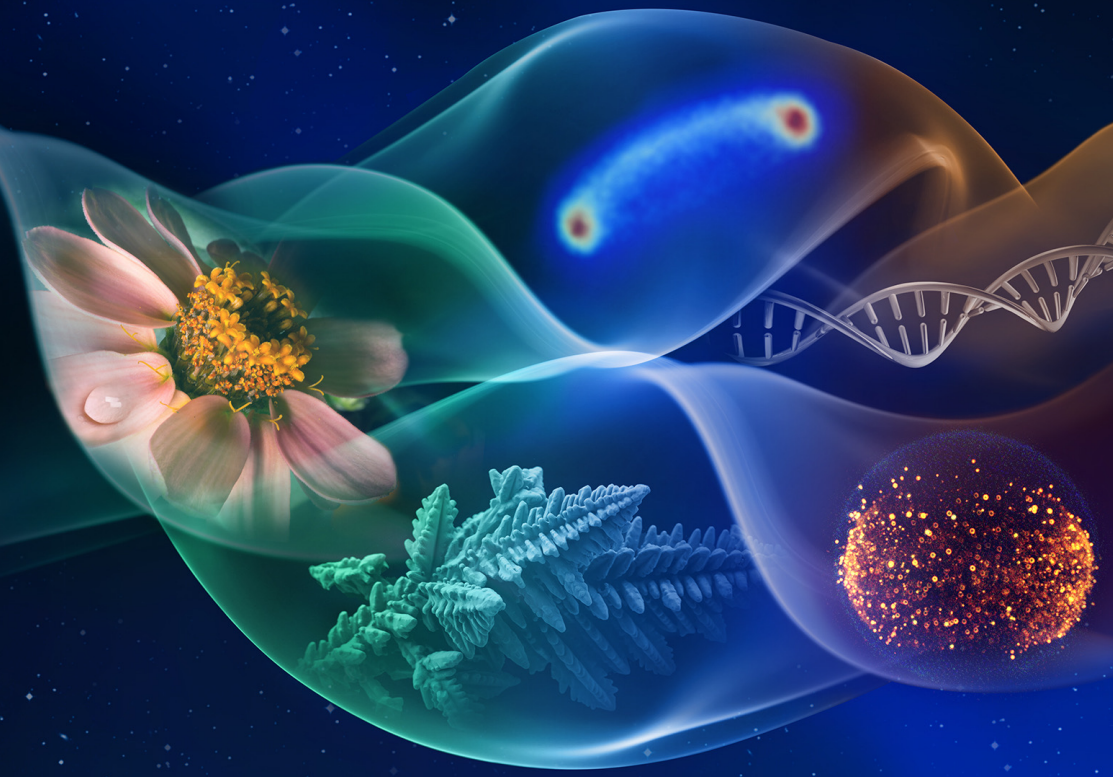
Bone Biology, Spaceflight, and Assays



National Aeronautics and Space Administration

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KBR
July 13, 2023
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Biological Responses of Space Exploration

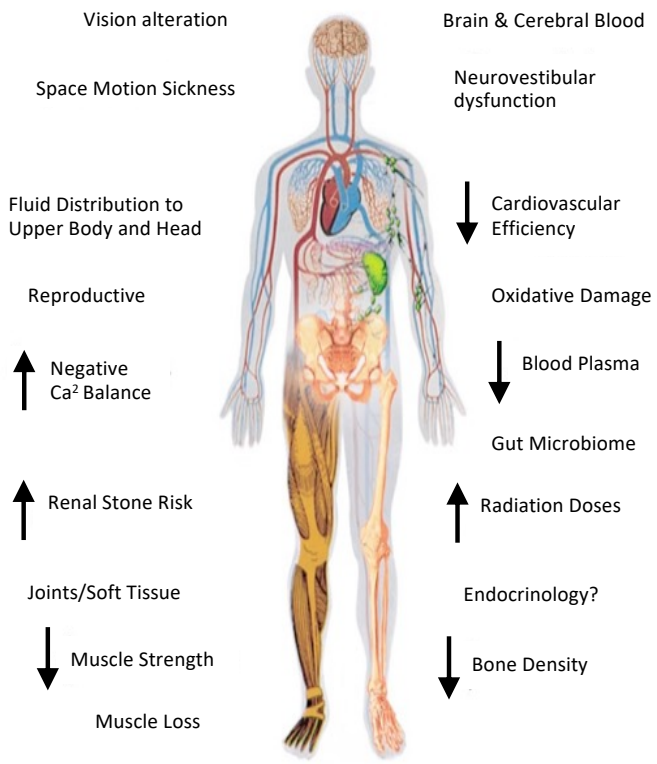
What's Occurring? Severity?

When? Time course?

Where? Whole system? Isolated?

How? Mechanics?

In Space vs On Earth?



Spaceflight and Risk- NASA Human Systems Risk Board

npj | Microgravity

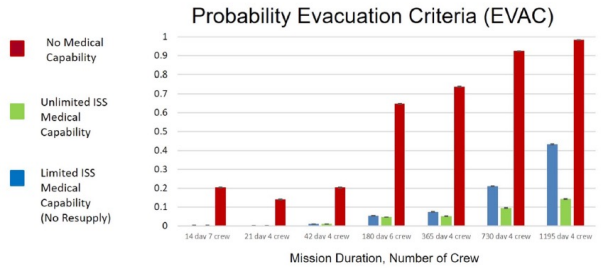
www.nature.com/npjmgrav

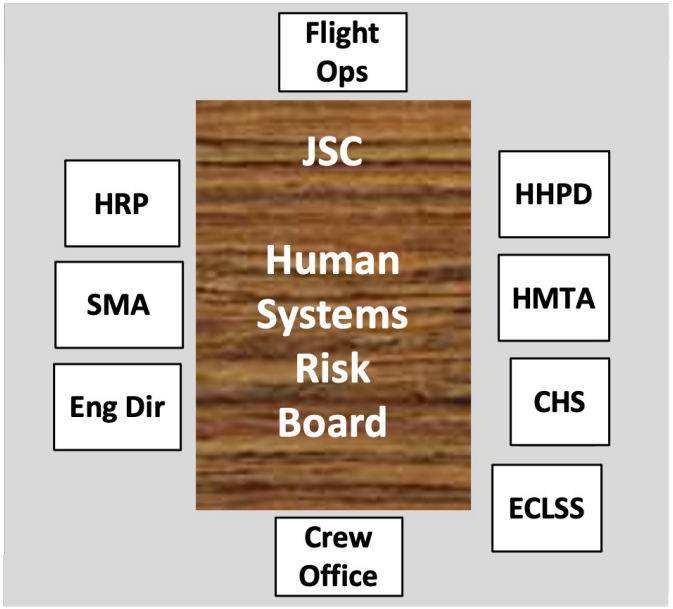
ARTICLE OPEN

Check for updates

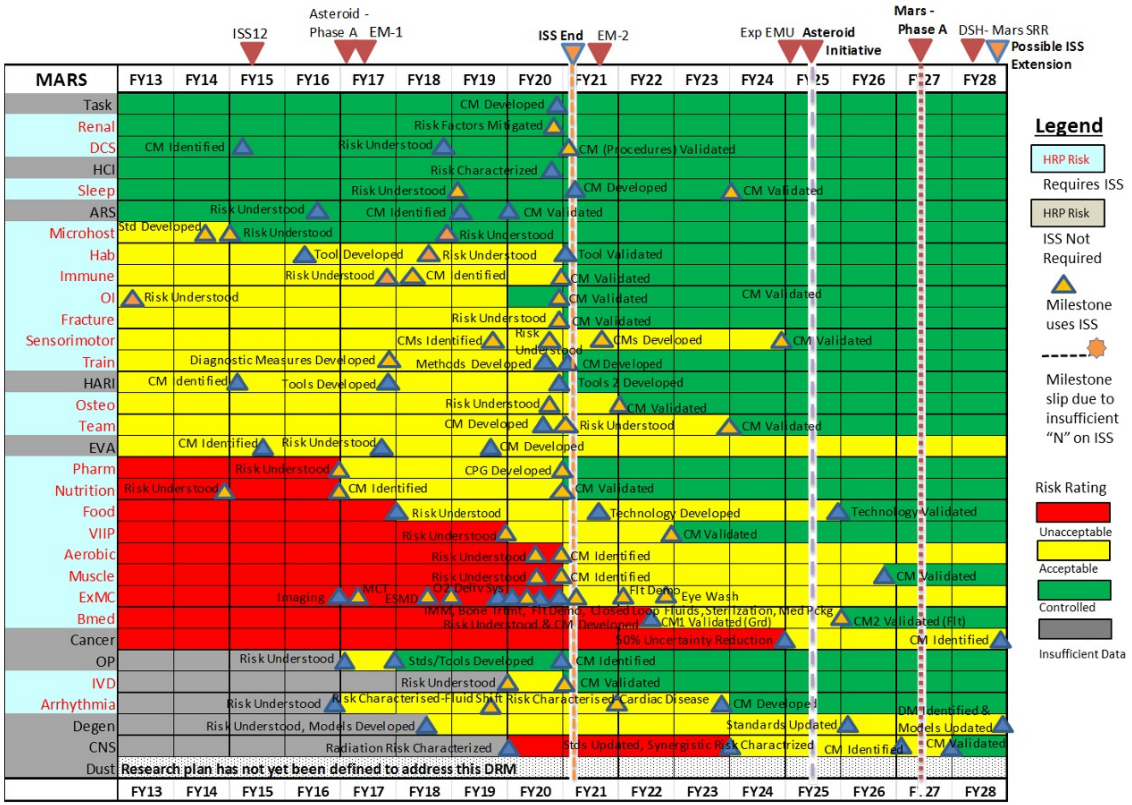
Estimating medical risk in human spaceflight

Erik L. Antonsen[1✉], Jerry G. Myers[2], Lynn Boley[3], John Arellano[4], Eric Kerstman[5], Binaifer Kadwa[6], Daniel M. Buckland[6,7] and Mary Van Baalen[6]

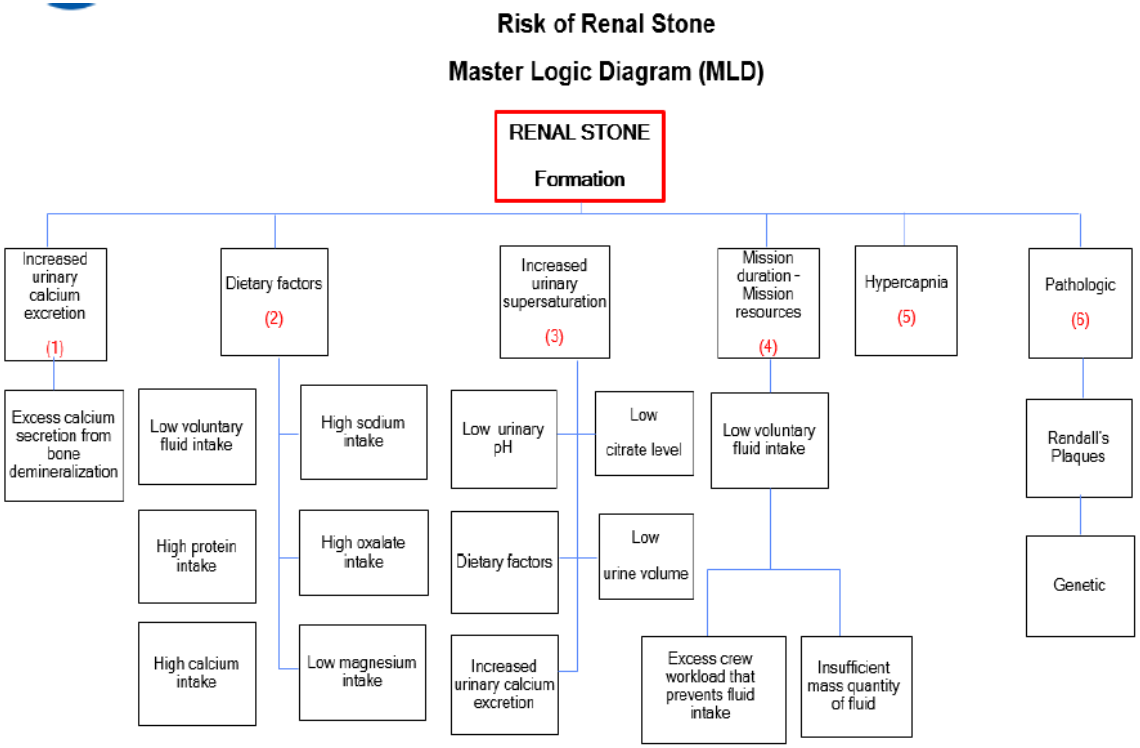




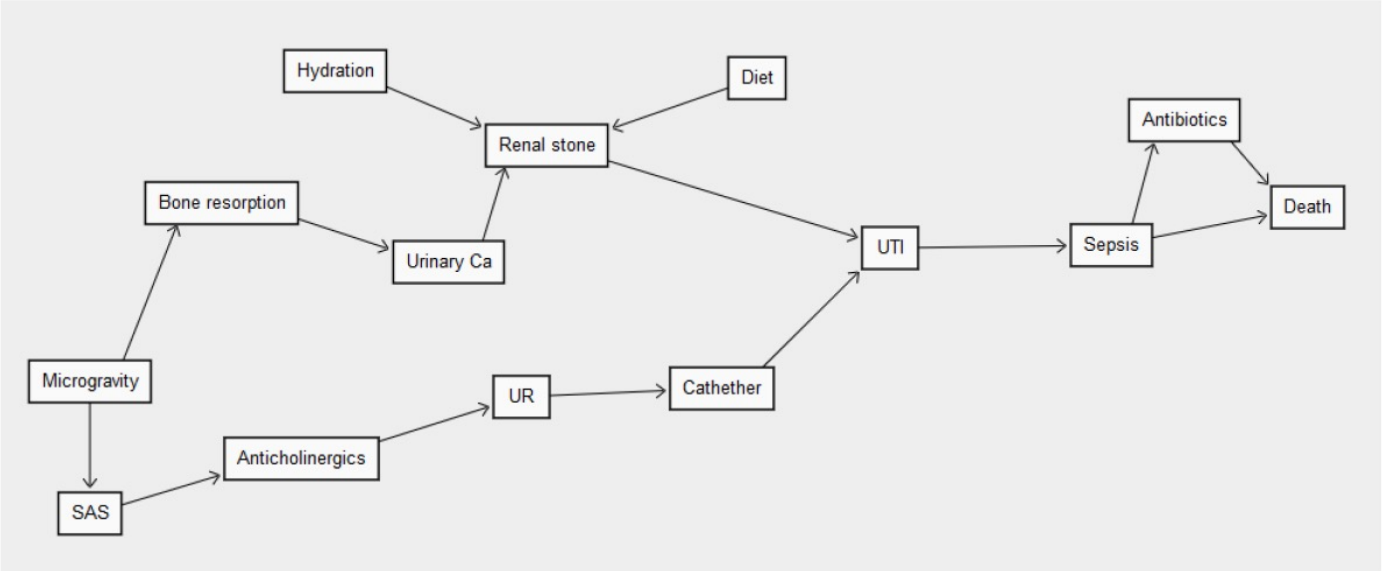
Risk Reduction Path



Master Logic Diagram

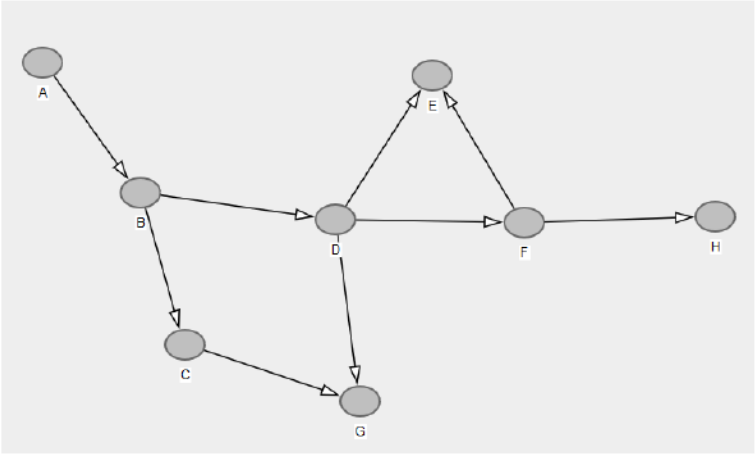


Example UTI

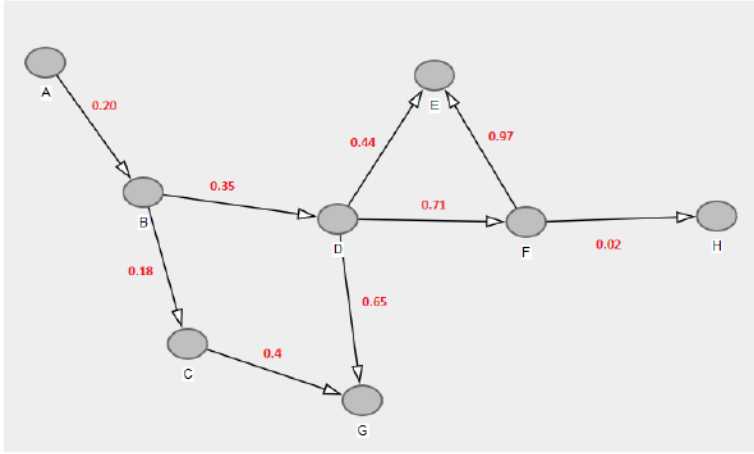


Novel question: How does use of anticholinergics modify our total probability of death from sepsis after UTI?

Where this leads to

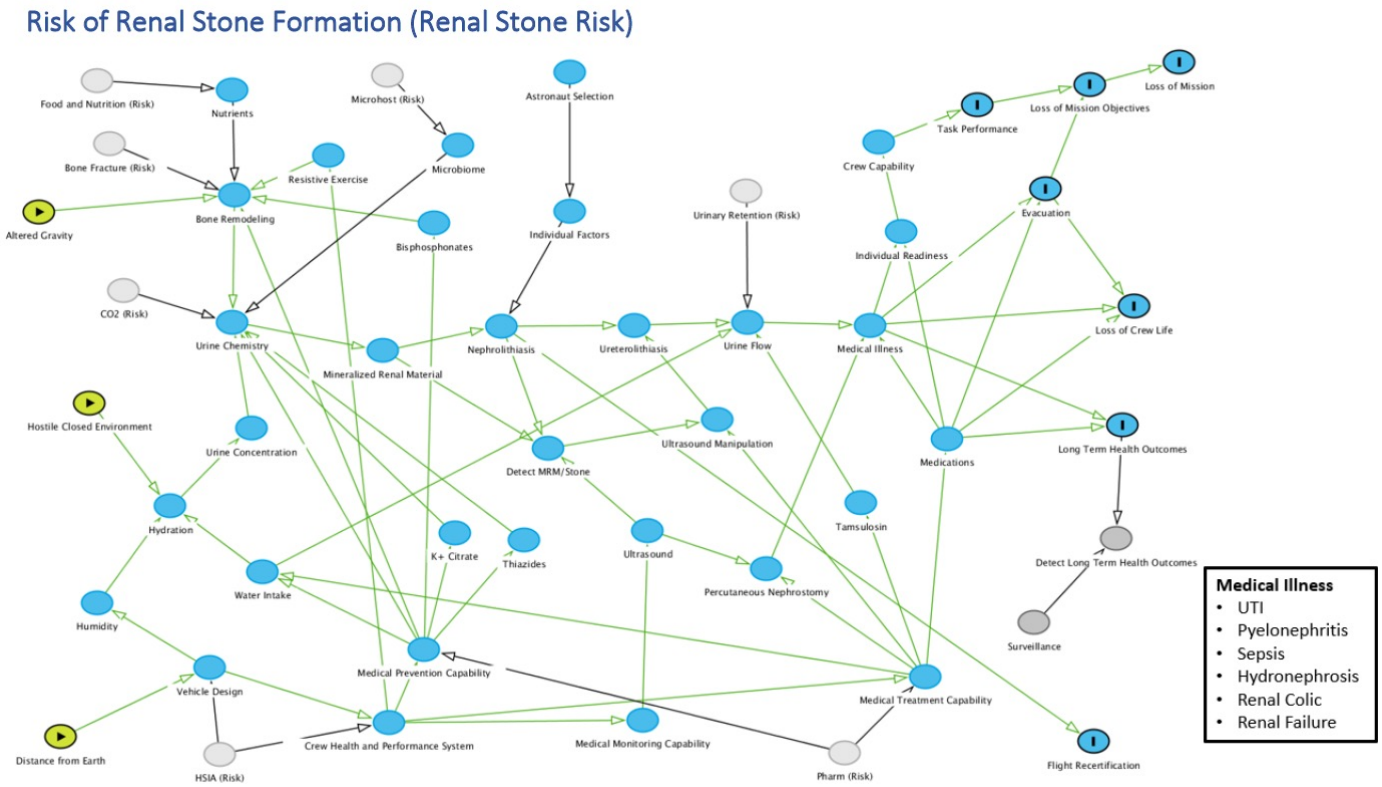


DAG



Bayesian Network

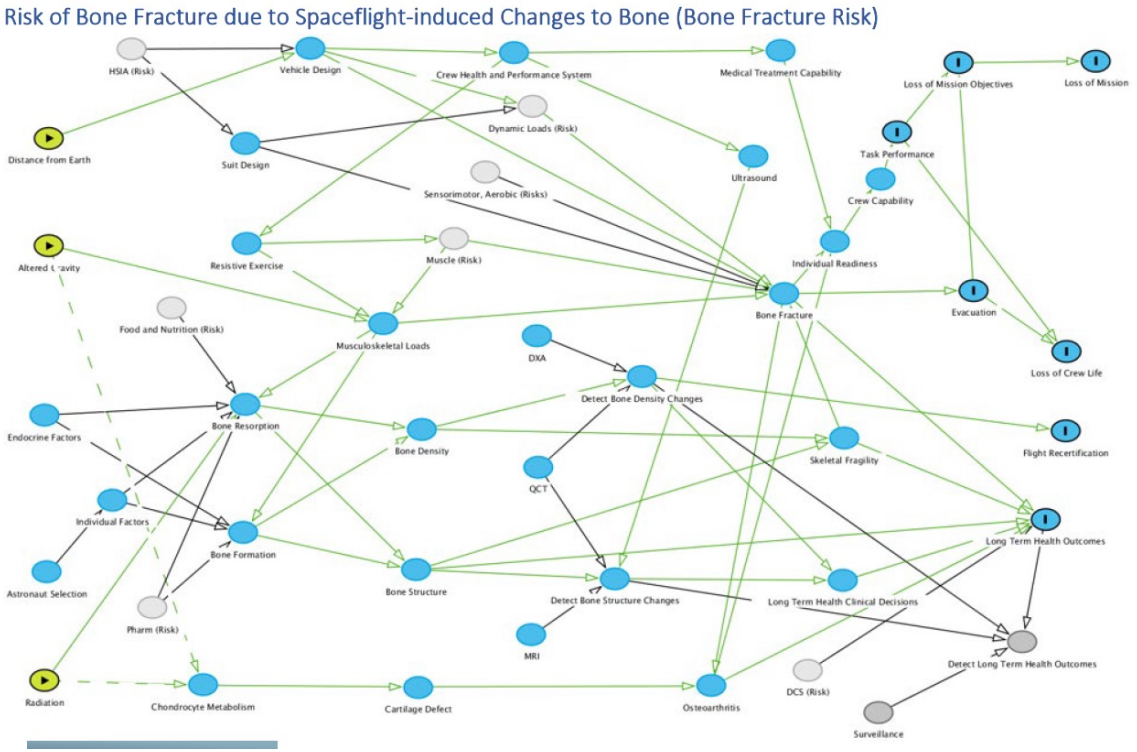
Renal Stone Risk DAG



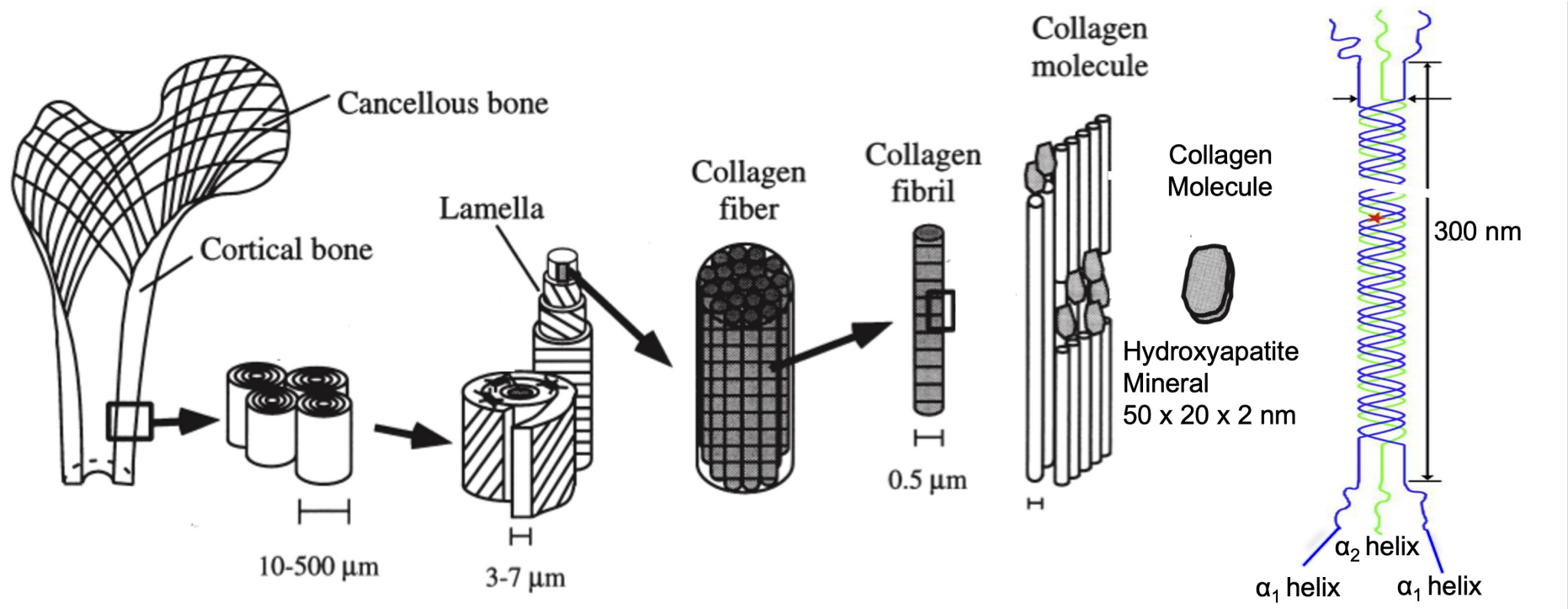
SMEs involved in creation of DAGs

Risk Title	Risk Custodian: Epidemiology	Risk Custodian: Ops	Risk Custodian: Research
Aerobic Risk	Maners, Jillian	Roden, Sean	Rivas, Eric (Acting)
Behavioral Risk	Petersen, Devan	Picano, James	Whiting, Sara
Bone Fracture Risk	Monti, Avalon	Kreykes, Amy	Sibonga, Jean
Cardiovascular Risk	Charvat, Jaqueline	Suresh, Rahul	Lee, Stuart
CO2 Risk	Osborne, Suzy	Alexander, David	Ryder, Valerie
Crew Egress Risk	Monti, Avalon	Haas, Christopher	Moore, Nathan
Decompression Sickness (DCS) Risk	Murray, Jocelyn	Sanders, Bob	Norcross, Jason
Dust Risk	Springer, Tamara	Keprta, Sean	McCoy, Torin
Dynamic Loads Risk	Monti, Avalon	Pattarini, James	Somers, Jeff
Electrical Shock Risk	Coble, Chris	Suresh, Rahul	Rasbury, Jack
EVA Risk	Murray, Jocelyn	Scheuring, Rick	Norcross, Jason
Food and Nutrition Risk	Maners, Jillian	Wu, Xulei	Douglas, Grace; Smith, Scott
Hearing Loss Risk	Coble, Chris	Robinette, Martin	Allen, Chris
Human-System Integration Architecture (HSIA) Risk	Petersen, Devan	Vos, Gordon	Vera, Alonso
Hypoxia Risk	Murray, Jocelyn	Sanders, Bob	Norcross, Jason
Immune Risk	Babiak-Vazquez, Adriana	Pavela, James	Crucian, Brian
Medical Conditions Risk	Taiym, Wafa	TBD	TBD
Microhost Risk	Babiak-Vazquez, Adriana	Valencia, William	Ott, Mark
Muscle Risk	Maners, Jillian	Scheuring, Rick	Prejean, Brian (Acting)
Non-Ionizing Radiation (NIR) Risk	Charvat, Jaqueline	Brunstetter, Tyson	Gaza, Ramona
Pharm Risk	Charvat, Jaqueline	Bayuse, Tina	Daniels, Vernie
Radiation Carcinogenesis Risk	Charvat, Jaqueline	Semones, Eddie	Sishc, Brock
Renal Stone Risk	Mason, Sara	Cole, Rick	Williams, Spencer
SANS Risk	Mason, Sara / Osborne, Suzy	Brunstetter, Tyson	Laurie, Steve
Sensorimotor Risk	Nartey, Nicholas	Hart, Stephen	Rosenberg, Marissa
Sleep Risk	Babiak-Vazquez, Adriana	Hart, Stephen	Flynn-Evans, Erin
Team Risk	Babiak-Vazquez, Adriana	Holland, Al	Landon, Lauren
Toxic Exposure Risk	Petersen, Devan	Alexander, David	Ryder, Valerie
Urinary Retention Risk	Mason, Sara	Cole, Rick	N/A
Venous Thromboembolism (VTE) Concern	Charvat, Jaqueline; Mason, Sara	Pavela, James	Marshall-Goebel, Karina

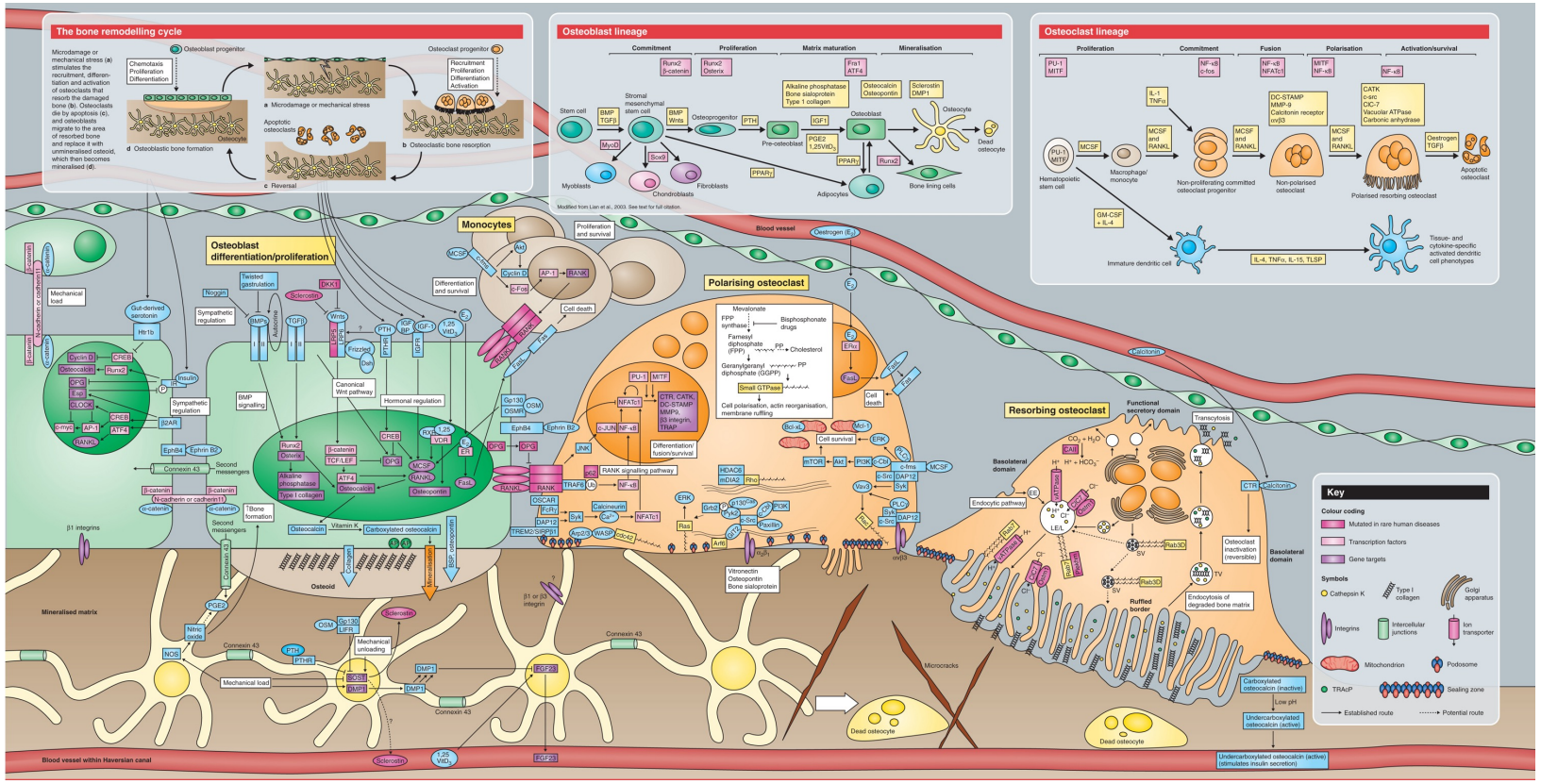
Bone Fracture Risk DAG



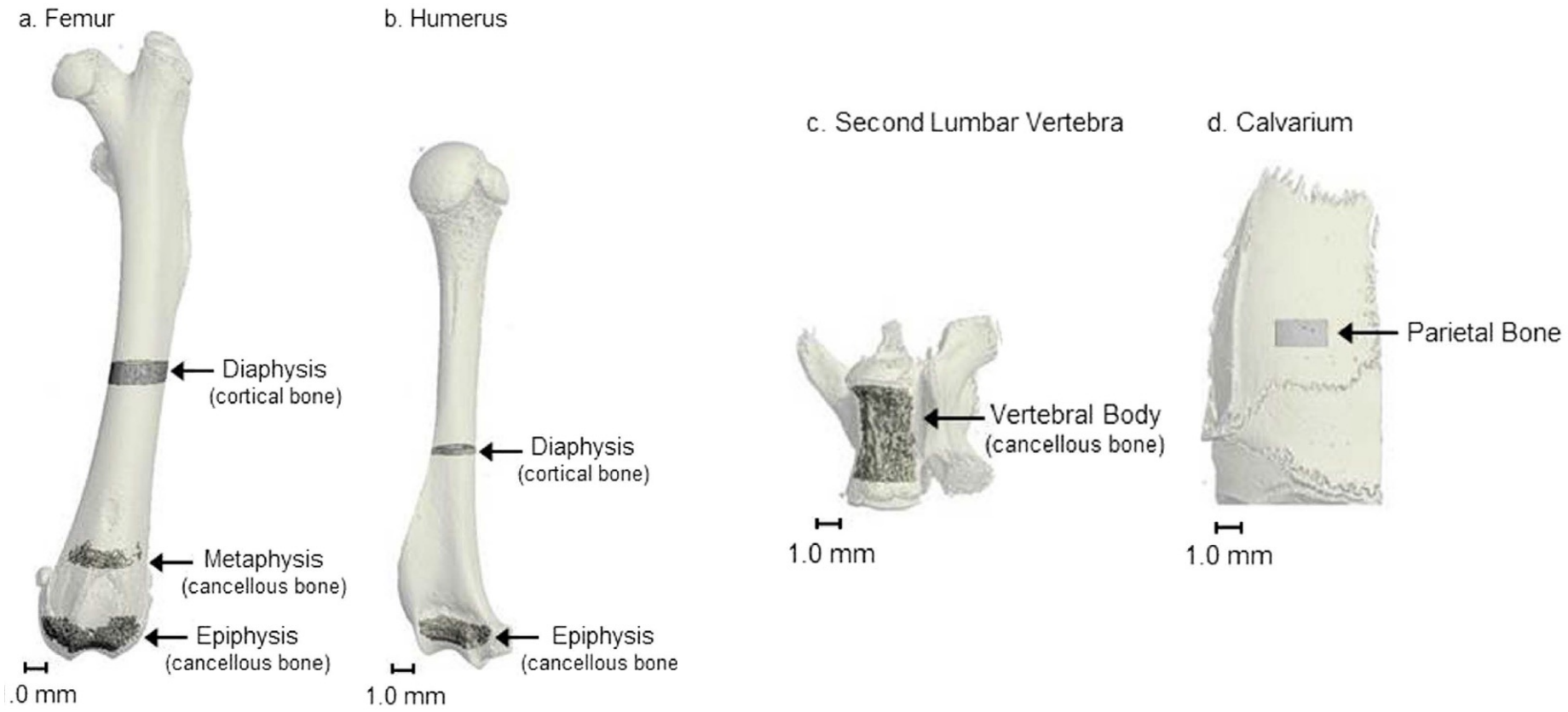
Basic Bone Biology



Bone Cell Biology



Bones


a. Femur
Diaphysis
(cortical bone)
Metaphysis
(cancellous bone)
Epiphysis
(cancellous bone)
.0 mm
b. Humerus
Diaphysis
(cortical bone)
Epiphysis
(cancellous bone
1.0 mm
c. Second Lumbar Vertebra
Vertebral Body
(cancellous bone)
1.0 mm
d. Calvarium
Parietal Bone
1.0 mm

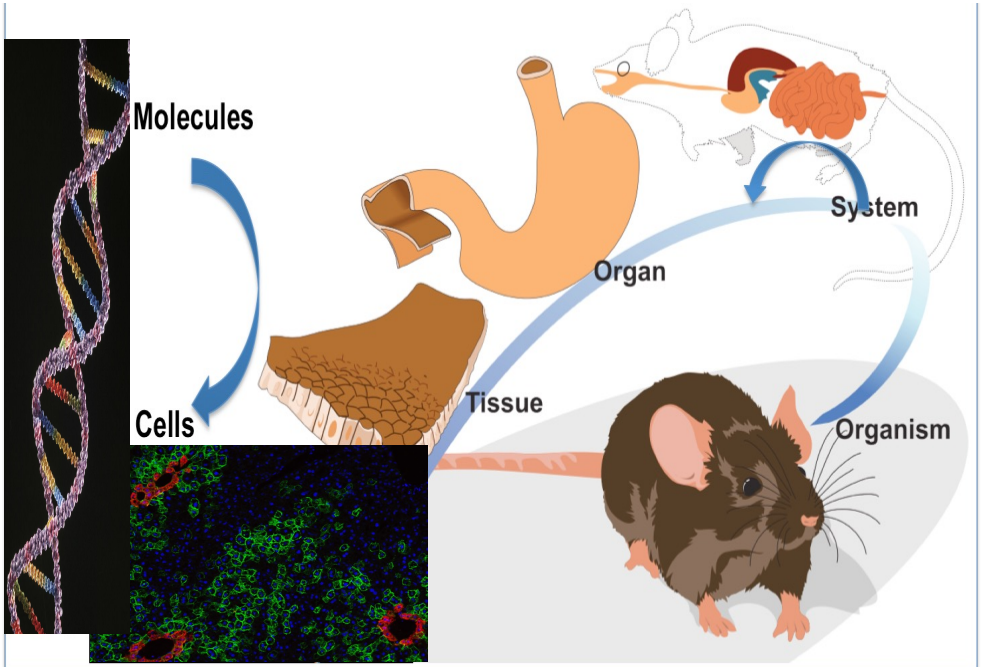
Levels of Evidence and Bradford Hill Criteria

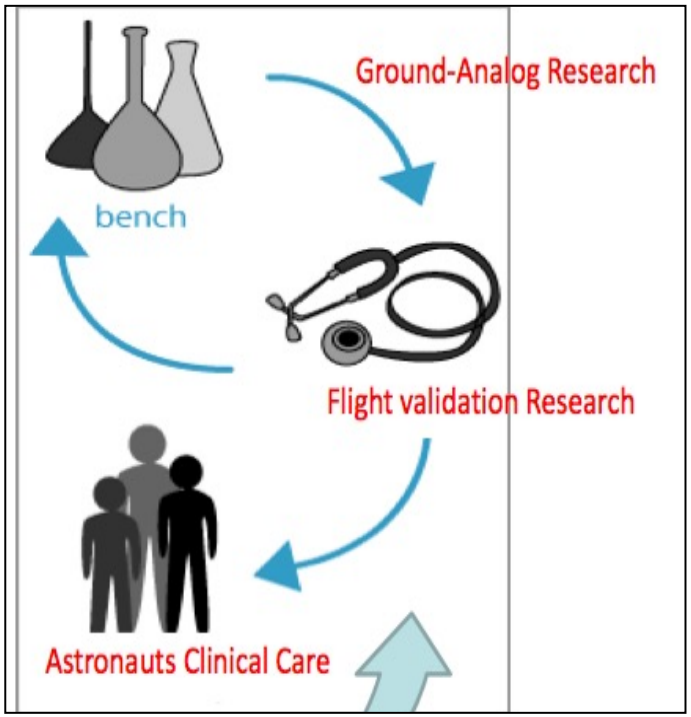
Criterion	Definition	Notes
Temporality	The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).	This is necessary for all posited causal effects, even speculative ones.
Analogy	The use of analogies or similarities between the observed association and any other associations.	Analogues can be in exposure, population, or both.
Mechanism	If there is a plausible theoretical mechanism that can explain how the causal effect works then the posited causal connection is more likely to be true.	
Reproducibility	Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an observed effect being causal.	
Specificity	Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.	This is the classic Person/Place/Time of epidemiology.
Coherence	Coherence between epidemiological and laboratory findings that validate the mechanistic assumptions increases the likelihood of an effect.	This is translational science.

Specificity, Reproducibility, and Mechanism may each fill the requirement for an additional category to name

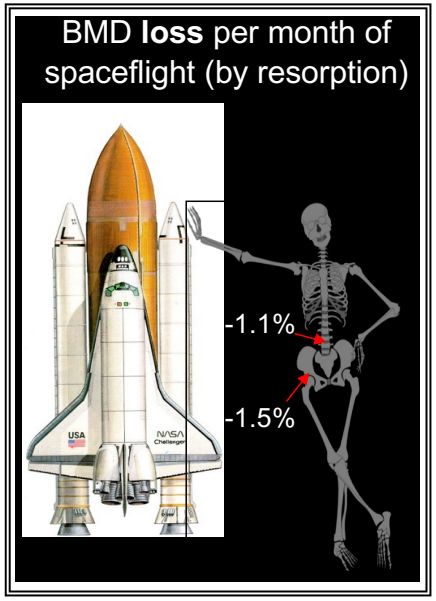
LOE	Temporality	Analogy	Mechanism	Reproducibility	Specificity	Coherence
4 - Speculative	✓	✓				
3 - Weak	✓	✓	✓			
2 - Moderate	✓	✓	✓	✓	✓	
1 - Strong	✓	✓	✓	✓	✓	✓

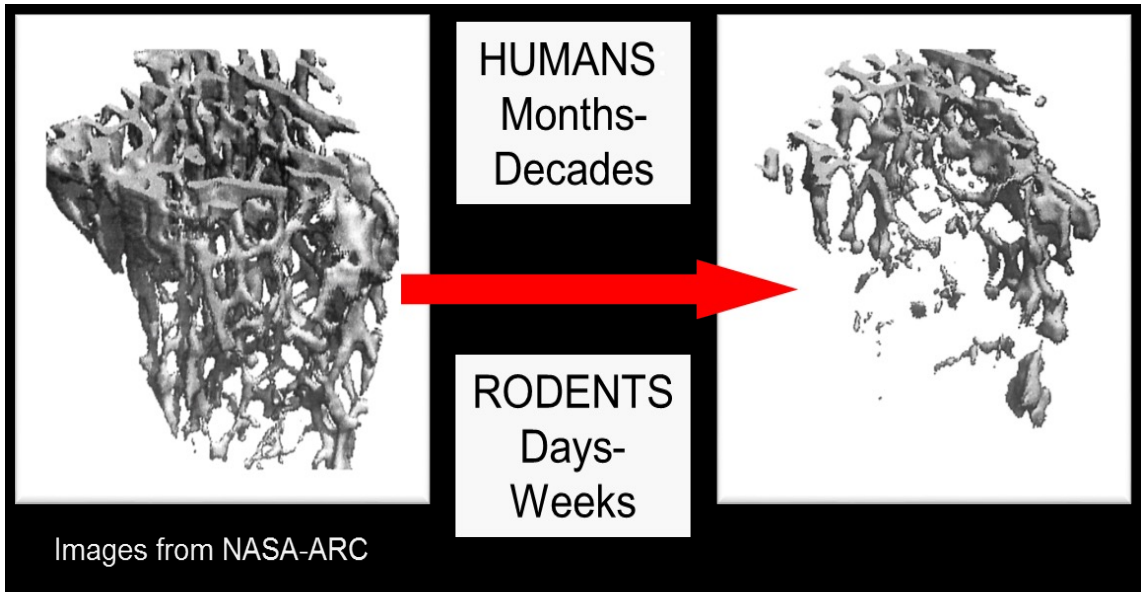
Levels of Scientific Research (Translational)



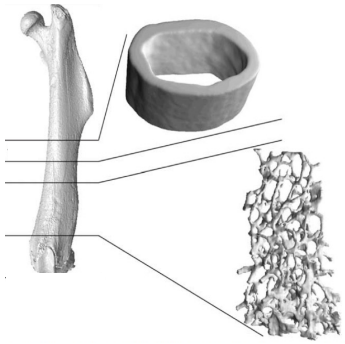


Bone Health and Spaceflight





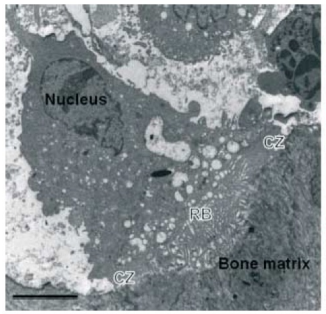
Basic Bone Analyses in Science



Microcomputed Tomography

1. Bone Structure
2. Tissue Mineral Density

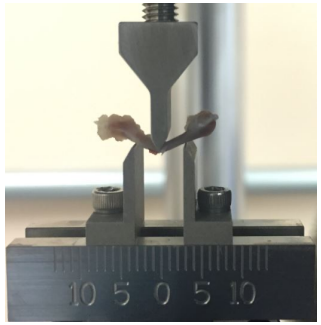
Cortical	
Ct. Ar, Ct. Th, I_{min}, I_{max}, J, Ma. Ar	TMD
Cancellous	
BV/TV,	



Histomorphometry

1. Osteoblast cells
2. Osteoclast cells

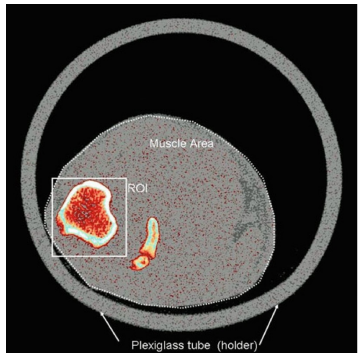
Osteoblasts
BFR
MAR
MS/BS
Osteoclasts
Oc.S



Mechanical Testing

1. Ex Vivo 3pt Bend

Stiffness (N/mm). Yield, Ultimate, and Fracture Loads (N). Postyield Displacement (mm), Work-to-fracture (Nmm), Strain, Stress equivalents



Peripheral Quantitative Computed Tomography

1. Bone Mineral Density

Mineral
Trab BMD, Cort BMD

Dual x-ray Absorptiometry

1. Bone Mineral Density

Mineral
Trab BMD, Cort BMD

Data from the Studies in DAG Effort

OSD-351

Effects of Spaceflight on Bone Microarchitecture in the Axial and Appendicular Skeleton in Growing Ovariectomized Rats

Jessica A. Keune[1], Adam J. Branscum[2], Urszula T. Iwaniec[1,3] & Russell T. Turner[1,3]

SCIENTIFIC REPORTS

STS-62; PSE.04; Rat

OSD-310

Spaceflight-induced vertebral bone loss in ovariectomized rats is associated with increased bone marrow adiposity and no change in bone formation

Jessica A Keune[1], Kenneth A Philbrick[1], Adam J Branscum[2], Urszula T Iwaniec[1,3] and Russell T Turner[1,3]

npj | microgravity

STS-62; PSE.04; Rat

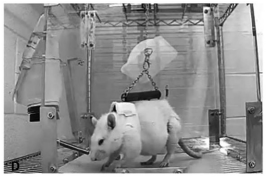
OSD-489

ISS; Rodent Research 1; Mouse

Quantifying Cancellous Bone Structural Changes in Microgravity: Axial Skeleton Results from the Rodent Research-1 Mission

Parker B. Dubée[1,2], R.T. Scott[3], N.H. Thomas[3], M.M. Pendleton[4], J.S. Alwood[5]. [1] Space Life Sciences Training Program (SLSTP), NASA Ames, Moffe Field, CA, USA, [2] Department of Biomedical Engineering, The Johns Hopkins University, Baltimore, MD, USA, [3] Blue Marble Space Institute of Scienc NASA Ames, Moffett Field, CA, USA, [4] University of California, Berkeley, CA, USA, [5] Bone and Signaling Laboratory, NASA Ames, Moffett Field, CA, U

OSD-477, 608



PWB; Harvard University; Rat

Dose-dependent skeletal deficits due to varied reductions in mechanical loading in rats

Frank C. Ko, Marie Mortreux, Daniela Riveros, Janice A. Nagy, Seward B. Rutkove & Mary L. Bouxsein

npj | microgravity

Gross Bone Anatomy