



An Integrated Genetic Approach to Detoxification

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The Truth about Toxins.

- ❑ A toxic cocktail of chemical pollutants in US drinking water resulted in more than 100 000 cancer cases in 2015.

(Environmental Working Group – 2019).

The Truth about Toxins.

- ❑ The air we breathe is laced with carcinogenic substances and was responsible for 223,000 deaths from lung cancer worldwide in 2013.

- ❑ *World Health Organization*

- ❑ *International Agency for Research on Cancer (IARC)*

Environmental Working Group Study (EWG)

- ❑ Study evaluating the toxic load in volunteers (none of which worked in factories or farming).
- ❑ 210 contaminants were tested.
- ❑ 91% of them were present in any given individual.
- ❑ Of the tested xenobiotics:
 - 53 compounds were linked to cancer
 - 62 compounds were toxic to the CNS and brain
 - 58 compounds were toxic to the endocrine system
 - 55 compounds were toxic to the immune system

Toxins and Genetics

- DNA methylation pattern in newborns is affected by maternal exposure to toxins.
- Mexican study looked at the effects of maternal exposure to low levels of arsenic in drinking water and the DNA methylation patterns in offspring.
- Significant alterations in DNA methylation in cord blood cells, especially in genes related to growth and development

Toxins and Genetics

- Phenotypically this resulted in lower birth weight, smaller head circumference, and lower placenta weight.
- Further compared the degree of symptoms with phase 2 detoxification genes.
- Those who were variant for one or more GST SNPS had significantly worse symptoms than those who were homozygote normal.

Toxicological Sciences. 2015;143(1):97–106. doi: 10.1093/toxsci/kfu210. ■

Phase 1 Detoxification and Genetics

- ❑ SNPS result in an increased or decreased production of CYP enzymes.
- ❑ **Increased expression** causes an over-production of phase 1 substrates **increasing inflammatory** and pre-carcinogenic substrate build-up.
- ❑ **Decreased expression** causes an abundant **build up** of the **intracellular toxin**.

❑ *HUGO Gene Nomenclature Committee (HGNC)*

❑ *Genetics Home Reference – US National Library of Medicine.*

Phase 2 Detoxification and Genetics

- ❑ SNPs decrease the production of GST.
- ❑ SNPS increase the production of ROS.
- ❑ SNPS decrease NRF2 pathways.
- ❑ All result in a decreased removal of toxins, increased inflammation, and the ability to alter other gene expression and the immune response.

Genes for Detoxification

- ❑ CYP1A2 rs762551
- ❑ CYP3A4 rs2740574
- ❑ GSTP1 rs1695
- ❑ SOD2 rs4880
- ❑ NQO1rs1800566

CYP1A2 rs762551

❑ Normal Allele is A

Variant Allele is C

- ❑ Crucial enzyme, that along with CYP3A4, metabolizes over 90% of drugs such as Ciprofloxacin, Flouoroquinones, Fluvoxamine and more.
- ❑ CYP1A2 comprises 13% of all CYP enzymes in the liver.
- ❑ CYP1A2 is key for the metabolism of xenobiotics.
- ❑ Important for the metabolism of 2-OH estrogen.
- ❑ A goldilocks gene!

CYP1A2 rs762551 A Allele

- ❑ **Fast Metabolizer** = Increased production of phase 1 substrates.
- ❑ Increased activation of carcinogenic PAH's and aromatic and heterocyclic amines >> breast and bladder cancer.
- ❑ Increased production of 2-OH estrogen >> decreased breast cancer.

❑ *Molecular Cancer Research AACR publication Feb 2005*

CYP1A2 rs762551 C Allele

- ❑ **Slow Metabolizer** – Decreased production of phase 1 substrates.
- ❑ Increased TNFa and inflammation.
- ❑ Increased risk of cardiovascular disease and heart attacks.
- ❑ Decreased production of 2-OH estrogen >> breast cancer.
- ❑ Increased risk of colon cancer and colorectal polyps especially with BBQ'd meats.

❑ Zhou SF et al. *Drug Metabolism Reviews*. 2010; 42:268-354

❑ UniProt. P05177 (CP1A2_HUMAN)

Support for CYP1A2 A Allele

- ❑ 2-3 cups of caffeine per day. (reduce your risk of a myocardial infarction).
- ❑ Curcumin
- ❑ COOK your cruciferous vegetables.
- ❑ Avoid Milk Thistle, mint and Echinacea.

Support for CYP1A2 C Allele

- ❑ Avoid caffeine
- ❑ Avoid acetaminophen (Tylenol).
- ❑ Avoid curcumin
- ❑ Increase RAW cruciferous vegetables.
- ❑ DIM
- ❑ Calcium-D-glucarate
- ❑ Hydroxymatairesinol (HMR)
- ❑ Milk Thistle

CYP3A4 rs2740574

- ❑ Normal Allele is C (G) Variant Allele is T (A)
- ❑ 2nd most abundant CYP enzymes in the liver and small intestines.
- ❑ Also highly expressed in the breast, prostate, stomach and colon.
- ❑ Metabolizes up to 50% of pharmaceutical medications such as phenobarbital, phenytoin and rifampicin.
- ❑ Significant catalyst in the hydroxylation of estrogens and testosterone.
- ❑ Detoxifies bile acids.
- ❑ *Carcinogenesis* 30, 1532–1535.
- ❑ *Tumor Biol.* 34, 649–660.

CYP3A4 C Allele

- ❑ Increased CYP enzyme production and activity.
- ❑ Faster phase 1 substrate production.
- ❑ Increased risk of breast and prostate via hydroxylation of hormones.
- ❑ Increased risk of breast cancer via worse 2-OH to 16-OH estrogen ratio.

❑ *Carcinogenesis* 18, 207–214

❑ *J. Pharmacol. Exp. Ther.* 298, 420–432.

CYP3A4 T Allele

- ❑ Decreased CYP enzyme production and activity.
- ❑ Slower phase 1 substrate production.
- ❑ Increased risk of breast, prostate, and colon disease via inflammatory response.
- ❑ Decreased risk of breast cancer via better 2-OH to 16-OH estrogen ratio.

Support for CYP3A4 C Allele

- ❑ 2-3 cups of caffeine per day. (reduce your risk of a myocardial infarction).
- ❑ Curcumin
- ❑ COOK your cruciferous vegetables.
- ❑ Bi-annual detox involves marginal slowing of phase 1 pathways and aggressively increasing phase 11 pathways.

Support for CYP3A4 T Allele

- ❑ Avoid caffeine
- ❑ Increase RAW cruciferous vegetables.
- ❑ DIM
- ❑ Calcium-D-glucarate
- ❑ Hydroxymatairesinol (HMR)
- ❑ Milk Thistle
- ❑ Quarterly detox involves increasing both Phase 1 and Phase 11 pathways.

GSTP1 rs1695

- ❑ Normal Allele = A Variant Allele = G
- ❑ Glutathione-S-Transferase P =phase 11 enzyme that catalyzes the conjugation of many toxic compounds, carcinogens, estrogens and cytotoxic medications.
- ❑ Widely spread in most cells. (except erythroid cells).
- ❑ Highest concentration in lungs and breasts.
- ❑ *Gene ID 2950- 2020*
- ❑ *Cancer Res 2008;68:4791-4801*

GSTP1 rs1695 A Allele

- ❑ Optimal/normal enzyme production.
- ❑ Can have increased inflammation (IL6) with vitamin E supplementation – especially over 75 IU

❑ *Am J Clin Nutr* 2010 Jun;95(6)

GSTP1 rs1695 G Allele

- ❑ Homozygote GG's far greater risk of developing breast cancer than AA's (0.73 times or a 1.4 OR).
- ❑ Lower risk of chemoresistance with Doxorubicin.
- ❑ Risks decrease greatly in those who ate high cruciferous vegetables.
- ❑ Greater risk of asthma and allergies.

- ❑ *BMC Med Genet* 2011
- ❑ *Ann Oncol* 2012 23(7).
- ❑ *Cancer Epidemiol Biomarkers Prev* 2009 18(5)

Support for GSTP1 A Allele

- ❑ Avoid higher doses of Vitamin E supplementation.
- ❑ Note: can still support A/A's with GST boosting when in polluted environment, vaccinating or on a longer-term medication with high inflammatory or toxic side effects.

Support for GSTP1 G Allele

- ❑ Liposomal Glutathione
- ❑ NAC
- ❑ DIM
- ❑ Cruciferous Vegetables
- ❑ Vitamin E

SOD2 rs4880

- ❑ Normal Allele is A (C) Variant Allele is G (T)
- ❑ Mitochondrial Superoxide dismutase - manganese-dependent enzyme that binds superoxide and ROS and converts them into hydrogen peroxide and diatomic oxygen.
- ❑ Main enzyme that protects mitochondria and DNA from oxidative damage.
- ❑ Decreases with age, cancer, inflammation and motor neuron diseases.

SOD2 rs4880 G (T) Allele

- ❑ Decreased enzyme production.
- ❑ Decreased clearance of ROS.
- ❑ Increased inflammation.
- ❑ Homozygote variant have 10-fold increased risk of cardiomyopathy – cardiac myocyte signaling.
- ❑ Increased risk of cancers – lung, non-Hodgkins lymphoma and colorectal.
- ❑ Decreased energy.

Support for SOD2 A (C) Allele

- ❑ High level athletes that generate more than normal amounts of ROS through exercise can still benefit from the support that the G allele carriers use.

Support for SOD2 G (T) Allele

- ❑ DIM
- ❑ Sulforphanes
- ❑ Astaxanthin
- ❑ Liposomal Glutathione
- ❑ NAC

❑ *Nutrients* 2018, 10(4)

❑ *Research Gate* June 2015

NQ01rs1800566

- ❑ Normal Allele is G (C) Variant Allele is A (T)
- ❑ NAD(P)H quinone dehydrogenase 1- main enzyme in the NRF2 pathways.
- ❑ Prevents redox reactions of quinones to inhibit the production of ROS.
- ❑ Binds and metabolizes toxins such as detergents and cleaners, pesticides, and cigarette smoke.
- ❑ Clears out estrogens.

❑ *Int J Cancer 2012 130(2)*

❑ *PLOS 1 2012 Jan 17*

NQO1rs1800566 A Allele

- ❑ Lower enzyme production
- ❑ Increased ROS and inflammation.
- ❑ 7-fold increase risk of bone marrow toxicity.
- ❑ Increased risk of breast, lung and colon cancer.
- ❑ Not responsive to epirubicin – chemo drug

❑ *Med Res 2012 43(1)*

❑ *Genetics in Medicine 2002; 4:62-70*

Support for NQ01 A Allele

- ❑ Exercise- especially HIIT if genes allow for it.
- ❑ DIM
- ❑ Sulphoraphanes
- ❑ Resveratrol
- ❑ Liposomal Glutathione
- ❑ NAC

❑ *J Clin Endocrinol Metab* 2011 96(5)

Genetic Integration

❑ CYP1A2 - C/C

❑ CYP3A4 - C/T

❑ GSTP1 G/G

❑ SOD2 – G/G

❑ NQ01- G/A

❑ IL6 – G/G

❑ CYP1A2 – A/A

❑ CYP3A4 - C/T

❑ GSTP1 A/A

❑ SOD2 – G/G

❑ NQ01- G/A

❑ IL6 – C/C

Case Study 1

- ❑ Mary is a 44-year-old runner who “feels like she is breaking down.”
- ❑ Increased joint inflammation, often with a skin rash on the chest and abdominal bloating/discomfort after a long run.
- ❑ Started taking acetaminophen (Tylenol) after hard workouts and curcumin daily but only got worse.
- ❑ No known allergies.
- ❑ Lives and runs in downtown Toronto.
- ❑ Ate a very clean diet rich in cruciferous veggies, but always cooked due to her bloating.

Case Study 1

- ❑ CYP1A2 - C/C – slowest clearance (curcumin, acetaminophen [Tylenol])
- ❑ CYP3A4 - C/T – slow clearance
- ❑ GSTP1 G/G – slowest clearance, allergenic response
- ❑ SOD2 – G/G – increased inflammation on exercise
- ❑ NQ01- G/A- slow clearance.
- ❑ IL6 – G/G - increase inflammation stimulating all above.

Case Study 1

- ❑ Off Curcumin and acetaminophen (Tylenol)
- ❑ Increased raw cruciferous vegetables – Greens powder for 6 weeks.
- ❑ Liposomal Glutathione – 1 BID empty stomach
- ❑ NAC – 1 BID empty stomach
- ❑ Querciten-Bromelain combo – 2 BID for 8 weeks empty stomach.
- ❑ DIM, Sulphorophane, Resveratrol combo – 2 BID for 4 weeks.

Case Study 1

- ❑ Within 2 weeks her inflammatory response was “50%” better.
- ❑ Her breathing improved (although she did not know if was poor until she felt it better).
- ❑ Rash post runs disappeared after 4 weeks, and joints felt much “younger”, but bloating remained. All symptoms better if she ran indoors.
- ❑ Continued her on the DIM combo for another 4 weeks.
- ❑ 7 weeks into the program all symptoms were 90% better.

Case Study 1

- ❑ 3 years later all inflammatory responses remain normal unless an apparent causal factor.
- ❑ Rotated the DIM combo in 1 week every 3 months.
- ❑ Increased her liposomal glutathione and NAC to 2 BID on days with high pollution, humidity and a long run.
- ❑ Uses Boswellia if she feels she needs extra joint support.

Case Study 2

- ❑ Julie is 44 years old and is Mary's running partner.
- ❑ She has a family history of osteoarthritis, but has no symptoms herself, but takes curcumin daily for prevention.
- ❑ She follows the same workout regime as Mary.
- ❑ Her diet is not as clean as Mary's, she often indulges in fried foods and drank 4 cups of coffee per day.

Case Study 2

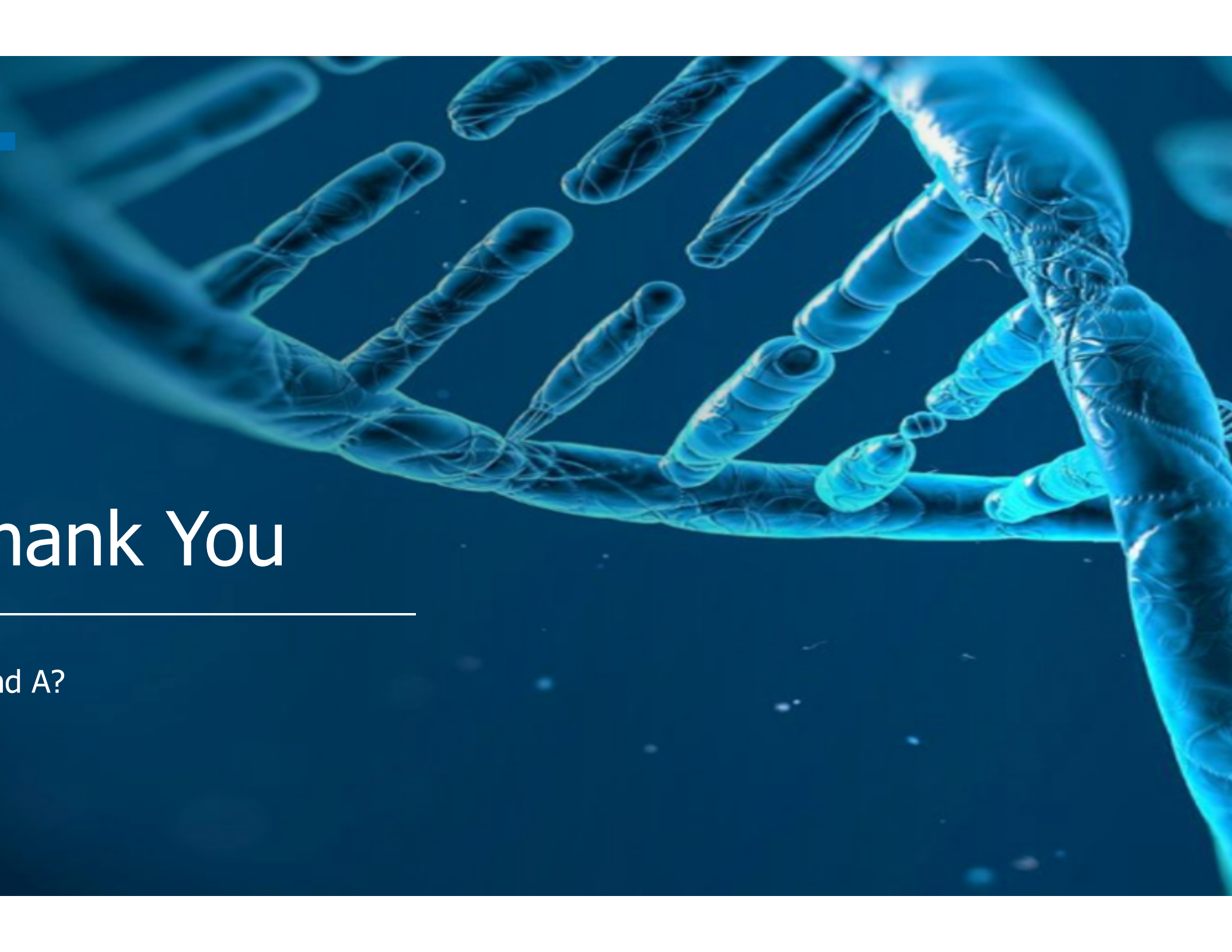
- ❑ CYP1A2 – A/A – increased phase 1 substrates
- ❑ CYP3A4 - C/T – slow clearance
- ❑ GSTP1 A/A- normal clearance
- ❑ SOD2 – G/G – increased inflammation on exercise
- ❑ NQ01- G/A - slow clearance
- ❑ IL6 – C/C- decreased inflammation.

Case Study 2

- ❑ Curcumin – 1 BID empty stomach
- ❑ Astaxanthin – 1 BID empty stomach
- ❑ Reduced coffee to 3 per day
- ❑ Increased cooked cruciferous vegetables

Case Study 2

- ❑ Julie did not have any symptoms to follow.
- ❑ Her OA family history came through her MMP3 and COL1A1 genes which we also added in Resveratrol and hydrolyzed collagen to help with prevention.
- ❑ 3 years later she remains feeling well and maintains the same workout regime with Mary.



Thank You

and A?