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Leveraging animal model populations for Precision Nutrition

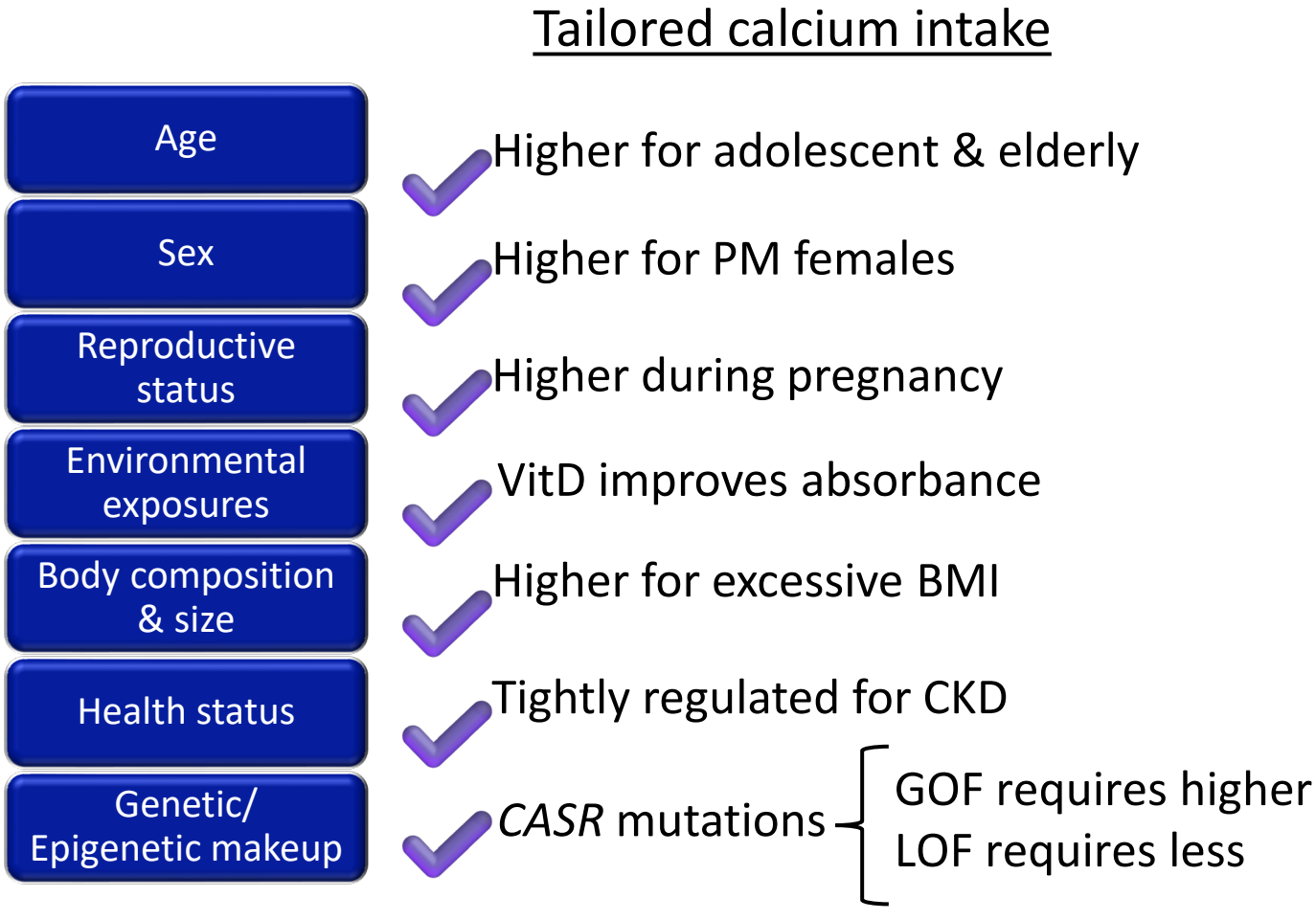
Folami Ideraabdullah, PhD
Associate Professor
Department of Genetics, Department of Nutrition
University of North Carolina at Chapel Hill

Precision Nutrition - One size does not fit all

❖ Nutrient needs differ by individual

Age	• Fetus vs. child vs. adult vs. aged adult
Sex	• Female vs. male
Reproductive status	• Pregnant vs. non pregnant
Environmental exposures	• Co-exposure interactions
Body composition & size	• Lean vs. fat mass, Tall vs. short
Health status	• Healthy vs. diseased
Genetic/ Epigenetic makeup	• ACGT vs. AGGT, methylation status

Precision Nutrition - Recommendations tailored to different needs



Gene-diet interactions (GxE) - Nutrients regulate the genome

- Nutrients are the building blocks of the genome and epigenome

nucleotides
Nucleic acids (DNA & RNA)

amino acids
proteins

Cofactors

Signaling molecules

Modifications
- methylation
- acetylation
- etc..

Reviewed in Ideraabdullah et al 2018, Physiol Rev

Gene-diet interactions (GxE) - The genome regulates nutrition

❖ Genes regulate essential **systemic** nutrient processing

Absorption in the GI tract

- Digestion
- Transport

Metabolism

- Enzymatic activity for activation and degradation
- Transport

Storage & bioavailability

Excretion

Reviewed in Nutrition for the 21st century 2025, Pediatric Nutrition 9th edition (AAP)

How do we define these gene x diet interactions?

Human studies ⟷ **Traditional animal models**

Measure range in differences
Identify causal factors driving variability
-Relevant mechanism
-Relevant tissue & timing
Measure interactions (gene x diet, gene x gene)
- Responsiveness across different genetic backgrounds/lineages

Limitations in humans

- Requires very large sample sizes
  - costly w/ complicated logistics
- Many uncontrollable confounders
  - impacts establishing causality
- Many inaccessible tissues/ timings

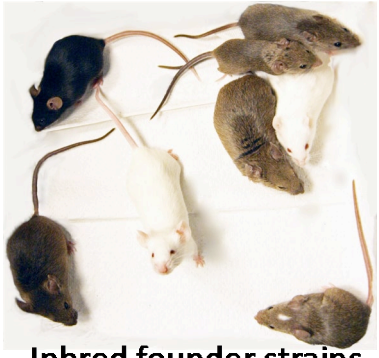
Limitations in traditional models

- Requires conserved mechanism
- Uses severe conditions/ gene knockouts that rarely/don't occur in nature
- Single genetic background
  - Lack population level data

Animal model genetic reference populations

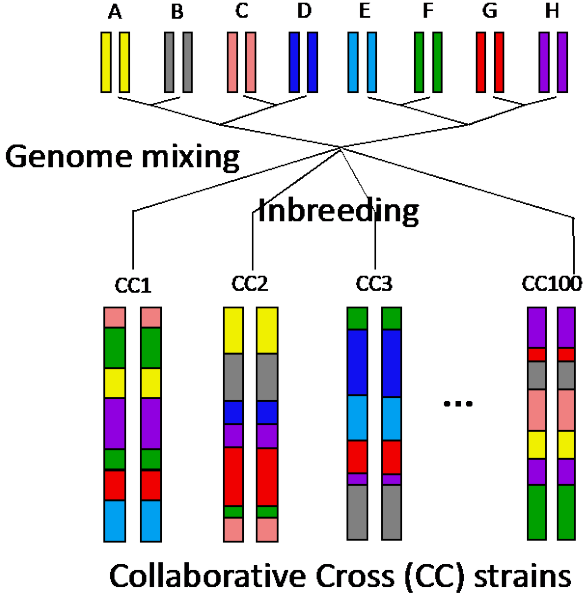
- A genetically diverse population of animal models (eg. mice)
  - 10-100 lines/strains
- Many populations contain inbred strains (genetically identical genomes)
- Ability to control & isolate environmental exposures
- Used to mimic & study effects from diverse human populations

Collaborative Cross (CC) – Mouse Model Population



A. A/J
B. C57BL/6J
C. 129S1/SvImJ
D. NOD/ShiLtJ
E. NZO/HlLtJ
F. CAST/EiJ
G. PWK/PhJ
H. WSB/EiJ

Inbred founder strains



~60 genetic backgrounds (strains)

- High level of ”naturally occurring” genetic differences among strains
- Novel gene x gene interactions that drive higher phenotypic diversity among strains including novel phenotypes
- Inbred - genetically identical within strains

Genome	SNPs
Human	10×10^6
CC	43×10^6

CC strains carry novel phenotypes that may better mimic humans

› Science. 2014 Nov 21;346(6212):987-91. doi: 10.1126/science.1259595. Epub 2014 Oct 30.

Host genetic diversity enables Ebola hemorrhagic fever pathogenesis and resistance

Angela L Rasmussen [1], Atsushi Okumura [2], Martin T Ferris [3], Richard Green [1], Friederike Feldmann [4], Sara M Kelly [1], Dana P Scott [4], David Safronetz [5], Elaine Haddock [5], Rachel LaCasse [4], Matthew J Thomas [1], Pavel Sova [1], Victoria S Carter [1], Jeffrey M Weiss [1], Darla R Miller [3], Ginger D Shaw [3], Marcus J Korth [1], Mark T Heise [6], Ralph S Baric [7], Fernando Pardo-Manuel de Villena [3], Heinz Feldmann [5], Michael G Katze [8]

› Mamm Genome. 2014 Apr;25(3-4):95-108. doi: 10.1007/s00335-013-9499-2. Epub 2014 Feb 1.

The Collaborative Cross as a resource for modeling human disease: CC011/Unc, a new mouse model for spontaneous colitis

Allison R Rogala [1], Andrew P Morgan, Alexis M Christensen, Terry J Gooch, Timothy A Bell, Darla R Miller, Virginia L Godfrey, Fernando Pardo-Manuel de Villena

› Front Behav Neurosci. 2022 Oct 5:16:886524. doi: 10.3389/fnbeh.2022.886524. eCollection 2022.

The collaborative cross strains and their founders vary widely in cocaine-induced behavioral sensitization

Sarah A Schoenrock [1 2], Leona Gagnon [2 3], Ashley Olson [2 3], Michael Leonardo [2 3], Vivek M Philip [2 3], Hao He [2 3], Laura G Reinholdt [2 3], Stacey J Sukoff Rizzo [2 3 4], James D Jentsch [2 5], Elissa J Chesler [2 3], Lisa M Tarantino [1 2 6]

CC strains used to map susceptibility loci/genes

G3 (Bethesda). 2017 Jun 7;7(6):1653-1663. doi: 10.1534/g3.117.041434.

Allelic Variation in the Toll-Like Receptor Adaptor Protein *Ticam2* Contributes to SARS-Coronavirus Pathogenesis in Mice

Lisa E Gralinski [1], Vineet D Menachery [1], Andrew P Morgan [2], Allison L Totura [3], Anne Beall [2], Jacob Kocher [1], Jessica Plante [1], D Corinne Harrison-Shostak [2], Alexandra Schäfer [1], Fernando Pardo-Manuel de Villena [2 4], Martin T Ferris [2], Ralph S Baric [5 3 4]

mBio. 2020 Mar 3;11(2):e00097-20. doi: 10.1128/mBio.00097-20.

Collaborative Cross Mice Yield Genetic Modifiers for Pseudomonas aeruginosa Infection in Human Lung Disease

Nicola Ivan Lorè [1 2], Barbara Sipione [3], Gengming He [4], Lisa J Strug [4 5], Hanifa J Atamni [6], Alexandra Dorman [6], Richard Mott [7], Fuad A Iraqi [6], Alessandra Bragonzi [1]

J Allergy Clin Immunol. 2024 Aug;154(2):387-397. doi: 10.1016/j.jaci.2024.03.027. Epub 2024 Apr 24.

A mutation in Themis contributes to anaphylaxis severity following oral peanut challenge in CC027 mice

Ellen L Risemberg [1], Johanna M Smeekens [2], Marta C Cruz Cisneros [3], Brea K Hampton [3], Pablo Hock [4], Colton L Linnertz [4], Darla R Miller [4], Kelly Orgel [2], Ginger D Shaw [5], Fernando Pardo Manuel de Villena [5], A Wesley Burks [2], William Valdar [6], Michael D Kulis [7], Martin T Ferris [8]

Leveraging the CC to study interindividual nutrient needs

Vitamin D

Primary biomarker

KIDNEY

Primary active metabolite

Calcidiol (biomarker)

Leveraged diverse genetic backgrounds and controlled diets

> Endocrinology. 2025 Sep 8;166(10):bqaf138. doi: 10.1210/endocr/bqaf138.

Interindividual Genetic Differences Drive Discordance Between Serum Calcidiol and Calcitriol Concentrations in Females

Elizabeth K Hutchins [1], Changran Niu [2], Jing Xue [1], Debin Wan [3], Carolina V Campos [1 4], Molly Warren [1 2], Megan M Knuth [1], Michael B Whalen [1], Venkata S Voruganti [2 5], Rafiou Agoro [6], James C Fleet [7], Bruce D Hammock [3 8], Folami Ideraabdullah [1 2 5 9]

Found

- Genetically determined variability in VitD status (calcidiol)
- Response to dietary VitD depletion differs by genetic background

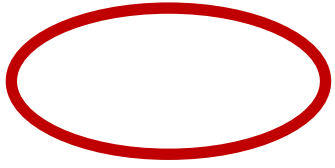
Leveraged genetically identical mice for repeated measures

Found

- Low calcitriol can be genetically determined – not predicted by biomarker

Hutchins et al 2019, Endocrinology

Leveraged simultaneous access to all tissues & cell types



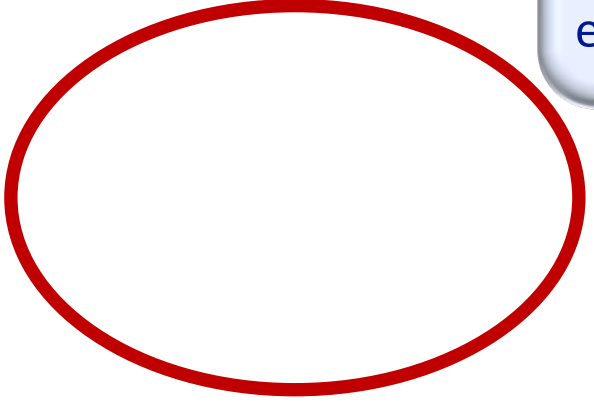
Found

– Candidate mechanism & genes:

Low calcitriol likely driven by impaired transport of calcidiol into the kidney for activation

Hutchins et al 2019, Endocrinology

Leveraged simultaneous access to all tissues & cell types



Found

– Potential physiological impact:

Strains with genetically determined low calcitriol exhibit evidence of impaired VitD signaling.

Hutchins et al 2019, Endocrinology

Summary

Animal model populations extend our reach for understanding the factors driving interindividual differences in human populations

1. **All the benefits of traditional single lineage models**
    - Access to tissues or developmental timings inaccessible in humans for systems biology approach
    - Controlled manipulation to study effects of individual ”normal” or “perturbed” conditions
    - Biological replicates improve statistical power (smaller sample size) and allow for integrating findings between studies
2. **Study “*naturally occurring*” genetic differences including gene-gene interactions**
    - Measure the range in phenotypic outcomes – population level effects
    - Measure efficacy of treatment/intervention on different backgrounds
3. **Define causality**
    - Gene discovery - Map causal genes through linkage analyses
    - Define biological mechanisms underlying vital biomarkers
    - Identify novel susceptibility markers that can be tested in human populations