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No Bones About It!

COMBINING NUTRIGENOMICS WITH THE CULINARY ARTS IN THE PREVENTION AND TREATMENT OF OSTEOPOROSIS

Susan Allen-Evenson, RDN, LDN, CCN:
Functional Nutrition
Amanda Archibald, RDN:
Nutrigenomics, Culinary Genomics

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Susan Allen-Evenson, RDN, CCN

Highly recognized Functional Nutrition expert, Susan Allen-Evenson incorporates an overall focus on the Integrative and Functional Medicine approach in her work as a speaker, mentor, author and nutrition consultant. In addition to her own private practice, she was involved in one of the first nationally-based Integrative Medicine clinics and consulted for the development of a major hospital system's Integrative Medicine Center in Chicago, IL. Ms. Allen has held board appointments with The International and American Association of Clinical Nutritionists, the Academy of Nutrition and Dietetics' sub-specialty group: Dietitian's in Integrative and Functional Medicine (DIFM), and on the Nutrition Board of the Institute for Functional Medicine (IFM).

In her more than two decades of practice, Susan has recognized the growing divide between traditional dietetics training and the emerging trends in Integrative and Functional Medicine. With her passion for educating and understanding many clinicians are missing a key opportunity; she originated a unique, first of its kind, international training initiative to provide advanced training in the nutritional aspects of this specialty. Considered an authority, she has appeared on numerous radio and television programs, has been invited to speak at many professional conferences, has been quoted extensively in the press, and is also a published author. She was Chief Nutritional Consultant for the Reader's Digest book; Food Cures: Breakthrough Nutritional Prescriptions for Everything from Colds to Cancer and she was a contributing author to the first college textbook of its kind, Integrating Therapeutic and Complementary Nutrition. Ms. Allen has also authored a chapter in AAPI's Nutrition Guide To Optimal Health: Using Principles of Functional Medicine and Nutritional Genomics – Part 2.

Although her professional training program keeps her very busy, Susan continues to enjoy a thriving private practice specializing in Integrative and Functional Medical Nutrition Therapy (IFMNT), where she also consults with healthcare professionals on their most challenging cases.

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Amanda Archibald RDN

Amanda's unique training as an analyst and a nutritionist (RDN), combined with her culinary expertise, has enabled her to develop a new lens through which we can understand the food and health conversation. Amanda's trailblazing work is redefining the food, nutrition and cooking education footprint in ways that are understandable, meaningful and fundamentally achievable for all Americans. Her cutting-edge work in Culinary Genomics, unveiled in 2015 in South Africa (Translational Nutrigenomics) and at the Institute for Functional Medicine AIC (2015), has created a new frontier uniting the fields of Genomic Medicine with the Culinary Arts. Through this work, Amanda is placing food, clinicians and chefs and the kitchen at the epicenter of healing, igniting a new food and nutrition conversation for the world. Her work has been showcased in more than 30 states, over 100 U.S. cities, and in 7 countries. Amanda is currently working with a global foodservice management company to build genomic principles onto the patient and retail menu for a Southern California hospital system. In its preliminary phase, this work received a culinary award in 2016, for its innovation in healthcare.

Amanda is the founder of The Genomic Kitchen, a system of choosing, preparing and understanding food based on culinary genomics, a term she coined to express this revolutionary merging of genomic science (nutrigenomics) and the culinary arts. Widely recognized for her trailblazing work as a culinary nutritionist and dietitian, Amanda has a longstanding commitment to redefining the food, nutrition and cooking education footprint in ways that make them understandable, meaningful and fundamentally achievable for all.

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No Bones About it!

Combining Nutrigenomics with the Culinary Arts in the Prevention and treatment of Osteoporosis

- The presenters have no conflicts of Interest
- This session is being recorded. Limited-time access will be shared tomorrow (NLFN Gold/Platinum members get extended access)
- CPE cert and slides are available in your control panel

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Agenda –

Susan Allen-Evenson, RDN, LDN, CCN

- Prevalence of bone disease
- Opportunity for Integrative and Functional Healthcare professionals to work at a deeper, more targeted and effective level
- Review of bone metabolism and factors affecting bone health
- Identify Genomic factors influencing and biomarkers to monitor both bone formation and degradation

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World-wide Statistics

- ~30% of women and 20% of men over 50 suffer from osteoporosis or osteoporotic fractures.
- Worldwide, osteoporosis causes >8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds.
- Osteoporosis is estimated to affect 200 million women worldwide
- Osteoporotic fractures are not only associated with increased mortality in both sexes, but are also responsible for about 1% of the worldwide disability caused by prevalent noncommunicable diseases.

Wu S et al. Genome-wide approaches for identifying genetic risk factors for osteoporosis. *Genome Medicine*2013 5:44 open access-BioMed Central Ltd 2013. May 29, 2013.

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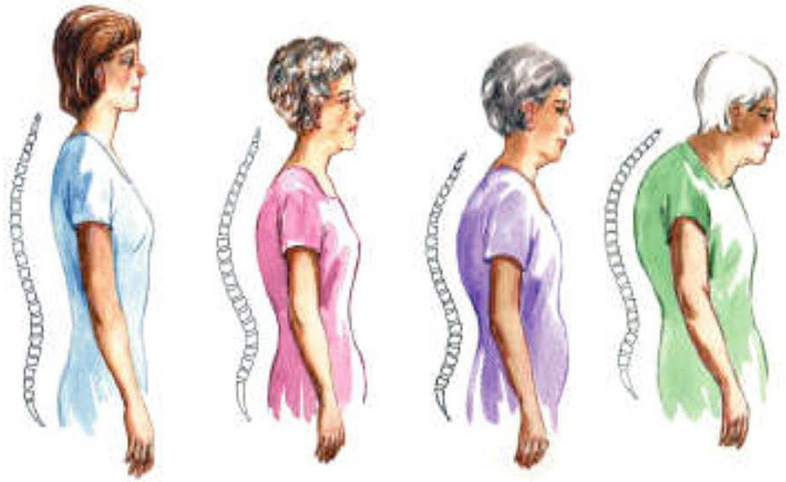
U.S. Statistics

NHANES: 10.2 million adults (8.2/women and 2.0/men) had osteoporosis and 43.4 million (27.3/women and 16.1/men) had low bone mass in 2010.



Wright,C,L et al, The Recent Prevalence of Osteoporosis and Low Bone Mass in the United States Based on Bone Mineral Density at the Femoral Neck or Lumbar Spine, J Bone Miner Res. 2014 Nov; 29(11): 2520–2526.

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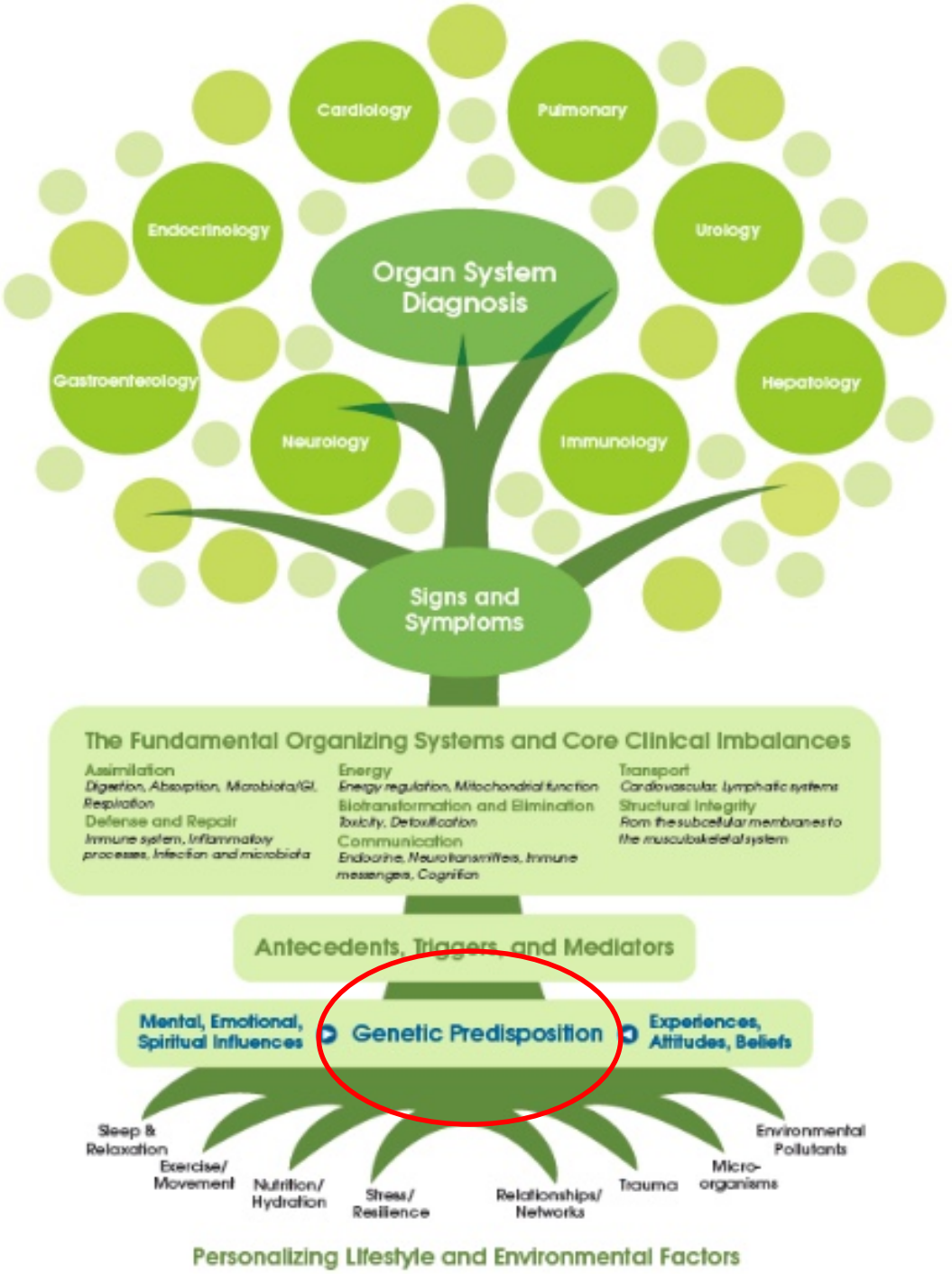
Health Care Providers Have a Golden Opportunity!

- The Functional Medicine model goes under the diagnosis to look at the root causes, or the set of circumstances that allows the progression of ill health to move into a disease state.
- Deeper assessment, food as medicine, and dietary supplements as indicated, are our valuable tools.
- The genomic assessment provides a missing piece to deeper understanding that we can now harness.

Systems Biology

Institute for Functional Medicine -

The Functional Medicine tree



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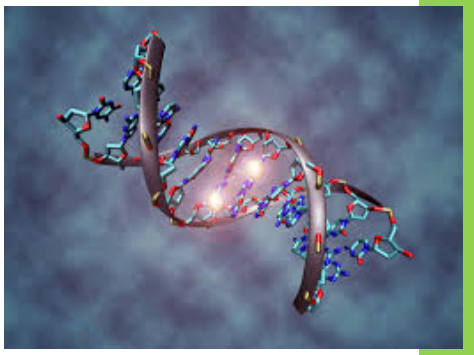
Genomics/ Epigenetics



- Modification of DNA can influence biochemical and metabolic pathways
  - Single Nucleotide Polymorphisms (SNPs) represent disease risk
- Epigenetics: changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself (e.g. environmental, stress, drugs/pharmaceuticals, diet, endotoxins).

Epigenetics: New Tool For Precision Medicine. Medical Xpress. https://medicalxpress.com/news/2016-06-epigenetics-tool-precision-medicine.html. Published June 27, 2016. Accessed February 21, 2017.

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Nutritional Genomics, or Nutrigenomics

- Study of gene-nutrient interactions; how foods affect our genes and how individual genetic differences can affect the way we respond to nutrients in the foods we eat
- Allows for personalized medicine and health, based upon an understanding of our nutritional needs, nutritional and health status, and our genotype
- New specialty – "Culinary Genomics"
  - Using food constituents/bioactives to mitigate the effects of gene SNPs

N. M. R. Sales, P. B. Pelegrini, and M. C. Goersch. Nutrigenomics: Definitions and Advances of This New Science. J Nutr Metab. 2014; 2014: 202759.

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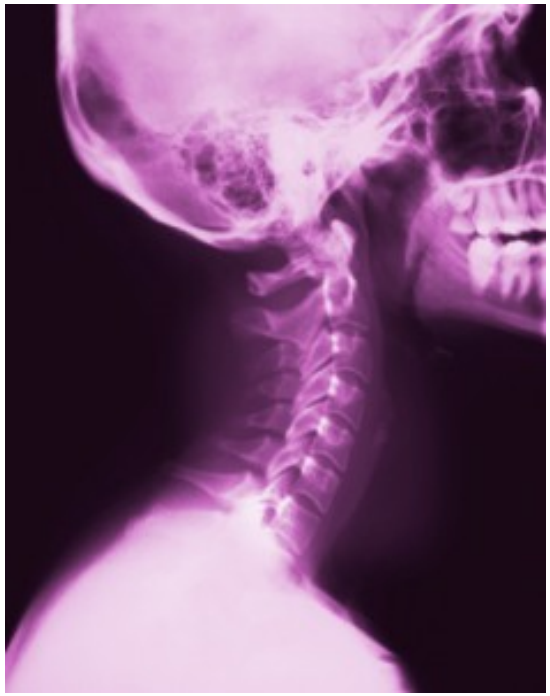
Bone Health

- Should be considered throughout all stages of women's life (not just menopause) and for men too!
- General Considerations:
  - Genetics/Genomics
  - Hormone balance
  - Diet/ Nutritional status
  - Exercise
  - Oxidative stress
  - Inflammation
  - Medication interactions/effects



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Drugs that may contribute to or exacerbate osteoporosis

- Aluminum-containing antacids
- Antiseizure medicines (only some) such as Dilantin® or Phenobarbital
- Aromatase inhibitors such as Arimidex®, Aromasin® and Femara®
- Cancer chemotherapeutic drugs
- Cyclosporine A and FK506 (Tacrolimus)
- Gonadotropin releasing hormone (GnRH) such as Lupron® and Zoladex®
- Heparin
- Lithium
- Medroxyprogesterone acetate for contraception (Depo-Provera®)
- Methotrexate
- Proton pump inhibitors (PPIs) such as Nexium®, Prevacid® and Prilosec®
- Selective serotonin reuptake inhibitors (SSRIs) such as Lexapro®, Prozac® and Zoloft®
- Steroids (glucocorticoids) such as cortisone and prednisone
- Tamoxifen® (premenopausal use)
- Thiazolidinediones ('glitazones' for DM2) such as Actos® and Avandia®
- Thyroid hormones in excess

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Bone Metabolism Review

- Bone resorption: removing of mature bone tissues from the skeleton via osteoclast cells
- Bone remodeling - the formation of new bone matrix via the process of ossification (osteogenesis) by osteoblast calls
- Bone health is homeostasis between these two
- The imbalance between bone formation and bone resorption leads to changes in bone mass. Osteoporosis is more resorption vs remodeling

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Inflammation and Bone Health

- Bone loss is due to the effects of inflammation, poor nutrition, oxidative stress, hormone balance, decreased lean body mass, hypothyroid, sedentary life and the effects of medications
- Chronic inflammatory diseases of almost any cause are associated with bone loss
  - Increase bone resorption (increased osteoclast activity)
  - Decrease bone formation (reduced osteoblast activity)

Hardy R, Cooper MS. Bone loss in inflammatory disorders. J Endocrinol. 2009 Jun;201(3):309-20.

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Oxidative Stress and Bone Health

- Oxidative stress may play a role by enhancing bone resorption
  - Increases bone-matrix degrading matrix metalloproteinases (MMPs)
- Example: Environmental pollution with cadmium and/or polychlorinated biphenyls (PCBs) are involved in the development of Osteoporosis

- Carlo Cervellati, Gloria Bonaccorsi, aet al. Oxidative Stress and Bone Resorption Interplay as a Possible Trigger for Postmenopausal Osteoporosis. BioMed Research International volume 2014, Article ID 569563
- Sheweita, Salah & Khoshhal, Khalid & Baghdadi, Hussam. (2014). Osteoporosis and Oxidative Stress – Role of Antioxidants. Systems Biology of Free Radicals and Antioxidants. 2973-2995. 10.1007/978-3-642-30018-9_128.

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Estrogen and Bone Health

- Plays a fundamental role in skeletal growth and homeostasis.
- Estrogen deficiency is the major factor in the pathogenesis of postmenopausal osteoporosis.
- With less estrogen, other factors become that much more important to identify and address.

1. Weitzmann M N and Pacifici R, Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest. 2006 May 1; 116(5): 1186–1194.
2. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Prz Menopauzalny 2014; 13(4): 213-220

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General Intervention/Support

- Supportive diet and optimal nutritional status (via diet or dietary supplements), especially bone building nutrients
  - Calcium, magnesium, other minerals
  - Vitamins D & K2 (MK-7), etc
  - Collagen supporting and sulfur containing amino acids
- Weight bearing exercise
- Monitor drug effects and drug-nutrient interactions
- Maintain optimal pH balance
- Avoid/reduce or counter oxidative stress
- Minimize inflammation

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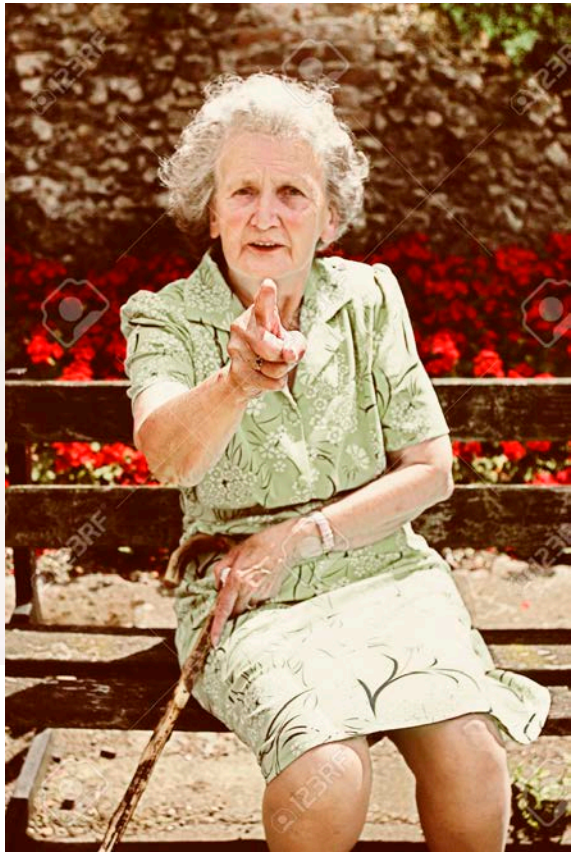
SOMETIMES IT'S JUST NOT ENOUGH.



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Genomics & Osteoporosis Risk

- **Bone Formation SNPs**
  - COL1A1
  - GSTT1
  - GSTM1
  - MTHFR
  - IGF-1
  - BMP4
  - LRP5
  - GSTT1
- **Inflammation SNPs**
  - IL-6/6R
  - CRP
  - TNF-alpha
  - APOE
  - DHCR7
  - GC
  - CYP2R1
  - CYP27A1
  - CYP27B1
  - VDRFokl
  - VDRBSml
- **Bone Resorption SNPs**
  - CYP1A2
  - MTHFR
  - BMP2
  - SOST
  - GSTM1
- **Calciotropic and Sex Hormone SNPs**
  - PTH/PTHR
  - CT/CTR
  - AR
  - CYP19A1
  - CaSR
  - GR
- **Other**
  - BCMO1?

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SNPs – Important to Know!

Expand your clinical toolbox:

- Identify your patient's SNPs that are actionable through diet & lifestyle modifications
- Look for signs, symptoms, and biomarkers that show evidence of SNP expression
- Polygenic vs Monogenic: It's not just about one SNP alone but how SNPs act together
- Apply appropriate intervention
- Monitor accordingly

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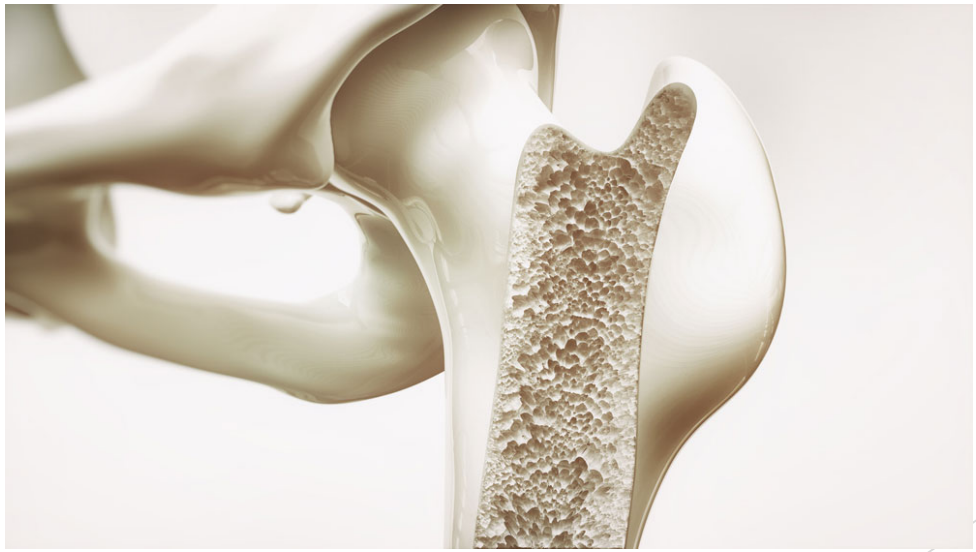
Bone Formation



Susan Allen RDN CCN. Amanda Archibald RDN

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COL1A1 (collagen type I alpha)

- Gene encodes for instructions for making part of a large molecule called type I collagen
  - most abundant form of collagen in the human body
  - major protein of bone matrix
- SNP: associated with decreased bone mass and osteoporotic fractures by reducing bone mineral density
- Smoking, low-protein diet/status and low calcium intake may negatively influence

1. https://www.snpedia.com/index.php/Rs1800012 (Date accessed: 8/28/2017)
2. https://ghr.nlm.nih.gov/gene/COL1A1#location (Date accessed: 8/28/2017)

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GSTT1 & GSTM1

(Glutathione S-Transferase theta 1 & Mu 1)

- A member of a superfamily of proteins that catalyze the conjugation of reduced glutathione
  - Detoxification of a broad range of toxic substances (like Estrogen!)
- Genetic polymorphisms can result in reduced enzyme activity due to the null phenotype of the GSTM1 and GSTT1
  - More prevalent in Caucasians
- Absence of gene, and therefore reduced enzymatic activity, is associated with decreased bone mineral density
  - Affects both formation and remodeling and indirectly increases oxidative stress
- Increased oxidative stress may negatively influence

1. Buchard A, Sanchez J, Dalhoff K, Morling N. Multiplex PCR Detection of GSTM1, GSTT1, and GSTP1 Gene Variants. J Mol Diagn. 2007 Nov; 9(5): 612–617.
2. Mlakar SJ, Osredkar J, Prezelj J, Marc J. Opposite effects of GSTM1--and GSTT1: gene deletion variants on bone mineral density. *Dis Markers*. 2011;31(5):279-87. doi: 10.3233/DMA-2011-0829.

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MTHFR:

Methylenetetrahydrofolate reductase

- Encodes for the protein that supports methylation by catalyzing the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine.
- MTHFR SNP associated with hyperhomocysteinemia, in some studies correlated with low BMD and Osteoporotic fracture
- Global methylation patterns of genes may also be directly associated with BMD in postmenopausal women
  - Major signaling pathways in osteoblasts affected by DNA methylation
  - DNA methylation affects osteoclast activity as well

Sjur Reppe, Harish Datta, and Kaare M. Gautvik. The Influence of DNA Methylation on Bone Cells. Curr Genomics 2015 Dec; 16(6): 384–392.

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Methylation and Sclerostin

- As a self-balancing mechanism, when necessary, Osteocytes produce the protein Sclerostin, which inhibits bone formation
- When bone density falls, our body normally counteracts this by inhibiting the expression of the Sclerostin-producing gene (SOST gene)
  - Inhibition achieved with increased methylation on the promoter region of the gene
- Proper methylation required to support SOST inhibition

Reppe S, Noer A, Grimholt RM. Methylation of bone SOST, its mRNA, and serum sclerostin levels correlate strongly with fracture risk in postmenopausal women. J Bone Miner Res. 2015 Feb;30(2):249-56.

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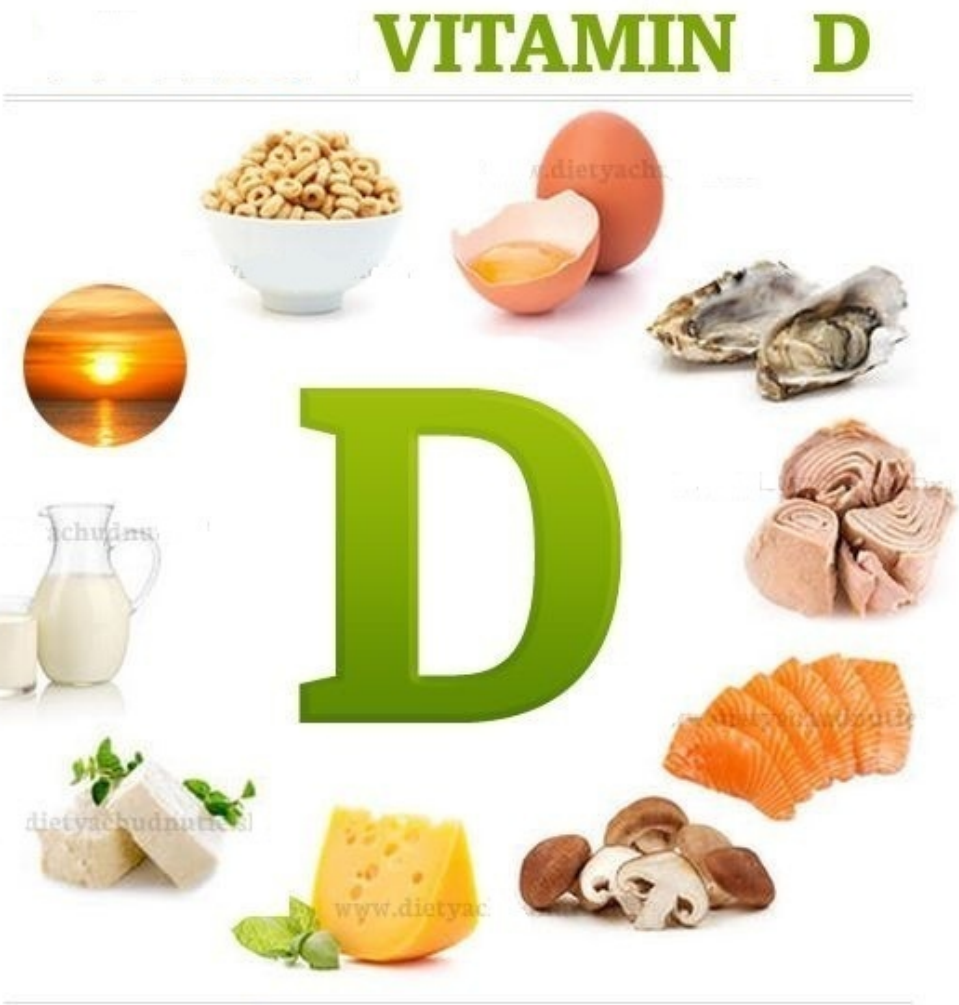
SNPs for



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At Risk for Deficiency

- Absorption issues
  - Low fat diets/malabsorption
  - Older individuals
  - Celiac or other mucosal damage issues
  - Taking supplements without fat-containing food
- Vit D receptor issues and SNPs for Vit D metabolism

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Vitamin D Metabolism Review

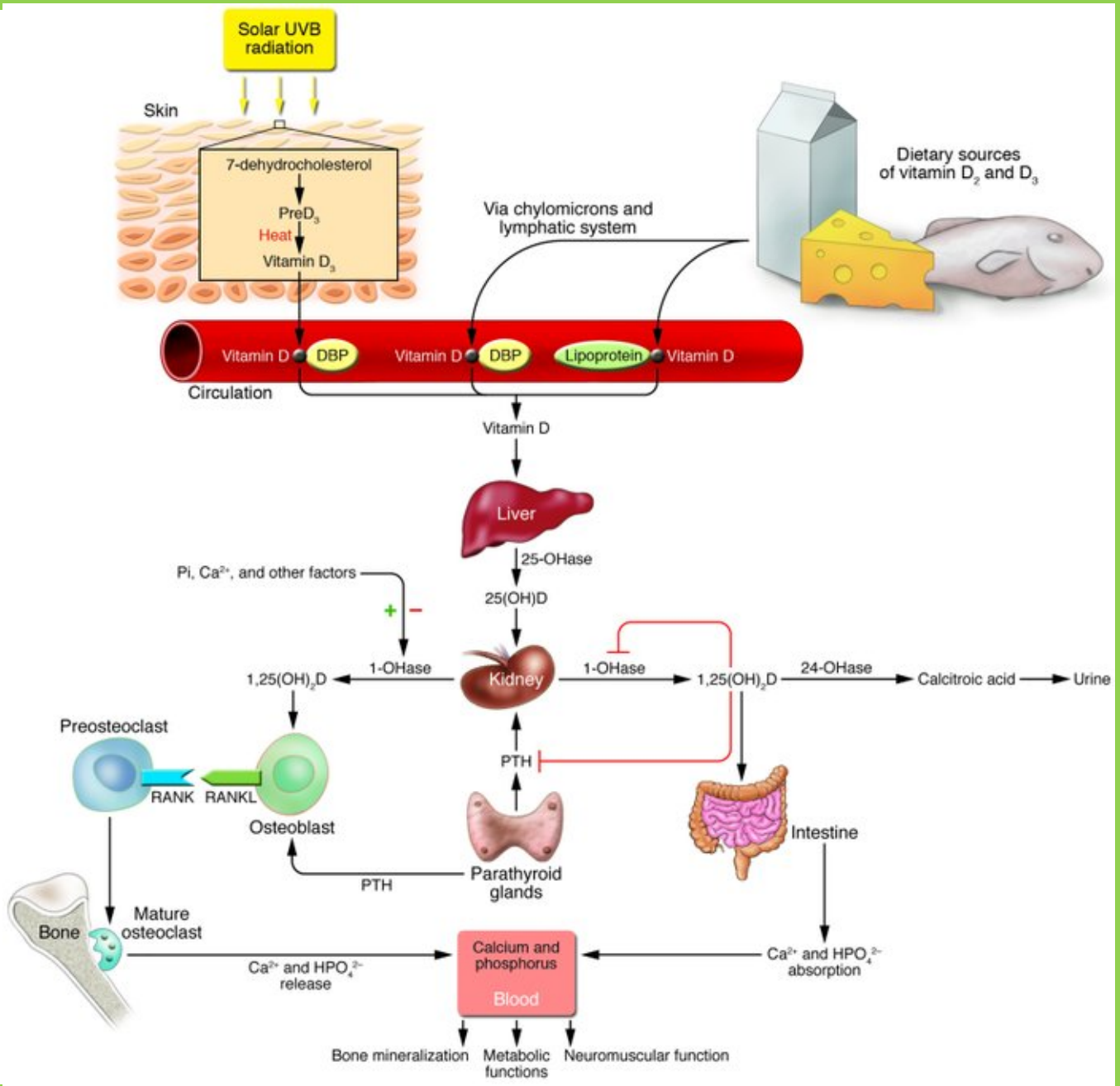

Image source: Holick M. Resurrection of vitamin D deficiency and rickets. *J Clin Invest.* 2006;116(8):2062-2072. doi:10.1172/JCI29449

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DHCR7

(7-Dehydrocholesterol Reductase)

- DHCR7 encodes 7-dehydrocholesterol reductase, which converts 7-dehydrocholesterol to cholesterol, thereby reducing availability for vitamin D synthesis in the skin
- Decreased enzyme activity = less vitamin D from sun
  - Increases risk for lower bone mineral density, osteoporosis and fractures.

KuanEmail V, Martineau A , Griffiths C, Hyppönen E and Walton R. DHCR7 mutations linked to higher vitamin D status allowed early human migration to Northern latitudes. BMC Evolutionary Biology201313:144

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CYP2R1

(Cytochrome P450 family 2 subfamily R member 1)

- Member of the cytochrome P450 superfamily of enzymes that converts vitamin D into the active ligand for the vitamin D receptor.
- SNP is associated with decreased enzymatic function, increased risk of vitamin D deficiency and therefore higher risk of Osteoporosis

1. https://www.ncbi.nlm.nih.gov/gene/120227 (Date accessed: 8/28/2017)
2. Cheng J et al. Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proc Natl Acad Sci U S A. 2004 May 18; 101(20): 7711–7715.

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GC (Vitamin D binding protein)

- Encodes for the major carrier protein of 25-hydroxyvitamin D in circulation (GC-globulin)
  - Linked with alterations in bone density
  - Roles in 1) maintaining stable levels during times of decreased 25(OH) availability and 2) in regulating delivery of 25(OH) D to target tissues
  - Role in inflammatory response and bone development independent of vitamin D as well.

Bhan I. Vitamin D Binding Protein and Bone Health. *International Journal of Endocrinology*, Volume 2014 (2014), Article ID 561214, 5 pages.

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VDR BsmI and VDR FokI (Vitamin D Receptors)

- The VDR gene encodes for the vitamin D receptor; variants have been reported to influence bone mineral density
- VDR Bsml (rs1544410): SNP in the VDR associated with increased risk of low BMD (especially in women).
- VDR FokI (rs2228570): SNP in the VDR related with osteoporosis risk
- Other potentially relevant receptor SNPs: Cdx2, ApaI, EcoRV and TaqI

1. https://www.snpedia.com/index.php/VDR (Date accessed: 8/28/2017)
2. Mohammadi Z.et al. Association between vitamin D receptor gene polymorphisms (Fok1 and Bsm1) and osteoporosis: a systematic review. *J Diabetes Metab Disord. 2014; 13: 98.* doi: 10.1186/s40200-014-0098-x .
3. SNPedia Members (September 6, 2017). Rs1544410. SNPedia (website). https://www.snpedia.com/index.php/Rs1544410. Accessed November 13, 2017.

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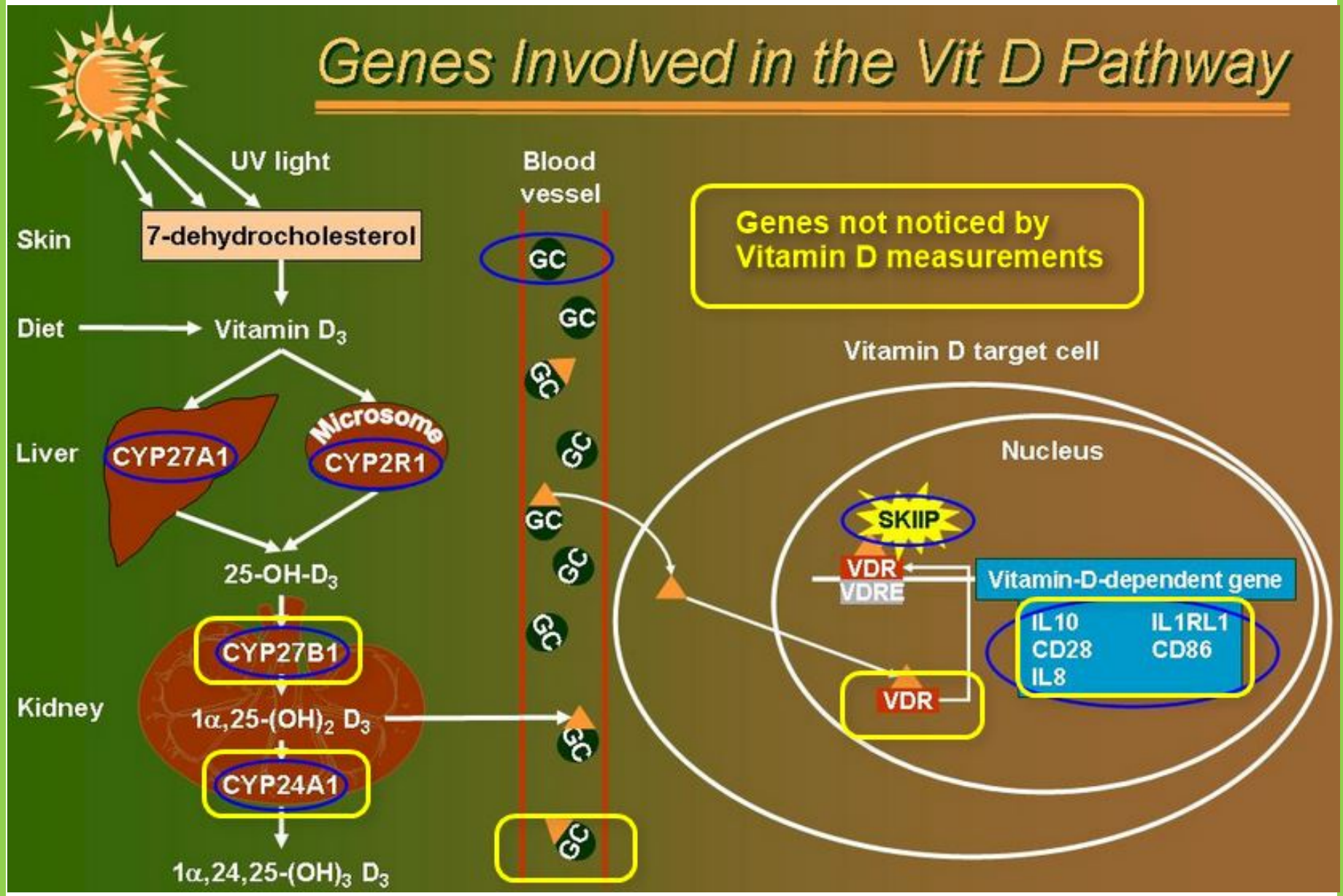
Other SNPs Related to Vit D

- **CYP24A1**: Regulates the level of vitamin D
  - Therefore, plays a role in calcium homeostasis and the vitamin D endocrine system
- **CYP27A1:** Might be responsible for the conversion of vitamin D to 25(OH)D3
- **CYP27B1**: Regulates the level of biologically active vitamin D and plays an important role in calcium homeostasis

1. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G, Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiological Reviews Jan 2016 Vol. 96 no. 1, 365-408.
2. Babiker AM, Al Gadi I, Al-Jurayyan NA, Al Nemri AM, Al Haboob AA, Al Boukai AA, Al Zahrani A, Habib HA. A novel pathogenic mutation of the CYP27B1 gene in a patient with vitamin D-dependent rickets type 1: a case report. BMC Res Notes. 2014 Nov 5;7:783.



Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G, Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiological Reviews Jan 2016 Vol. 96 no. 1, 365-408.

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Vitamin D 25-OH Lab Limited

- D3 depends on lab values (not season!)
  - Off supplements for 1 week prior
  - Labs drawn fasting
- Lab may be normal but conversion to active may be suboptimal with SNP affecting kidney conversion
  - Check 1,25 OH
- Lab may be normal but utilization suboptimal with receptor SNPs.
  - Look at alternative markers and associated signs/symptoms

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Bone Formation:

Monitor Labs, especially as you see risk in SNPS

- Bone mineral density
- Collagen cross-linking markers
- Vitamin D (25-OH & 1,25-OH)
- Magnesium RBC
- Vitamin A
- Homocysteine
- Folate
- Vitamin B12/MMA
- Hormones/related markers
- PTH/calcitonin
- Phosphorus

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Collagen Cross-linking Markers

- In post-menopausal women, the markers that have been studied the most and also have the strongest negative correlations with BMD are:
  - Alkaline phosphatase (ALP)
  - Carboxylated Osteocalcin (OC) – for K2 status
  - Type 1 cross-linked C-telopeptide (CTx)
  - Type 1 cross-linked N-telopeptide (NTx)
- Mostly used in research and perhaps more in functional medicine (may not be covered well by insurances)

1. Collagen Crosslinks and Biochemical Markers of Bone Turnover. UnitedHealthcare Commercial Medical Policy Effective 03/01/2017 PDF
2. Talwar SA, et al. Bone Markers in Osteoporosis Medscape online. http://emedicine.medscape.com/article/128567. Updated: Jan 12, 2017 (Accessed 5/15/17)

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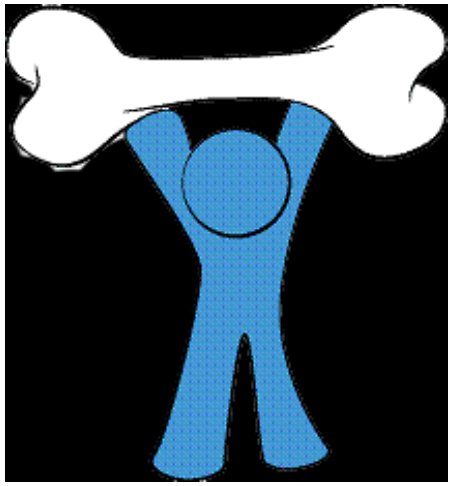
Bone Formation:
Supplement Support



- Vitamin D3
- Calcium
- Magnesium
- Hydroxyapatite
- Choline-stabilized orthosilica
- Strontium
- Boron
- MSM, SAMe
- Good-quality multi vitamin-mineral supplying: Vit C, A, E, Cu, Zn, and Mn
  - Additional antioxidants as needed
- K2 (as MK 7) – often needed in higher amt than what occurs in many supplements

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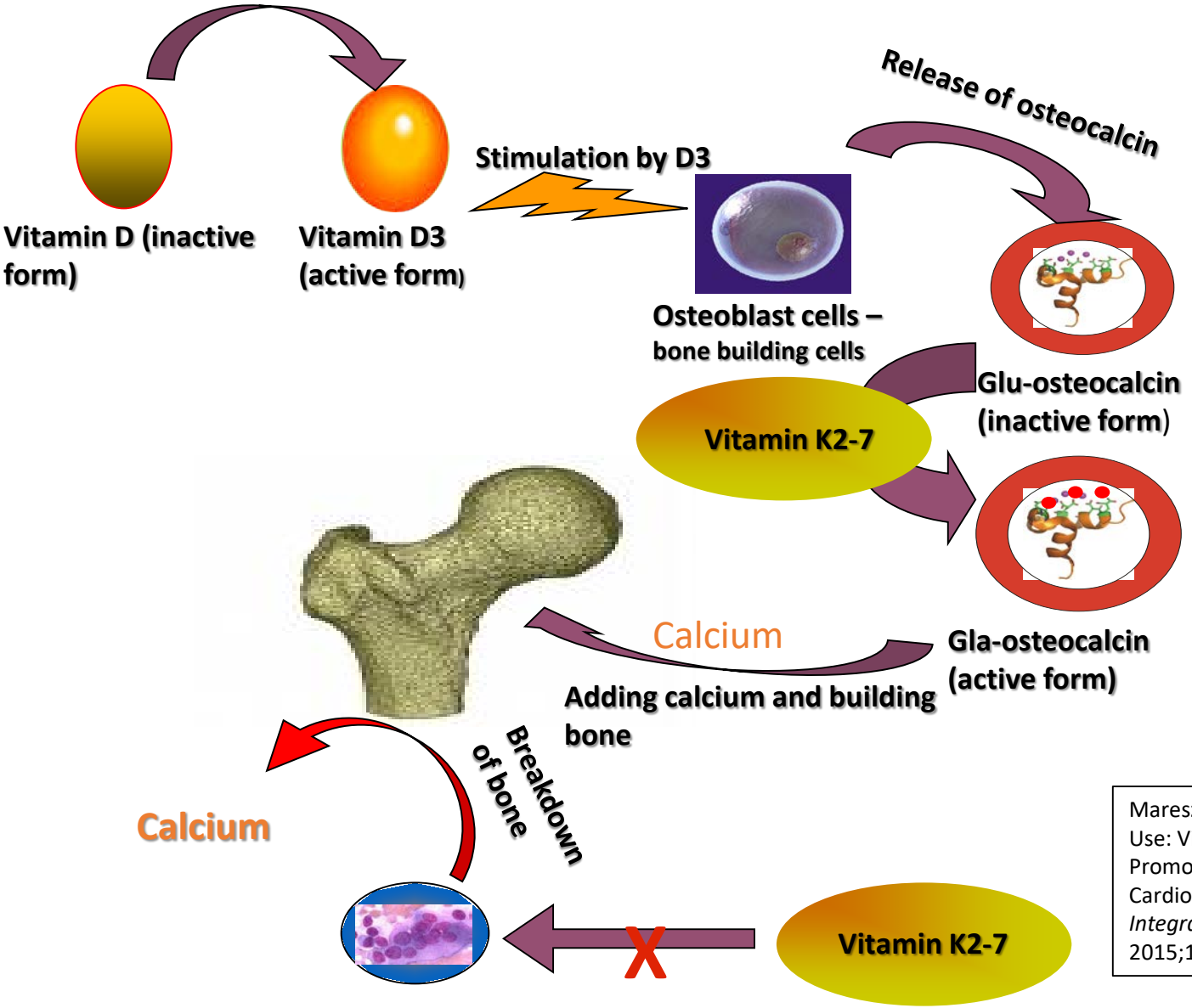
More on Vitamin D/K2 Supplementation

- If any gut problems of malabsorption, dysbiosis, hx gall bladder removal – may be best to use an emulsified form of D so not dependent on adequate bile and absorption chemistry
- Be sure Calcium fasting blood level is not high before giving higher dose D
- Consider Vit K2 status & supplement K2-7
- Vit D and Vit A can use some same receptor sites – monitor both if supplementing D

The Role of K2 in Building Bone and Preventing Bone Loss



Maresz K. Proper Calcium Use: Vitamin K2 as a Promoter of Bone and Cardiovascular Health. *Integrative Medicine*. 2015;14(1):34-39

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Antioxidant Support

- Vitamins: A, C, and E
- Minerals: zinc and Selenomethionine (active selenium)
- Green tea extract
- Milk thistle
- Flavanoids
- Lipoic acid
- NAC/Reduced Glutathione
- CoQ 10 (Ubiquinol if NQ01 SNP)

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Bone Formation Diet and Lifestyle

- Adequate dietary protein intake
  - especially containing proline and glycine (collagen forming amino acids) and sulfur containing amino acids (methionine and cysteine)
- Ensure adequate intake of foods rich in folate, vit B6 & 12, silica, antioxidants, and bone building nutrients like Ca, Mg, vit D, K2-7, boron, etc
- Reduce Oxidative stress: smoking and other toxins
- Get regular (not excessive) exposure to sun – mind the DHCR7 SNP
- Exercise on a regular basis with strength/resistance training

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Bone Resorption

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CYP1A2
(Cytochrome P450 1A2)

- CYP1A2 is a member of the cytochrome P450 superfamily of enzymes, involved in the metabolism of xenobiotics/caffeine.
- Related to low bone mineral density with caffeine intake.
  - Fast metabolizers may have an effect based on an increased concentration of caffeine metabolites (men in the literature , more then women)
  - Slow metabolizers may have an effect through increased concentration of caffeine itself.

Hallström H, Melhus H, Glynn A , Lind L , Syvänen A C , Michaëlsson K. Coffee consumption and CYP1A2 genotype in relation to bone mineral density of the proximal femur in elderly men and women: a cohort study. Hallström et al. Nutrition & Metabolism 2010, 7:12

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GSTT1 & GSTM1

- Addressed earlier: A member of a superfamily of proteins that catalyze the conjugation of reduced glutathione.
  - Involved in the detoxification of a broad range of toxic substances.
- Absence of gene and therefore enzymatic activity associated with decreased bone mineral density.
  - Affects both formation **and remodeling.**
- May counter benefits of Nrf2 pathway
  - Compounded by TNF-a

Buchard A, Sanchez J, Dalhoff K, Morling N. Multiplex PCR Detection of GSTM1, GSTT1, and GSTP1 Gene Variants. J Mol Diagn. 2007 Nov; 9(5): 612–617.

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MTHFR:

Methylenetetrahydrofolate reductase

- Addressed earlier: Encodes for the protein that supports methylation by catalyzing the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate
- A relationship exists between DNA methylation and level of transcription of genes highly associated with BMD

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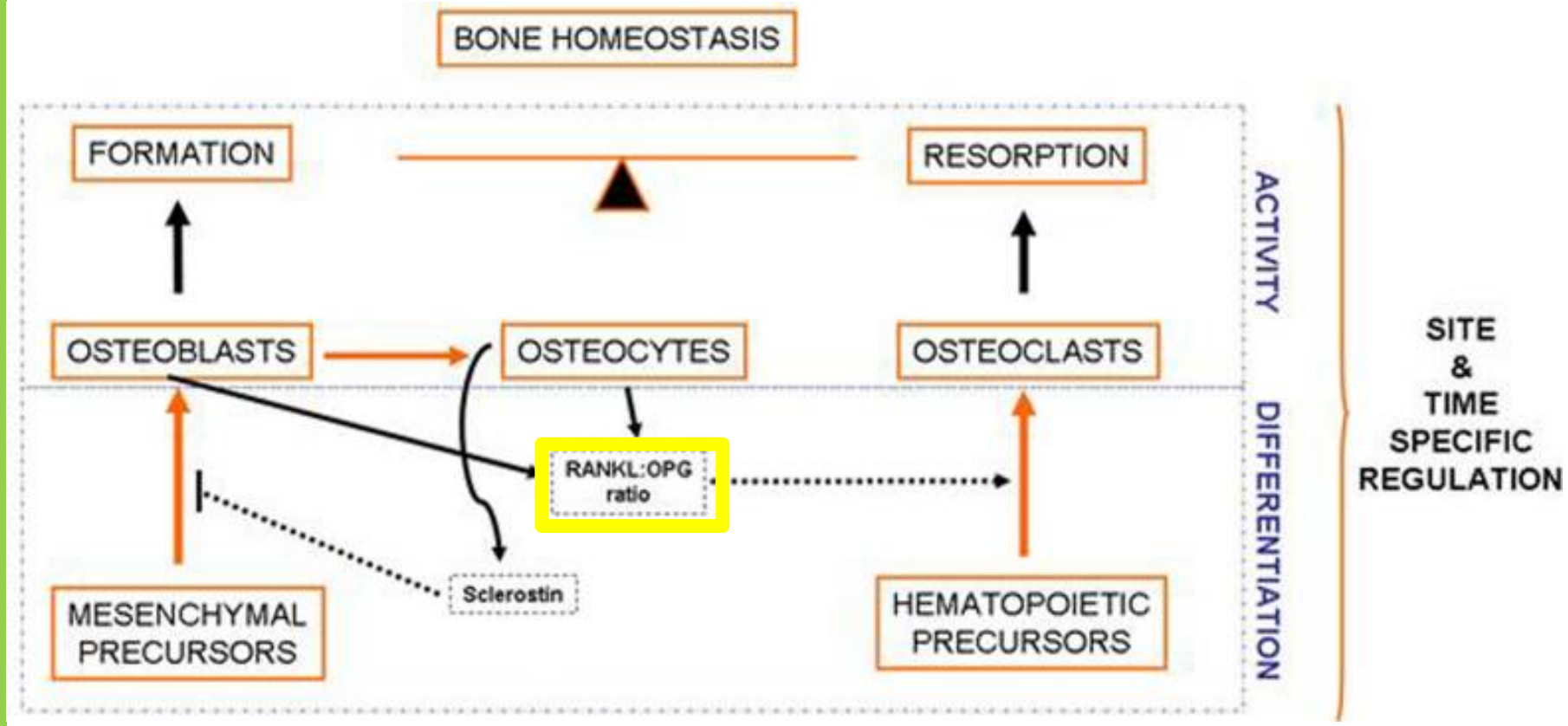
Methylation and (NF-kB Ligand) RANKL Gene

- Receptor activator of nuclear factor-kB ligand (RANKL) is a key mediator of osteoclast differentiation, promoting the activation and survival of bone-resorbing cells
- For bone homeostasis, RANKL can be opposed by osteoprotegerin (OPG), which blocks RANKL from stimulating osteoclast formation and activation
- Increased DNA methylation in the RANKL transcriptional start site is associated with epigenetic silencing of RANKL.
- Supporting DNA methylation capability may help to regulate RANKL expression and modulate bone resorption.

Sjur Reppe, Harish Datta, and Kaare M. Gautvik. The Influence of DNA Methylation on Bone Cells. Curr Genomics 2015 Dec; 16(6): 384–392.

Methylation Influences RANKL and Sclerostin



Adapted from Image in Delgado-Calle J and Riancho JA. The Role of DNA Methylation in Common Skeletal Disorders. Biology (Basel). 2012 Dec; 1(3): 698–713.

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APOE (Apolipoprotein E)

- ApoE4 associated with reduced fat soluble vitamin absorption
- ApoE2 is genetic risk factor for low trabecular bone mass and vertebral fractures.
  - May have impaired lipoprotein-associated vitamin K delivery affecting osteoblasts, via a lower degree of carboxylation of osteoblast-derived gla-proteins (carboxylated osteocalcin) which in turn contributes to a higher bone turnover and development of a lower trabecular bone mass.

1. Huebbe P, Lange J, Lietz G, Rimbach G. Dietary beta-carotene and lutein metabolism is modulated by the APOE genotype. Biofactors. 2016 Jul 8;42(4):388-96
2. Dieckmann M, Beil F T, Mueller B, et al. Human Apolipoprotein E Isoforms differentially affect Bone Mass and Turnover in vivo. J Bone Miner Res. 2013 Feb; 28(2): 236–245. doi: 10.1002/jbmr.1757.

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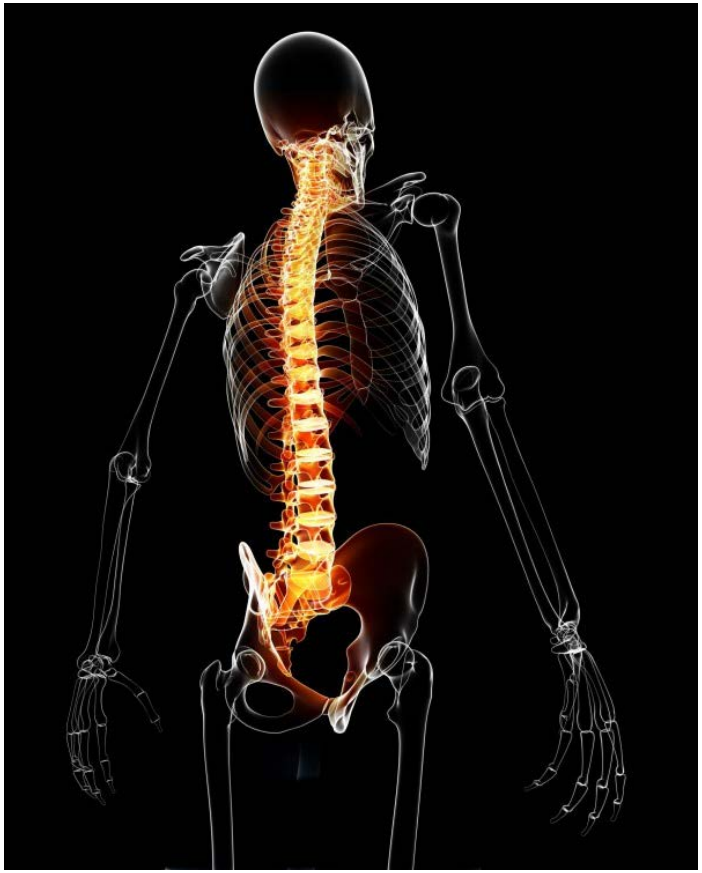
More Inflammation SNPs



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IL-6 (Interleukin 6)
IL-6R (Interleukin 6 Receptor)

- Gene encodes a cytokine that functions in inflammation and the maturation of B cells and plays a central role in inflammatory response
- IL-6 stimulates the development of osteoclasts and thereby the process of bone resorption, it is likely to be a pathogenic factor in bone loss, especially that triggered by estrogen deficiency.
  - SNP (GG Genotype) associated with decreased bone density
- IL6R associated with increased C-reactive protein and inflammation

Wang Z, Yang Y, He M, Wang R, Ma J, Zhang Y, Zhao L, Yucorresponding K. Association Between Interleukin-6 Gene Polymorphisms and Bone Mineral Density: A Meta-Analysis. Genet Test Mol Biomarkers. 2013 Dec; 17(12): 898–909.
https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=3570 (Date accessed 8/25/2017)

Next Level Functional Nutrition™

CRP (C-Reactive Protein)

- C-reactive protein (CRP), a marker of inflammation and a hallmark of the acute-phase response, has been observed in immune and inflammatory diseases.
- Higher CRP concentration in premenopausal women was found to significantly correlate with decreases in BMD.
- SNPs on CRP can influence plasma levels of CRP ⬆ or ⬇
  - Note: SNP on rs1205 can lower CRP and consequently mask an inflammatory status - look for other markers and symptoms of inflammation

1. Hage F G, Szalai A J. C-Reactive Protein Gene Polymorphisms, C-Reactive Protein Blood Levels, and Cardiovascular Disease Risk. Journal of the American College of Cardiology, Vol. 50, No. 12, 2007
2. Lim H S, Park Y H, Kim S K. Relationship between Serum Inflammatory Marker and Bone Mineral Density in Healthy Adults. J Bone Metab 2016;23:27-33
3. Carlson C S, Aldred S F, Lee P K, et al. Polymorphisms within the C-Reactive Protein (CRP) Promoter Region Are Associated with Plasma CRP Levels. AJHG. The American Journal of Human Genetics. Volume 77, Issue 1, July 2005, Pages 64-77. DOI:10.1086/431366.
4. Almeida OP1, Norman PE, Allcock R, et al. Polymorphisms of the CRP gene inhibit inflammatory response and increase susceptibility to depression: the Health in Men Study. Int J Epidemiol. 2009 Aug;38(4):1049-59.

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TNF-alpha (Tumor Necrosis Factor)

- Gene encodes for tumor necrosis factor alpha, a pro-inflammatory cytokine.
- Induces ROS production that activates NF-κB
  - There is a strong consensus that TNFα and RANKL can act synergistically to induce osteoclastogenesis
- Specifically, NF-κB controls the differentiation/activity of the main skeletal cell types – osteoclasts, osteoblasts, osteocytes and chondrocytes. Activation increases inflammation - negatively affects bone health

1. https://www.ncbi.nlm.nih.gov/gene/7124 (Date accessed: 9/1/2017)
2. http://www.pathwaycommons.org/pc/record2.do?id=543635 (Date accessed: 9/22/2017)
3. Lawrence T. The Nuclear Factor NF-κB Pathway in Inflammation. Cold Spring Harb Perspect Biol. 2009 Dec; 1(6): a001651.
4. Kastl L, Sauer S W, Ruppert T, Beissbarth T, Becker M S, Süss D, Krammer P H, Gülow K. TNF-a mediates mitochondrial uncoupling and enhances
5. ROS-dependent cell migration via NF-jB activation in liver cells. FEBS Letters 588 (2014) 175–183

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NF-κB (Nuclear Factor- κB)

- Encodes this protein complex that controls DNA transcription, cytokine production, and cell survival
- NF-κB activation has been associated with
  - Low-grade inflammation
  - Accumulation of reactive oxygen species
- Inappropriate activation of NF-κB enhances RANKL-mediated osteoclastogenesis and bone resorption and may also inhibit bone formation by osteoblasts

1. Veis Novack D V. Role of NF-κB in the skeleton. Cell Res. 2011 Jan; 21(1): 169–182.
2. Abu-Amer Y. NF-κB signaling and bone resorption. Osteoporos Int. 2013 Sep; 24(9): 10.1007/s00198-013-2313-x.

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Monitor Labs, especially as you see risk in SNPS

- Inflammation Markers
  - IL-6
  - TNF-a
  - Additional cytokines - look at balance between pro and anti-inflammatory (IL 4, IL 10 etc)
  - hsCRP and other acute phase reactants (Ferritin, Albumin, etc)
  - Sed rate (ESR)
  - EFA balance

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Other SNPs Related to Bone Health

Calciotropic and sex hormones and their receptors

- Parathyroid hormone (PTH) and PTH receptor (PTHR).
  - Calcium homeostasis, endogenous vitamin D synthesis and regulation of bone cells activity.
- Calcitonin (CT) and its receptor (CTR).
  - Increases osteoblast activity, retains calcium in bones and prevents phosphorus and calcium loss.
- Aromatase (CYP19A1).
  - Catalyzes androgens conversion to estrogens.

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Other SNPs Related to Bone Health

Calciotropic and sex hormones and their receptors

- Androgen receptor (AR).
  - Regulates osteoblast function and suppresses action on bone resorption.
- Calcium-sensing receptor (CaSR).
  - Regulates calcium homeostasis at parathyroid, kidney, bowel and bone level.
- Glucocorticoid receptor (GR).
  - Inhibition of bone formation, suppression of calcium absorption.

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Other SNPs Related to Bone Health

Growth factors and local regulators

- Insulin-like growth factor 1 (IGF-I).
  - Stimulates bone formation, recruits pre-osteoblasts, growth factor for osteoblasts.
- Bone morphogenetic protein 4 (BMP4).
  - Involved in bone and cartilage development and in fracture repair.
- Bone morphogenetic protein 2 (BMP2).
  - Stimulates the differentiation and/or activity of osteoclasts.

Miscellaneous

- Low-density lipoprotein receptor-related protein 5 (LRP5).
  - Regulates osteoblasts proliferation and bone formation.
- Sclerostin (SOST).
  - Potent osteocyte expressed negative regulator of bone formation in vitro.

Marini F. and Brandi M. L. Genetic Determinants of Osteoporosis: Common Bases to Cardiovascular Diseases? International Journal of Hypertension Volume 2010 (2010), Article ID 394579, 16 pages

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General Intervention/Support & To Quiet SNP Expression

- Supportive/varied diet and optimal nutritional status, especially bone building nutrients
  - 8-12 srvgs fruit/veggies a day (all colors of rainbow!)
  - Keep insulin in check
  - Keep processed foods to a minimum
  - Assure good protein balance and amino acid status
  - Avoid excessive caffeine intake, especially if CYP1A2 SNP
  - Stay hydrated
- Identify and reduce inflammation from all sources
  - Gut health/Microbiome diversity
  - Diet
    - Balance fatty acid intake

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Anti-inflammatory Supplements

(Many cross over for oxidative stress!)

- EPA/DHA
- Curcumin
- Quercetin
- Ginger
- Alpha-lipoic acid
- Resveratrol

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General Intervention/Support & To Quiet SNP Expression

- Reduce Oxidative stress
  - Monitor/Reduce heavy metals/toxic burden
  - Remember oil quality/cooking methods
- Exercise, but not too much
- Maintain optimal pH balance
- Maintain optimal Microbiome
- Monitor drug effects and drug-nutrient interactions
- Get enough good quality sleep
- Balance work/play – stress management
- Experience joy and gratitude everyday

And to get more targeted….

The Face of Culinary Genomics

Agenda

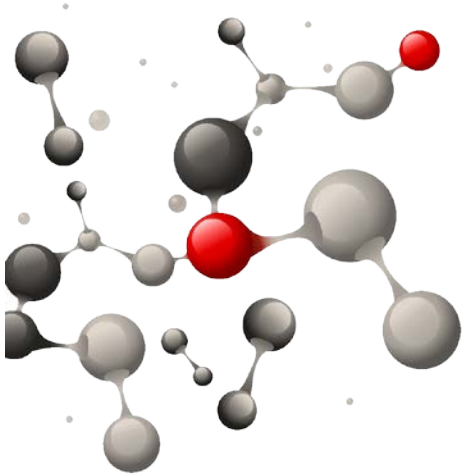
- Definitions
- Culinary Genomics: the art of translating biochemistry to the plate: example: oxidative stress
- Applying Culinary Genomics to Bone Formation SNPs
- Applying Culinary Genomics to Bone Resorption SNPs
- Case Study: Polygenic thinking and applied culinary genomics

Definitions

- **Nutrigenomics**: sometimes called nutritional genomics, investigates how nutrients and bioactive compounds in the food we eat interact with our genes to affect our health

- **Culinary Genomics**: uniting the science of genomics with the knowledge of the kitchen. Preparing & serving specific nutrient rich foods to trigger specific genes on/off and promote overall health. Or *Cooking the Language of our DNA*

Slide courtesy of Genoma International/Genomic Kitchen



The application of the culinary arts to the science of genomics…
yields a new food conversation

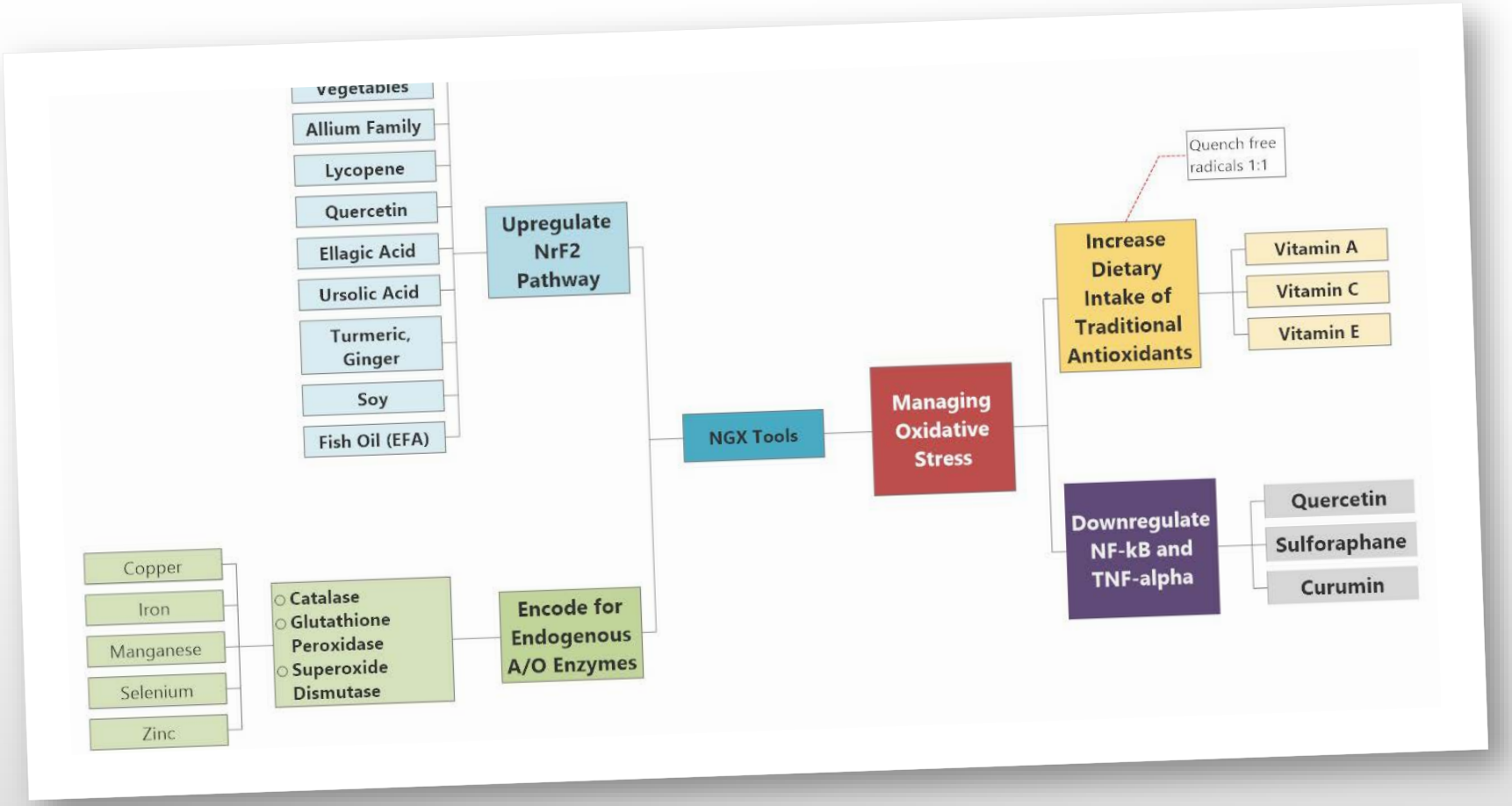
Culinary Significance

- Nutrigenomics elevates the importance of food for our innate biochemistry
- Culinary genomics showcases the power, relevance and potential of the kitchen

Culinary Genomics requires an implicit understanding of the following:

- How genes function
- Which ingredients contain bioactives that can trigger genes into action, or turn them off
- Which nutrients are needed to support the functionality of the proteins that our genes produce
- How to cook with these ingredients!

CULINARY GENOMICS EXAMPLE: OXIDATIVE STRESS



Painting biochemistry on the plate

1

Bioactives + Gene NrF2 *plus* target nutrient cofactors (vitamins and minerals) = successfully reduced oxidative stress

2

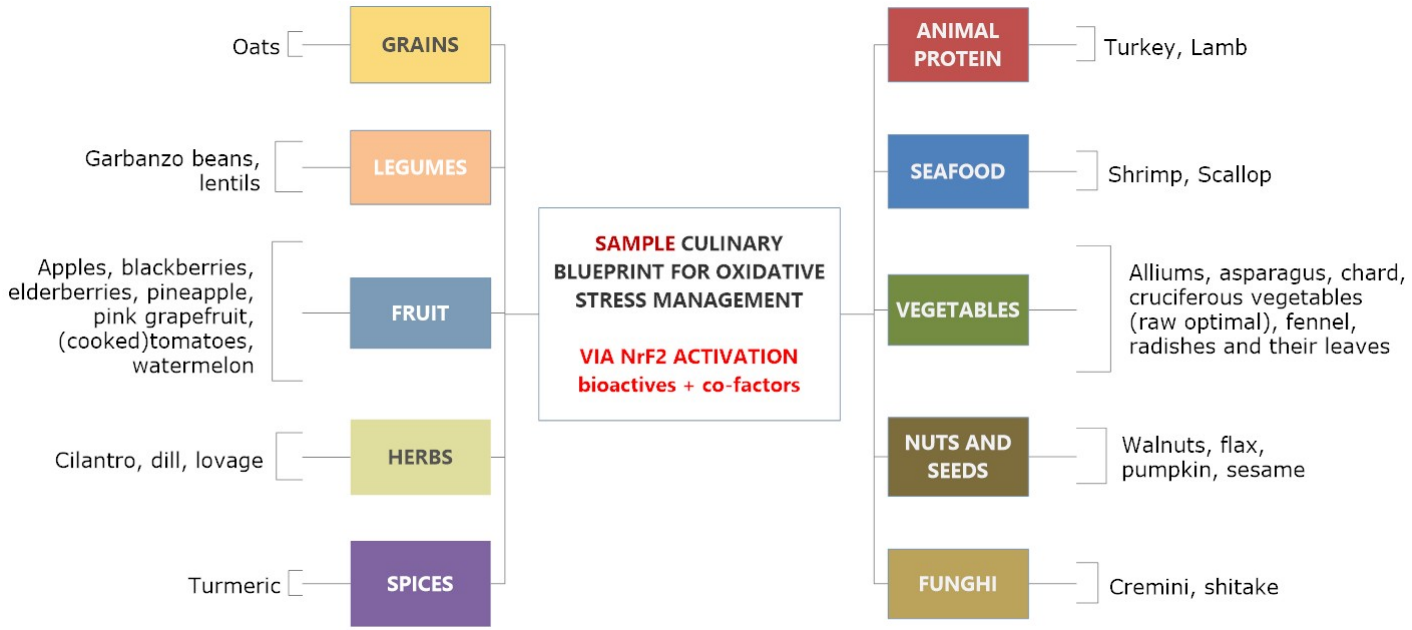
Bioactives + Gene NrF2 ***minus*** **nutrient cofactors** = unmitigated oxidative stress via endogenous enzymes

Putting biochemistry on the plate

Bioactives + Gene NrF2 = Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GPX)

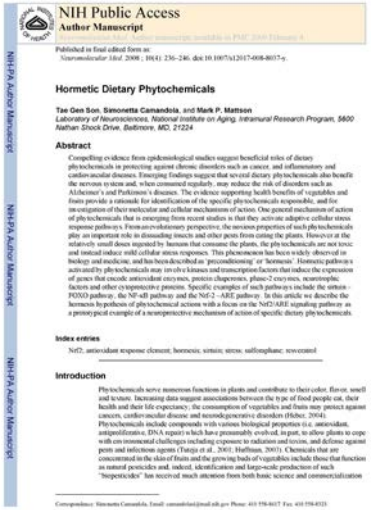
SOD, CAT and GPX + selenium, copper, manganese, iron and zinc

Oxidative stress mitigation =**bioactives + NrF2** = (SOD + CAT + GPX + se + cu + mn+ zn +fe) + (Exogenous antioxidants)



THE GENOMIC KITCHEN

Culinary Genomics creates recipes from biochemistry for biochemistry



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Hormetic Dietary Phytochemicals

Tae Geo Son, **Simonetta Camandola**, and **Mark P. Mattson**
Laboratory of Neurosciences, National Institute on Aging, Intramural Research Program, 5600 Nathan Shock Drive, Baltimore, MD, 21224

Abstract

Compelling evidence from epidemiological studies suggest beneficial roles of dietary phytochemicals in protecting against chronic disorders such as cancer, and inflammatory and cardiovascular diseases. Emerging findings suggest that several dietary phytochemicals also benefit the nervous system and, when consumed regularly, may reduce the risk of disorders such as Alzheimer's and Parkinson's diseases. The evidence supporting health benefits of vegetables and fruits provide a rationale for identification of the specific phytochemicals responsible, and for investigation of their molecular and cellular mechanisms of action. One general mechanism of action of phytochemicals that is emerging from recent studies is that they activate adaptive cellular stress response pathways. From an evolutionary perspective, the noxious properties of such phytochemicals play an important role in dissuading insects and other pests from eating the plants. However at the relatively small doses ingested by humans that consume the plants, the phytochemicals are not toxic and instead induce mild cellular stress responses. This phenomenon has been widely observed in biology and medicine, and has been described as 'preconditioning' or 'hormesis'. Hormetic pathways activated by phytochemicals may involve kinases and transcription factors that induce the expression of genes that encode antioxidant enzymes, protein chaperones, phase-2 enzymes, neurotrophic factors and other cytoprotective proteins. Specific examples of such pathways include the sirtuin - FOXO pathway, the NF-κB pathway and the Nrf-2 – ARE pathway. In this article we describe the hormesis hypothesis of phytochemical actions with a focus on the Nrf2/ARE signaling pathway as a prototypical example of a neuroprotective mechanism of action of specific dietary phytochemicals.

Index entries

Nrf2; antioxidant response element; hormesis; sirtuin; stress; sulforaphane; resveratrol

Introduction

Phytochemicals serve numerous functions in plants and contribute to their color, flavor, smell and texture. Increasing data suggest associations between the type of food people eat, their health and their life expectancy; the consumption of vegetables and fruits may protect against cancers, cardiovascular disease and neurodegenerative disorders (Heber, 2004). Phytochemicals include compounds with various biological properties (i.e. antioxidant, antiproliferative, DNA repair) which have presumably evolved, in part, to allow plants to cope with environmental challenges including exposure to radiation and toxins, and defense against pests and infectious agents (Tateja et al., 2001; Huffman, 2003). Chemicals that are concentrated in the skin of fruits and the growing buds of vegetables include those that function as natural pesticides and, indeed, identification and large-scale production of such "biopesticides" has received much attention from both basic science and commercialization

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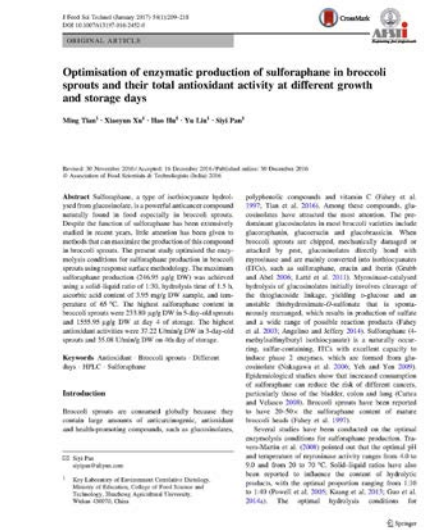

J Food Sci Technol (January 2017) 54(1):209–218
DOI 10.1007/s13197-016-2452-6

ORIGINAL ARTICLE

Optimisation of enzymatic production of sulforaphane in broccoli sprouts and their total antioxidant activity at different growth and storage days

Ming Tian[1] · **Xiaoyun Xu**[1] · **Hao Hu**[1] · **Yu Liu**[1] · **Siyi Pan**[1]

Revised: 30 November 2016 / Accepted: 16 December 2016 / Published online: 30 December 2016

Abstract Sulforaphane, a type of isothiocyanate hydrolyzed from glucoraphanin, is a powerful anticancer compound naturally found in food especially in broccoli sprouts. Despite the function of sulforaphane has been extensively studied in recent years, little attention has been given to methods that can maximize the production of this compound in broccoli sprouts. The present study optimised the enzymolysis conditions for sulforaphane production in broccoli sprouts using response surface methodology. The maximum sulforaphane production (266.95 μg/g DW) was achieved using a solid–liquid ratio of 1:30, hydrolysis time of 1.5 h, ascorbic acid content of 3.95 mg/g DW sample, and temperature of 45 °C. The highest sulforaphane content in broccoli sprouts were 253.80 μg/g DW in 5-day-old sprouts and 1555.95 μg/g DW at day 4 of storage. The highest antioxidant activities were 37.22 U/min/g DW in 3-day-old sprouts and 35.08 U/min/g DW on 4th day of storage.

Keywords Antioxidant · Broccoli sprouts · Different days · HPLC · Sulforaphane

Introduction

Broccoli sprouts are consumed globally because they contain large amounts of anticarcinogenic, antioxidant and health-promoting compounds, such as glucosinolates, polyphenolic compounds and vitamin C (Fahey et al. 1997; Tian et al. 2016). Among these compounds, glucosinolates have attracted the most attention. The predominant glucosinolates in most broccoli varieties include glucoraphanin, glucoerucin and glucobrassicin. When broccoli sprouts are chipped, mechanically damaged or attacked by pest, glucosinolates directly bond with myrosinase and are mainly converted into isothiocyanates (ITCs), such as sulforaphane, erucin and iberin (Gruhb and Abel 2006; Latté et al. 2011). Myrosinase-catalyzed hydrolysis of glucosinolates initially involves cleavage of the thioglucosidic linkage, yielding D-glucose and an unstable thiohydroximate-O-sulfonate that is spontaneously rearranged, which results in production of sulfate and a wide range of possible reaction products (Fahey et al. 2003; Angelino and Jeffery 2014). Sulforaphane (4-methylsulfinylbutyl isothiocyanate) is a naturally occurring, sulfur-containing, ITCs with excellent capacity to induce phase 2 enzymes, which are formed from glucosinolate (Nakagawa et al. 2006; Yeh and Yen 2009). Epidemiological studies show that increased consumption of sulforaphane can reduce the risk of different cancers, particularly those of the bladder, colon and lung (Cortes and Velasco 2008). Broccoli sprouts have been reported to have 20–50× the sulforaphane content of mature broccoli heads (Fahey et al. 1997).

Several studies have been conducted on the optimal enzymolysis conditions for sulforaphane production. Travers-Martin et al. (2008) pointed out that the optimal pH and temperature of myrosinase activity ranges from 4.0 to 9.0 and from 20 to 70 °C. Solid–liquid ratios have also been reported to influence the content of hydrolytic products, with the optimal proportion ranging from 1:10 to 1:40 (Powell et al. 2005; Kuang et al. 2015; Guo et al. 2016a). The optimal hydrolysis conditions for

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Plus Food Science & Technology

Recipe Formulation Considerations

- Genes / SNPs + their impact
- Prioritization of culinary intervention based on level of impact on critical biochemical pathways
- Recipe formulation utilizing bioactives and supporting nutrients
- Knowledge of impact of heat (turmeric = example)
- Outcomes measurement and adjustment of intervention


Culinary
innovation &
translation
just got more
real…

Culinary Genomics in action.

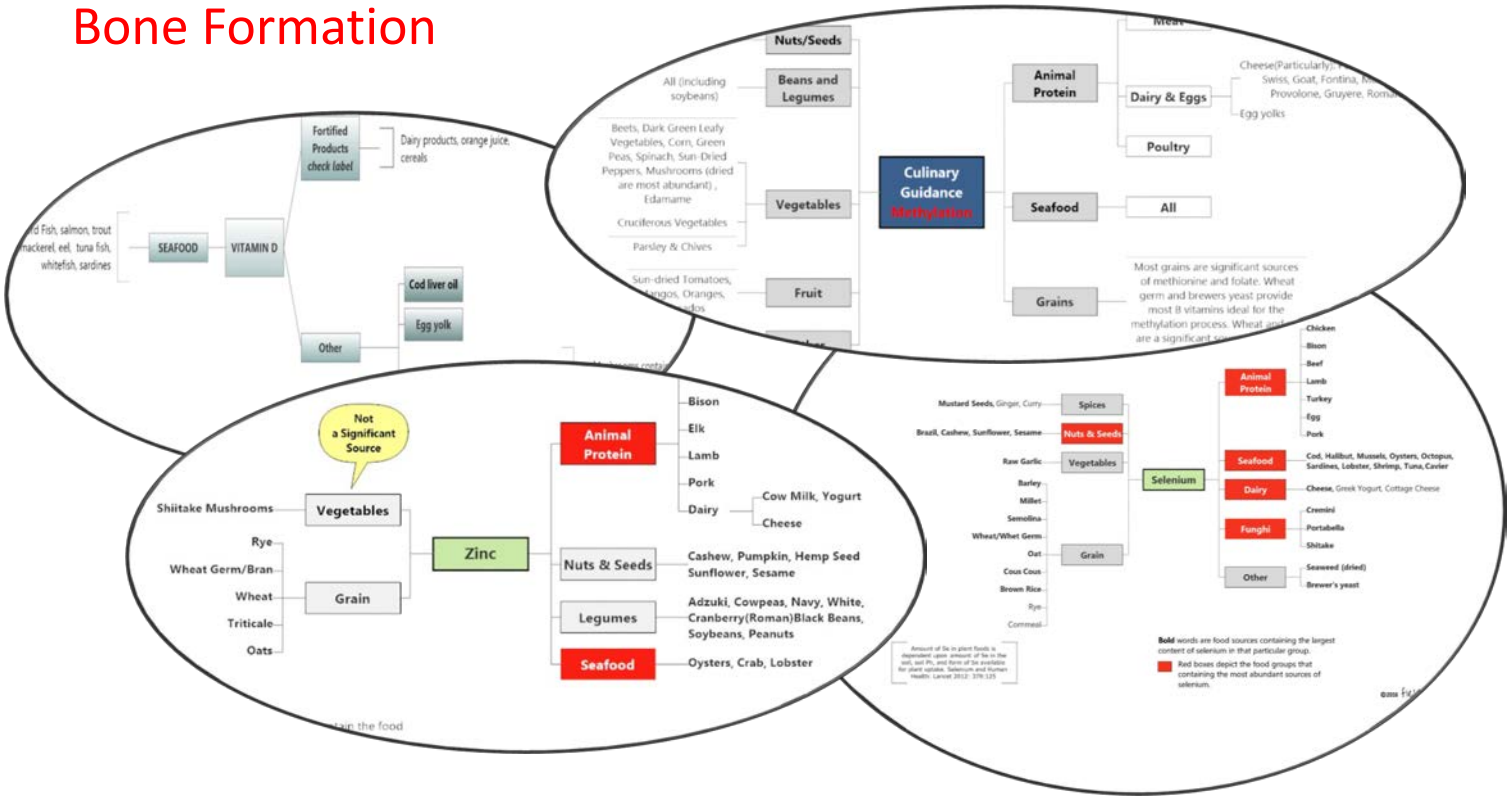
Genomic specific: Bone Formation

- Bone formation SNPs, including Vitamin D SNPs
  - Ca, MG, Vitamin D rich foods
  - Mineral-rich
  - Add fermented foods
- Oxidative stress SNPs
  - Cruciferous vegetables
  - Alliums/quercetin-rich foods

Polygenic thinking drives culinary solutions

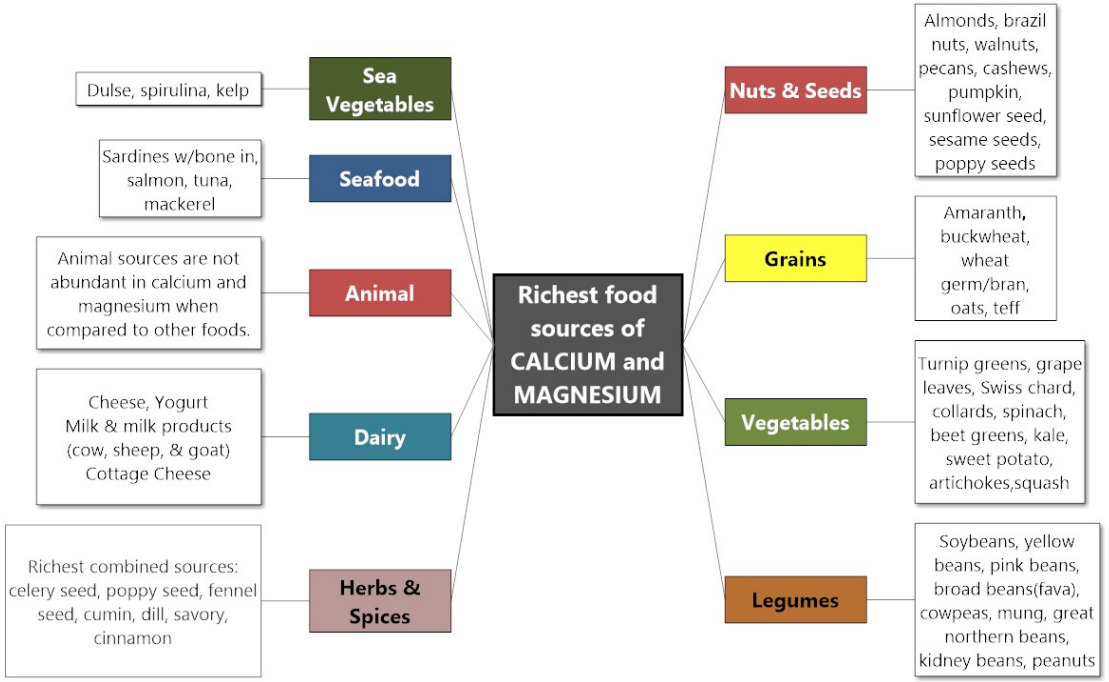
Food-Gene Cross Talk

Bone Formation

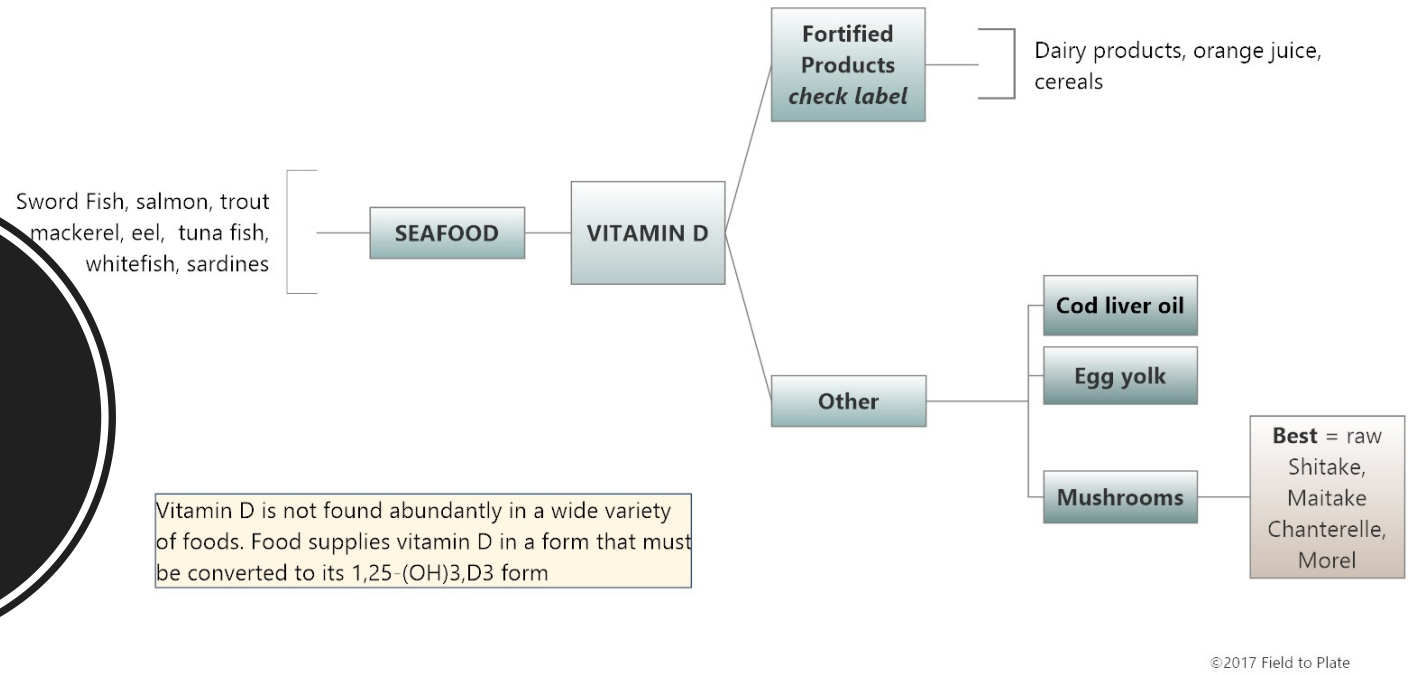


……100 foot painting of assorted biochemistry for the plate

Build an ingredient matrix specific to SNPs in relevant Biochemical Pathways

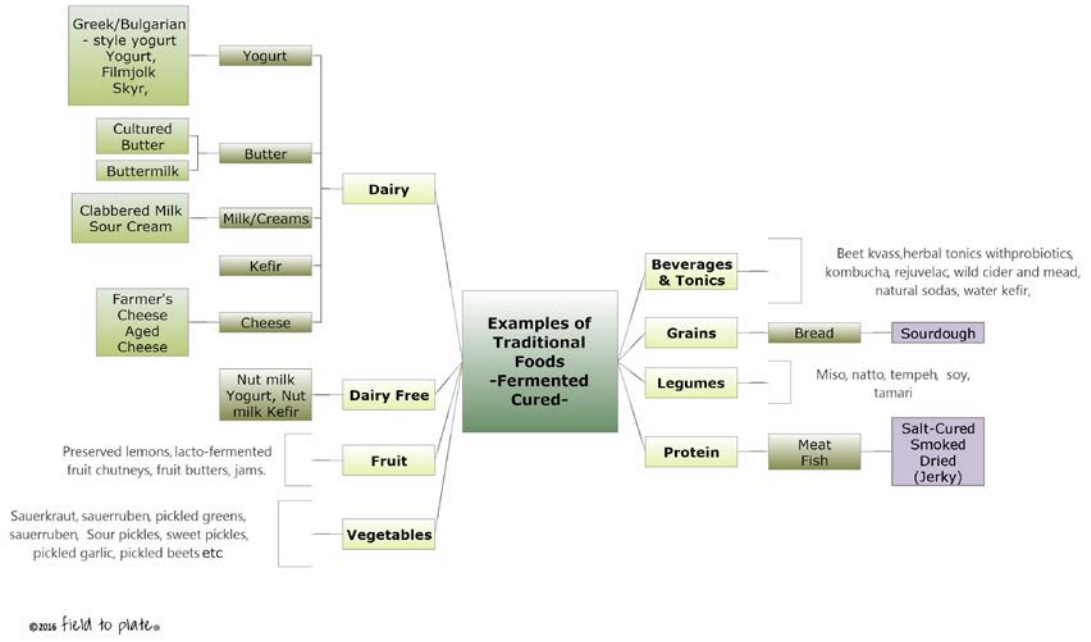


Build an ingredient matrix



Vitamin D is not found abundantly in a wide variety of foods. Food supplies vitamin D in a form that must be converted to its 1,25-(OH)3,D3 form

Build an ingredient matrix specific to SNPs in relevant Biochemical Pathways



frontiers in Microbiology

REVIEW

Functional Properties of Microorganisms in Fermented Foods

Jyoti P. Tamang[1], Dong-Hwa Shin[2,3], Su-Jin Jung[2] and Soo-Wan Chae[2,3]*

[1] Department of Microbiology, School of Life Sciences, Sikkim University, Gangtok, India, [2] Microorganism Resources Research Institute, Jeonju, South Korea, [3] Clinical Trial Center for Functional Foods, Chonbuk National University Hospital, Jeonju, South Korea, [4] Division of Pharmacology, Chonbuk National University Medical School, Jeonju, South Korea

Fermented foods have unique functional properties imparting some health benefits to consumers due to presence of functional microorganisms, which possess probiotics properties, antimicrobial, antioxidant, peptide production, etc. Health benefits of some global fermented foods are synthesis of nutrients, prevention of cardiovascular disease, prevention of cancer, gastrointestinal disorders, allergic reactions, diabetes, among others. The present paper is aimed to review the information on some functional properties of the microorganisms associated with fermented foods and beverages, and their health-promoting benefits to consumers.

Keywords: fermented foods, microorganisms, functional properties, health benefits, bioactive compounds

OPEN ACCESS

INTRODUCTION

Existing scientific data show many fermented foods have both nutritive and non-nutritive components in foods, which have the potential to modulate specific target functions in the body relevant to well-being and health of the consumers. However, 90% of naturally fermented foods and alcoholic beverages in different countries and regions of the world are still at home production under traditional conditions. Naturally fermented foods and beverages contain both functional and non-functional microorganisms (Tamang et al., 2016). Functional microorganisms transform the chemical constituents of raw materials of plant/animal sources during food fermentation thereby enhancing the bio-availability of nutrients, enriching sensory quality of the food, imparting bio-preservative effects and improvement of food safety, degrading toxic components and anti-nutritive factors, producing antioxidant and antimicrobial compounds, stimulating the probiotic functions, and fortifying with some health-promoting bioactive compounds (Tamang et al., 2009, 2016; Rafiul et al., 2010; Bourdichon et al., 2012; Thapa and Tamang, 2017). Among bacteria associated with fermented foods and alcoholic beverages, lactic acid bacteria (LAB) mostly species of *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Weissella*, etc. are widely present in many fermented foods and beverages (Axelsson et al., 2012; Holzapfel and Wood, 2014). Species of *Bacillus* are also present in legume based fermented foods (Kubo et al., 2011; Tamang, 2015). Species of *Bifidobacterium*, *Brachybacterium*, *Enterobacterium*, and *Propionibacterium* are isolated from cheese, and species of *Arthrobacter* and *Bafinia* from fermented meat products (Bourdichon et al., 2012). Several genera with hundred of species of yeasts have been isolated from fermented foods, alcoholic beverages and non-food mixed amylolytic starters which mostly include *Candida*, *Debaryomyces*, *Geotrichum*, *Hanseniula*, *Kluyveromyces*, *Pichia*, *Rhodotorula*, *Saccharomyces*, *Saccharomycopsis*, *Schizosaccharomyces*, *Torulopsis*, *Wickerhamomyces*, and *Zygosaccharomyces* (Tamang and Sarkar, 2008; Ye et al., 2013). Species of *Actinomucor*, *Amylomyces*, *Aspergillus*, *Monascus*, *Mucor*, *Neurospora*, *Penicillium*, *Rhizopus*, and *Umbiga* are reported for many fermented foods. Asian non-food amylolytic starters, and alcoholic beverages (Chen et al., 2014).

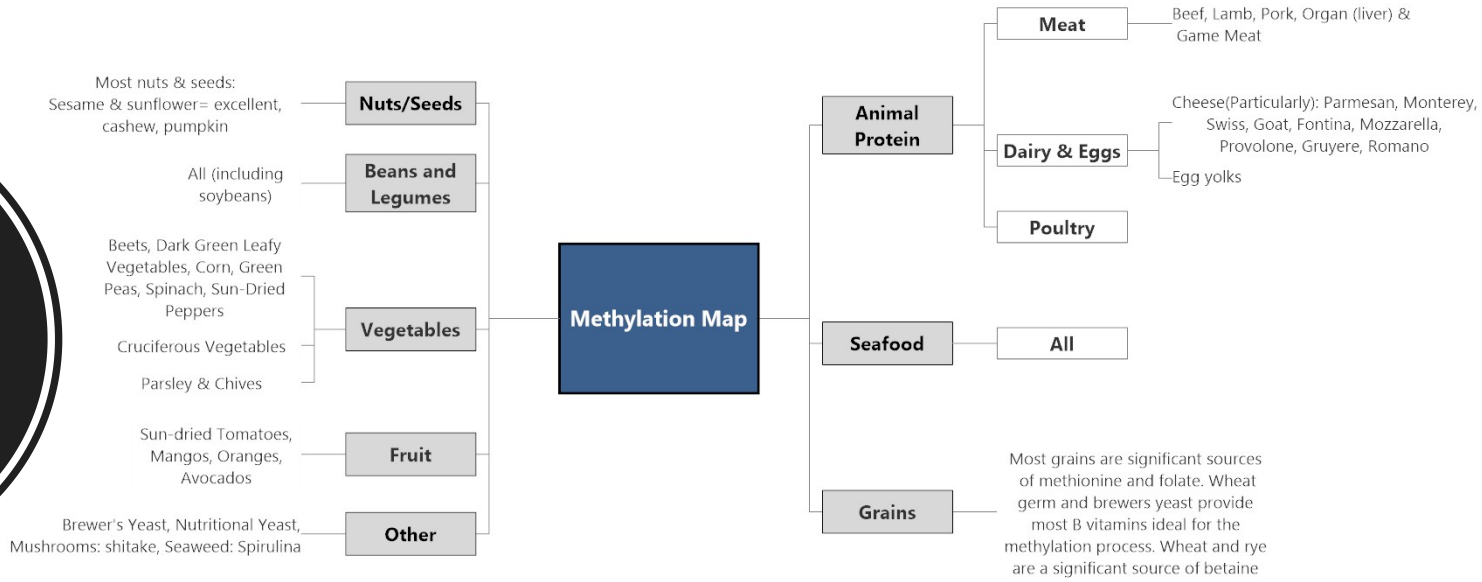
Bioactive compounds	Synthesized in fermented foods	Health benefits	Reference
Genistein	*Doenjang*	Facilitates the β-oxidation of fatty acid, reducing body weight	Kwak et al., 2012
Lipoteichoic acid from *L. rhamnosus* GG	Fermented milk	Oral photoprotective agent against UV-induced carcinogenesis	Weill et al., 2013
Isocyanate and sulphide indole-3-carbinol	*Kimchi*	Prevention of cancer, detoxification of heavy metals in liver, kidney, and small intestine	Kwak et al., 2014
Ornithine		Anti-obesity efficacy	Park et al., 2012
Vitamin A, Vitamin C, fibers		Suppression of cancer cells	Han et al., 2015
Capsaicin, Allicin		Prevention of cancer, suppression of *Helicobacter pylori*	Lim and Im, 2009
Chlorophyll		Helps in prevention of absorbing carcinogen	Ferruzzi and Blakeslee, 2007
S-adenosyl-L-methionine (SAM)		Treatment of depression	Lee and Lee, 2009
HDMPPA (an antioxidant)		Therapeutic application in human atherosclerosis	Kim et al., 2007
Nattokinase, antibiotics, Vitamin K	*Natto*	Antitumor, immunomodulating	Nagai, 2015
Vitamin C	Sauerkraut	Scurvy	Peñas et al., 2013
Glucosinolates		Activation of natural antioxidant enzymes	Martínez-Villaluenga et al., 2012
Antioxidant genestein, daidzein, tocopherol, superoxide dismutase	*Tempe*	Prevents oxidative stress causing non-communicable disease such as hyperlipidemia, diabetes, cancer (breast and colon), prevents the damage of pancreatic beta cell	Astuti, 2015
Phenolics- resveratrol	*Wine (red)*	Anti inflammatory	Jeong et al., 2010
Phenolics, succinic acid		Digestive aid	Jackson, 2008
Phenolics, resveratrol, flavonoids – quercitin, Vitamins C and E, mineral selenium		Prevent cardiovascular diseases, reduce incidence of heart attacks and mortality rate	Walker, 2014
Melatonin, resveratrol		Antioxidant and anti-aging property	Fernández-Mar et al., 2012
Resveratol		Anti-diabetic	Ramadori et al., 2009

Culinary thought informed by science

Genomic specific: Bone Resorption

- **Bone Resorption SNPS**
  - Vitamin D rich foods
  - Crucifers (induce) (Cumin/turmeric/grapefruit inhibit)
- **Methylation SNPs**
  - Vitamin B complex rich foods, choline, betaine
- **Inflammation SNPs**
  - Upregulate NrF2 /downregulate TNF-alpha/NfkB cascade +
  - Omega-3 FA

Methylation



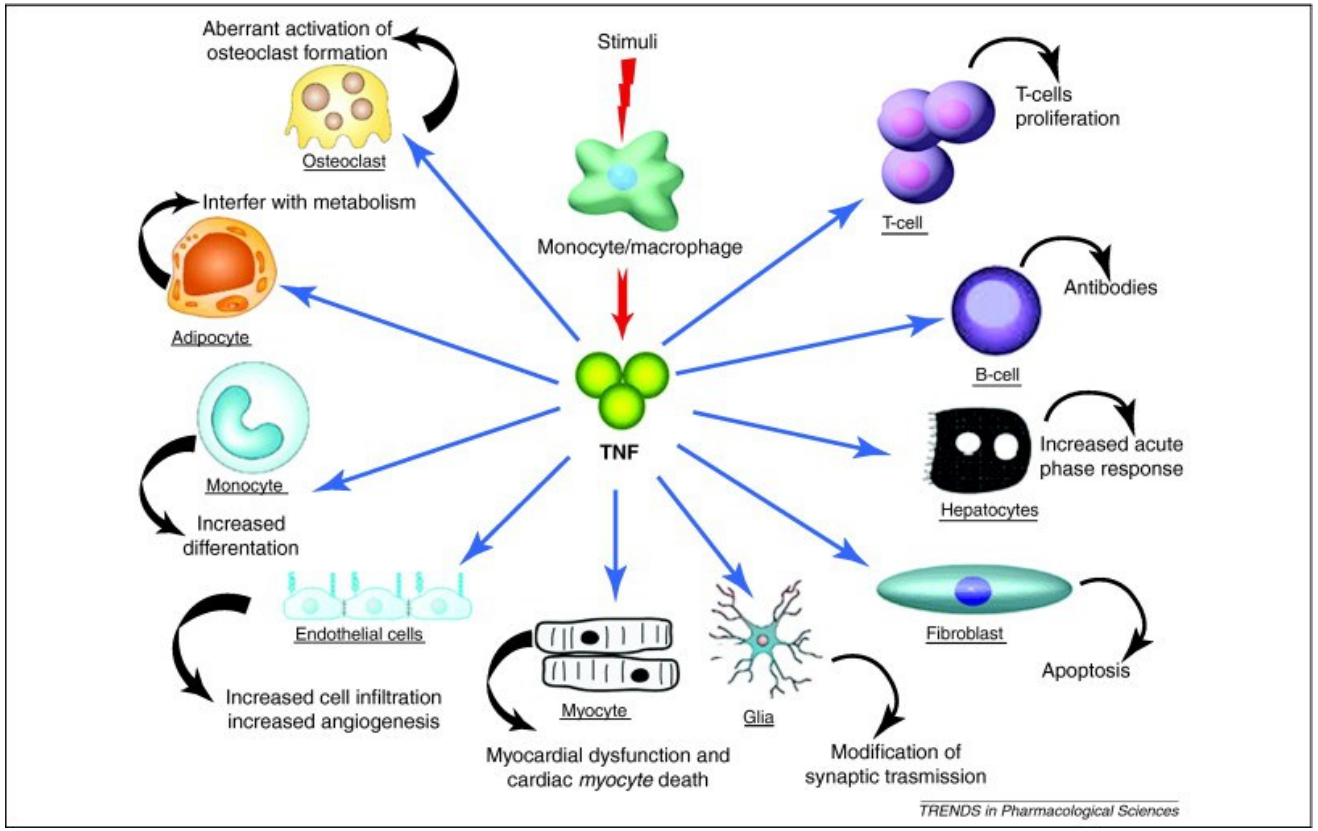
The **methylation cycle** is dependent on many cofactors including B vitamins and amino acids.
Critical nutrient drivers of the cycle are **B2, B6, B12, folate, magnsium, zinc, methionine, betaine, choline.**This roadmap illustrates foods which, when combined, provide a rich source of both of these key nutrients. **NOTE: Animal proteins are the richest source of Methionine.**
All other food groups are poor sources of methionine. B
est plant sources are Brazil nuts, sesame seeds, seaweed (spirulina)

Culinary Genomics for Inflammation

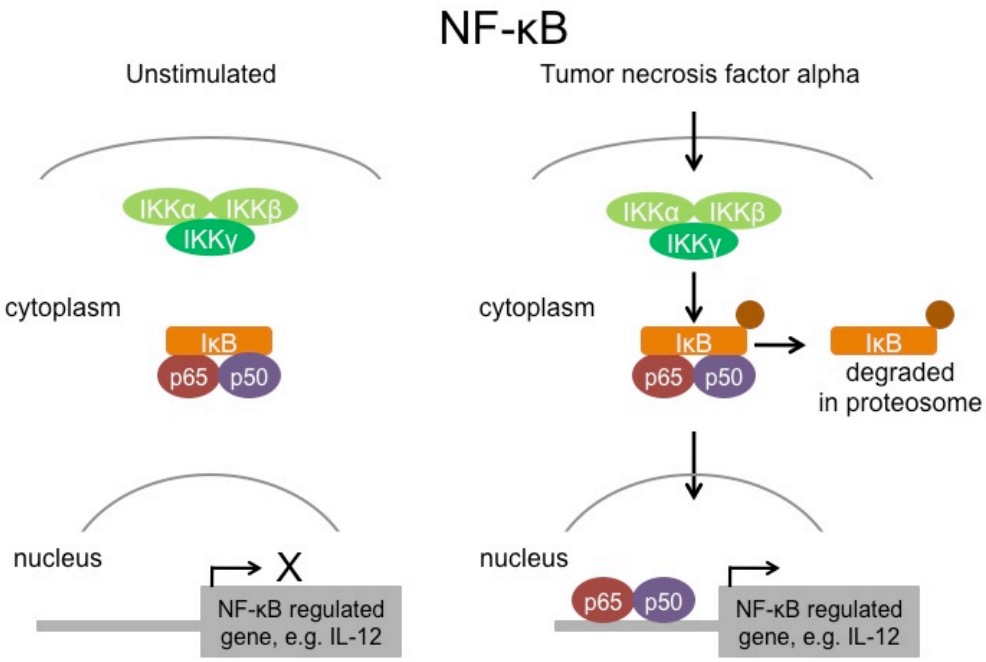
Target
CRP, TNF-alpha, IL6/6R cascade
Genomic Intervention
Balance Omega-3:Omega-6
Upregulate NrF2: Sulforaphane/Quercetin
Downregulate TNF-alpha/NfkB: Quercetin/curcumin

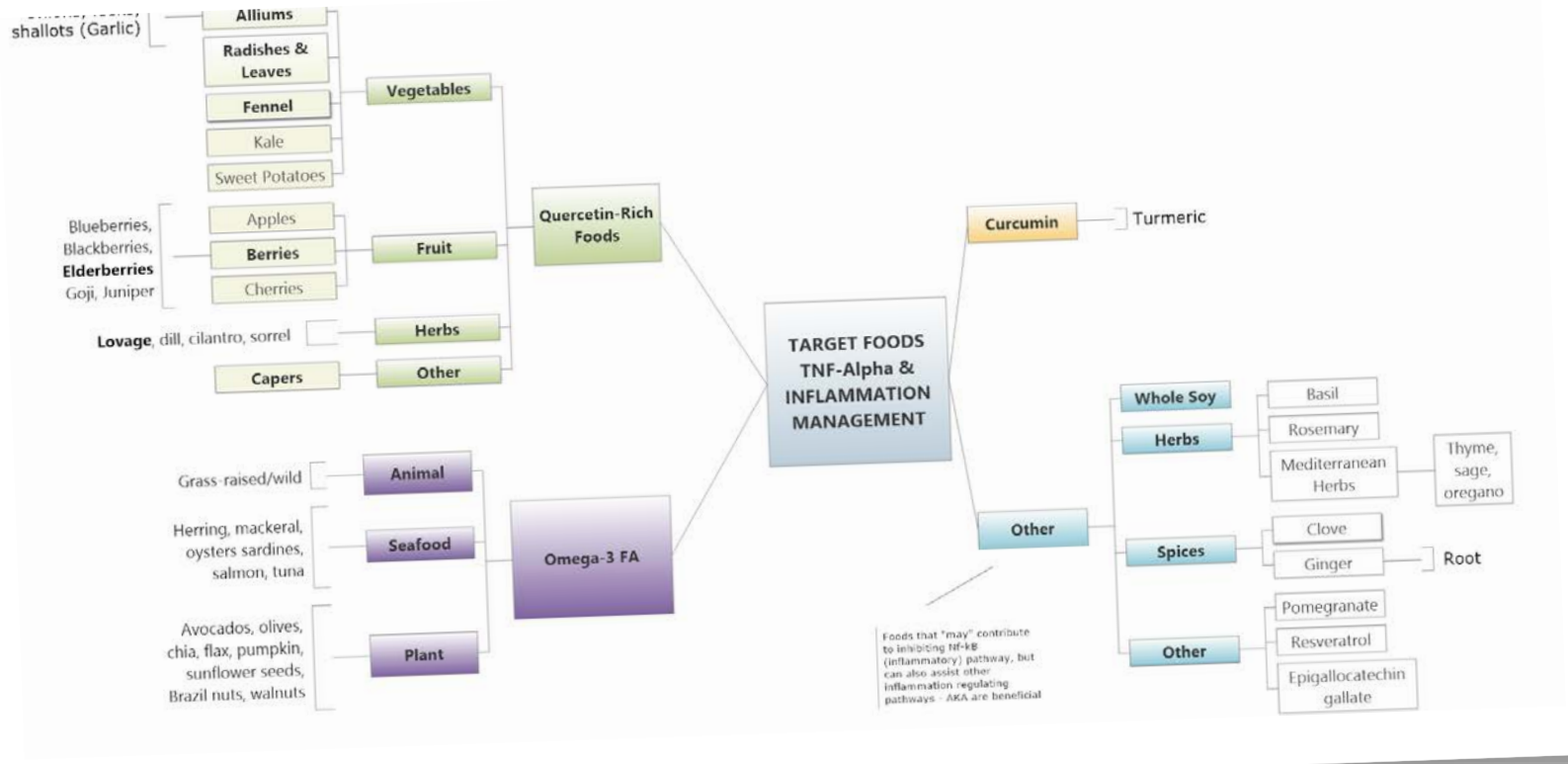
Upregulate NrF2: Offset oxidative stress

TNF-alpha: widespread implications



Tamp down TNF-alpha & NF-kB




shallots (Garlic)
Alliums
Radishes & Leaves
Fennel
Kale
Sweet Potatoes
Vegetables
Blueberries, Blackberries, Elderberries Goji, Juniper
Apples
Berries
Cherries
Fruit
Lovage, dill, cilantro, sorrel
Herbs
Capers
Other
Quercetin-Rich Foods
Grass-raised/wild
Animal
Herring, mackeral, oysters sardines, salmon, tuna
Seafood
Avocados, olives, chia, flax, pumpkin, sunflower seeds, Brazil nuts, walnuts
Plant
Omega-3 FA
TARGET FOODS TNF-Alpha & INFLAMMATION MANAGEMENT
Curcumin
Turmeric
Other
Whole Soy
Herbs
Basil
Rosemary
Mediterranean Herbs
Thyme, sage, oregano
Spices
Clove
Ginger
Root
Other
Pomegranate
Resveratrol
Epigallocatechin gallate
Foods that "may" contribute to inhibiting Nf-kB (inflammatory) pathway, but can also assist other inflammation regulating pathways - AKA are beneficial

Case Studies

Female, age 52

Ht 62”/Wt 125#

Med Hx: Lap Chole, Tubal Ligation, 2 x breast abcess

Family Hx: mother – bilateral hip replacement, curvature of spine

Activity level: high but not excessive. Road-mountain cycling/yoga/hike

Diet: healthy and varied. Lots of vegetables, adequate protein intake (includes fish and animal protein), healthy fats, fermented foods

Caffeine: 1 cup coffee/day, 2 teas

Alcohol: avg 1 glass of wine/day

Meds: none

Supplements: Woman over 50, Omega 3, D3/K2, DIM, Ubiquinol, Calcium: 900 mg/d (in supplements). Diet: avg 500mg/d

Polygenic Assessment and Application Bone Formation & Resorption

High Impact

- VDR FokI
- VDR Taq1
- IL 10

Moderate Impact

- DHCR7
- GC
- GSTT1
- CRP
- IL-6
- IL-6R
- MTHFR-1

Polygenic Assessment and Applications

Beyond Bone: looking deeper under the hood

- NQ01 (Inflammation/ estrogen metabolism)

- **FUT2 (folate/HCY)**
- **TCN2 (folate/HCY)**
- **CβS (folate/HCY)**

- **COMT**
- **SOD2**
- **GPx**
- **HMOX1**
- **NRF2L2**

Genomics Was Key!

- Genomic results showed potential risk
- With family history, dictated a closer look at lab biomarkers
  - Dexa
  - Blood

DEXA Results: Osteopenia-Osteoporos

L1-L4
BMD 0.814 g/cm2
T-score -3.1 STD
Z -score -2.3 STD

Left Femoral neck
BMD 0.924 g/cm2
T-score -0.8 STD
Z -score 0.2 STD

Left Femur Total
BMD 0.895 g/cm2
T-score -0.9 STD
Z-score -0.2 STD

Right Femoral Neck
BMD 0.847 g/cm2
T-score -1.4 STD
Z-score -0.3 STD

Right Femur Total
BMD 0.903 g/cm2
T-score -0.8 STD
Z-score -0.1 STD

Bloodwork

- B12: 613 pg/mL (180-914 pg/mL)
- Folate: >20 ng/mL (>5.9 ng/mL)
- Vit B6 (P5P): 342.6 nmol/L (20.0 125.0 nmol/L
- Plasma Homocycteine: 7 umol/L (5-15 umol/L)
- hsCRP: 1.303 mg/L (0.000 – 3.000 mg/L)
- Vit D 25-OH: 33 ng/mL (13 – 62 ng/mL)
- Vit D 1,25-OH: 61.4 pg/mL (19.9 – 79.3 pg/mL)

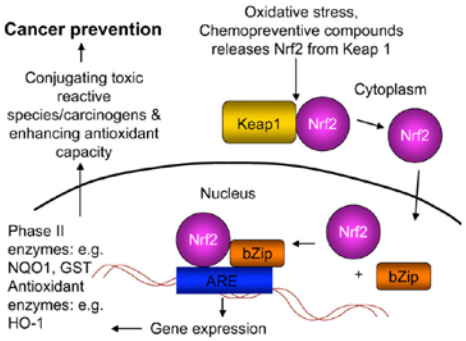
- Other markers earmarked for future testing…
- Osteocalcin
- IL-6
- TNF-a
- Collagen cross-linking markers
- C-telopeptide
- EFA testing

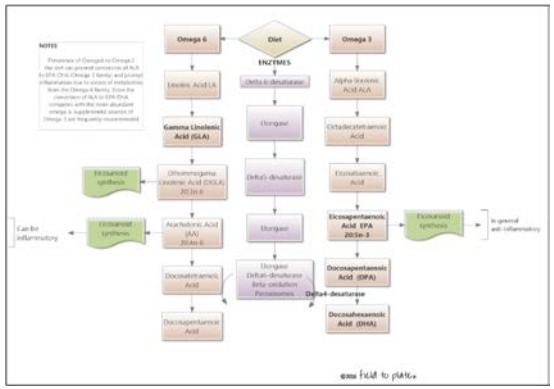
Genomic Informed Culinary Intervention

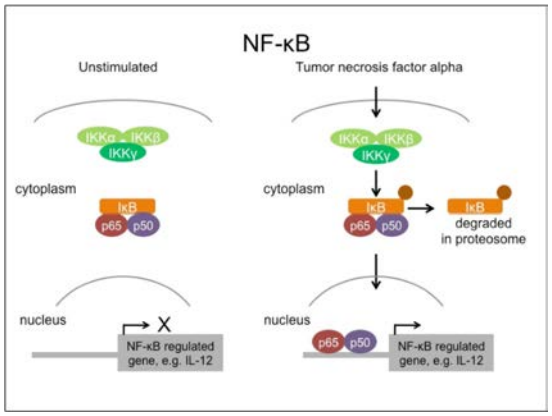
- **Preventive Inflammation management**
  - CRP
  - IL-6
  - IL-6R
  - SOD2
  - GPx
  - HMOX1
  - NRF2L2
  - + Omega-3 foods

- **Optimizing bone metabolism**
  - Fermented Foods
  - D-rich +mineral rich

- **Strength regimen**







Knowledge of how biochemical pathways work, drives selection of ingredients and recipe/menu formulation




Culinary Translation

Female, age 55

Ht 65”/Wt 130#

Med Hx: IBS (since childhood), Diverticulosis, Raynaud's, Frequent Sinusitis, Thyroid nodules, Osteopenia (Spine) – BMD: 9% loss 2010 to 2013.

Family Hx:Cancer, CVD, Thyroiditis, Osteopenia (paternal)

Activity level: 3x/week, varied and included wt bearing.

Diet: Varied, avoids lactose, focuses on calcium rich foods. Eats modified FODMAPS, consumes coffee.

Sun exposure – seasonal and with travel. Always wears sunscreen

Alcohol: 2 glasses wine/wk

Meds: none

Supplements: Woman over 50, Omega 3

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Dexa Results – Spine Before Intervention

Yr	BMD	T score	Z score
2010	1.015	-0.3	
2013	.919 (9.5% loss)	-1.2	-0.2

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Previous Bloodwork

2015

- T Pro, albumin – functionally low
- CRP – WNL
- Folate - elevated
- Vit D 34 – WNL (no intervention needed?)
- Monos – elevated (inflammation)

2016

- Mag RBC - fxn low
- 1,25 OH Vit D – WNL
- Phos – WNL

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Polygenic Assessment

High Impact	Moderate
• COL1A1	• VDR Bsml
• CYP2R1	• VDR FokI
• DHCR7	• CRP
• CG	• Cyp1A2
• GSTT1	• MTFHR-1/2
• IL6	• SLC19A1
• FUT2	• Gpx

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Intervention

- Add Vitamin D, 2000mg qd
- Add Calcium Citrate, 250 mg qd
- Add Vitamin K2 (MK7), 160 mg bid
- Add Magnesium citrate 150 mg bid
- Add Curcumin/Boswellia combo qd
- Add beta-sitosterol (address IL-6/optional)
- Add spore-based Probiotic
- Protein at every meal
- Off coffee
- No dairy, focus on other calcium rich food sources
- Focus on antioxidant, magnesium, and K2 foods
- Anti-inflammatory diet
- Address source of inflammation – GUT/SIBO confirmed!

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Current Bloodwork

- C-Telopeptide – WML
- Calcitronin WNL
- Osteocalcin – WNL
- Protein and calcium – WNL
- Monos – WNL
- Mag – WNL
- 25 OH – 97 (forgot to go off supplement)
- Folate – WNL
- Still need IL6

Next Level Functional Nutrition™

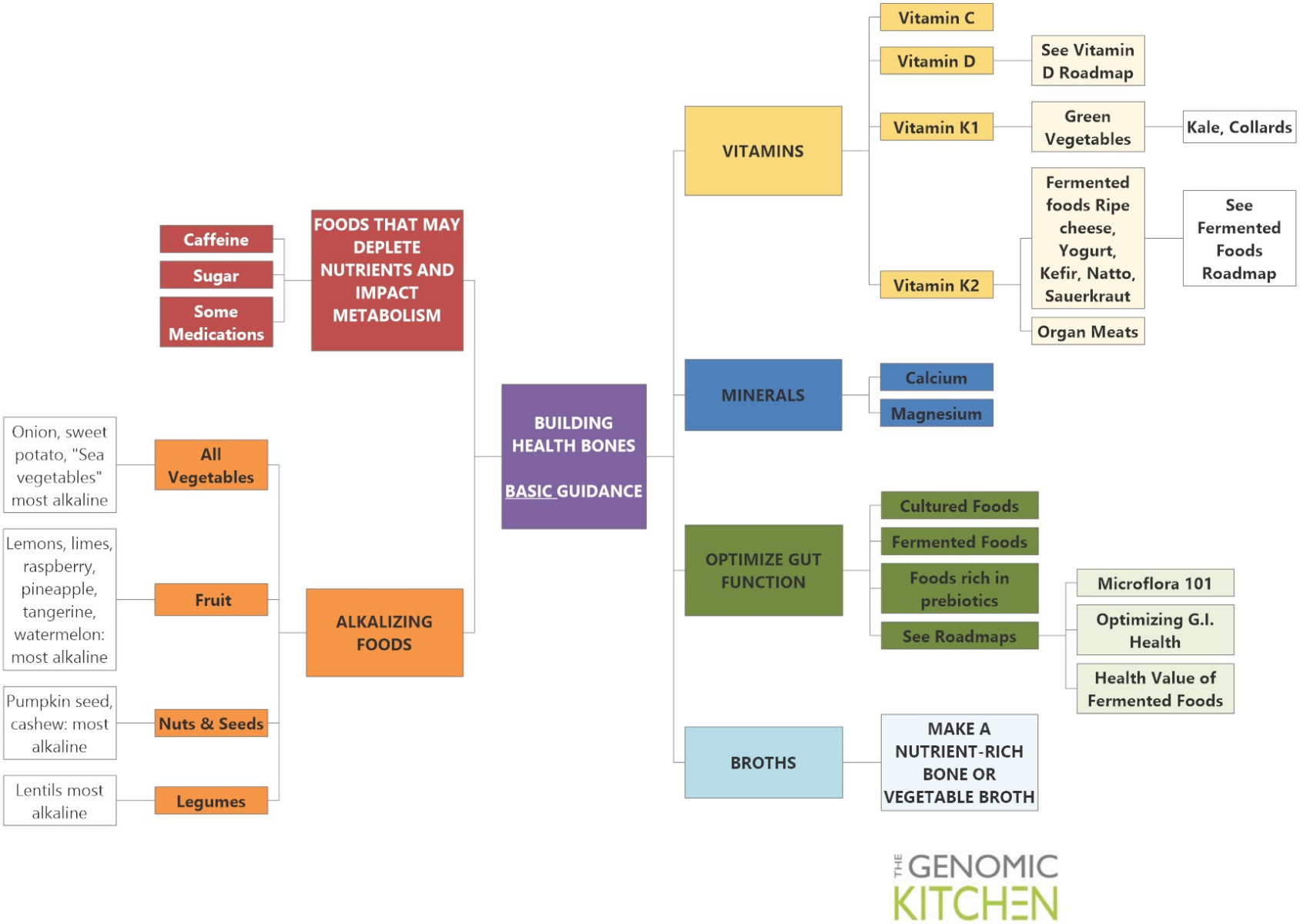
Dexa Results – Spine After Intervention

Yr	BMD	T score	Z score
2010	1.015	-0.3	
2013	.919 (9.5% loss)	-1.2	-0.2
2016	.897 (only 3% loss)	-1.4	-0.2

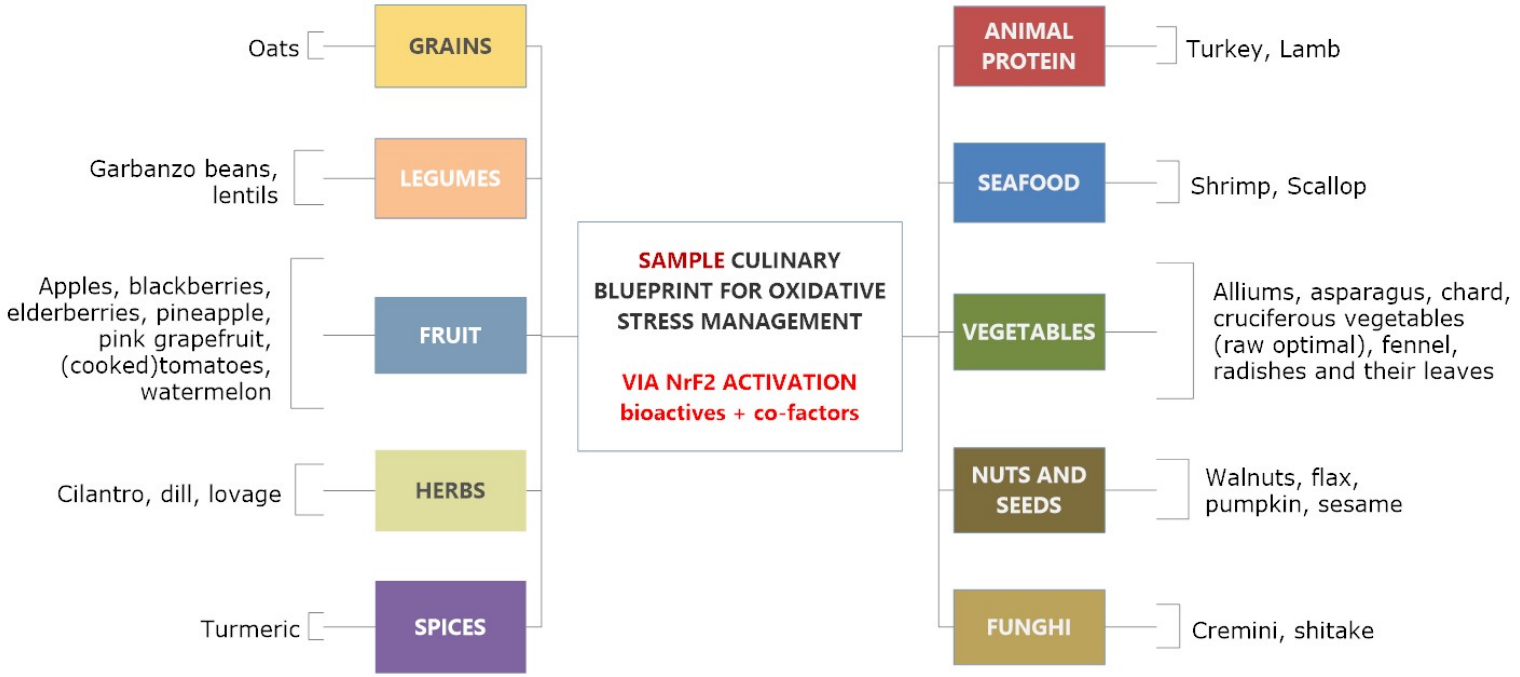
Culinary Intervention

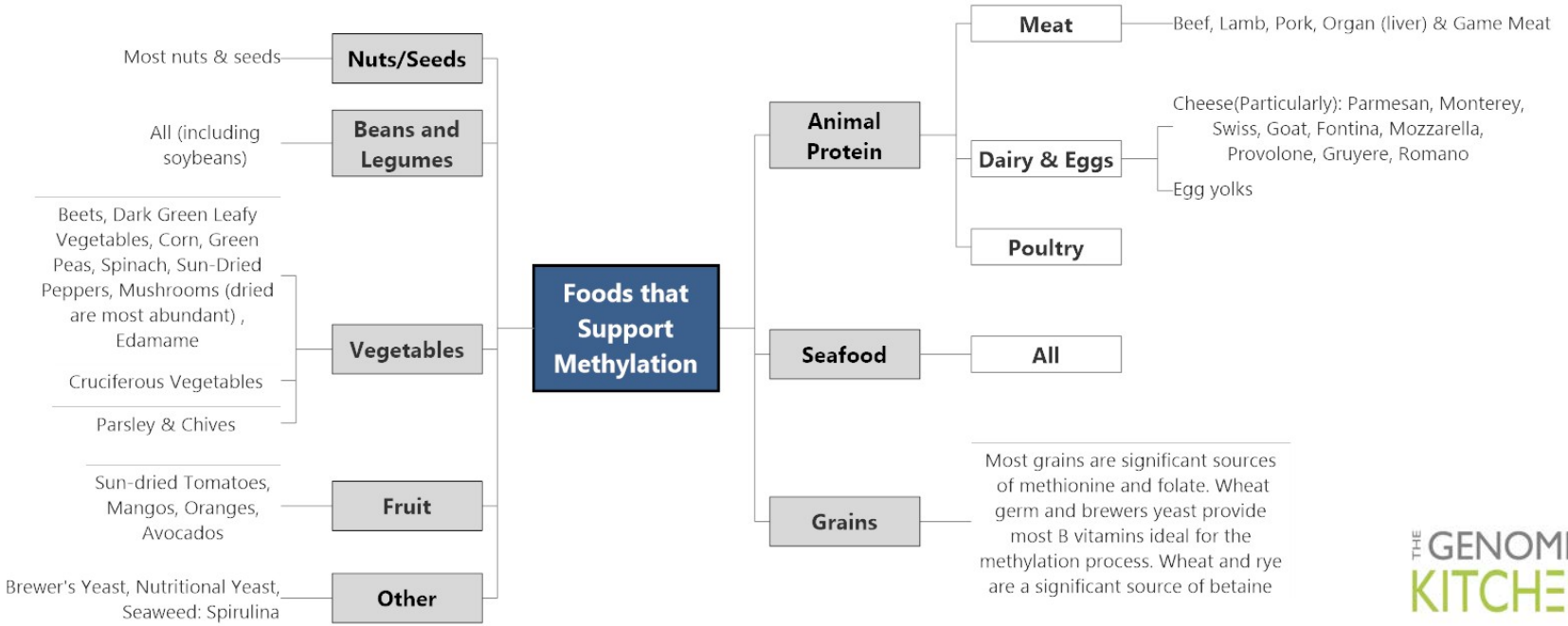
Goals

- Support anti-inflammatory protocol (multiple SNPs)
- Optimize dietary folate/methylation cycle
- Optimize protein intake/sources
- Magnesium
- Gut support as tolerated



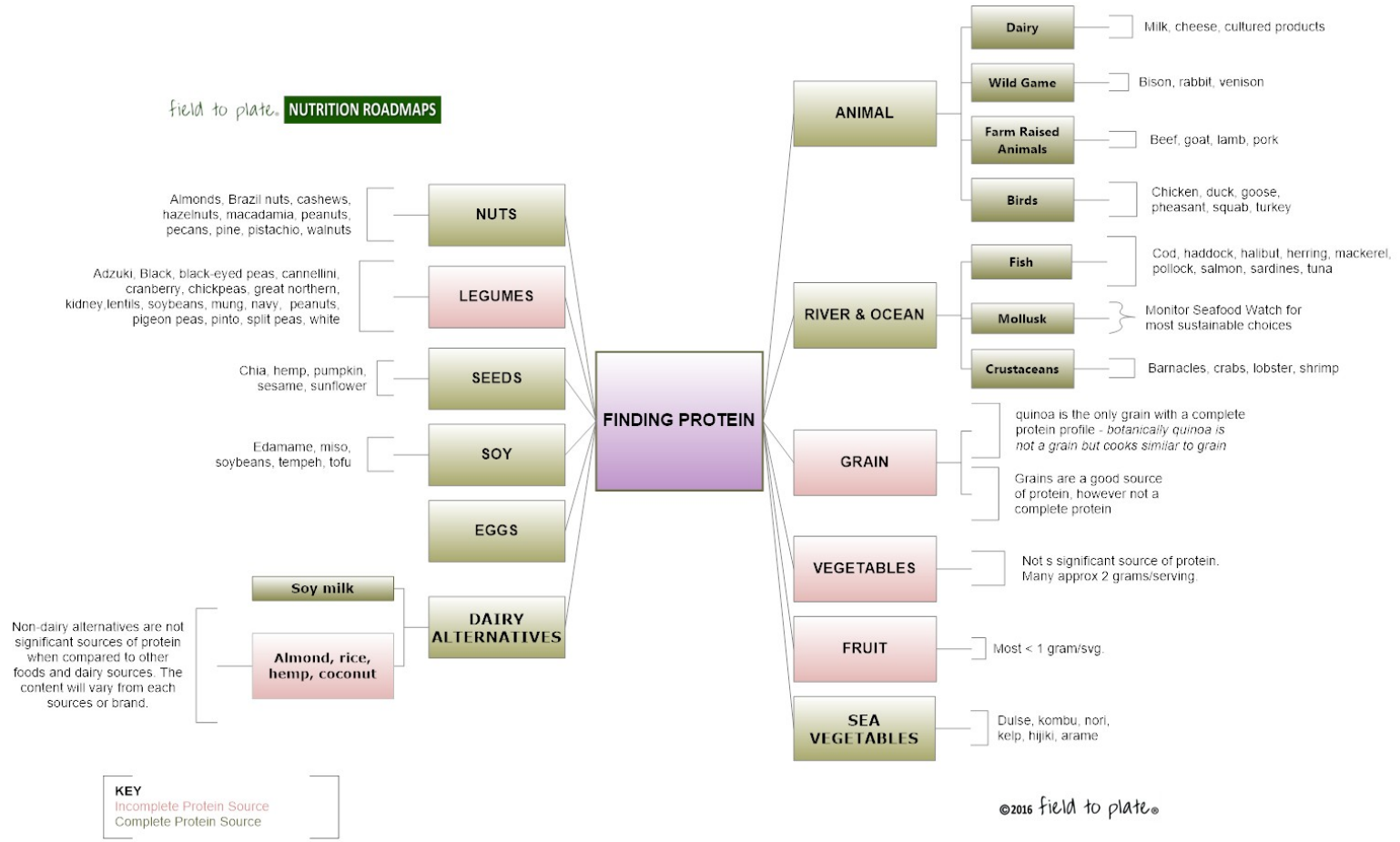
THE GENOMIC KITCHEN

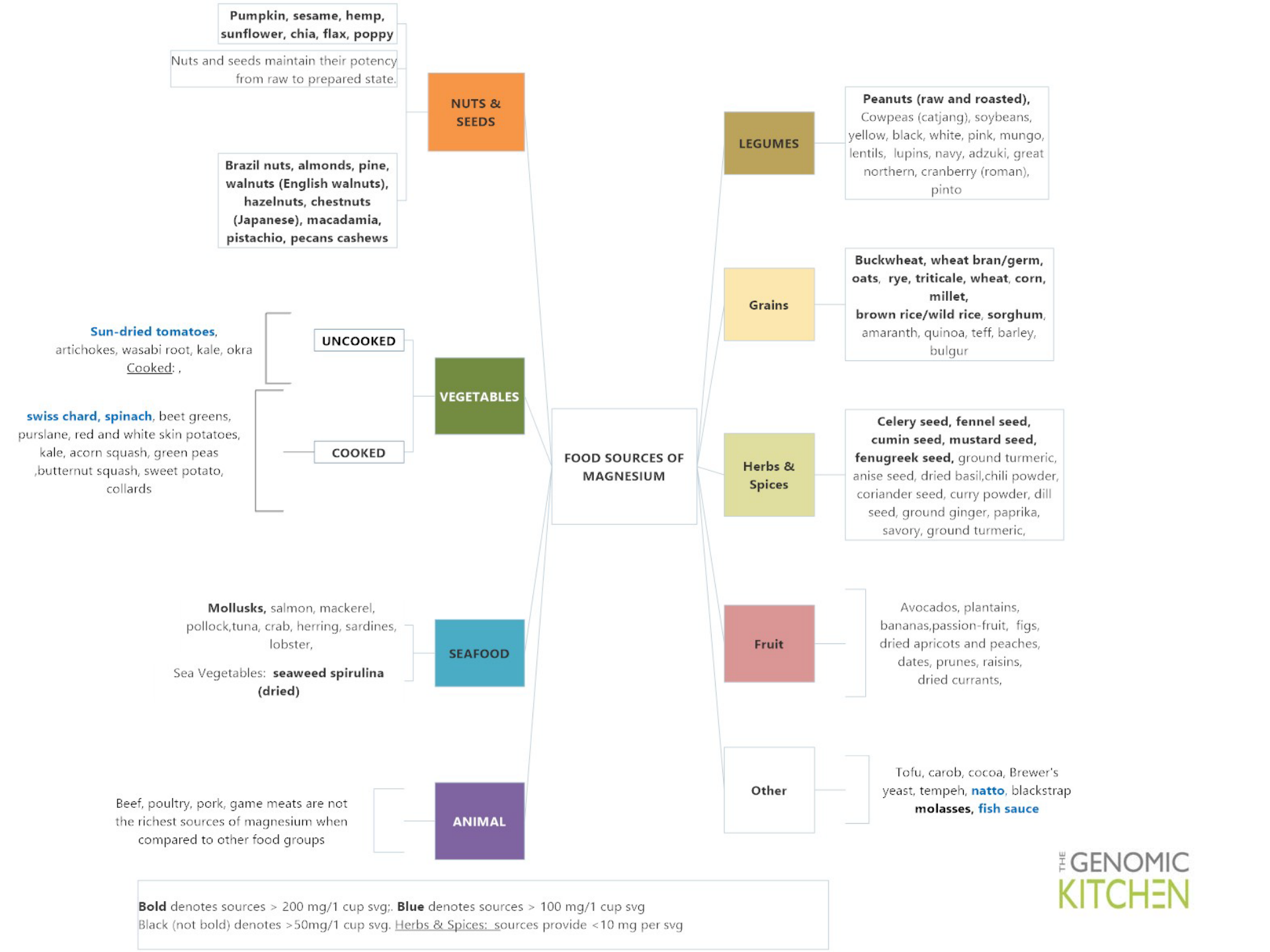


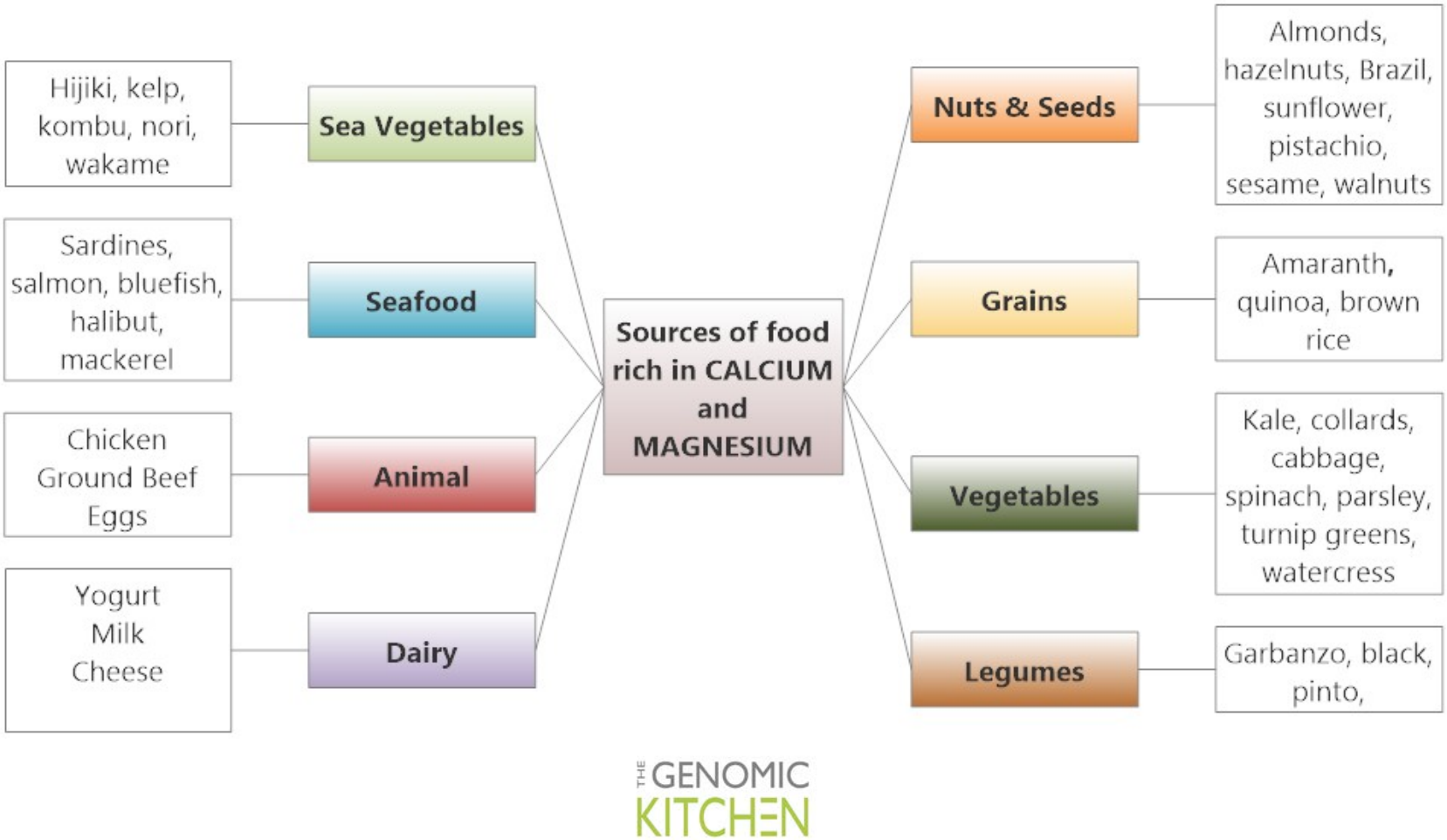


Support methylation

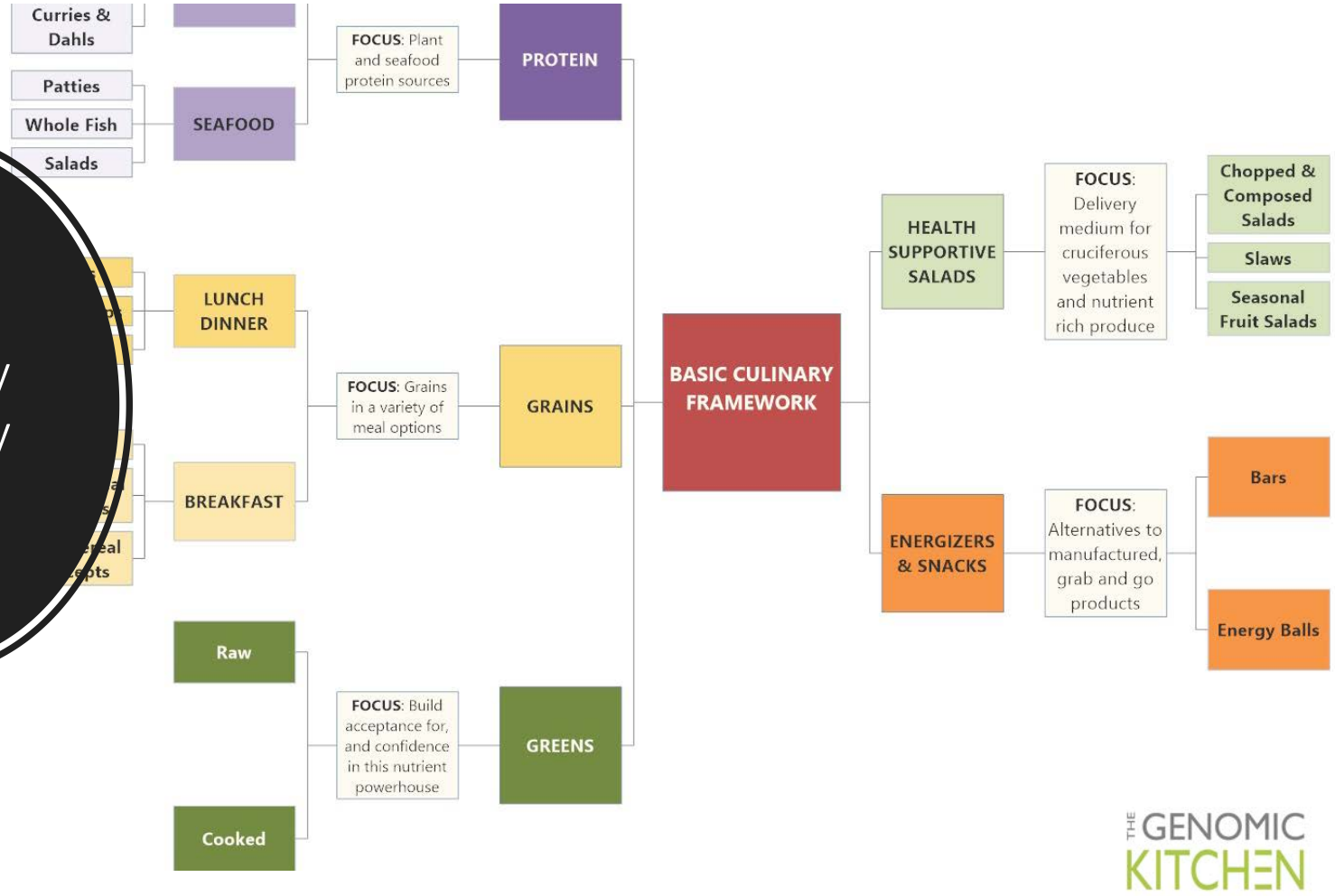
Optimize protein




FOOD SOURCES OF MAGNESIUM
NUTS & SEEDS
Pumpkin, sesame, hemp, sunflower, chia, flax, poppy
Nuts and seeds maintain their potency from raw to prepared state.
Brazil nuts, almonds, pine, walnuts (English walnuts), hazelnuts, chestnuts (Japanese), macadamia, pistachio, pecans cashews
VEGETABLES
UNCOOKED
Sun-dried tomatoes, artichokes, wasabi root, kale, okra
Cooked: ,
COOKED
swiss chard, spinach, beet greens, purslane, red and white skin potatoes, kale, acorn squash, green peas ,butternut squash, sweet potato, collards
SEAFOOD
Mollusks, salmon, mackerel, pollock,tuna, crab, herring, sardines, lobster,
Sea Vegetables: seaweed spirulina (dried)
ANIMAL
Beef, poultry, pork, game meats are not the richest sources of magnesium when compared to other food groups
LEGUMES
Peanuts (raw and roasted), Cowpeas (catjang), soybeans, yellow, black, white, pink, mungo, lentils, lupins, navy, adzuki, great northern, cranberry (roman), pinto
Grains
Buckwheat, wheat bran/germ, oats, rye, triticale, wheat, corn, millet, brown rice/wild rice, sorghum, amaranth, quinoa, teff, barley, bulgur
Herbs & Spices
Celery seed, fennel seed, cumin seed, mustard seed, fenugreek seed, ground turmeric, anise seed, dried basil,chili powder, coriander seed, curry powder, dill seed, ground ginger, paprika, savory, ground turmeric,
Fruit
Avocados, plantains, bananas,passion-fruit, figs, dried apricots and peaches, dates, prunes, raisins, dried currants,
Other
Tofu, carob, cocoa, Brewer's yeast, tempeh, natto, blackstrap molasses, fish sauce
Bold denotes sources > 200 mg/1 cup svg;. Blue denotes sources > 100 mg/1 cup svg
Black (not bold) denotes >50mg/1 cup svg. Herbs & Spices: sources provide <10 mg per svg
THE GENOMIC KITCHEN


Sources of food rich in CALCIUM and MAGNESIUM
Sea Vegetables
Hijiki, kelp, kombu, nori, wakame
Seafood
Sardines, salmon, bluefish, halibut, mackerel
Animal
Chicken
Ground Beef
Eggs
Dairy
Yogurt
Milk
Cheese
Nuts & Seeds
Almonds, hazelnuts, Brazil, sunflower, pistachio, sesame, walnuts
Grains
Amaranth, quinoa, brown rice
Vegetables
Kale, collards, cabbage, spinach, parsley, turnip greens, watercress
Legumes
Garbanzo, black, pinto,
THE GENOMIC KITCHEN

Culinary Strategy



THE GENOMIC KITCHEN

BOWL CONCEPTS

Supportive References: Culinary Genomics

- The Nrf2-Antioxidant Response Element Signaling Pathway and Its Activation by Oxidative Stress: J Biol Chem. 2009 May 15; 284(20): 13291–13295
- Omega-3 fatty acids protect the brain against ischemic injury by activating Nrf2 and upregulating heme oxygenase 1. J Neurosci. 2014 Jan 29;34(5):1903-15
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- Downregulation of tumor necrosis factor and other proinflammatory biomarkers by polyphenols: Archives of Biochemistry and Biophysics 559 (2014) 91–99
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- Carotenoids, inflammation and oxidative stress - implications in cellular signaling pathways: Nutrition Research · November 2014
- Omega-3 Fatty Acids and Inflammatory Processes: Nutrients 2010, 2, 355-374
- Culinary Herbs and Spices: Their Bioactive Properties, the Contribution of Polyphenols and the Challenges in Deducing Their True Health Benefits: Int J Mol Sci. 2014 Oct; 15(10): 19183–19202

Genomic Testing: What to Look For…

- Evaluate Genomic Testing Companies
  - Are SNPs relevant, modifiable, measurable
    - Do specialty panels fit clinical needs
  - Are reports and interpretation user-friendly
    - Name/show biochemical pathways for SNP relevance and interplay (polygenic versus monogenic)
    - Provide evidenced-based recommendations
    - Listing of biomarkers to monitor SNP expression
  - Clinical Lab or Research Lab
    - Want more than just raw data
  - Clinical/educational support provided

Concluding Remarks

- Genomic information is one tool among many in the clinician toolbox
- Genomic information provides informed insights into the individual health blueprint and deep insights into prioritizing health intervention
- Polygenic versus monogenic approach requires an understanding of the multiple nutrients and compounds that inform our innate biochemistry
- Biochemistry informs culinary intervention

Concluding Remarks

- Deep level assessment, and corresponding nutritionally-focused intervention, represent the pinnacle of a personalized approach to patient care and ensure better outcomes

- Additional learning is recommended. Further still, Medical practitioners and their patients can benefit from the services of a Dietitian/Nutritionist who is comprehensively trained in Integrative and Functional Medical Nutrition Therapy (IFMNT), genomics/nutrigenomics and culinary genomic application!

Thank you to genomics experts, Dr Joe Veltman PhD, DCCM, FAAIM and Dr Roberta Kline MD, FACOG, for all their guidance and expertise

Next Level Functional Nutrition™

Additional Resources

- The “Genomic Resources” research group: http://www.genomic-resources.eus/
- Human Genome Resources at NCBI: https://www.ncbi.nlm.nih.gov/projects/genome/guide/human/
- Human Ageing Genomic Resources: http://genomics.senescence.info/
- Genomia International – Education/Training:
- https://genomainternational.com/clinician-training-certification/
- SNPedia: https://www.snpedia.com/
- International Osteoporosis Foundation : https://www.iofbonehealth.org/facts-statistics#category-14

Next Level Functional Nutrition™

Thank You!

This webinar was recorded – Limited time access is available to all registrants starting tomorrow.

Next Level Functional Nutrition™

Announcements

- IFMNT Spring training starts April 24!
- NLFN members get 10% off! (get in on NLFN Spring membership special savings now!)
- Spring Special (Through April 17 ONLY):
  Use code: S18 to receive an *additional* 10% off!
  (Yes, both discounts apply)
- Visit: https://www.nextlevelfunctionalnutrition.com/

IFMNT Grand Rounds coming soon!