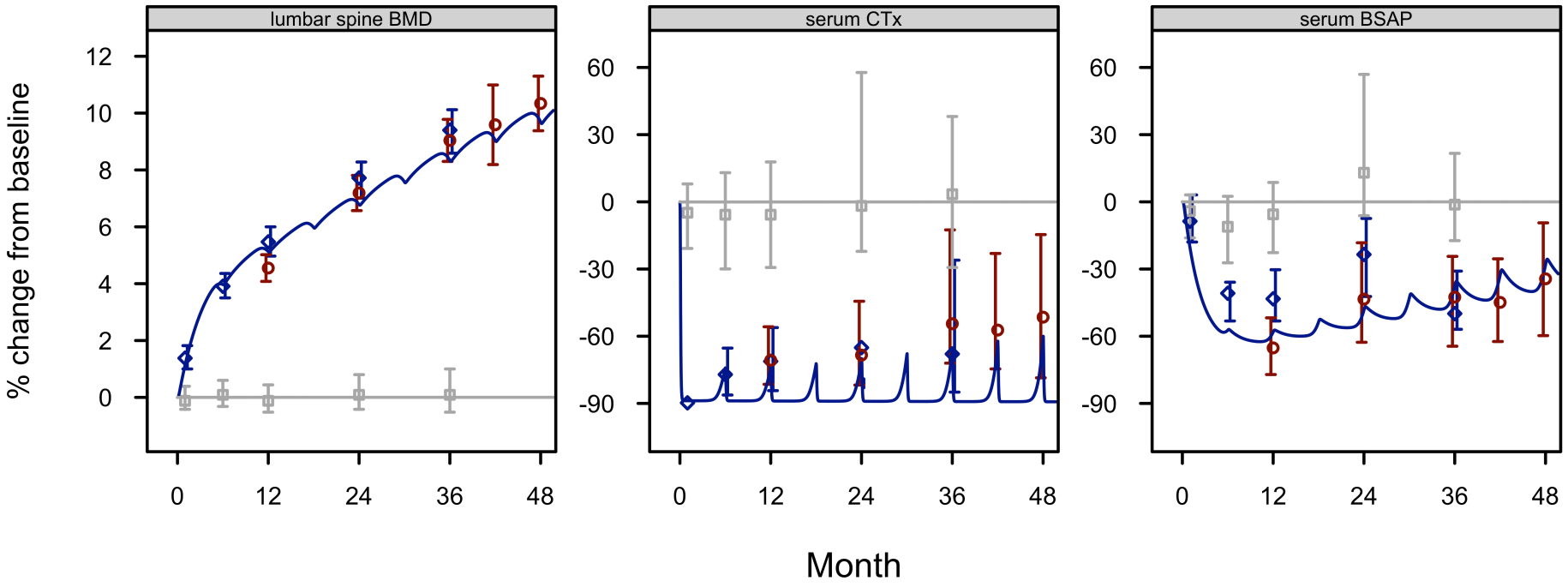


Fig.5; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

Denosumab Model Evaluation

FREEDOM (Phase 3) Trial Data



Observed (symbols) and simulated (lines) BMD, CTx, and BSAP during during treatment with 60mg Q6M denosumab for 4 years. Observed values from denosumab treatment groups: NCT00089791 (FREEDOM, blue symbols) and NCT00043186 (red symbols); and placebo treatment group: NCT00089791 (grey symbols).

Matthew M. Riggs, Kyle T. Baron, Elodie L. Plan, Marc R. Gastonguay. Qualification of a Physiologically-Based Model for Predicted Bone Marker and Bone Mineral Density Changes Associated with Denosumab Treatment. Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Minneapolis, MN; October 14, 2012 (Abstract# SU0363). **Available at: http://metrumrg.com/index.php/publications**

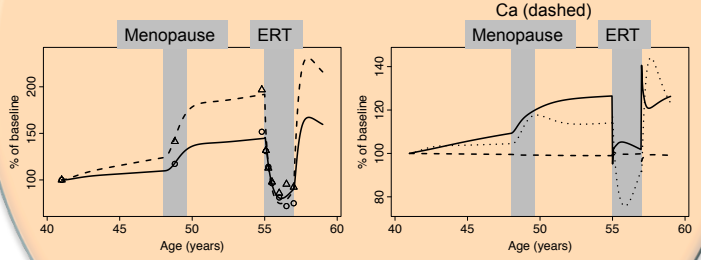
Applications: Disease Response

AGE + MENOPAUSE

Includes longitudinal estrogen loss
Predicts Ca & bone estrogen-related effects

Bone Markers
Resorption (dashed)
Formation (solid)

Maintain Ca Balance
PTH (solid)
Active TGF-beta (dotted)
Ca (dashed)

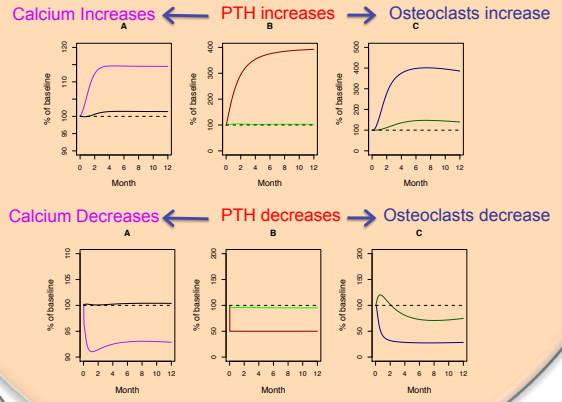


Riggs MM, Gillespie WR, Gastonguay MR, Peterson MC. NIGMS Quantitative Systems Pharmacology Workshop II: September 9, 2010.

DISEASE PROGRESSION

1⁰ HYPER- & HYPO-PARATHYROIDISM

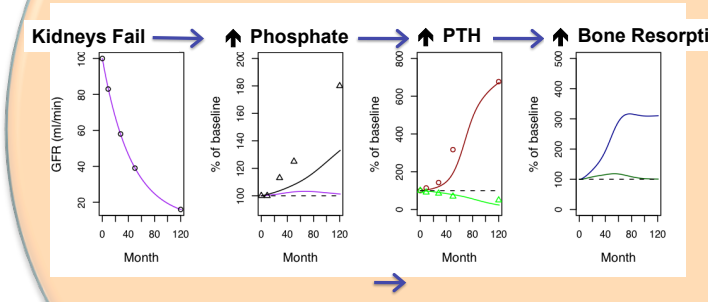
Predicts Ca and bone effects



Peterson and Riggs (2010)
Bone 46:49-63 (Fig 5 & 7)

CKD-MBD

Predicts Secondary hyperPTH
Predicts increased bone turnover



Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010: Poster # W4403

Estrogen Loss During Menopause Transition

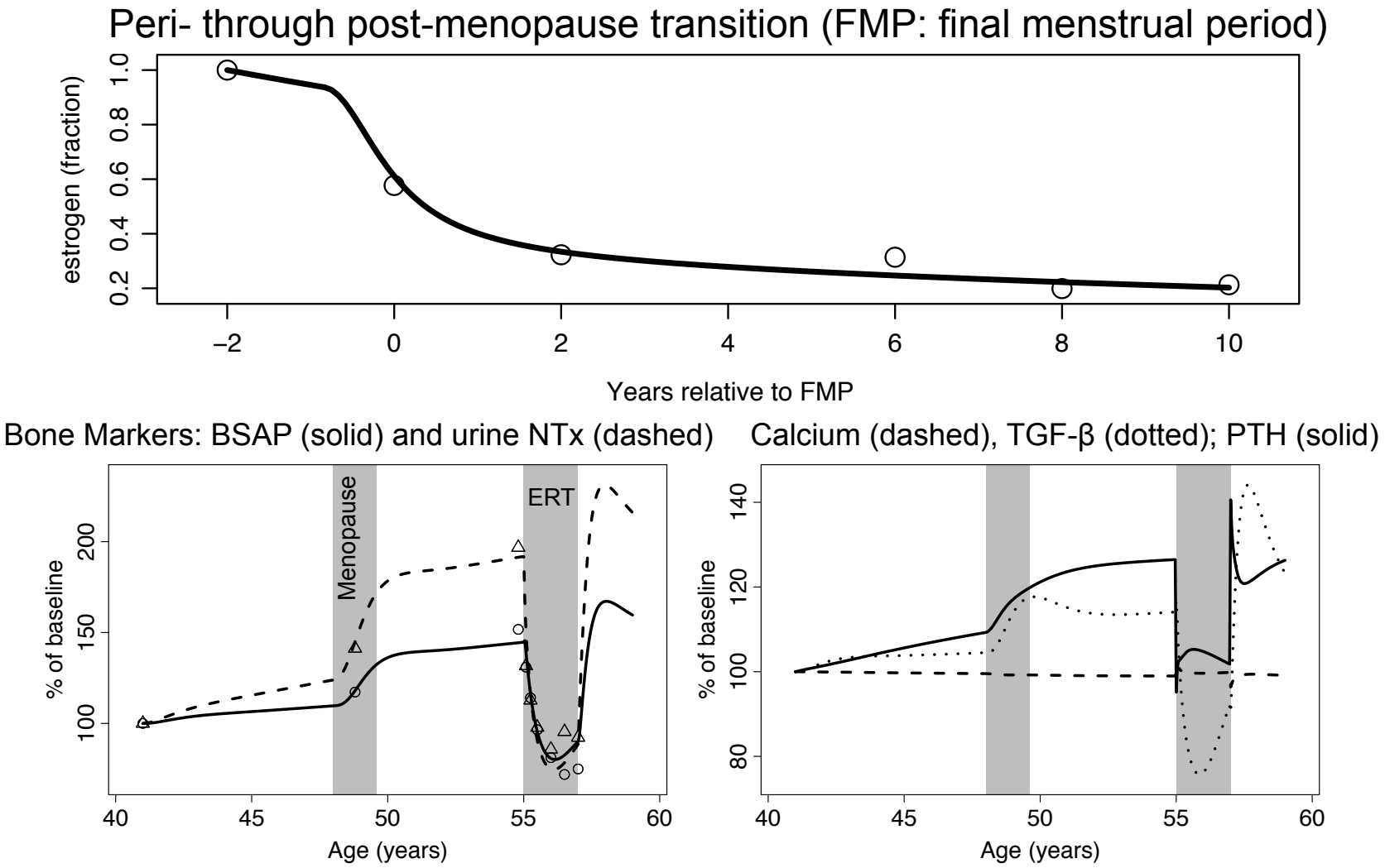


Figure 2 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f2.html#figure-title

Translate to GnRH Modulation: Estrogen Loss → BMD

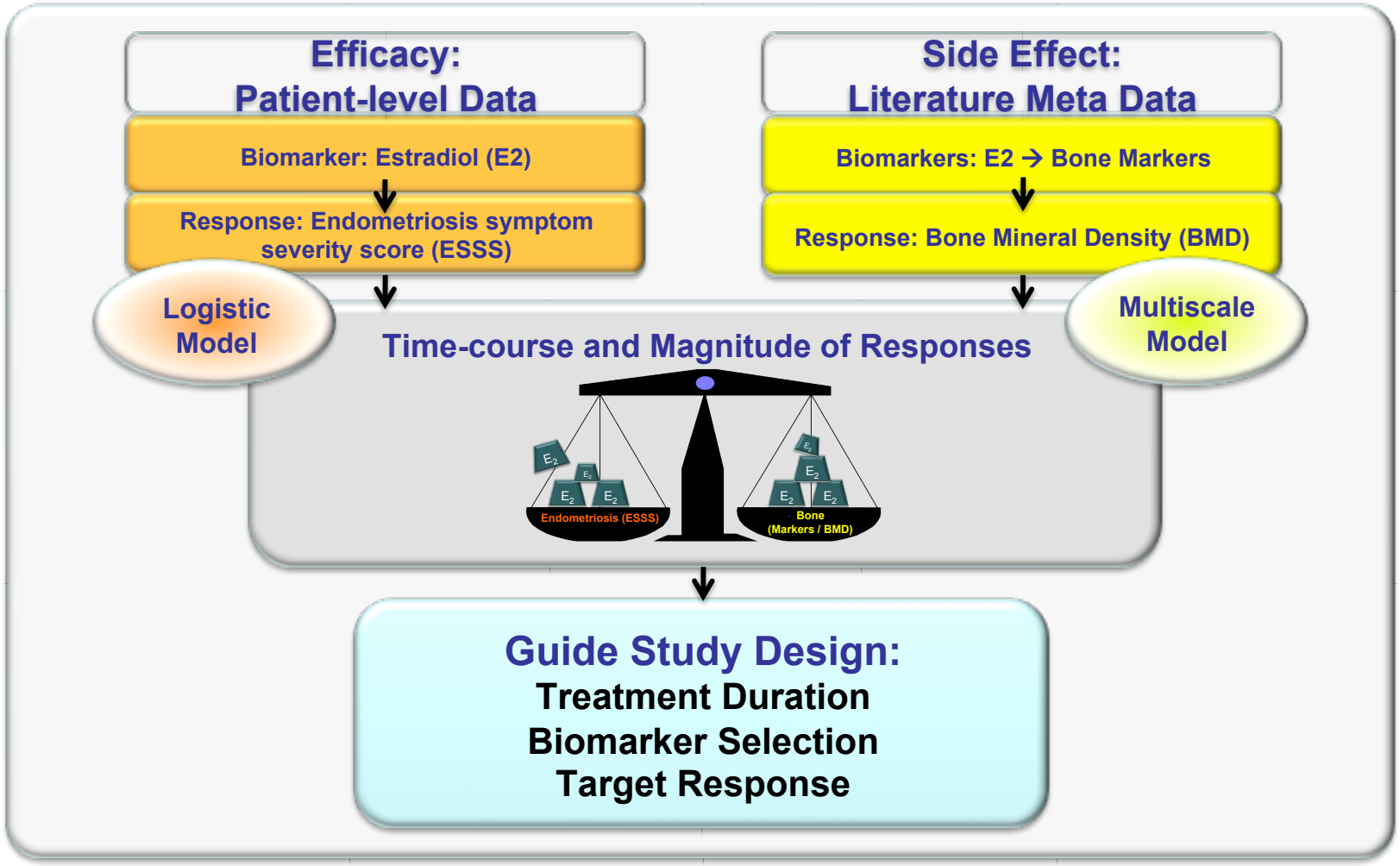
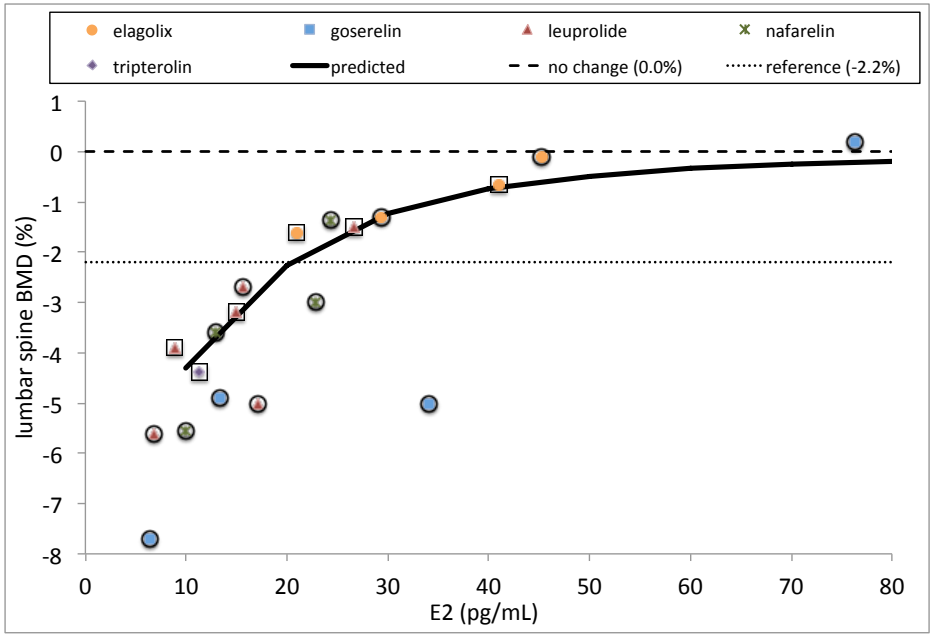


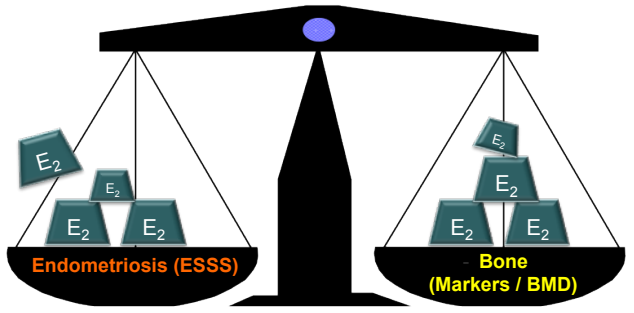
Figure 1 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

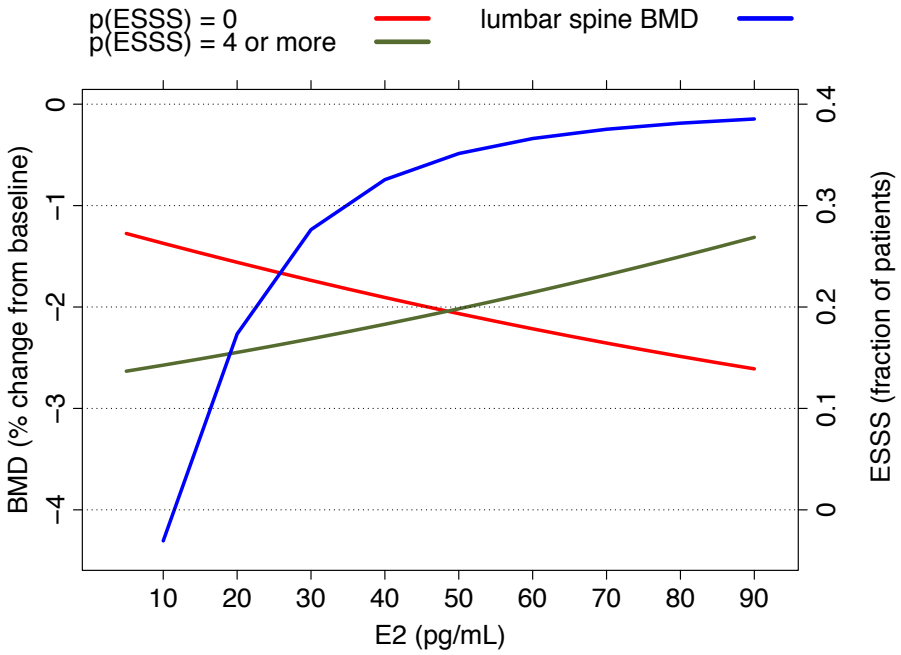
http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f1.html#figure-title

Translate to GnRH Modulation: Estrogen Loss → BMD

External Evaluation of BMD Response







Figures 4 and 6 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210ft.html

- Ongoing Extensions ("Middle-Out")

- Bone markers → Bone Mineral Density → Fracture Risk
- Vitamin D kinetics and biotransformation

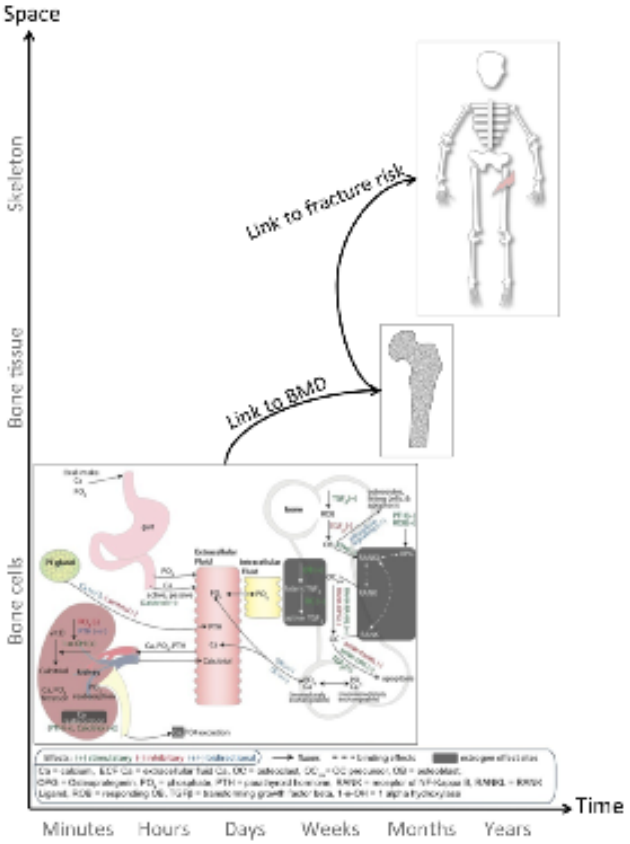
- Future Plans

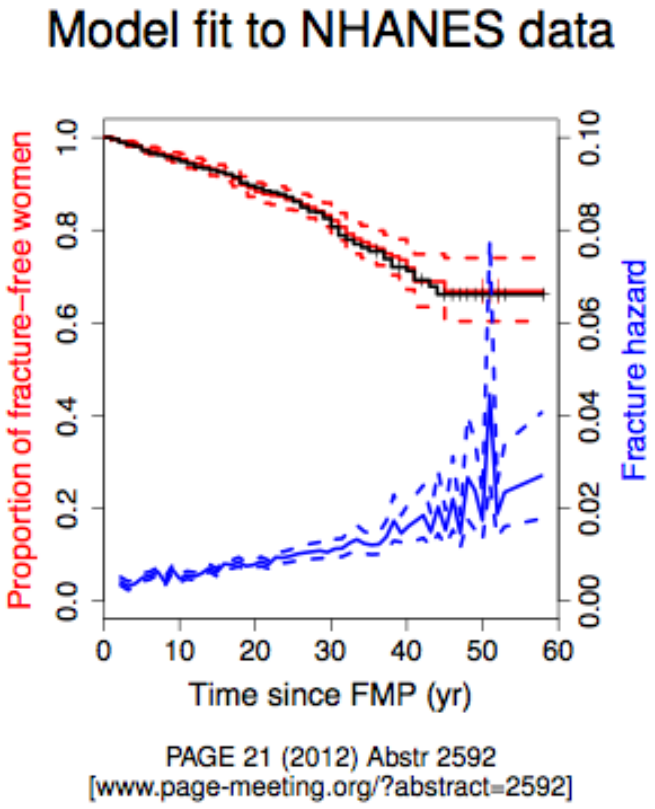
- WNT/SOST/DKK-1 pathways
- FGF-23
- Oncology
- Glucocorticoid-induced bone loss

R&D – Fracture Risk Modeling

- **Bayesian Joint Modeling of Bone Mineral Density and Repeated Time-To-Fracture Event for Multiscale Bone Systems Model Extension**. PAGE 21 (2012) Abstr 2592 [www.page-meeting.org/?abstract=2592]

BMD-Fracture Model





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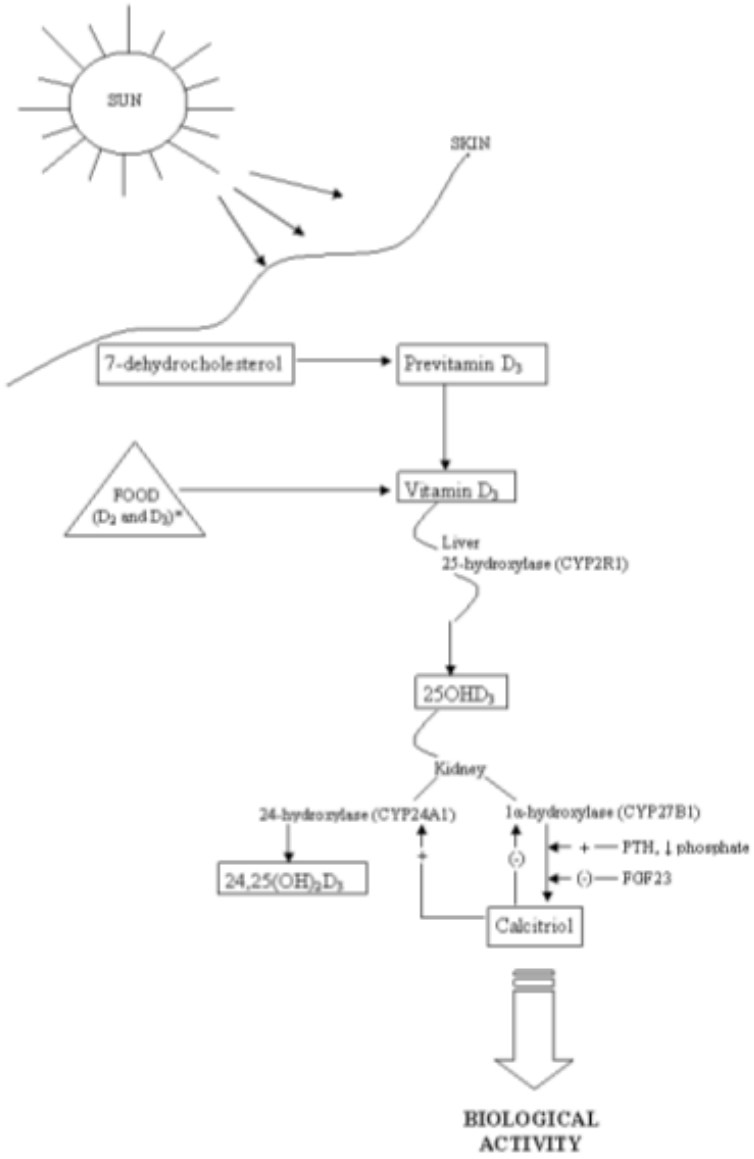
[www.page-meeting.org/?abstract=2592]

R&D -- Vitamin D kinetics and biotransformation



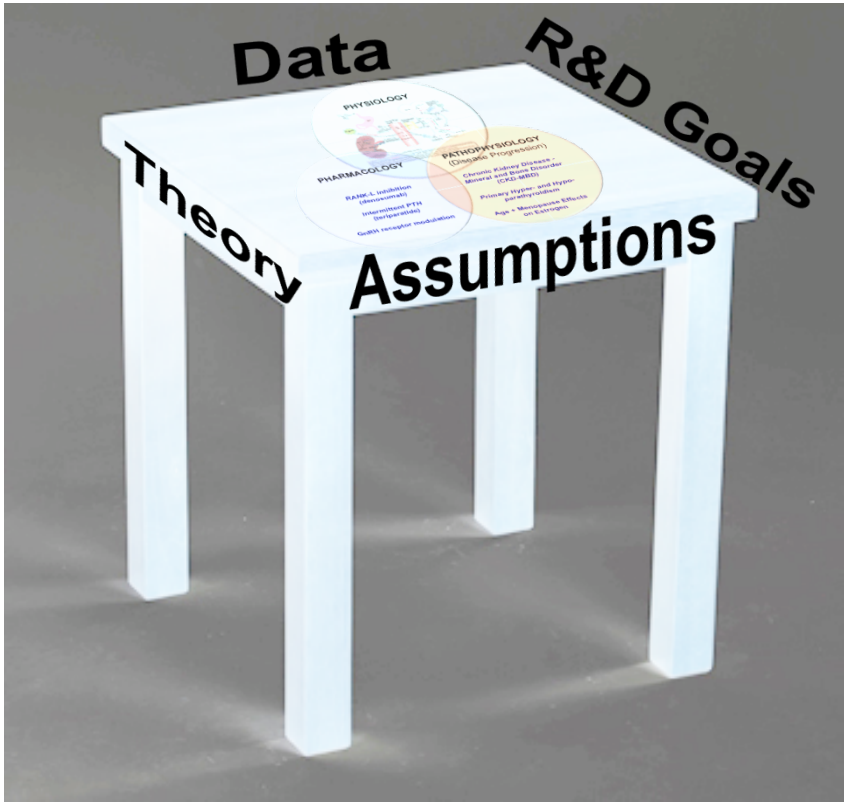
*Vitamin D can also be in the diet as vitamin D_2, which undergoes the same metabolic steps shown here for vitamin D_3.

- Vitamin D input: diet and sun
- Biotransformation: involves liver and kidney
- Pharmacology: active Vit D = calcitriol
- Applications: disease states evaluations, trial design, supplemental recommendations

Figure 3-1 of Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press, 500 Fifth Street, N.W. Wasihngton, DC 20001, 2011.*

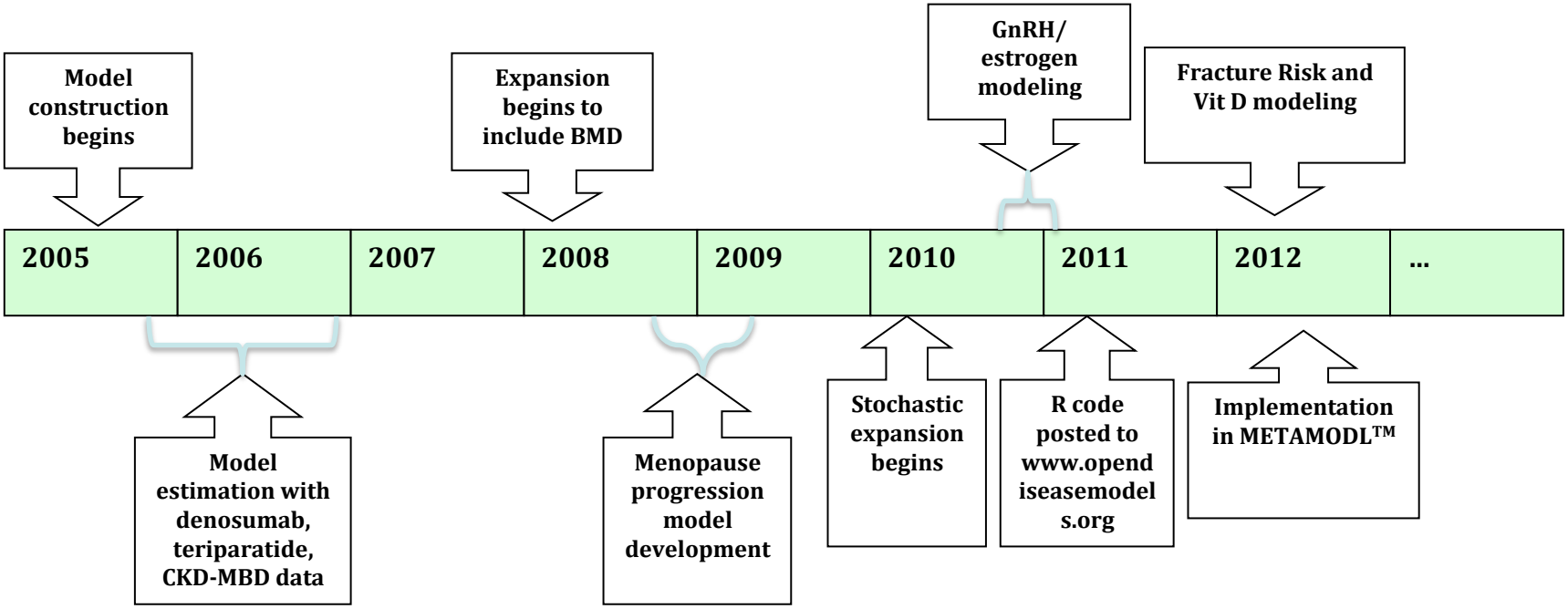
SUMMARY

- Multiscale Models as a Knowledge Platform / Repository



- Include supporting data
- Input emerging research
  - New data = learn/confirm hypotheses and assumptions
  - Information becomes knowledge (translational, model-based R&D)
- Sharing within and across R&D teams
  - Portable across drug and disease states
  - Expandable to new drug and disease states

MSPM as an expandable R&D platform



- Construct in adaptable framework: address broad research questions
- Offer efficient, timely extension and application
- Repository of known mechanisms, hypotheses (theory), assumptions, and ongoing R&D goals

- Acknowledgements

- Metrum RG
  - Kyle Baron, Ph.D.
  - Marc Gastonguay, Ph.D.
  - Alanna Ocampo-Pelland, M.S., Ph.D. Student
  - Elodie Plan, Ph.D. (now @ Uppsala U)
- Mark Peterson, Ph.D., Pfizer (formerly Amgen)
- Pfizer (GnRH modulation modeling)
  - Steve Martin, Ph.D.
  - Piet van der Graaf, Ph.D. (now @ Leiden U)

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Tariffville, CT

- Parting Thoughts

- The scales do not need to be all inclusive…
  - but should match the question(s) at hand
- Model validation/evaluation?
  - Consider model validation at different scales
- Team ownership: biologists, pharmacologists, clinicians
  - Shared consensus on assumptions
  - Appropriate representations
    - » the known
    - » the unknown
    - » the ‘to be determined’
- These models *are* complicated, but…
  - biology, pathphysiology and pharmacology are even more complicated

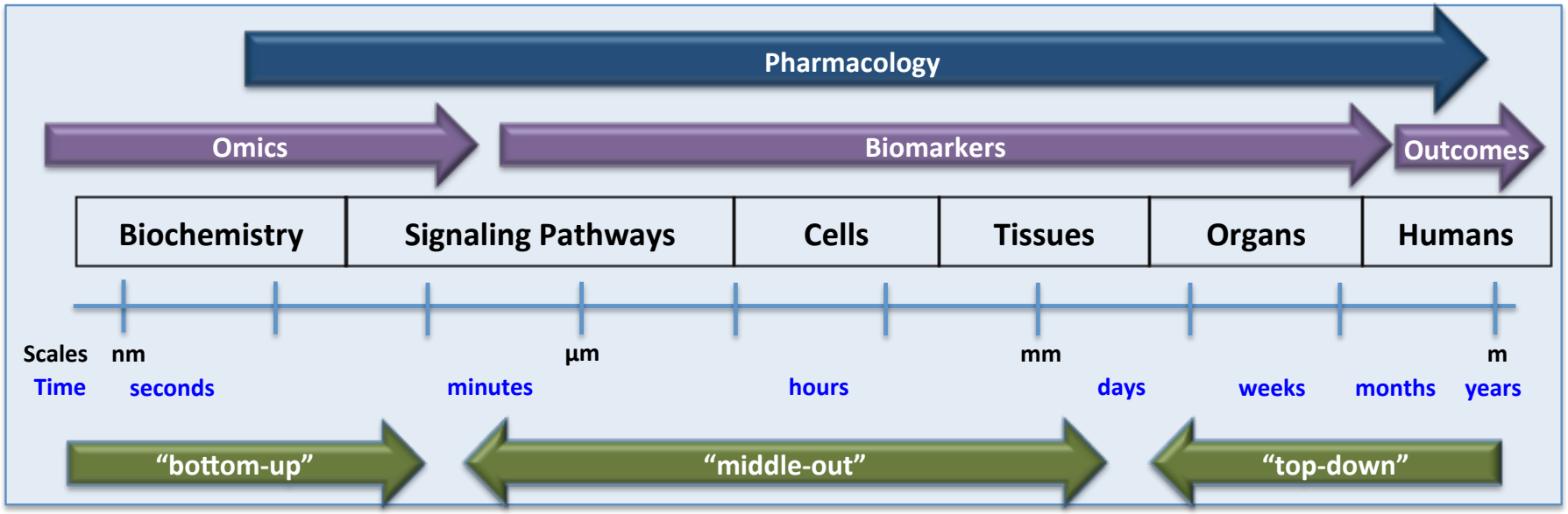
- Benefits: What's to be Gained?

- selection of therapeutic modality
- hypothesis driven experimentation
- holistic drug design
- selection of target pathways and patient populations
- dose / regimen selection
- broad scale understanding of intended (and unintended) effects associated with disease, genetic variants and drug intervention,
- trial (experiment) simulation/optimization
- simultaneous predictions of all involved co-factors -- potential for biomarker identification
- can serve as repository of known, suspected, and assumed effects with supporting data ... information sharing within and across R&D teams
- …

- Challenges/Barriers: What's holding us back?

- differing role(s) on R&D teams
- sufficient resources (time, people and/or $)
- training -- broad skill set required
- leadership investment in defining opportunities for real impact
- intellectual inertia (differing discipline nomenclatures, perspectives, and motivations to develop models),
- data (formatting, availability, quality)
- …

- What is a Multiscale Systems Model?



From Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. *AAPS Newsmagazine (December, 2011)*

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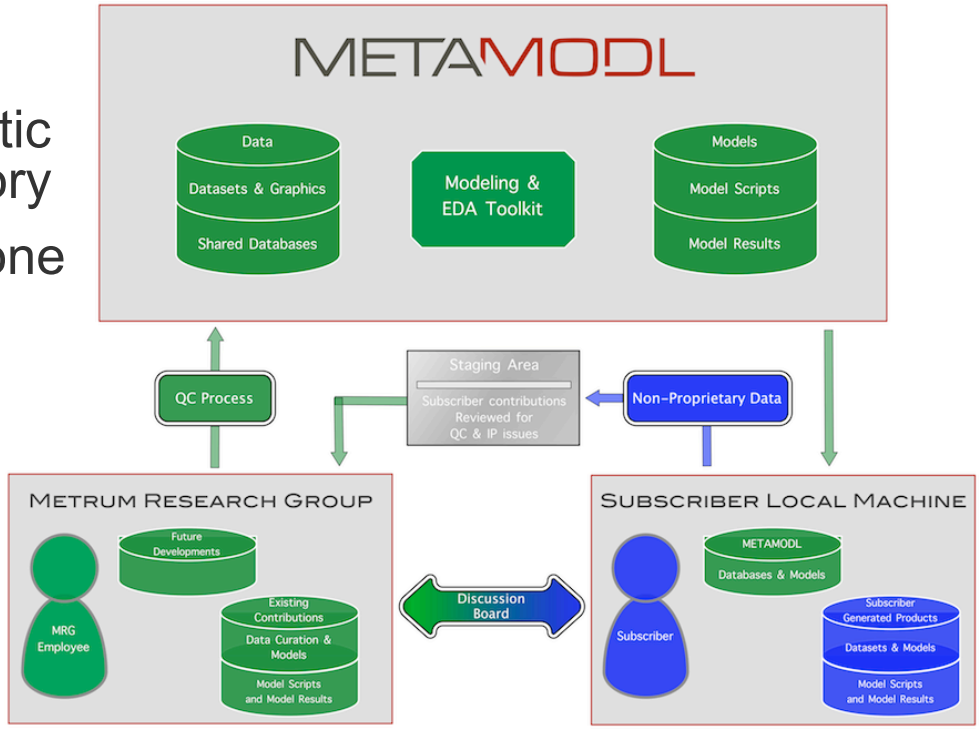
- METAMODL™

- Subscription-Based, Therapeutic Area Model and Data Repository
- Incorporates All Current Ca-Bone Model Extensions



Chronic Kidney Disease-Mineral Bone Disorder

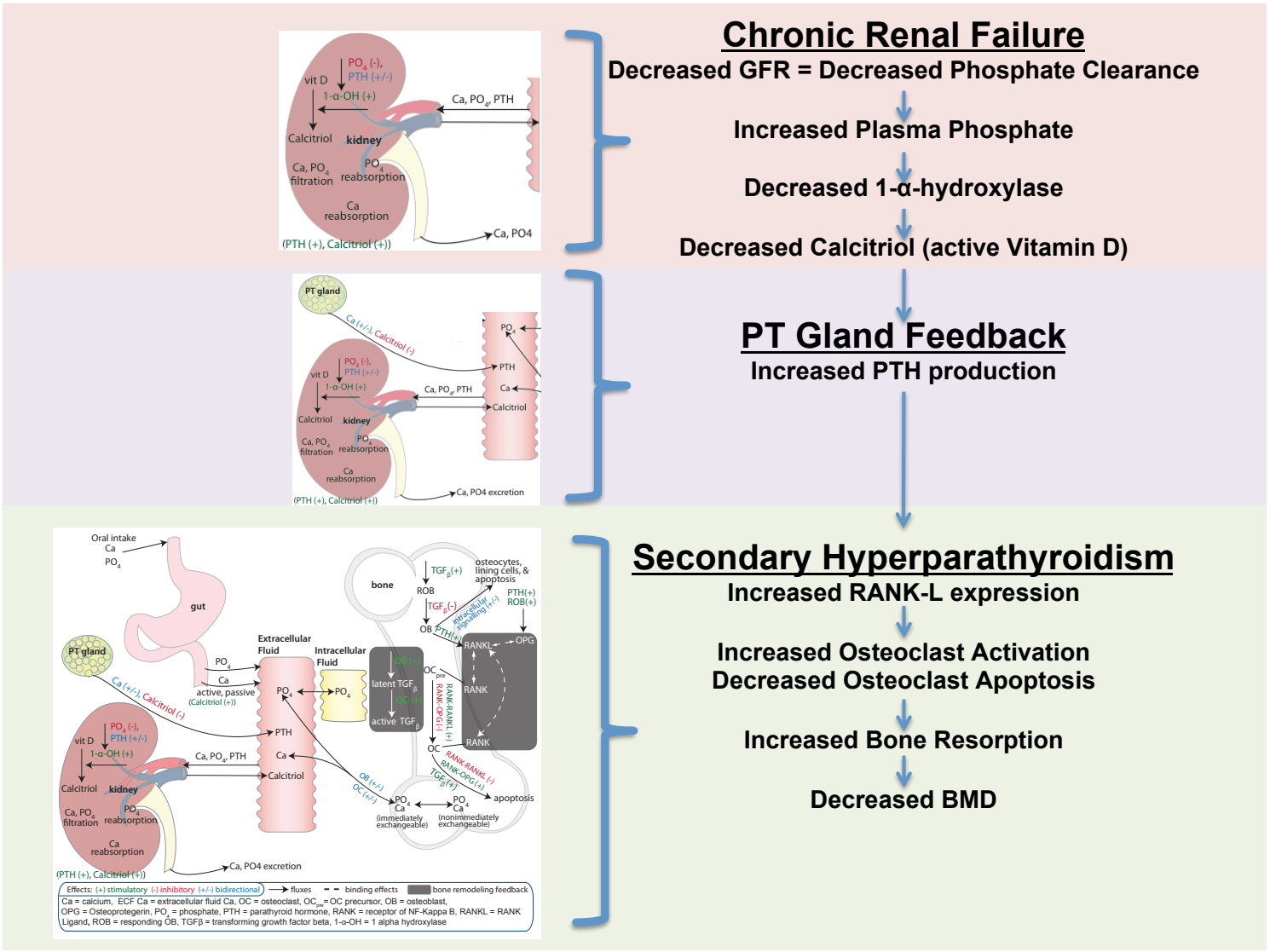


Fig. 1; M. M. Riggs, M. C. Peterson, and M. R. Gastonguay. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.

Chronic Kidney Disease-Mineral Bone Disorder

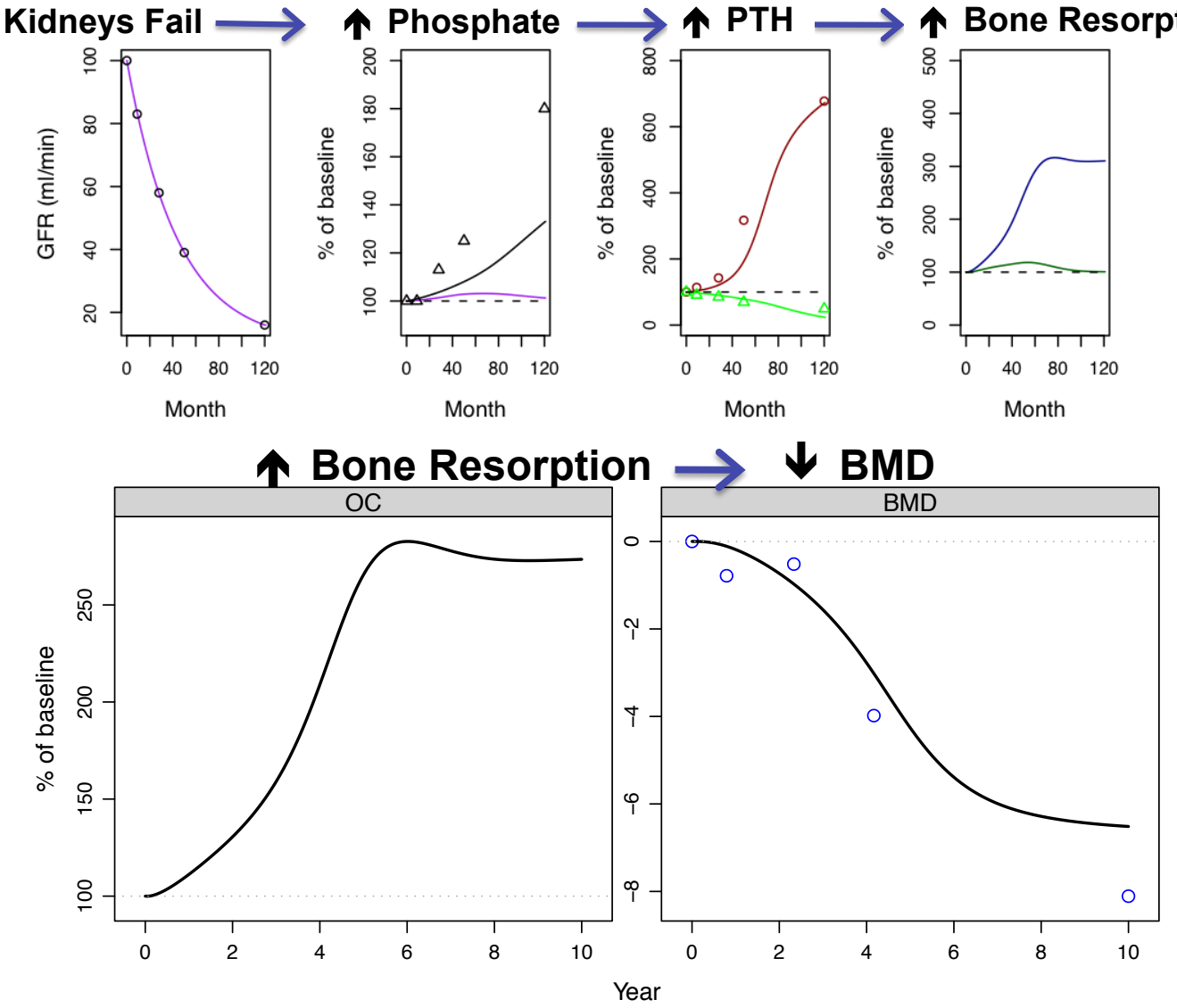
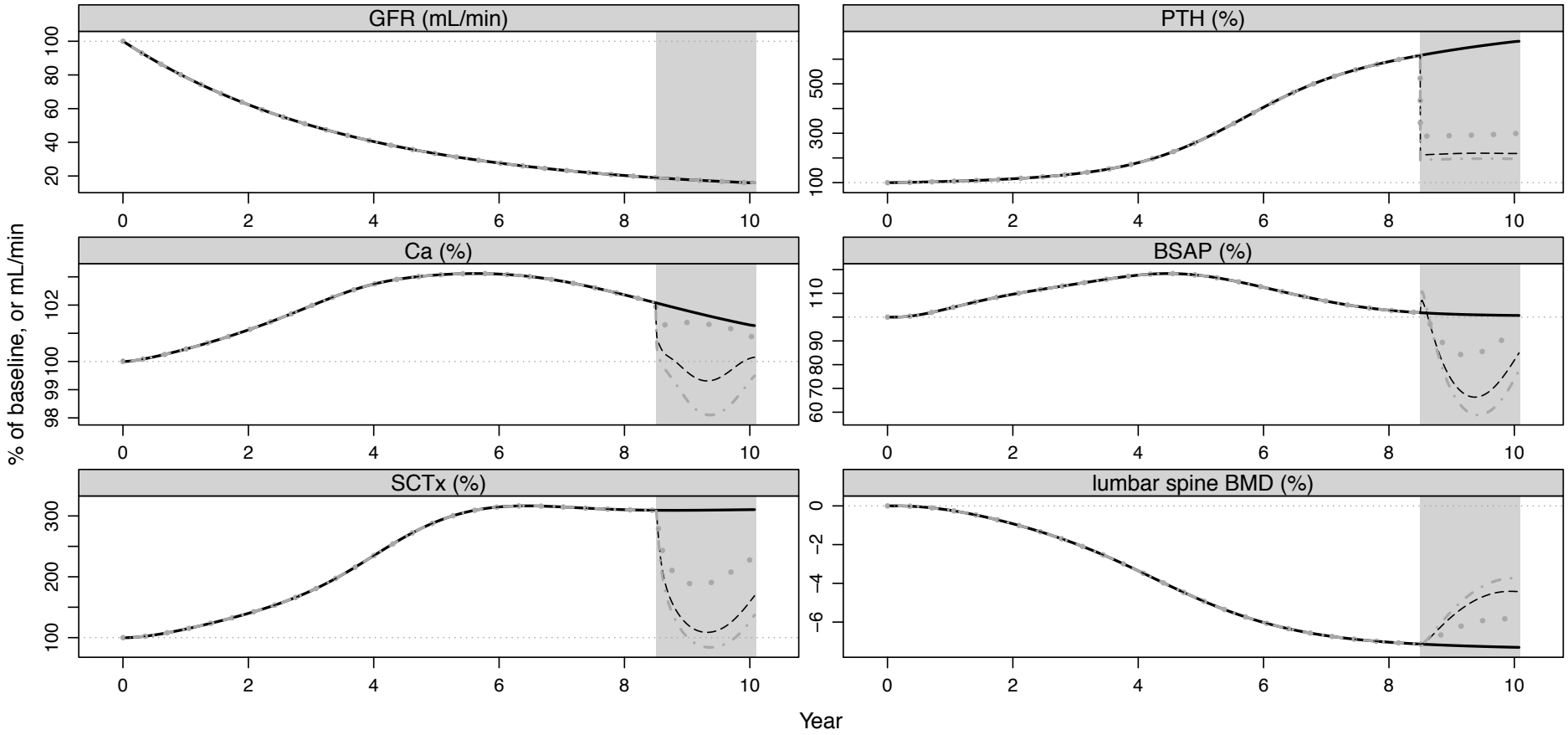


Fig. 2, 3; M. M. Riggs, M. C. Peterson, and M. R. Gastonguay. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of CaSR agonism

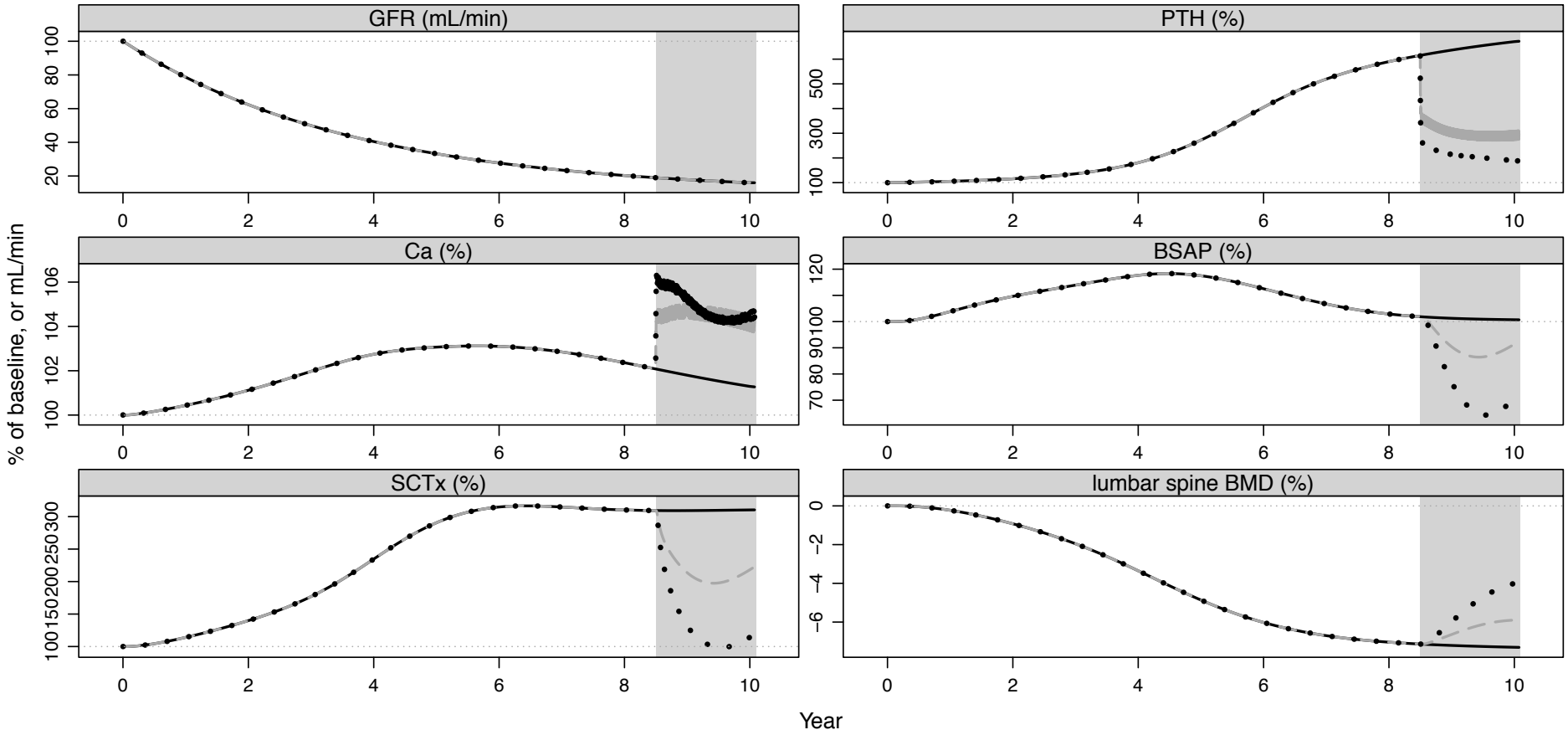


black solid = no intervention; gray dot = 0.33 mmolar Ca Eq; black longdash = 0.67 mmolar Ca Eq; gray dotdash = 1.0 mmolar Ca Eq

Fig. 4; M. M. Riggs, M. C. Peterson, and M. R. Gastonguay. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of Calcitriol Infusion



black solid = no intervention; gray dash = 1.25 mcg QOD; black dot = 2.5 mcg QOD

Fig. 5; M. M. Riggs, M. C. Peterson, and M. R. Gastonguay. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.