

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

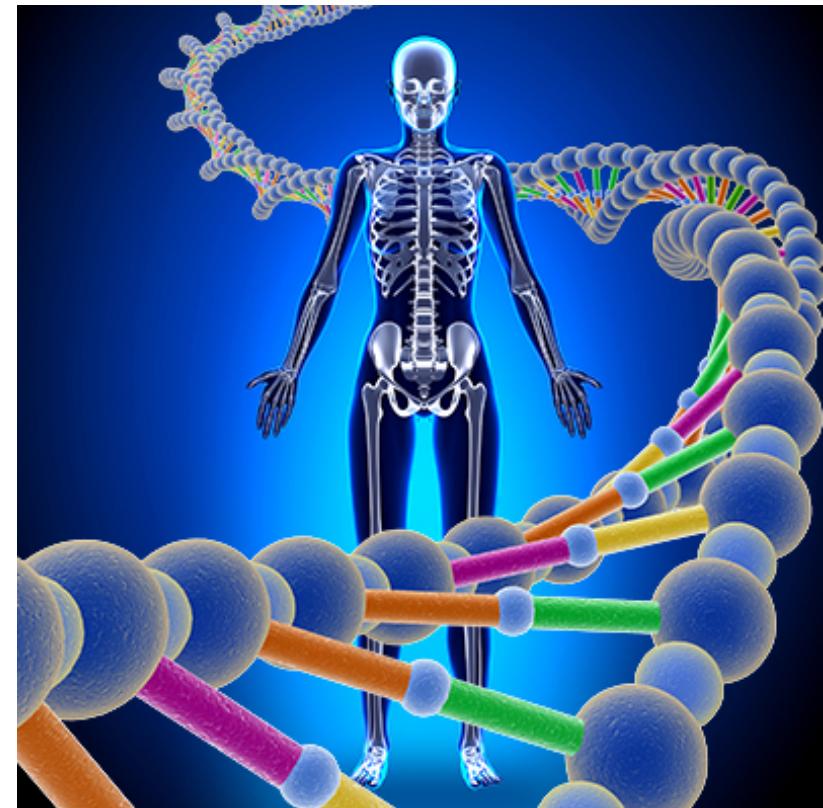
Amanda Archibald, RDN: Nutrigenomics; Culinary Genomics

Integrative Healthcare Symposium 2018



No Bones About it! Combining Nutrigenomics with the Culinary Arts in the Prevention and treatment of Osteoporosis

- We have no conflicts of Interest with this presentation





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



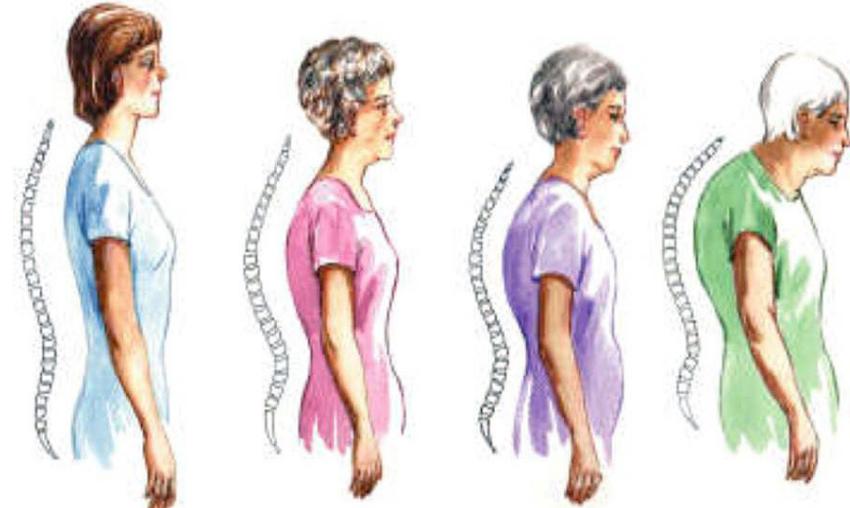
World-wide Statistics

- ~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.



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.

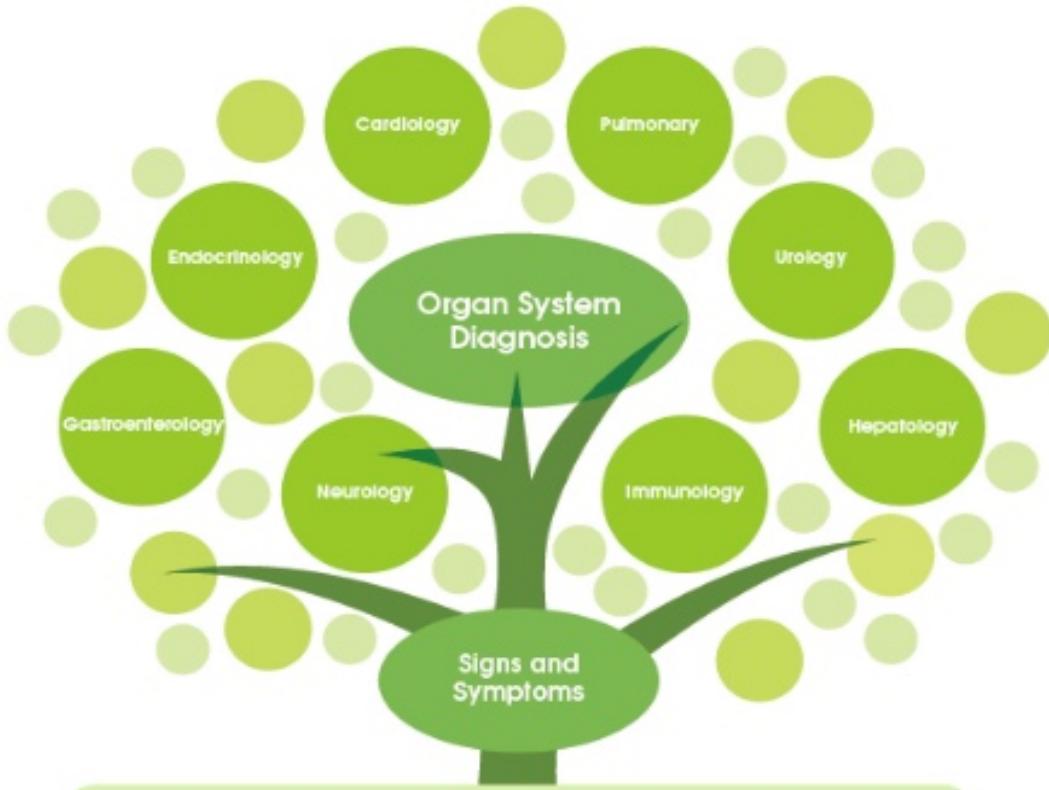




Health Care Providers Have a Golden Opportunity!

- 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



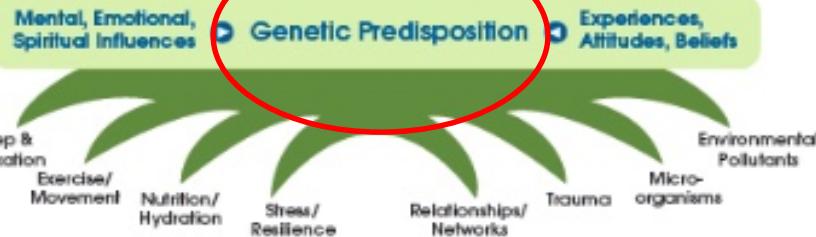
The Fundamental Organizing Systems and Core Clinical Imbalances

Assimilation
Digestion, Absorption, Microbiota/GI,
Respiration
Defense and Repair
Immune system, Inflammatory
processes, Infection and microbiota

Energy
Energy regulation, Mitochondrial function
Biotransformation and Elimination
Toxicity, Detoxification
Communication
Endocrine, Neurotransmitters, Immune
messengers, Cognition

Transport
Cardiovascular, Lymphatic systems
Structural Integrity
From the subcellular/membrane to
the musculoskeletal system

Antecedents, Triggers, and Mediators



Personalizing Lifestyle and Environmental Factors

Institute for Functional Medicine
The Functional Medicine tree



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).



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



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





Drugs that may contribute to 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



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



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)



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, et 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.



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



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
- Support optimal microbiome





SOMETIMES IT'S JUST
NOT ENOUGH.





Genomics & Osteoporosis Risk

- **Bone Formation SNPs**

- COL1A1
- GSTT1
- GSTM1
- MTHFR
- IGF-1
- BMP4
- LRP5
- GSTT1

- **Inflammation SNPs**

- IL-6/6R
- CRP
- TNF-alpha
- APOE

- **Vitamin D SNPs**

- DHCR7
- GC
- CYP2R1
- CYP27A1
- CYP27B1
- VDRFok1
- VDRBSm1

- **Bone Resorption SNPs**

- CYP1A2
- MTHFR
- BMP2
- SOST
- GSTM1

- **Calciotropic and Sex Hormone SNPs**

- PTH/PTHR
- CT/CTR
- AR
- CYP19A1
- CaSR
- GR

- **Other**

- BCMO1?



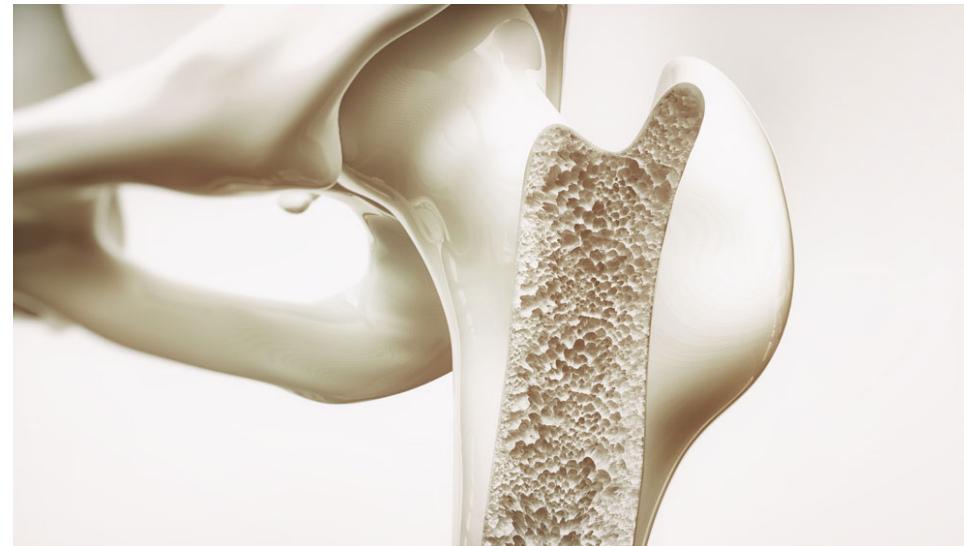
SNPs – Important to Know!

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



Bone Formation



Susan Allen RDN CCN. Amanda Archibald RDN



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 and low calcium intake may negatively influence



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
- Genetic polymorphisms can result in lack of enzyme activity due to the null phenotype (no functional genes) of the GSTM1 and GSTT1
 - More prevalent in Caucasians
- Absence of gene, and therefore 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.



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

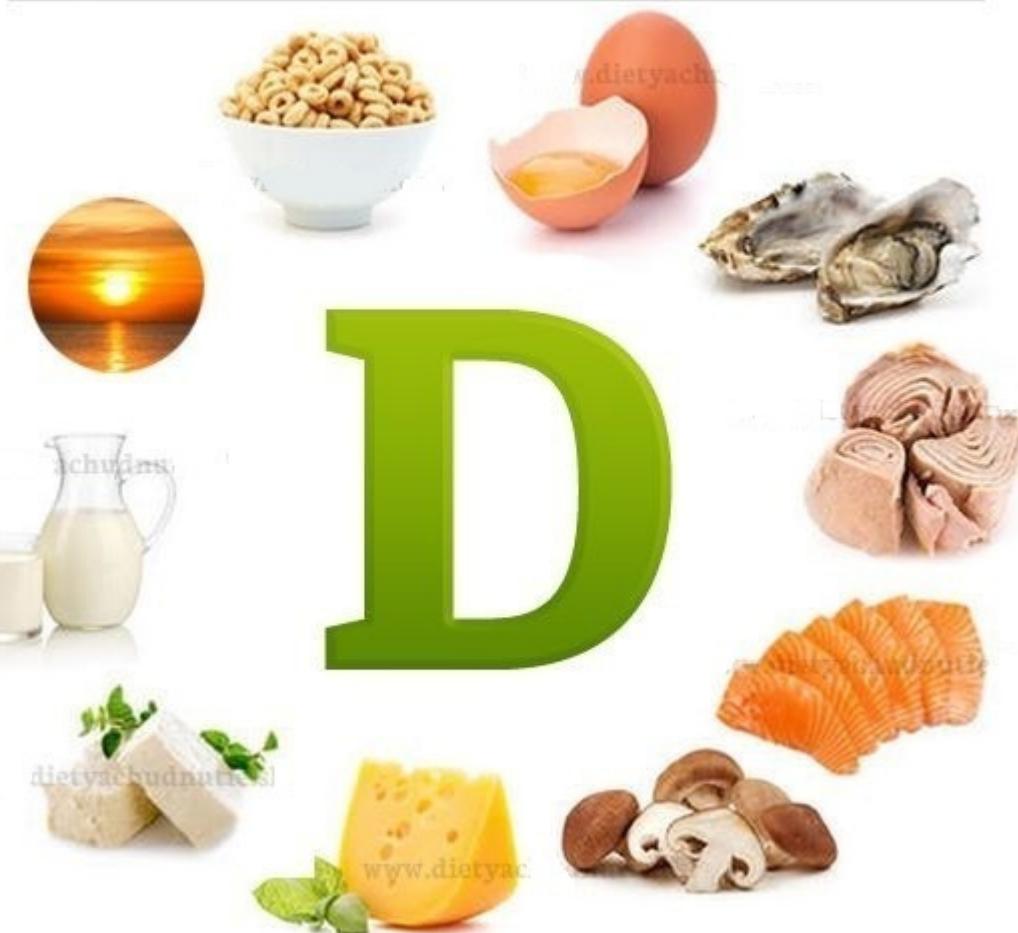


Methylation and Sclerostin

- 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, the *SOST* gene
 - Inhibition achieved with increased methylation on the promoter region of the gene
- Proper methylation required to support *SOST* inhibition



SNPs for VITAMIN D





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





Vitamin D Metabolism Review

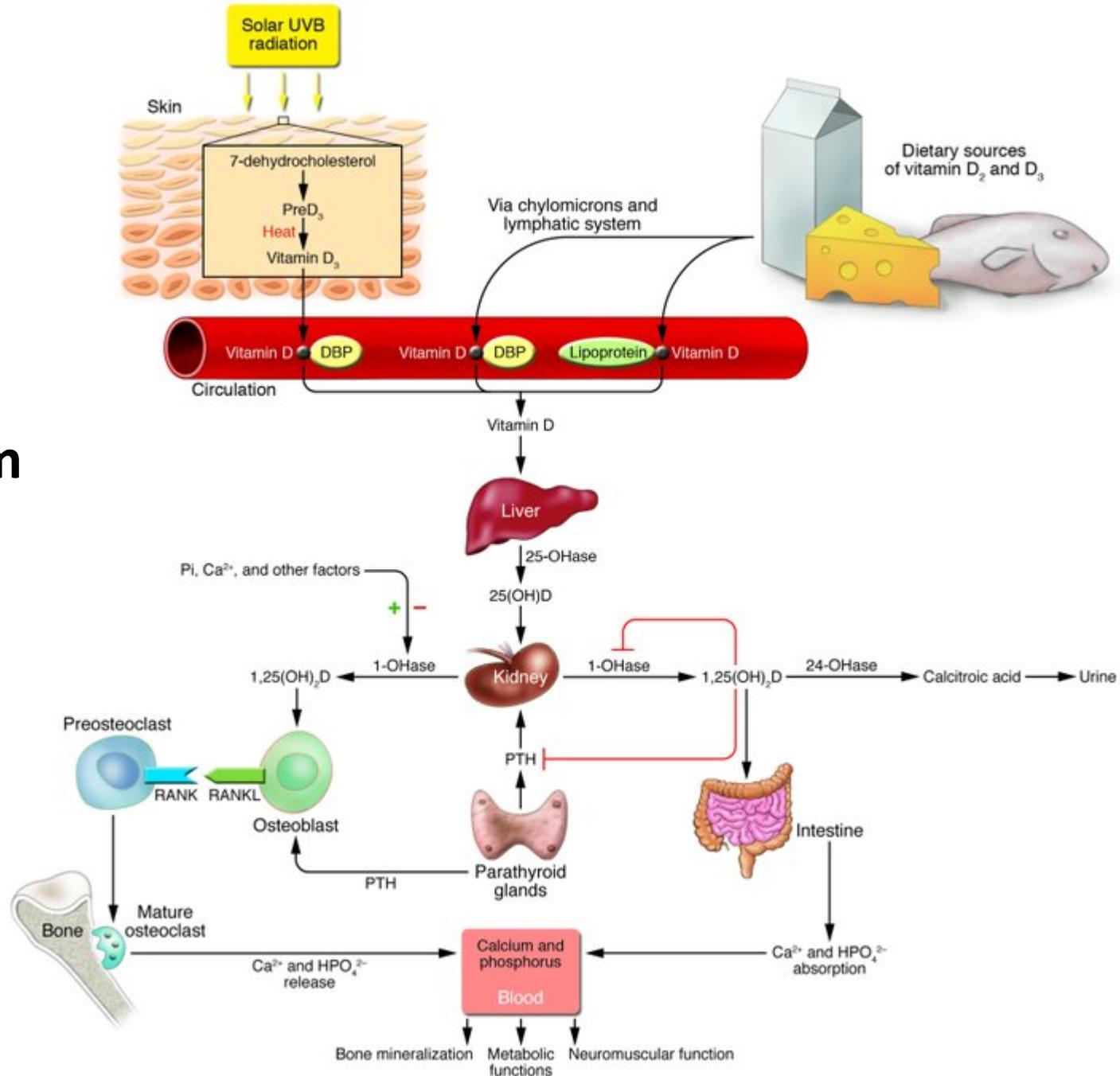


Image source: Holick M. Resurrection of vitamin D deficiency and rickets. *J Clin Invest.* 2006;116(8):2062-2072.
doi:10.1172/JCI29449



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.



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.



GC (Vitamin D binding protein)

- Encodes for the major carrier protein of 25-hydroxyvitamin D in circulation (GC-globulin)
 - 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.
- Polymorphisms of GC lead to phenotypic changes in the protein that may affect affinity, activity, and concentration.
 - Linked with alterations in bone density



VDR Bsml 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, Apal, EcoRV and Taql

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.



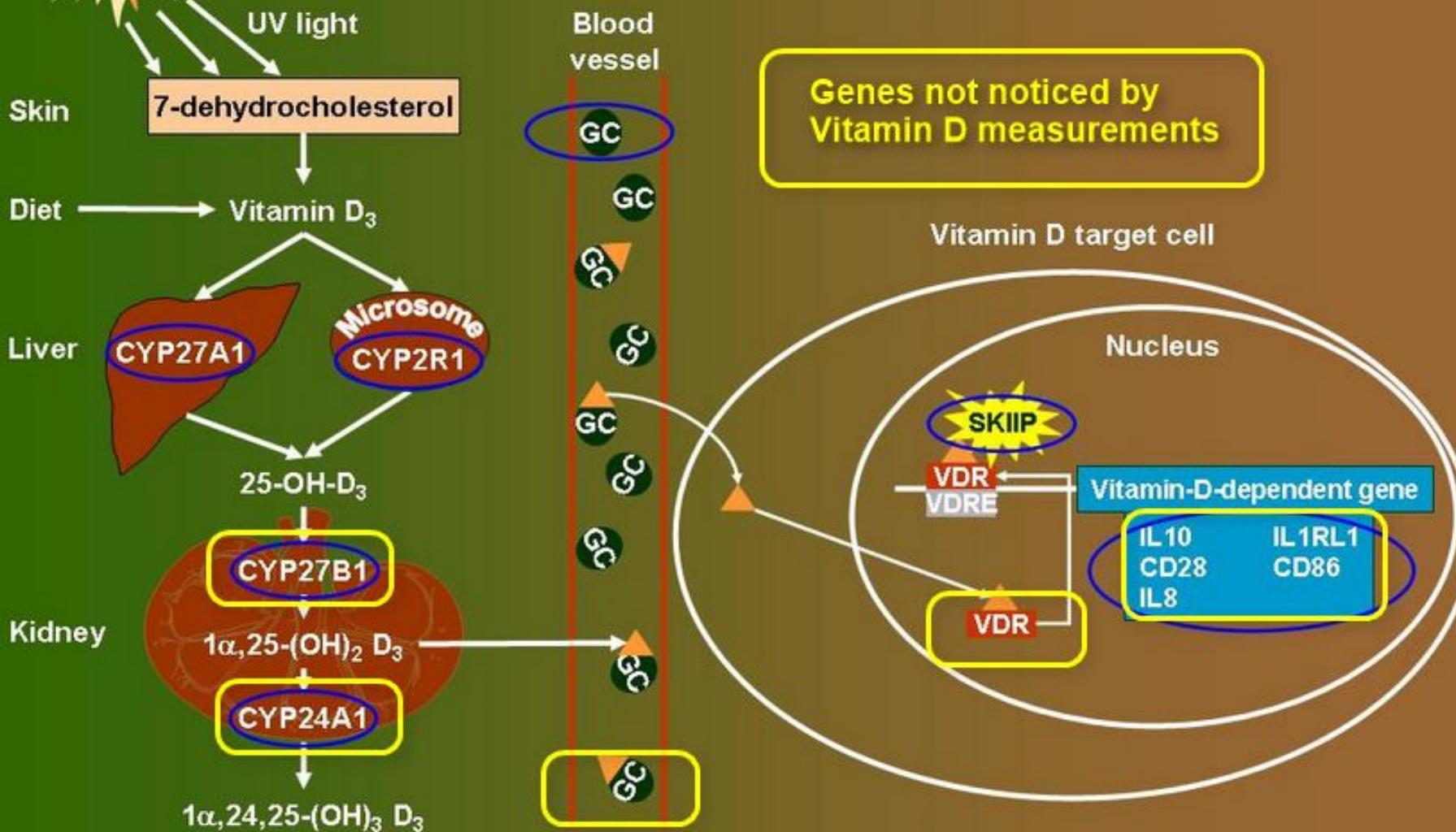
Other SNPs Related to Vit D

- **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 Zahraeni 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.



Genes Involved in the Vit D Pathway



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.



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



Bone Formation:

Monitor Labs, especially as you see risk in SNPs

- Bone mineral density
- Collagen cross-linking markers
- C-telopeptide
- Carboxylated Osteocalcin (K2 status)
- Vitamin D (25-OH & 1,25-OH)
- Magnesium RBC
- Vitamin A
- Homocysteine
- Folate
- Vitamin B12/MMR
- Hormones/related markers
- PTH/calcitonin
- Phosphorus





Collagen Cross-linking Markers

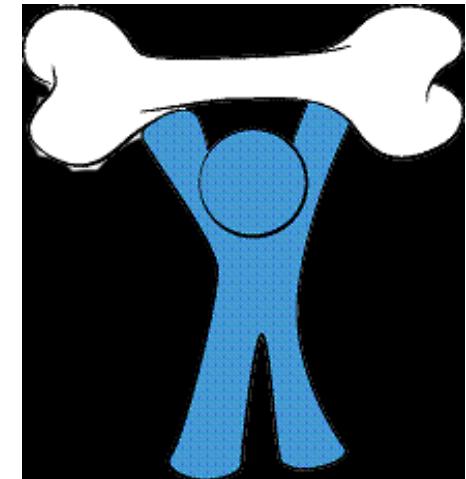
- In post-menopausal women, the markers that have been studied the most and also have the strongest negative correlations with BMD are:
 - Alkaline phosphatase (ALP)
 - Osteocalcin (OC)
 - Type 1 cross-linked C-telopeptide (CTx)
 - Type 1 cross-linked N-telopeptide (NTx)
- Mostly used in research and 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)



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

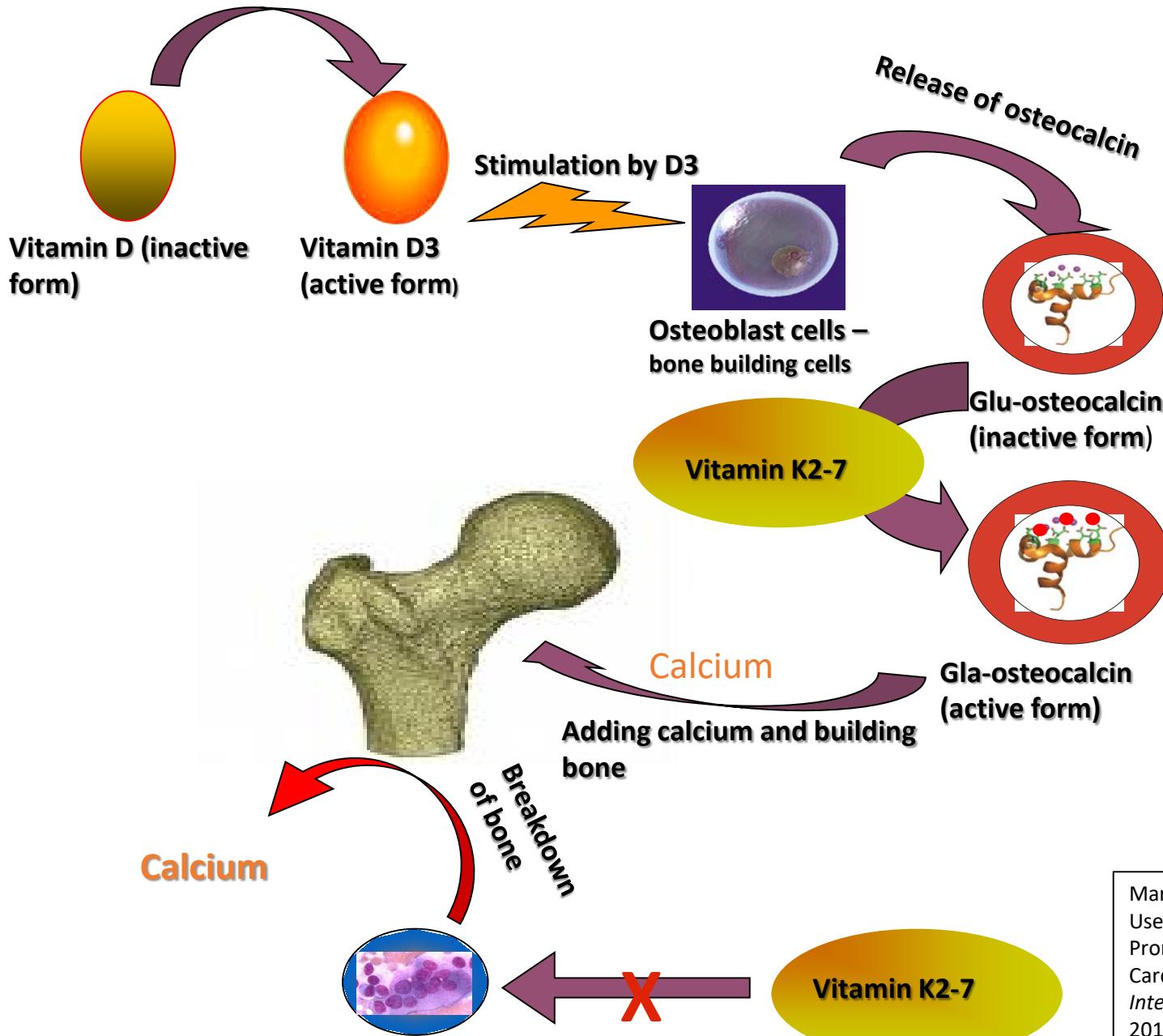




More on Vitamin D/K2 Supplementation

- 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



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 NQO1 SNP)



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



Bone Resorption



Susan Allen RDN. Amanda Archibald RDN



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 than women)
 - Slow metabolizers may have an effect through increased concentration of caffeine itself.



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



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

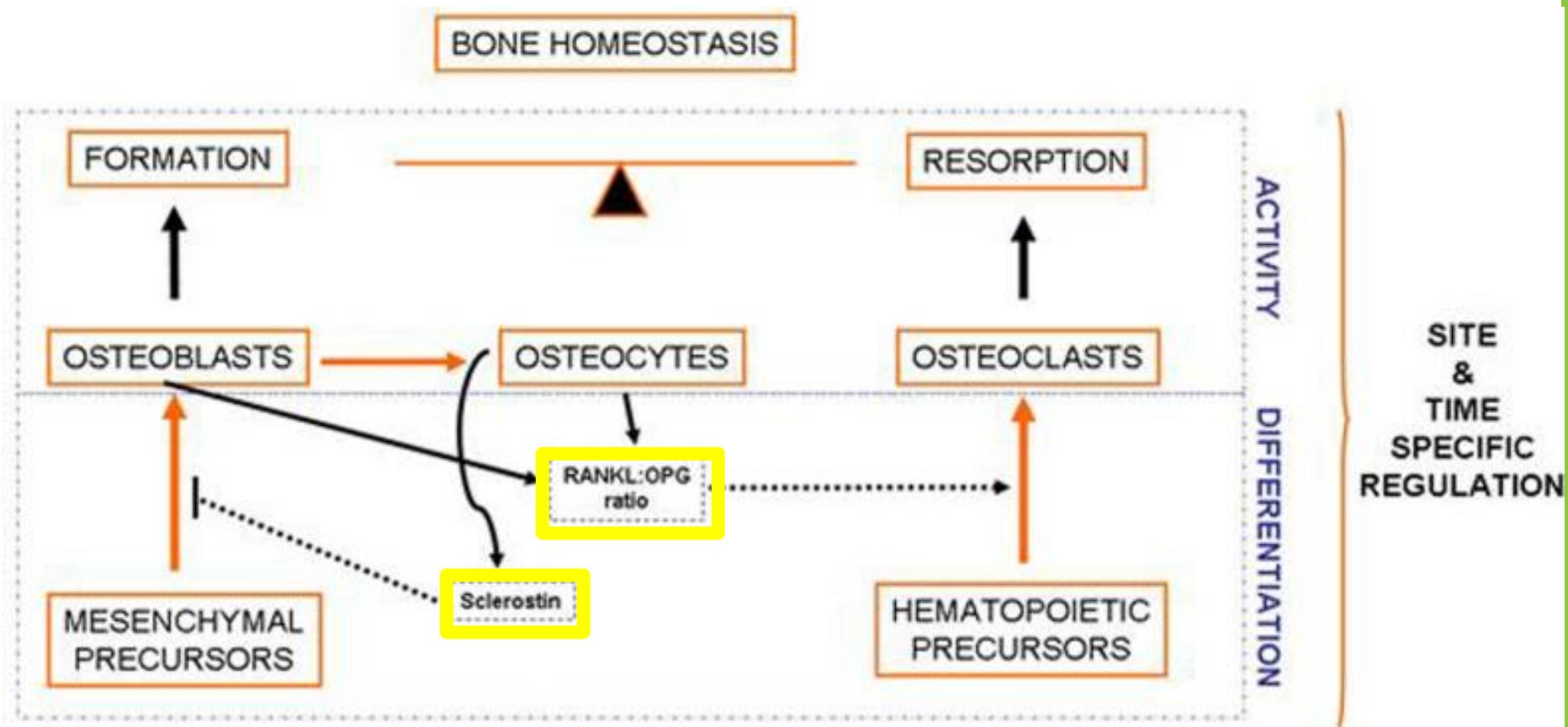


Methylation and (NF- κ B Ligand) RANKL Gene

- Receptor activator of nuclear factor- κ B 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.



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.



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.



More Inflammation SNPs





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



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.



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 TNF α 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 ROS-dependent cell migration via NF- κ B activation in liver cells. *FEBS Letters* 588 (2014) 175–183



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.



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





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.



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.



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.



General Intervention/Support & To Quiet SNP Expression

- Supportive/varied diet and optimal nutritional status, especially bone building nutrients
 - 8-12 svrgs 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



Anti-inflammatory Supplements

(Many cross over for oxidative stress!)

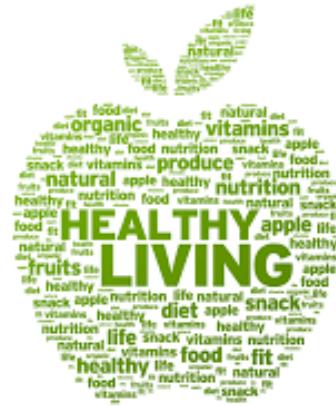
- EPA/DHA
- Curcumin
- Quercetin
- Ginger
- Alpha-lipoic acid
- Resveratrol





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
- Monitor drug effects and drug-nutrient interactions
- Get enough good quality sleep
- Balance work/play – stress management
- Experience joy and gratitude everyday!



The Face of Culinary Genomics





Agenda – Amanda Archibald, RDN

- 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*



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

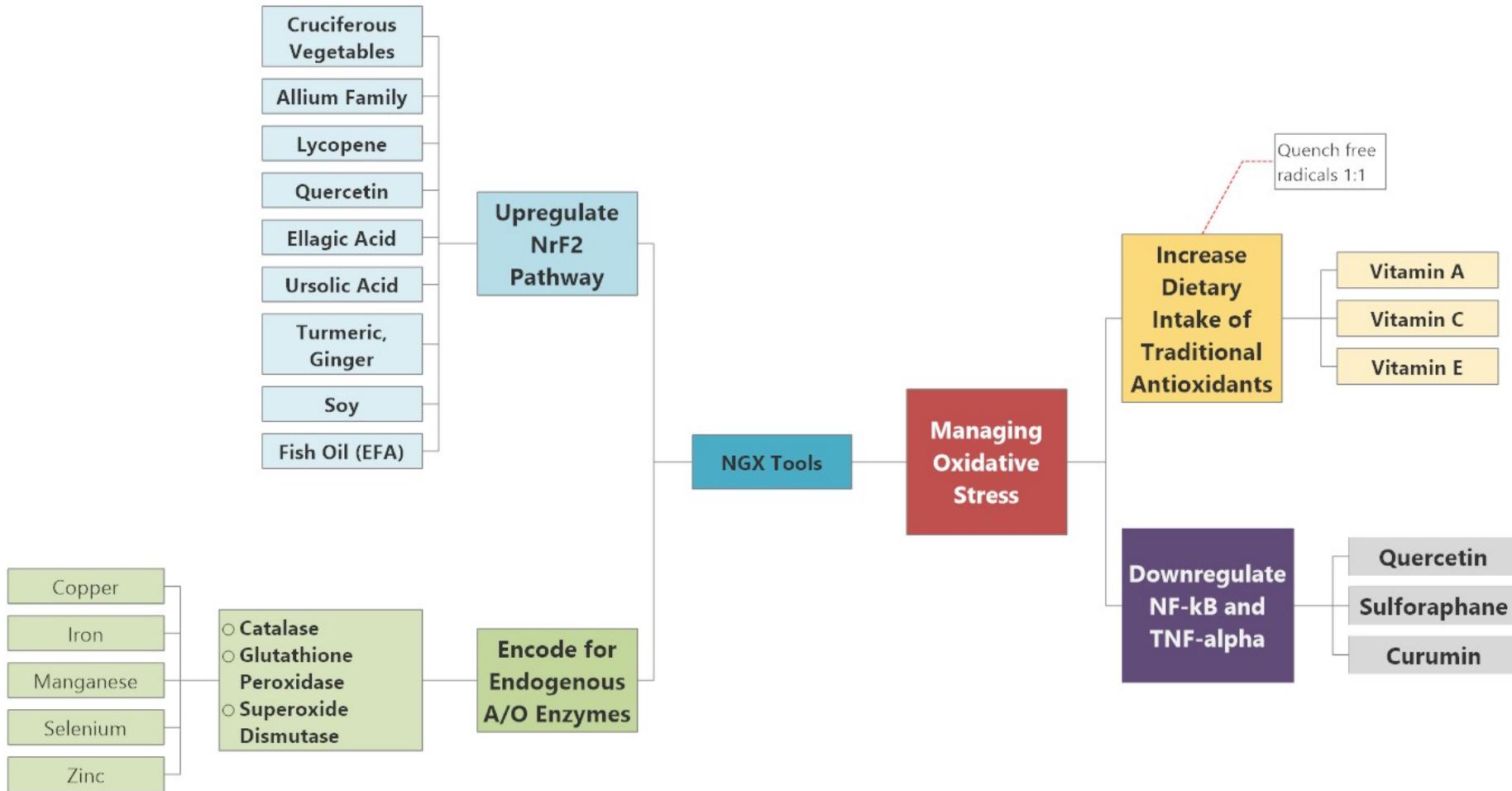
Culinary Significance

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



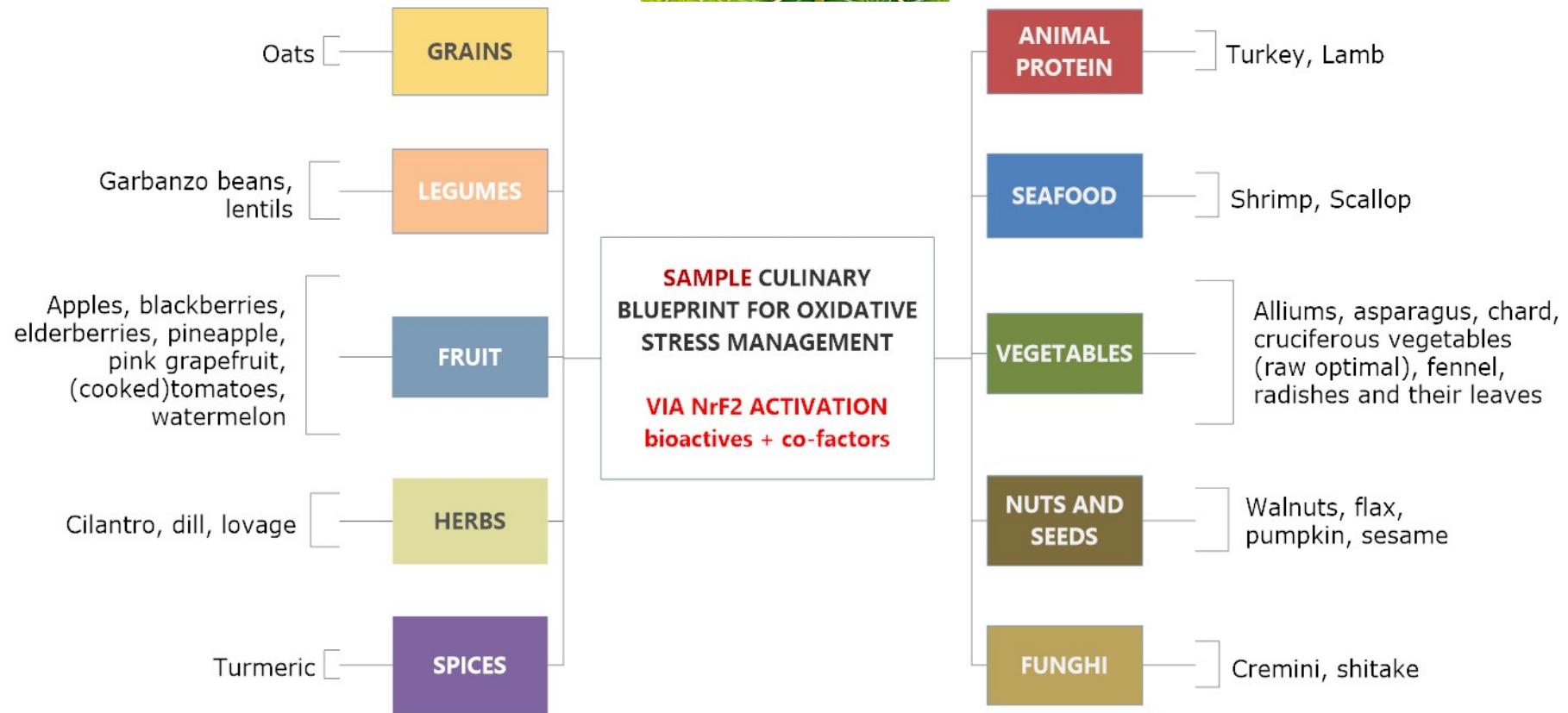
Culinary Genomics requires an implicit understanding of the following:

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



**CULINARY GENOMICS LINKS TO
INGREDIENTS THAT INFLUENCE GENE
BEHAVIOR AND BIOCHEMICAL PATHWAYS**





Culinary Genomics creates recipes from biochemistry for biochemistry





Recipe Formulation



1. SNPs + their impact
2. Prioritization of culinary intervention based on level of impact on critical biochemical pathways
3. Recipe formulation utilizing bioactives and supporting nutrients
4. Outcomes measurement

Culinary
innovation just
got more
real...





Culinary
Genomics in
action.



Genomic specific: Bone Formation

- Bone formation SNPs, including Vitamin D SNPs

- Oxidative stress SNPs

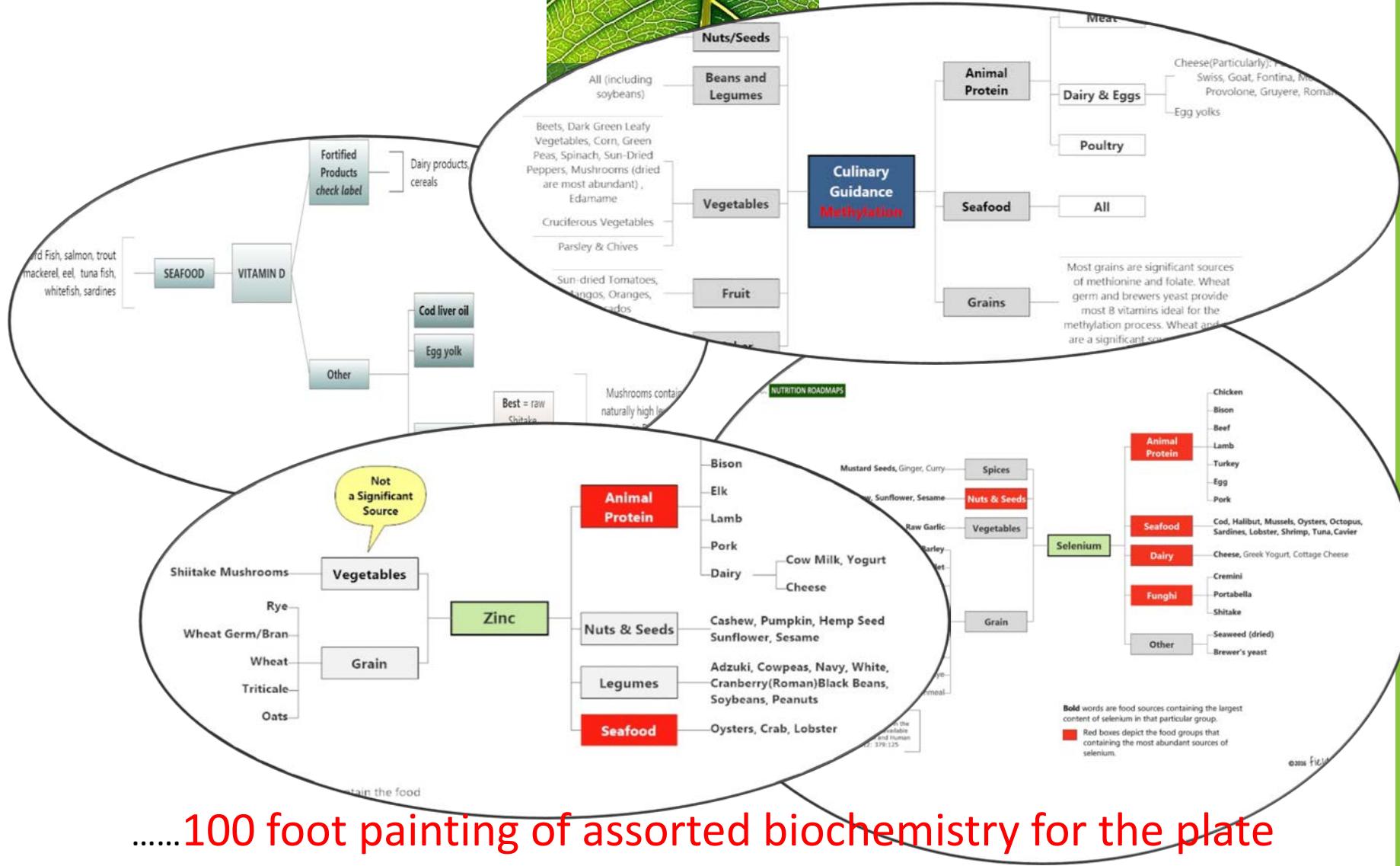
- Ca, MG, Vitamin D rich foods
- Mineral-rich
- Add fermented foods

- Cruciferous vegetables
- Alliums/quercetin-rich foods

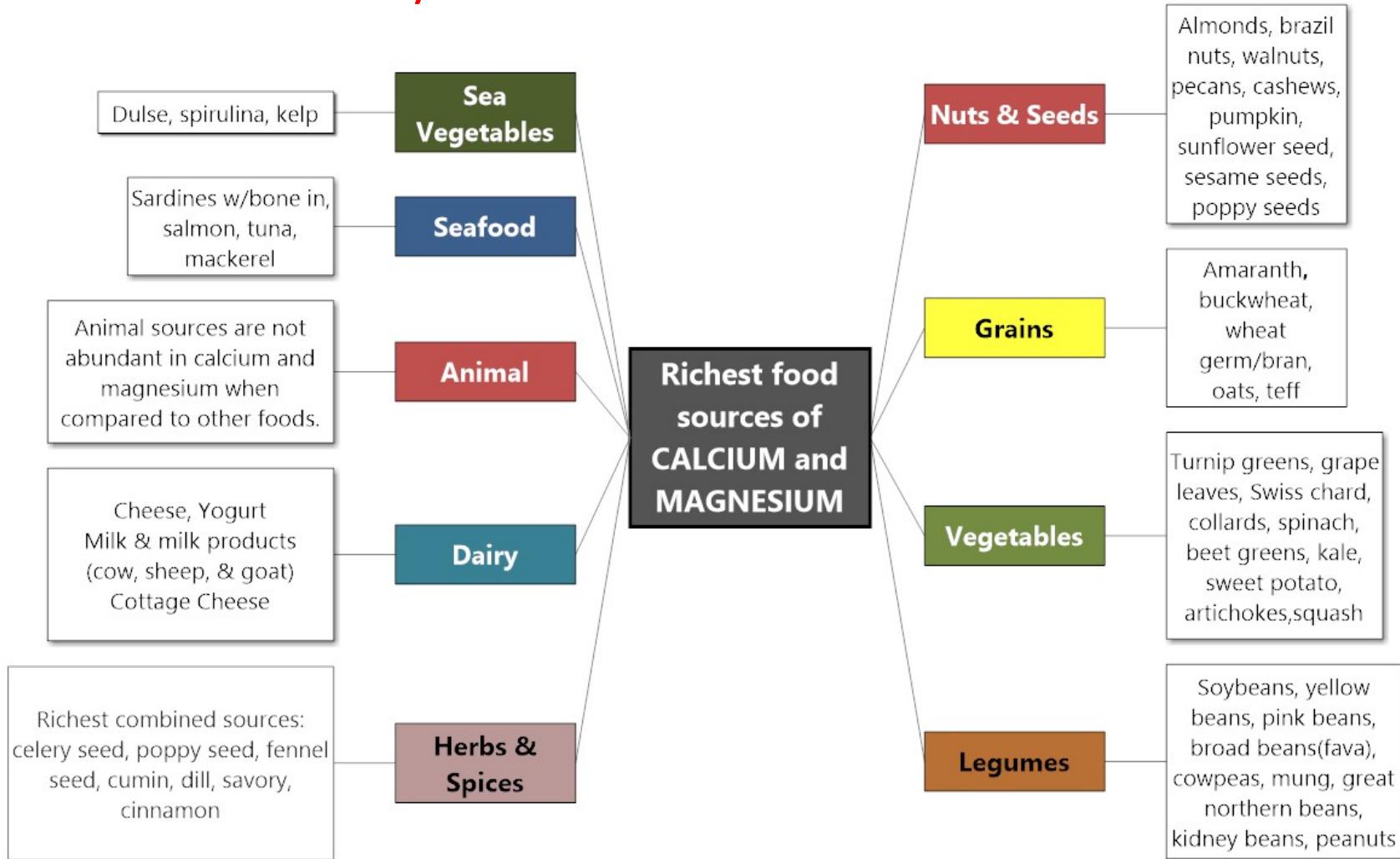
Polygenic thinking drives culinary solutions

Food-Gene Cross Talk

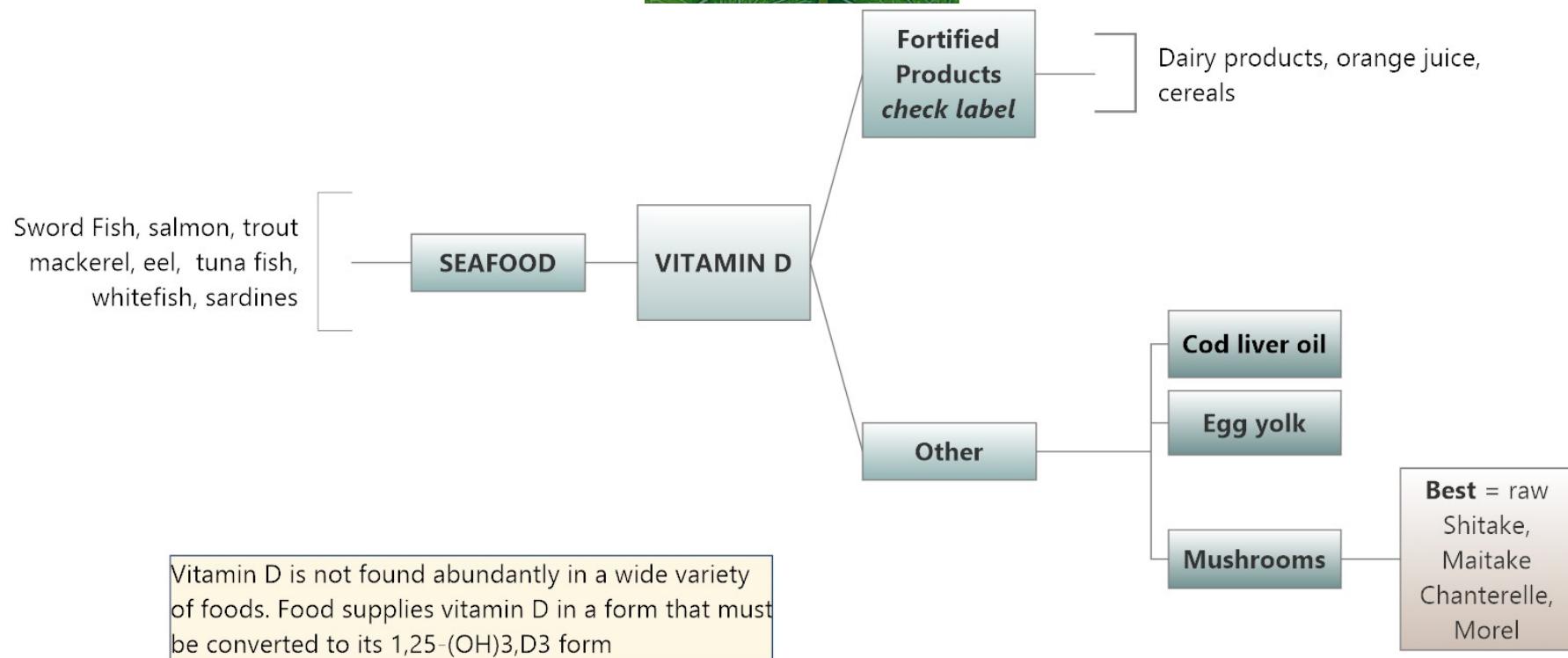
Bone Formation

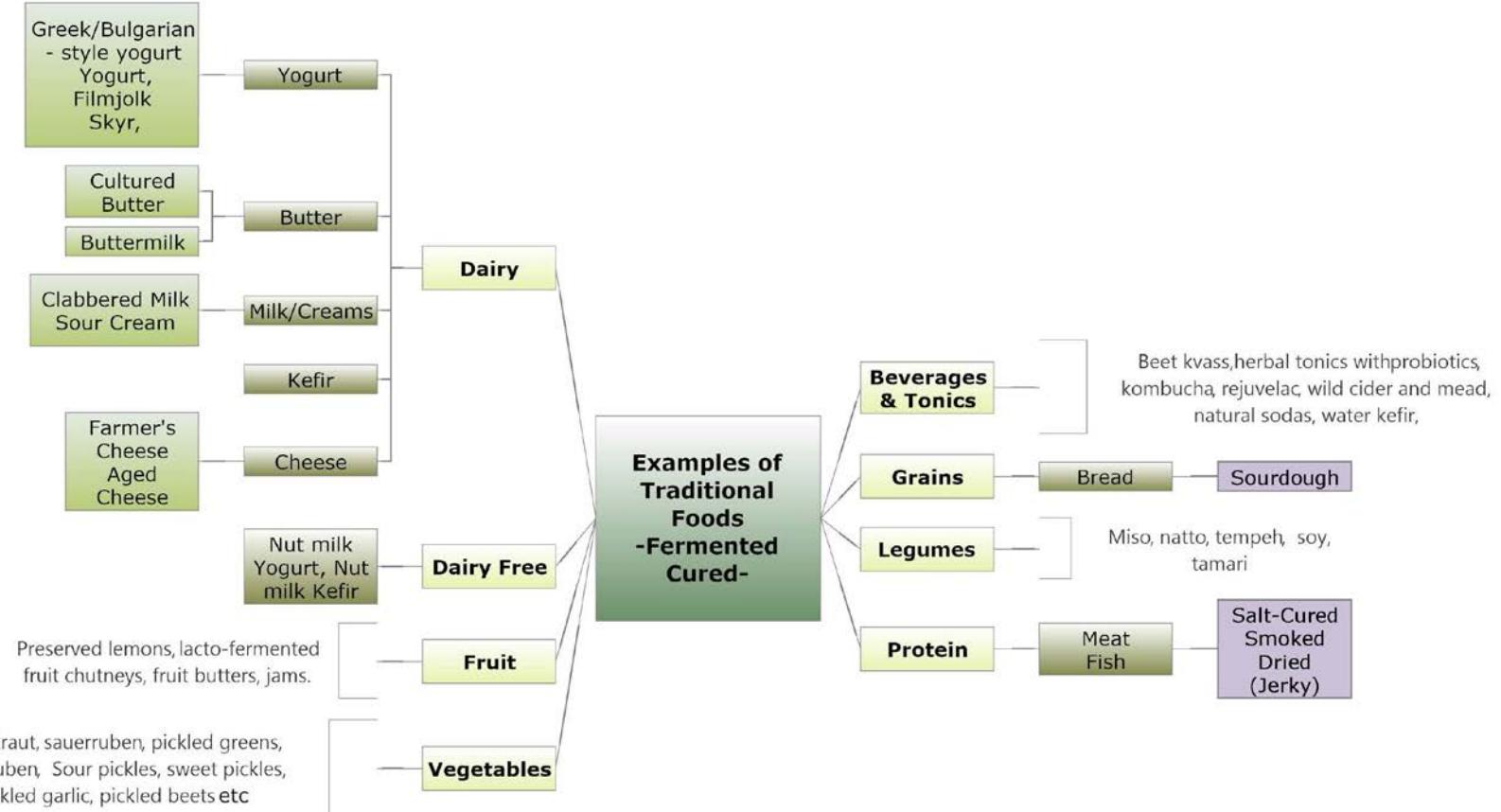


Build an ingredient matrix Specific to SNPs in relevant Biochemical Pathways



Build an ingredient matrix





Biochemistry

GSTT1 & GSTM1

The Nrf2 Pathway



"Absence of gene and therefore enzymatic activity associated with decreased bone mineral density"

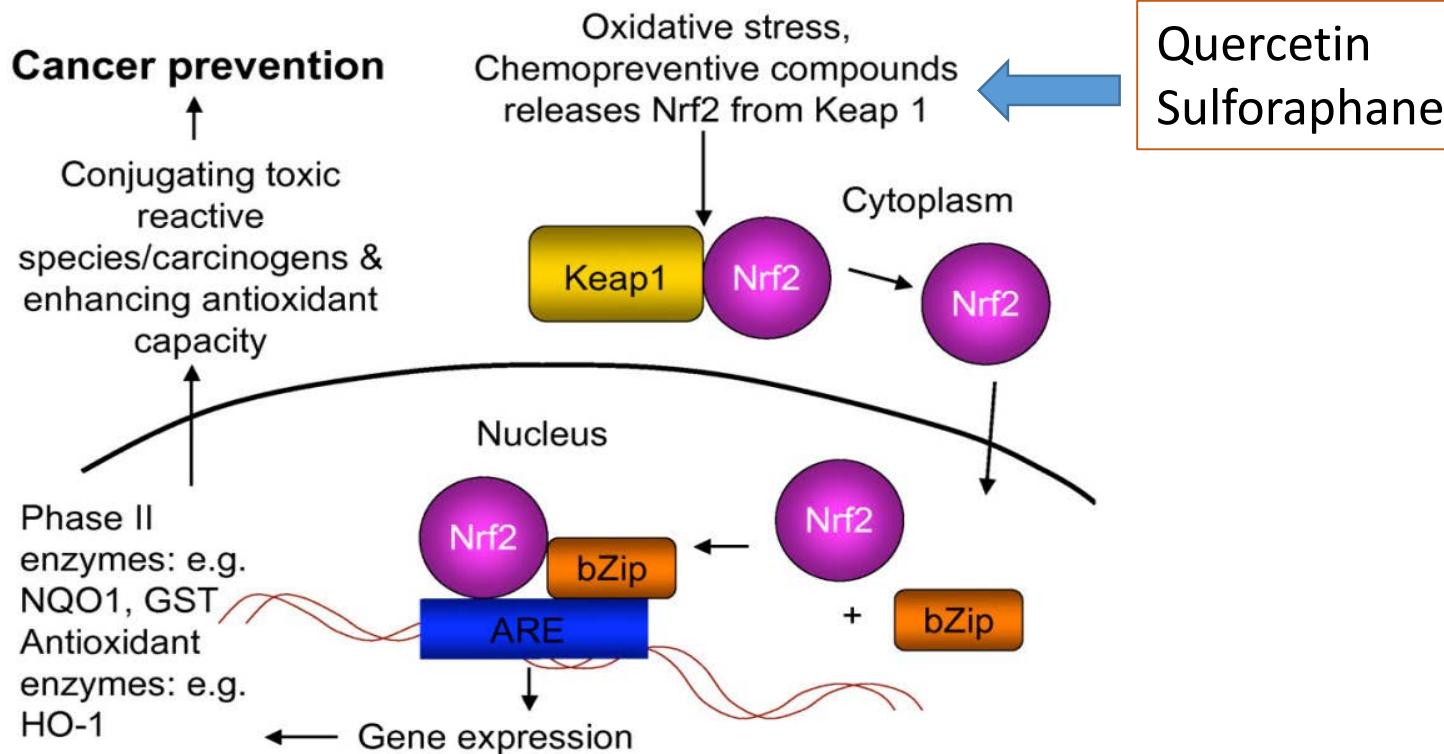
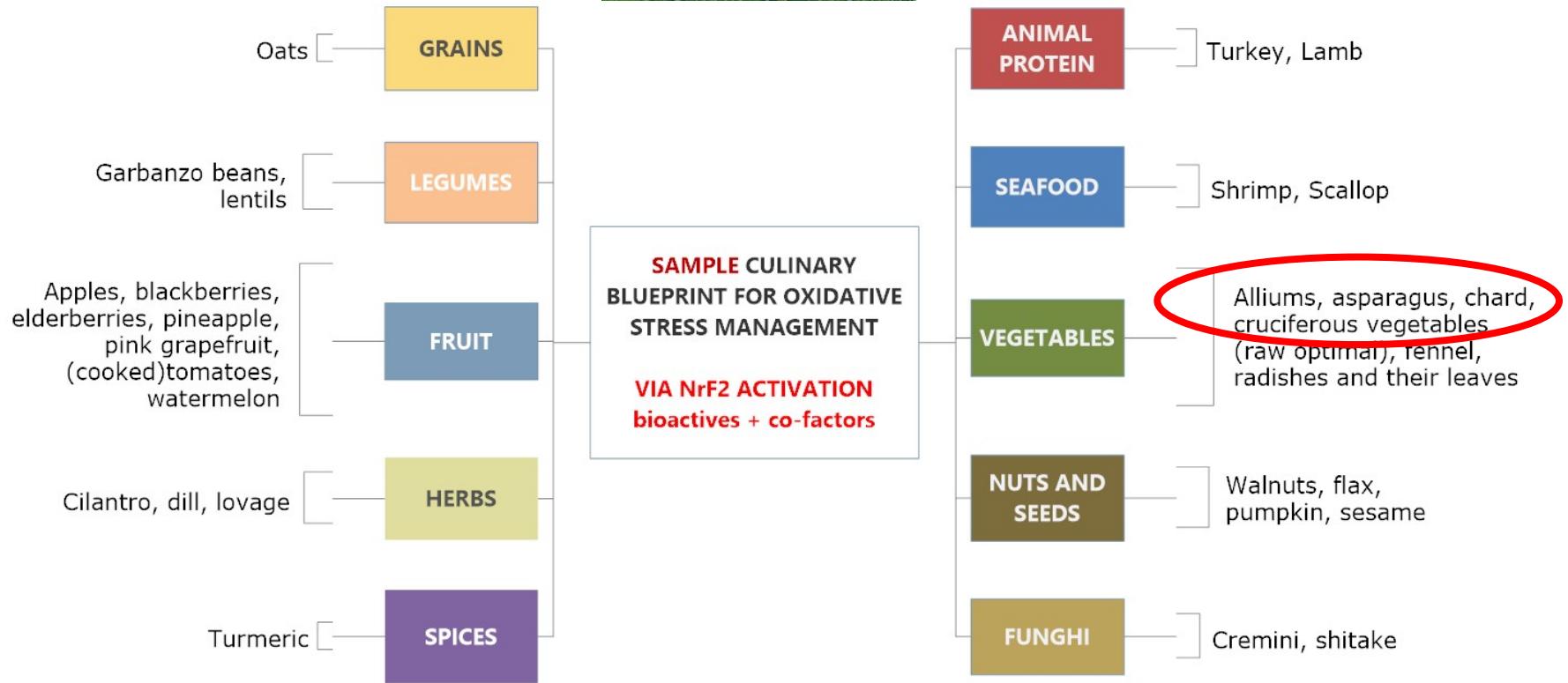
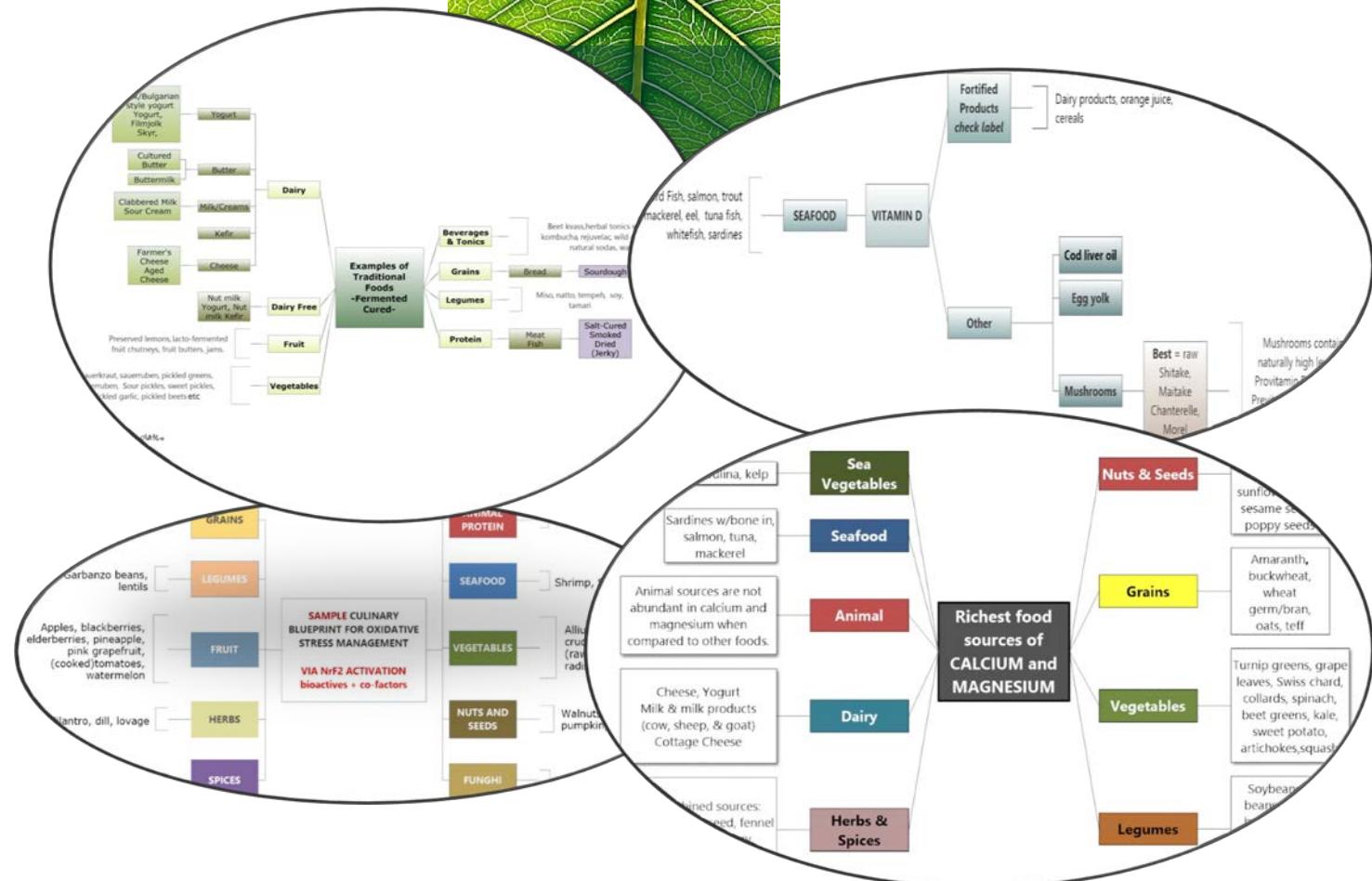


Image source: <http://drjockers.com/nrf2-the-anti-oxidant-amplifier/>



Food-Gene Cross Talk

Bone Formation



.....100 foot painting of assorted biochemistry for the plate



Genomic specific: Bone Resorption

- **Bone Resorption SNPs**
- **Methylation SNPs**
- **Inflammation SNPs**

Vitamin D rich foods

Crucifers (induce)
(Cumin/turmeric/grapefruit inhibit)

Vitamin B complex rich foods,
choline, betaine

Upregulate NrF2/downregulate TNF-alpha/NfkB cascade + Omega-3 FA



Culinary Genomics for Inflammation

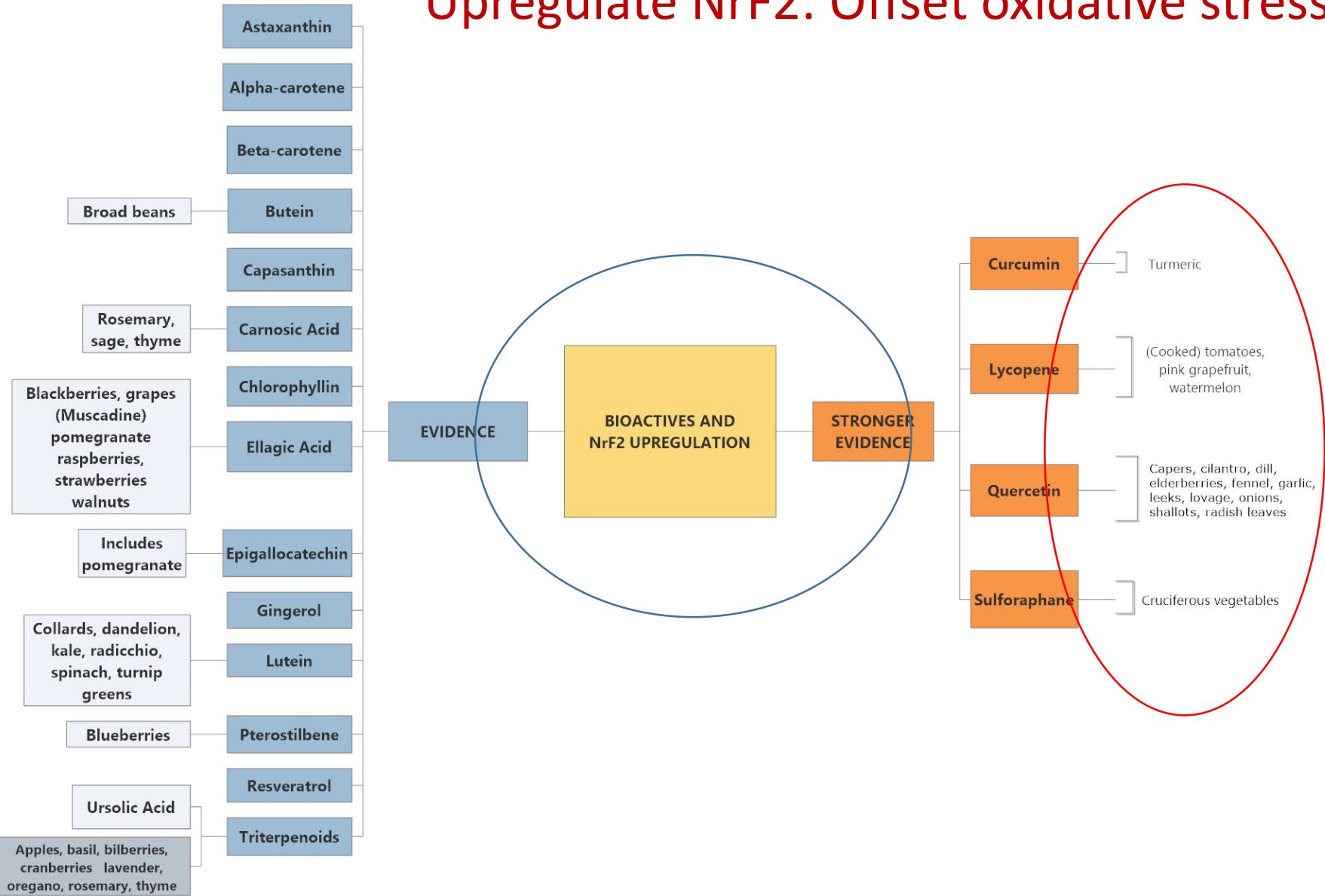
Targets

- CRP, TNF-alpha, IL6/6R cascade

Genomic Intervention

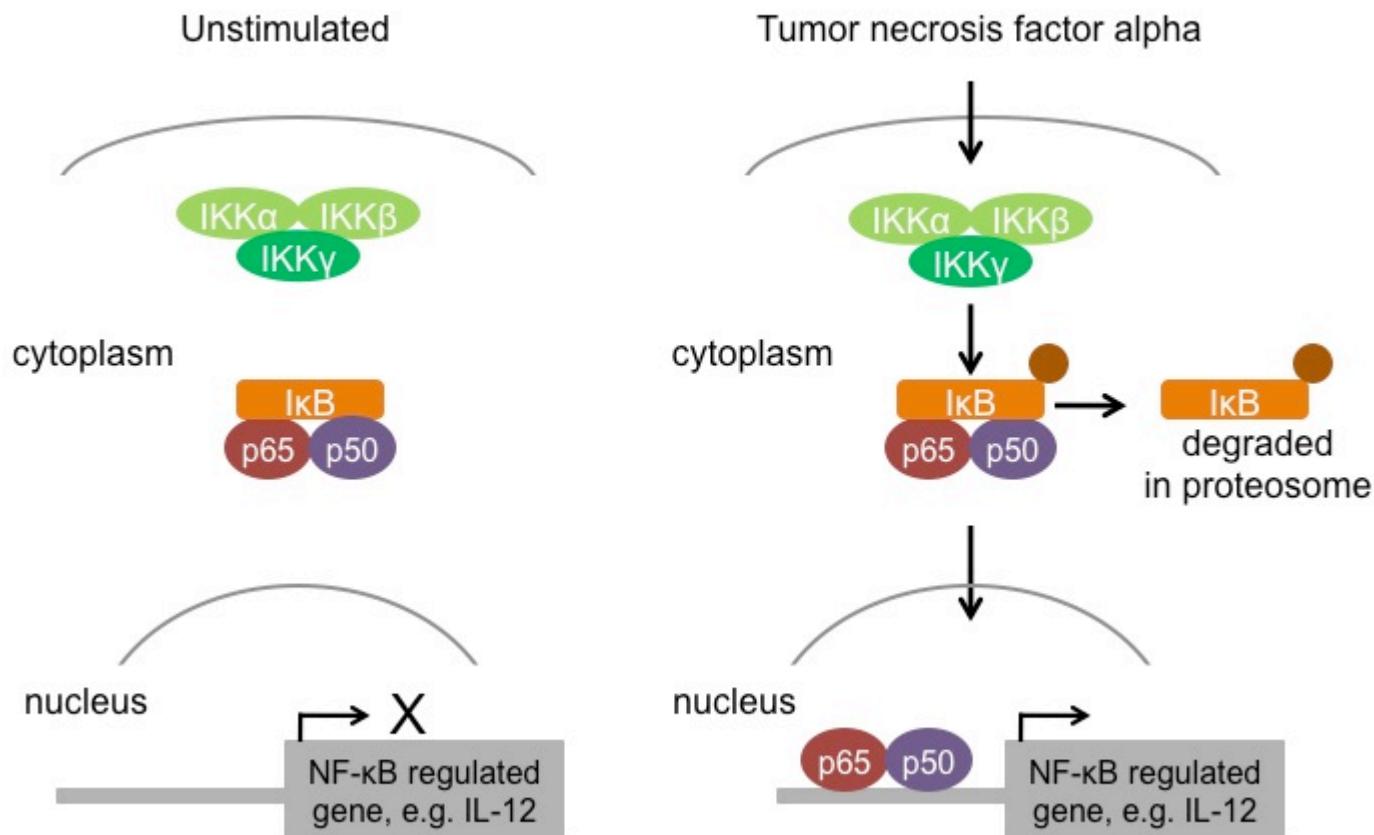
- Balance Omega-3:Omega-6
- Upregulate NrF2: Sulforaphane/Quercetin
- Downregulate TNF-alpha/NfkB: Quercetin/curcumin

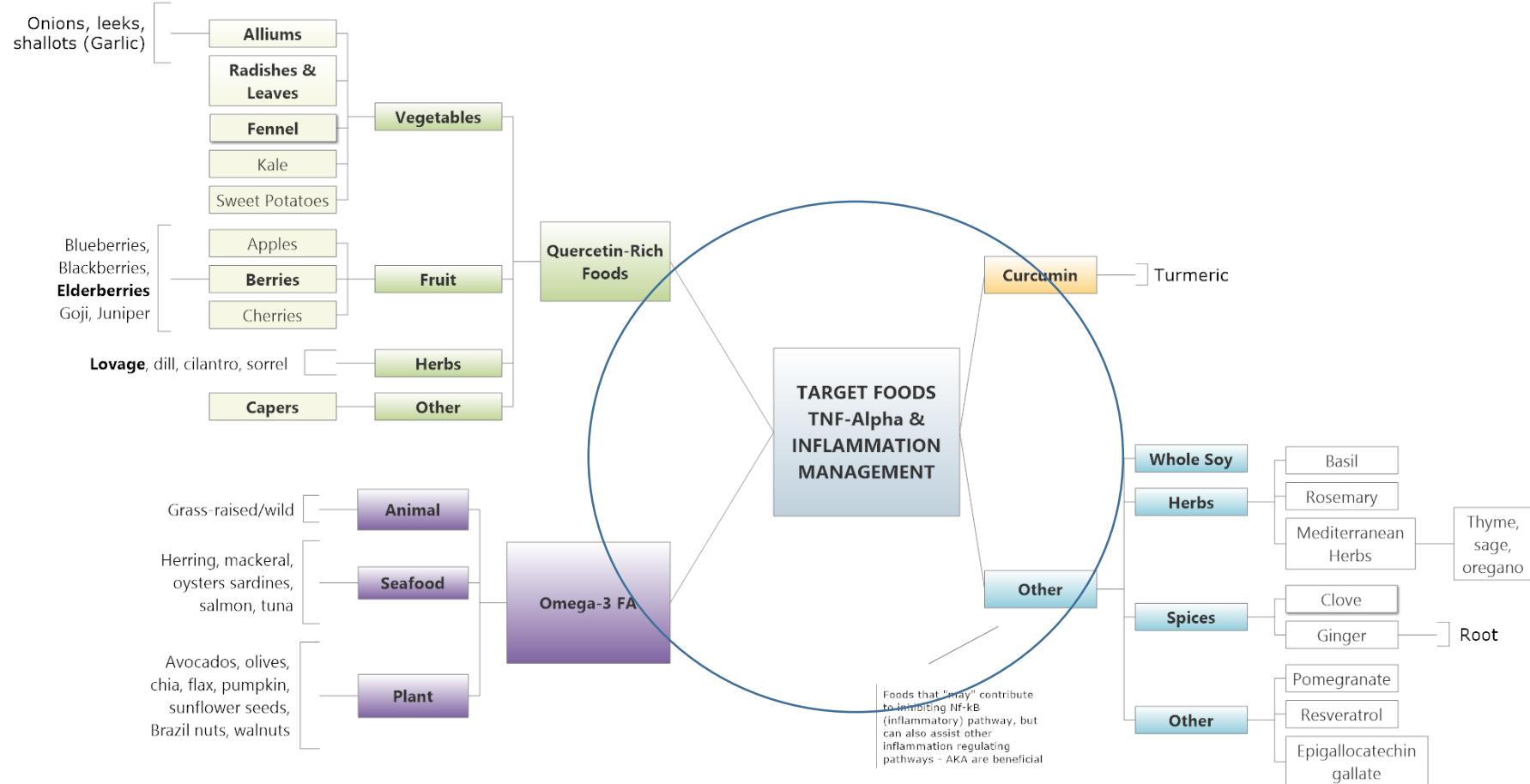
Upregulate NrF2: Offset oxidative stress



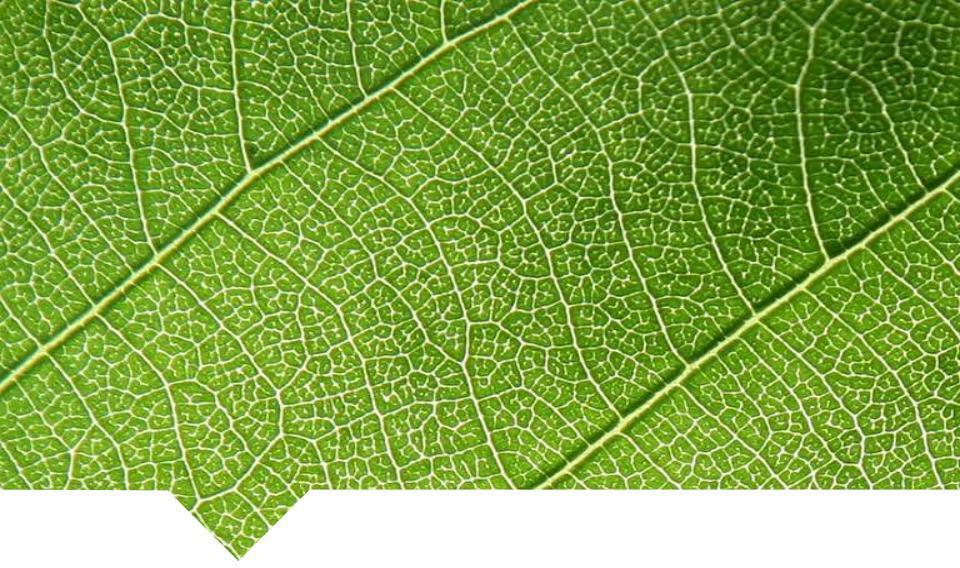


Tamp down TNF-alpha & NF- κ B





Case Study





Female, age 52

- Ht 62"/Wt 125#
- Med Hx: Lap Chole, Tubal Ligation, 2c breast abscess
- Family Hx: mother – bilateral hip replacement, curvature of spine
- Activity level: high but not excessive
- Diet: healthy and varied. Lots of vegetables, adequate protein intake (includes fish and animal protein)
- Caffeine: 1 cup coffee/day, 2 teas
- Alcohol: avg 1 glass of wine/day
- Meds: none
- Supplements: Woman over 50, Omega 3, D3/K2



Polygenic Assessment and Application

Bone Formation & Resorption

High Impact

- VDR Fok1
- VDR Taq1

Moderate Impact

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



Polygenic Assessment and Applications Beyond Bone: looking deeper under the hood

- NQO1
(Inflammation/
estrogen metab)
- FUT2
(folate/HCY)
- TCN2 (folate/HCY)
- C β S (folate/HCY)
- LI-13 (Cardio)
- IL-1B (Cardio)
- 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, borderline Osteoporosis

<u>L1 - L4</u>			
BMD	0. 814		
g/cm ²			
T- score	- 3. 1 STD	<u>Right Femoral Neck</u>	
Z - score	- 2. 3 STD	BMD	0. 847 g/cm ²
		T- score	- 1. 4 STD
<u>Left Femoral neck</u>		Z- score - 0. 3 STD	
BMD	0. 924 g/c		
m ²			
T- score	- 0. 8 STD	<u>Right Femur Total</u>	
Z - score	0. 2 STD	BMD	0. 903 g/cm ²
<u>Left Femur Total</u>		T- score - 0. 8 STD	
BMD	0. 895		
g/cm ²			
T- score	- 0. 9 STD	Z- score	- 0. 1 STD
Z- score	- 0. 2 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 Homocysteine: 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



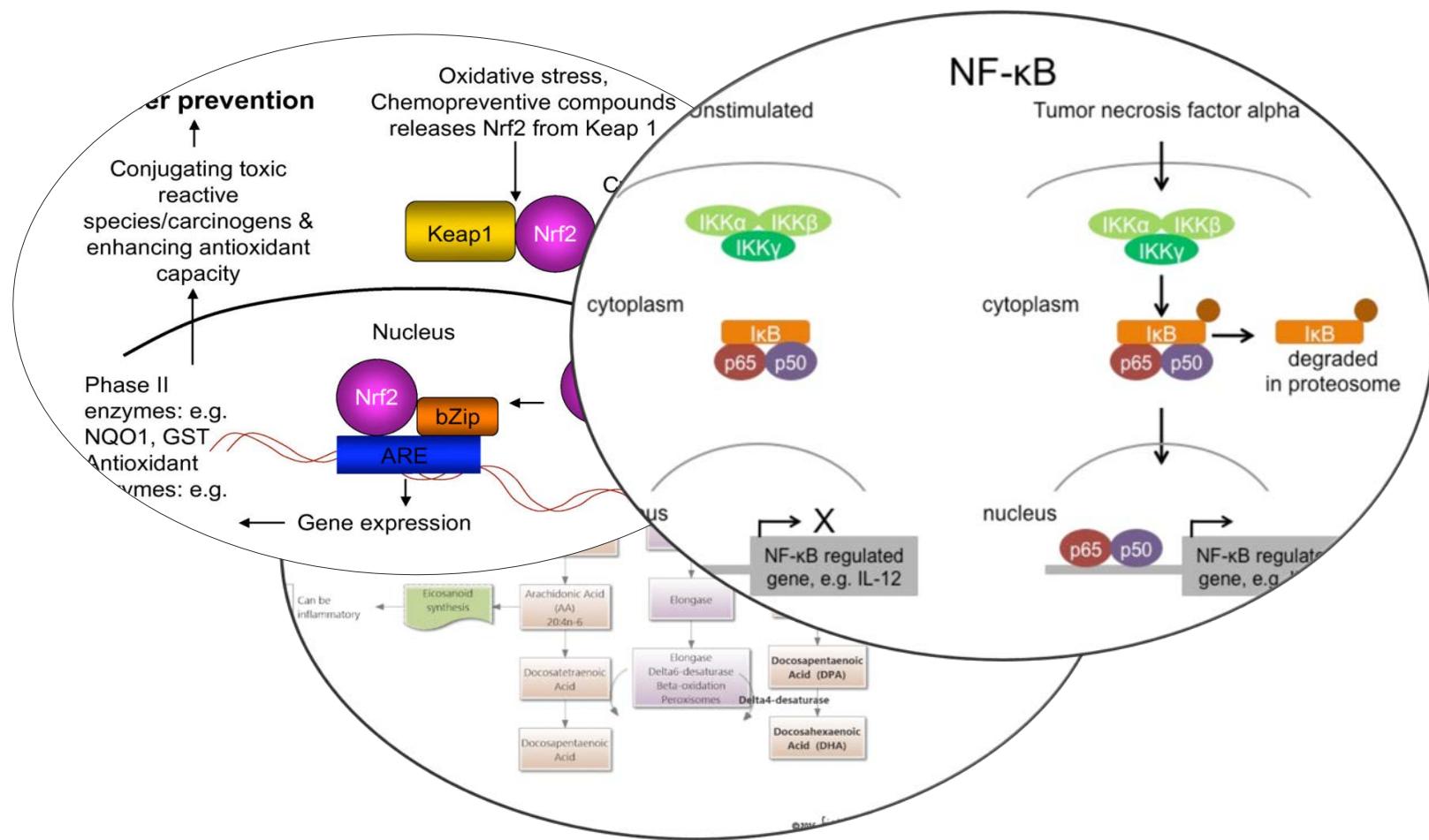
Genomic Informed Culinary Intervention

- Preventive Inflammation management
 - CRP
 - IL-6
 - IL-6R
 - SOD2
 - GPx
 - HMOX1
 - NRF2L2
 - + Omega-3 foods
- Optimizing bone metabolism
 - Fermented Foods
 - D-rich +mineral rich





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



Culinary Translation





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
- The cytoprotective role of the Keap1-Nrf2 pathway. [Arch Toxicol](#). 2011;85:241–272
- Crosstalk of reactive oxygen species and NF-κB signaling: [Cell Research](#) (2011) 21:103-115
- The Nuclear Factor NF-κB Pathway in Inflammation: [Cold Spring Harb Perspect Biol](#). 2009 Dec; 1(6)
- Downregulation of tumor necrosis factor and other proinflammatory biomarkers by polyphenols: [Archives of Biochemistry and Biophysics](#) 559 (2014) 91–99
- Bioactive Nutrients and Nutrigenomics in Age-Related Diseases. [Molecules](#). 2017 Jan 8;22(1).
- 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 a valuable 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 professional 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



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/>
- GeneCards: <http://www.genecards.org/>
- International Osteoporosis Foundation :
<https://www.iofbonehealth.org/facts-statistics#category-14>