Epigenetics
Influencing Health Trajectories

1. Nutrition influences health status
2. Genetic expression effects specific health conditions
Background

• 12 years in ER
• 7 years in practice
  - Center for integrative medicine focused on women and children’s health
• Various vantage points
  - Chinese & Ayurvedic Medicine
Are we the way we are due to:

- Genetic predisposition describes potential but not necessarily expression of genes
- Diet and lifestyle can influence genetic expression and activate genetic potential
- Nutrition influences epigenetic modification and balance to express genetic potential

**NATURE**

Genes inherited from our parents?

**NURTURE**

Experiences during our life?
What is Genomics?

Genetic Information

Provides the building blocks for the manufacture of all proteins needed for cell function activity.

Epigenetic Information

Provides instructions on how, where and when the genetic information should be used.
Epigenetic Mechanisms May Account for Our Response to the “Wear and Tear” of Life
The “Health-Ome” Influences Expression of Health
The “Health-Ome” Axis: Managing Wellbeing

Chronic Inflammation

Genetic Instability
Epigenetic Influences

Reduced Resilience of Host Defense

Neuro-Endocrine and Oxidative Stress
Focus on Health Outcomes and Status

Health and Patient Management
• Supports the foundations of health and manages disease

Genetic Predisposition and Health Potential
• Identifies levels of risk and manages its influence

Epigenetic Expression and Influence
• Manages expression of health & its influence on wellbeing

Metabolic Pathways and Stability of Methylation
• Optimize cellular capacity and balance

Association to disease states
• Eliminate problems with methylation for clinical management
Epigenetics Today

- Autism
- Autoimmune Disease
- ADHD
- Dyslexia, Apraxia
- Anxiety
- Depression
- Breast Cancer
- Cancer
- Mental Health- Bipolar, Schizophrenia, OCD
The Patient is Waiting
Focus on Select Patient Segments and Health Conditions

Typical Clinical Presentation of Health Conditions

Genetic Information

- Vitamin deficiencies (B12, Folic Acid, Choline)
- Genetic predisposition and risk of non-optimized expression
- Chronic stress and fatigue
- Mood disorders, anxiety and ‘brain fog’
- Cardiovascular conditions
- Diabetes and carbohydrate intolerance
- Frequent use of prescription medications
- Hormone therapy, specifically estrogen use
- Thyroid conditions and therapy
- Pre ‘Detox’ Program
Methylation

• Buzz word in the field of epigenetics

• **Definition** - DNA methylation is an epigenetic mechanism used to control gene expression- epigenetic signaling tool.

• Homocysteine produced as a byproduct of methylation.

  High Homocysteine associated with malfunction of methylation cycle, disease risk.
Clinical Conditions Caused by Elevated Homocysteine

Single Nucleotide Polymorphisms (SNPs), gene mutations that affect enzymatic activity

Includes riboflavin (B2), B12, B6, folate (B9), and the cofactor betaine
Evolution of epigenetics

4 Key Health Trajectories
First 1000 days

- Prenatal exposure to chemicals disrupts fetal epigenome
- Results in lifelong risk of disease- evolving field of research
Study Looked at 2 Chemicals

PAH (polyaromatic hydrocarbons) + BPA (bisphenol A)

- Found Key Points where methylation involved
- Father's sperm (demethylates more quickly)
- Mother's Egg - maternal diet
- Blastocyst
- Embryo Implantation

Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171169/
Critical Transition (Ages 25-40)

- Chronic Inflammation triggers epigenetic changes
- Changes in methylation
- Pro-inflammatory diet
- Increased immunogenicity or aging of the immune system
- Increases autoimmune phenomenon- autoimmune disease, cancer, inflammation, infection
- Shortening of DNA (telomeres)

Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2850145/
Critical Transition  (Ages 25-40)

- Increased Paternal Age, associated with more epigenetic changes
- Increased incidence of autism, bipolar disease, schizophrenia and childhood leukemia
- Oxidative stress and reduced antioxidant reserve connected to DNA fragmentation (80%)

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455614/
Critical Transition (Ages 25-40)

• Expression of Cardiovascular Disease

• Methyl nutrient status influences CVD pathophysiology.¹

Role of NF-kB in CVD- controls DNA transcription, affects cytokines- triggers inflammation.²

¹: Ncbi.nlm.nih.gov/pubmed/23661599
²: ncbi.nlm.nih.gov/pmc/articles/PMC4049125
Healthy Aging (Ages 50-65)

- Epigenetics are a factor in aging.
- Only 20-30% of aging is determined by genetics.
- Remaining 80% from environment, nutrient, stress and other factors
- Predispose to colorectal cancer

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3014766/
Vitality  (Ages 65+)

• Effects of social stress
• Exercise
• Mental Health
• Pharmogenomics
• All factors that play into epigenetics
Current Stats/Info on Epigenetics

DNA methylation most well known - histones that surround DNA and expression of noncoding RNA
Interconnected Metabolic Pathways

Key Methylation Activity Starts Here!
Activation of Epigenetic Expression:

Bringing together the Genome with the Metabolome to Create the Healthome!

Activation of epigenetic expression is determined by the capacity of metabolic pathways.

Metabolic load and capacity can be monitored by testing blood for the biomarkers of the Methylation Axis:

- SAMe
- SAH
- Homocysteine
The primary function of this system is to maintain *cellular methylation capacity* so proper genetic activation and influence may be managed.

- Maintain the SAM : SAH ratio with optimal SAM, SAH, and homocysteine levels.
- Imbalance in SAM:SAH ratio (methylation capacity) can impair methylation reactions.
- High SAH inhibits methyltransferases, impairing 1-carbon metabolism and intersecting biochemical and epigenetic processes, such as the gene COMT.
Current Stats/Info on Epigenetics

DNA methylation most well known - histones that surround DNA and expression of noncoding RNA
Health Potential is Determined by Specific Genes

### Hypertension

<table>
<thead>
<tr>
<th>Gene/Locus</th>
<th>Marker</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCAT1</td>
<td>rs7961152</td>
<td>C/C</td>
</tr>
<tr>
<td>PPARGCA</td>
<td>Rs8192678</td>
<td>A/G</td>
</tr>
</tbody>
</table>

### Genetic Risk for Elevated LDL Cholesterol

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<tr>
<th>Gene/Locus</th>
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<tbody>
<tr>
<td>Intergenic</td>
<td>rs1501908</td>
<td>G/G</td>
</tr>
<tr>
<td>LDLR</td>
<td>rs6511720</td>
<td>G/G</td>
</tr>
<tr>
<td>MAFB</td>
<td>rs6102059</td>
<td>C/T</td>
</tr>
<tr>
<td>NCAN</td>
<td>rs10401969</td>
<td>T/T</td>
</tr>
<tr>
<td>PCSK9</td>
<td>rs11206510</td>
<td>T/T</td>
</tr>
</tbody>
</table>

- Gene/Locus refers to the gene or intergenic region.
- Marker refers to the unique identifier of the tested marker.
- Genotype refers to the combination of nucleotides at a particular marker. The letters on each side of the slash refer to the two copies of the patient’s DNA.

Clinical Evidence Validates Use of Gene as a Marker of Health Potential.
## Selected Genes Influence Nutritional Needs and Health Outcomes

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Gene Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic risk for decreased folate</td>
<td>MTHFR</td>
</tr>
<tr>
<td>Genetic risk for decreased vitamin A</td>
<td>BCMO1</td>
</tr>
<tr>
<td>Genetic risk due to decreased vitamin B2</td>
<td>MTHFR</td>
</tr>
<tr>
<td>Genetic risk for decreased vitamin B6</td>
<td>NBPF3</td>
</tr>
<tr>
<td>Genetic risk for decreased vitamin B12</td>
<td>FUT2</td>
</tr>
<tr>
<td>Genetic risk for decreased vitamin C</td>
<td>SLC23A1</td>
</tr>
<tr>
<td>Genetic risk for decreased vitamin D</td>
<td>GC</td>
</tr>
<tr>
<td>Genetic risk for increased vitamin E</td>
<td>INTERGENIC</td>
</tr>
</tbody>
</table>
## Selected Genes Influence Metabolic Systems, Determine Nutrient Availability & Health Status

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Gene Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produces 5-methyltetrahydrofolate (5-MTHF)</td>
<td>MTHFR</td>
</tr>
<tr>
<td>Recycles homocysteine back into methionine, B12 dependent</td>
<td>MTR</td>
</tr>
<tr>
<td>Recharges MTR via re-methylation. B12 dependent</td>
<td>MTRR</td>
</tr>
<tr>
<td>Catalyzes conversion of betaine and homocysteine to dimethylglycine and methionine.</td>
<td>BHMT</td>
</tr>
<tr>
<td>Catalyzes the conversion of homocysteine to cystathionine, the first step in the transsulfuration pathway, involves the degradation of sulfur-containing amino acids. B6 is a cofactor.</td>
<td>CBS</td>
</tr>
<tr>
<td>Catalyzes phase II detoxification (metabolism) of neurotransmitters dopamine, epinephrine, and norepinephrine, as well as estrogen.</td>
<td>COMT</td>
</tr>
<tr>
<td>Encodes for nitric oxide synthases which catalyze the reaction of oxygen with l-arginine generating citrulline and nitric oxide.</td>
<td>NOS</td>
</tr>
</tbody>
</table>
36 year old woman with chronic yeast infections, hypothyroidism.

Biomarkers

• High homocysteine
• Low B6, Low B12
• High folate
• Candida Positive
COMT

- 50 year old women- Breast cancer history
- Post Hysterectomy, Mastectomy
- Placed on pellets for testosterone, estrogen replacement
- New Dx Lung Cancer
- Biomarkers - COMT gene, High estrone, high homocysteine
By The Numbers:  
4 Easy Steps to Epigenetics

Four Easy steps to understanding and using Epigenetics and Methylation: Know your Health **Potential**, Determine Metabolic **Capacity**, Manage **Balance** in Methylation, and Achieve the **Expression** of your New Health Status

Three Influential Parts of Epigenetics – Gene Expression and Influence, Metabolic Pathway Control and Precision Medicine & Outcome. Fix the Foundation and Manage the Disease

Simple Diagnostic Tools to Assess and Monitor Patients. Relevant Clinical Results Supporting Precision Medicine

Therapeutic Program for Patient Management Supporting Condition Specific Health with Medical Nutrition Therapy
By The Numbers:
4 Steps to Epigenetics

Four Steps to Understanding and Using Epigenetics and Methylation in Clinical Practice
Four Steps to Understanding and Using Epigenetics and Methylation

**Potential**
Knowing your health potential through diagnostics can help identify risk factors to design precision medicine programs.

**Capacity**
Metabolic processes should support optimal whole body and DNA methylation at healthy capacity.

**Balance**
Whole body and DNA methylation must be kept in balance and can be supported by clinical nutrition solutions.

**Expression**
Patient management can optimize epigenetic influences and keep or return patients to health and wellbeing.
By The Numbers:
4 Steps to Epigenetics

Three Influential Parts of Epigenetics
Three Influential Parts of Epigenetics

Gene Markers Relevant to Health Outcomes and Influences
• Genetic Predisposition and Risk Factors
• Genetic Controls and Influence on Metabolic Systems

Metabolic Pathways that Determine Epigenetic Outcomes and Controls
• Availability of Methyl Groups for System Viability and Control
• Functional Metabolic Pathways and Capacity
• Balance the System to Enable Health Management

Health and Condition-Specific Management Systems
• Balance the underlying metabolic system and its influences
• Focus on Patient Management Therapeutic Regimen
• Improve Patient Outcomes and Reduce Risk Factors
By The Numbers: 4 Steps to Epigenetics

Two Simple Diagnostic Tools to Assess and Monitor Patients
Two Diagnostic Tools for Monitoring

Gene Diagnostics
- Genetic Markers of Condition-Specific Health Risks
- Genetic Markers and Influencers of Metabolic Processes

Biomarkers Reflective of Metabolic Controls and Response
- Blood Diagnostics of Methylation Capacity and Balance
- Condition-Specific Health Panels for Metabolic Response
By The Numbers: 4 Steps to Epigenetics

One Therapeutic Program for Total Patient Care
Nutrition and Epigenetics

Most important piece
**Epigenetics**

- Control of gene expression by factors other than the DNA sequence.
- Our Genotype Means Nothing Without Knowing our Phenotype.

**Epigenome**
Comprised of chemical compounds and proteins which attach to DNA and direct actions such as turning genes on and off.

**Nutritional Epigenetics**
Nutrient-induced change in epigenetic patterns that can alter gene expression and hence, long term health outcomes.

Niculescu MD, Nutritional Epigenetics. ILAR J. 2012;53(3-4):270-8
Epigenetic Mechanisms

DNA Methylation
Methyl groups added to the DNA through action of DNA methyltransferase (DNMT) enzymes

Methyl groups are donated for reactions by S-adenosylmethionine (SAM)

Methylation is a key biochemical process and common epigenetic signaling tool cells use to turn genes on or off.

Because methylation occurs a billion times per second in the body, it must be optimized.

Research has linked alterations in methylation to a variety of health consequences including several diseases.
DNA Methylation and Health: What is Optimal?

- Wear and tear of living includes hypo- and hyper-methylation of genes associated with various diseases.
- Non-optimal activation or loss of gene expression may result due to imbalanced methylation.
- Balance in methylation is critical, not “more” or “less.”

Influence of Epigenetic Mechanisms on Cardiovascular Disease – Potential Determined by Methylation

What is the association between DNA methylation and CVD?

DNA methylation patterns associated with disease states from 31 studies including n=12,648 individuals with 4037 CVD events
Influence of Epigenetic Mechanisms on Cardiovascular Disease – Potential Determined by Methylation

34 metabolic genes involved in fetal growth, glucose and lipid metabolism, inflammation, atherosclerosis and oxidative stress

5 of these loci were validated:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Methylation Event</th>
<th>Associated Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2RL3</td>
<td>Hypomethylation</td>
<td>Smoking</td>
</tr>
<tr>
<td>C1QLR</td>
<td>Hypermethylation</td>
<td>Weight Loss</td>
</tr>
<tr>
<td>HSP90B3P</td>
<td>Hypermethylation</td>
<td></td>
</tr>
<tr>
<td>KCNQ1</td>
<td>Hypermethylation</td>
<td>20 Med. Diet plan</td>
</tr>
<tr>
<td>STRADA</td>
<td>Hypermethylation</td>
<td></td>
</tr>
</tbody>
</table>

Muka et al. Manuscript In Press
Epigenetic Interaction of SNPs and Precision Medicine

- Studying only SNPs for precision medicine is not sufficient – metabolomic analysis is critical to managing methylation pathways.

- Identifying specific and relevant genes is important as they have specific roles and sites of activity

- Since the gene SNP regulates metabolic processes and balance of methylation, metabolic process and output must be balanced and measured

Genic predisposition does not necessarily mean the gene is activated!

- Metabolic activation can be measured

Ensuring healthy methylation balance first, allows the practitioner to then successfully manage the health issue.
DNA Methylation: Good or Bad?

- DNA methylation usually silences a gene, acting as an off-switch (location dependent).

- In certain areas of the genome, DNA methylation is important to prevent genome instability associated with the expression of these elements.

- DNA methylation of other areas of the genome, such as tumor suppressor genes, may be associated with negative health outcomes.

The impact of more or less methylation depends on the gene site affected.

Epigenetics in Practice

Putting it All Together
Improved Clinical Management and Precision Medicine Programs Outcomes

• Understand individual health risks and predispositions
• Understand if influential genes are activated
• Understand relevant metabolic systems and their balance
• Manage the epigenetic system of genes and metabolism
• Manage the condition for better health
Focus on Health Outcomes and Status

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Supports the foundations of health and manages disease

Genetic Predisposition and Health Potential
Identifies levels of risk and manages its influence

Epigenetic Expression and Influence
Manages expression of health & its influence on wellbeing

Metabolic Pathways and Stability of Methylation
Optimize cellular capacity and balance

Association to Disease States
Eliminate problems with methylation for clinical management
DNA is not Destiny
Genetic Predisposition and At-Risk Profile

Methylation Pathway Capacity Out of Balance?

Blood Markers

Yes?

Genetic Test Reveals Risk

No?

Elevated?

Rebalance
Normalize
Maintain

Manage Health Condition Based on Genetic Potential

Moderate?

Normalize
Maintain

Normal?

Maintain

Manage Health Condition Based on Genetic Potential
Patient Assessment Guide & Algorithm for Epigenetic Influence & Management

**Three Test Results Critical to Accurate Diagnosis and Care**

**Condition Specific Genetic Predisposition**
- Elevated Biomarkers
- High Homocysteine
- SNP Risk Profile
- Nutrient Deficiencies
- High Use Rx Meds

**High Risk Profile**
- 12 Week Methylation Balance Therapy
- Transition to Maintenance Therapy, Manage Condition

**Genetic Methylation Influence**
- Biomarkers Out of Range
- SNP Risk Profile
- Nutrient Deficiencies
- Lifestyle Management

**Moderate/At Risk**
- Normalize Biomarkers Balance Therapy
- Monitor Blood Biomarkers to within Normal Range
- Manage Health Condition

**Metabolic-Based Biomarker (Metagenics Methylation Axis)**
- Biomarkers in Normal Range
- SNP Normal or At Risk

**Normal**
- Maintenance Therapy
- Manage Health Condition
<table>
<thead>
<tr>
<th>Elevated &amp; Impaired Capacity</th>
<th>Mild to Moderately Impaired Capacity</th>
<th>Normal Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(HCY&gt;11; SAH elevated and SAM:SAH ratio &lt; 4 and SAM low; SnPs at risk)</td>
<td>(HCY 8-11; SAH within normal range; SAM:SAH ratio &lt;4; SAM within normal; SnPs at risk)</td>
<td>(HCY&lt;6; SAH normal; SAM:SAH ration normal; SAH normal; SnPs may be at risk)</td>
</tr>
<tr>
<td>ReBalance SAM:SAH &amp; lower HCY</td>
<td>Reset Methylation Capacity</td>
<td>Maintain Methylation Balance</td>
</tr>
<tr>
<td><strong>Therapeutic Plan</strong></td>
<td></td>
<td><strong>Therapeutic Plan</strong></td>
</tr>
<tr>
<td><strong>Cardio Risk Related Patients:</strong></td>
<td></td>
<td><strong>Specific Health Management:</strong></td>
</tr>
<tr>
<td><strong>Vessel Care 6 - 12 weeks</strong></td>
<td></td>
<td>PhytoMulti or Wellness Essentials with Glutaclear and CoQ10</td>
</tr>
<tr>
<td><strong>Mood Related Complaints:</strong></td>
<td></td>
<td>Medical Foods including Ultra Glucose Control, or UltraMeal Advance Protein or UltraInflammx360</td>
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<tr>
<td><strong>Blisphora 6 - 12 weeks</strong></td>
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Patient management can optimize epigenetic influences and keep or return patients to health and wellbeing.