

The background image is a scenic landscape. In the foreground, there are several purple flowers with five petals, growing on green stems with long, thin leaves. The flowers are in various stages of bloom. In the background, there are rolling hills and mountains under a cloudy sky. The mountains are covered in green vegetation, and some peaks are visible in the distance. The overall tone of the image is natural and serene.

Investigating Ayurveda in the Genomics Era: A Brief Research Review

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Disclosure Statement

The background of the slide is a vibrant photograph of a mountain landscape. In the foreground, several tall, slender purple flowers with green foliage stand prominently. Beyond them, a light-colored, possibly snow-covered or sandy, ridge line runs across the middle ground. The background is filled with a series of rolling mountain ranges under a bright blue sky with scattered white clouds. The overall scene is bright and clear, suggesting a high-altitude environment.

Dr. Sudha Prathikanti has no relevant relationships with commercial interests to disclose.

Learning Objectives

At the end of this session, participants will be able to:

1. Define the concept of Ayurvedic constitution and explain its role, according to Ayurveda, in restoring and maintaining an individual's health.
2. Describe at least one genome-wide study that provides some support for the concept of Ayurvedic constitution.
3. Identify at least two Ayurvedic therapies associated with epigenomic changes.

Genetics and Epigenetics

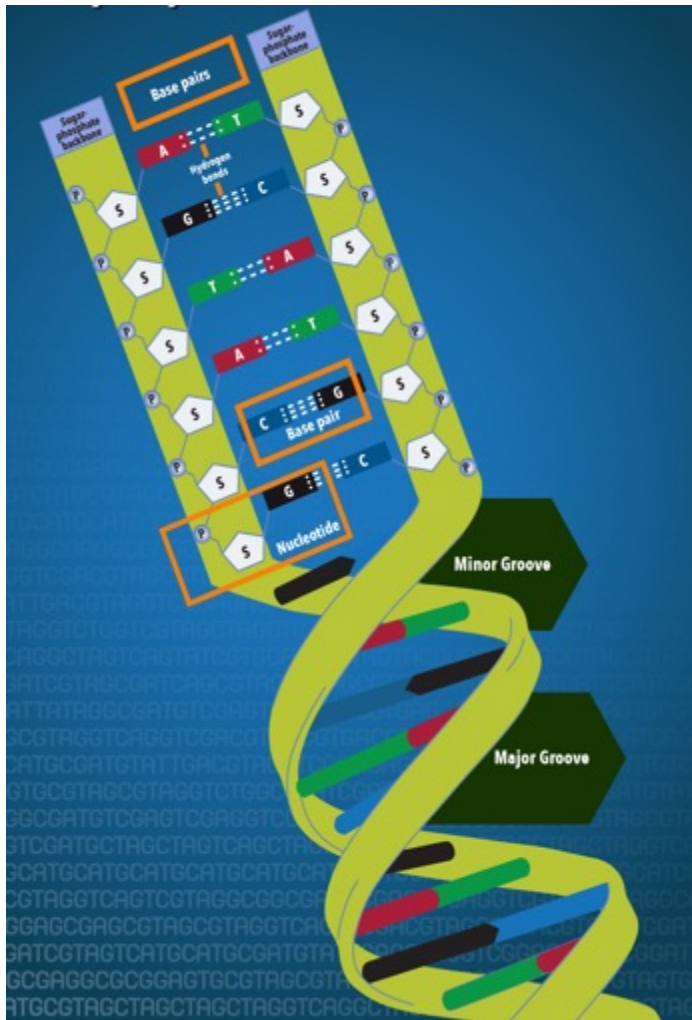


Image: NIH Genetics Home Reference

Human DNA (Deoxyribonucleic acid)

- Double helix of base pairs along sugar-phosphate backbones
- Four nitrogen bases: adenosine, thymine, guanine, cytosine
- Genome (total DNA in a person) contains ~3 billion base pairs
- Coiled tightly into 46 chromosomes in each cell nucleus
- 1-2% of DNA codes for genes to make proteins (23K+ genes)
- Remaining 98-99% of DNA is non-coding for genes:
 - Regulatory elements: promoters, enhancers, silencers
 - Instructions to form tRNA, rRNA, other RNA molecules
 - Structural elements: telomeres, centromeres

Genetics:

The study of genes and their role in inheritance – how specific genes and their traits are passed down from one generation to another

Epigenetics:

The study of biological mechanisms that affect the expression of genes (turn genes on or off) without changing their DNA code

Epigenetic Mechanisms

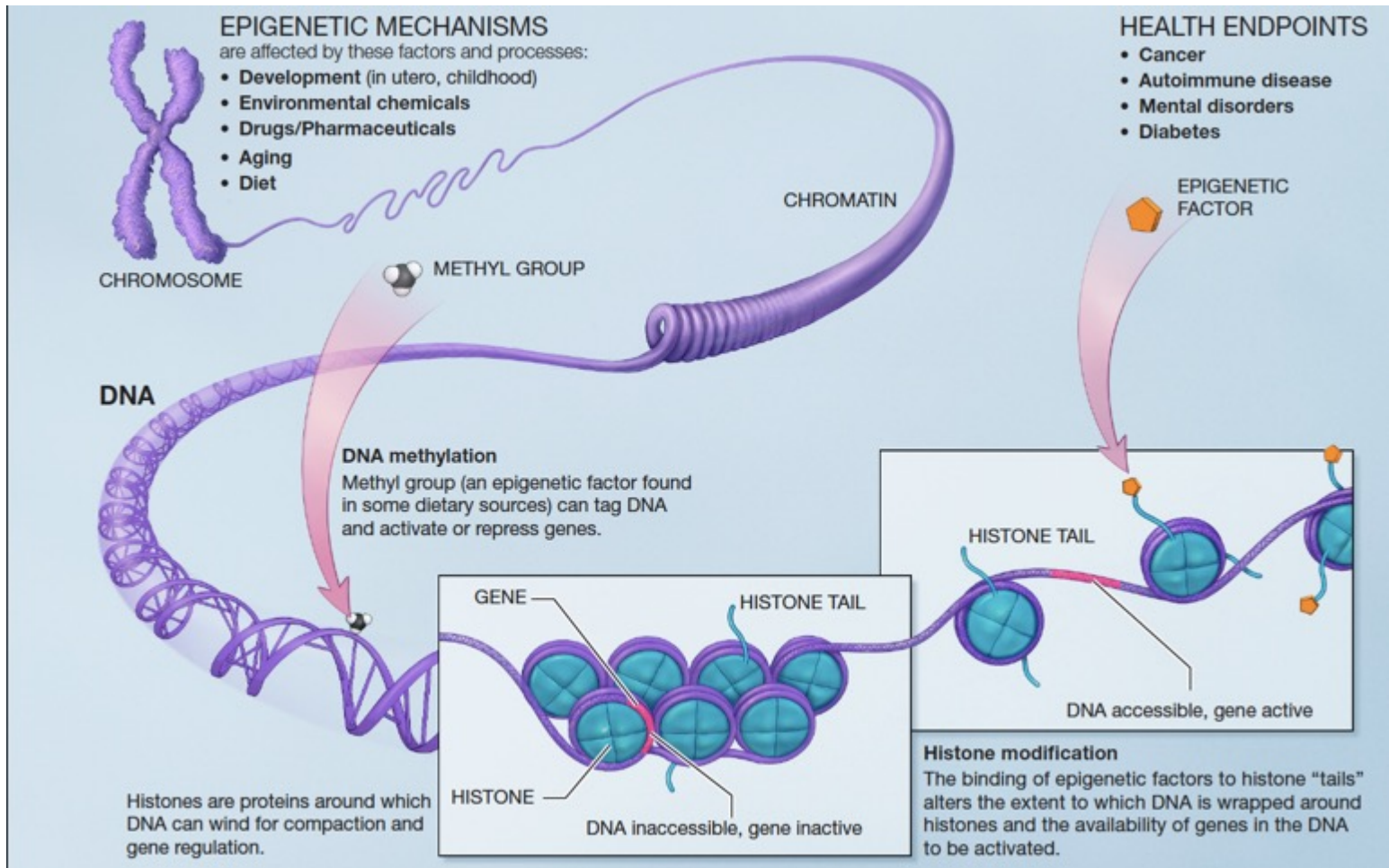
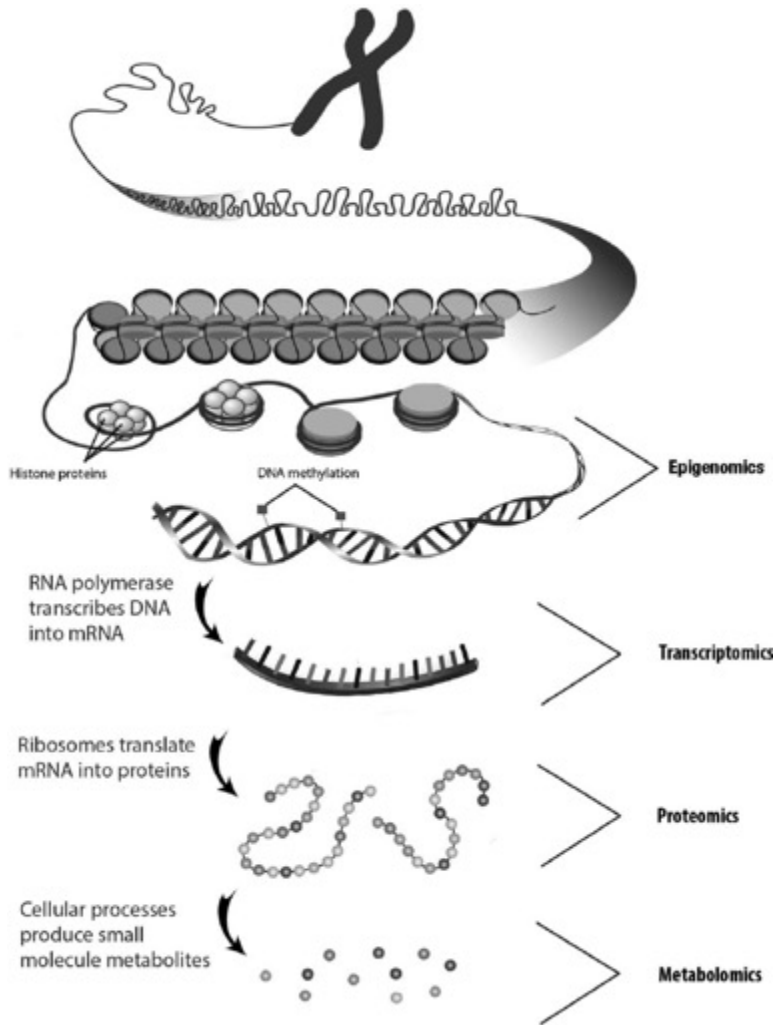


Image: National Institutes of Health via Wikimedia

Genomics



Genomics:

The study of an individual's entire set of genes (genome), including interactions of genes with each other and with the environment.

- Relies on high-performance computing & math techniques (bioinformatics)
- Searches thru 3 billion DNA bases across 23K genes to find variations that affect a person's health, disease or drug response
- Discovers unique molecular profile of each person

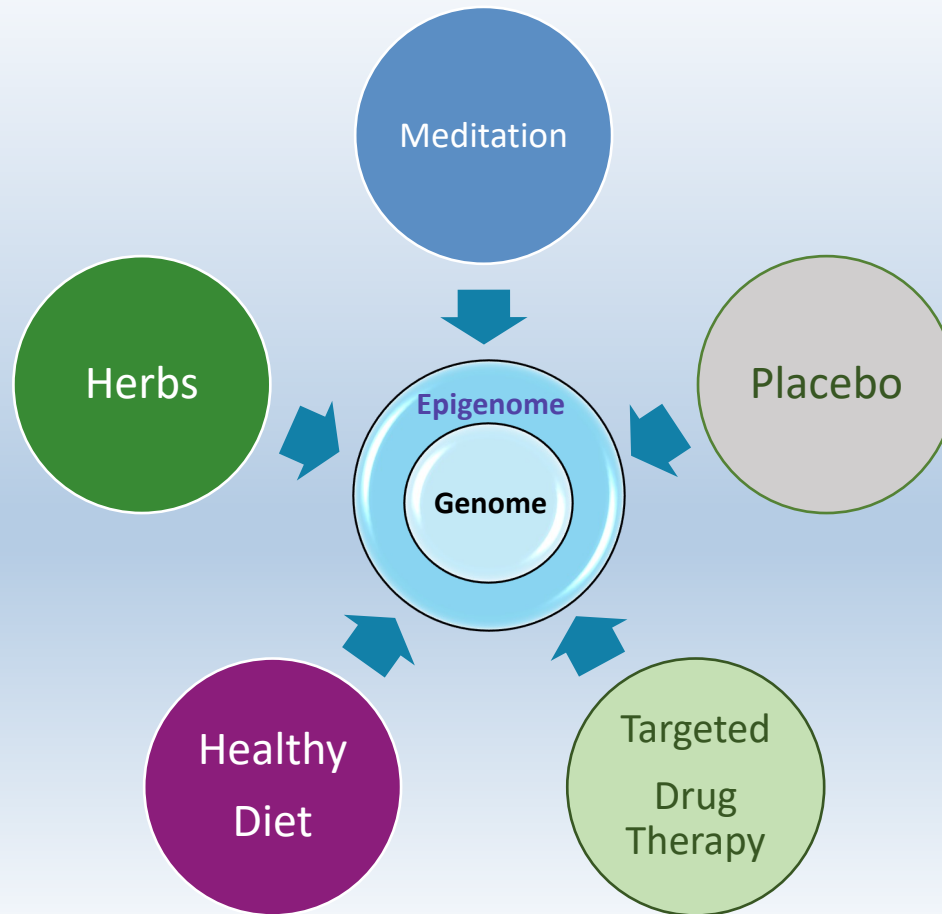
Epigenomics analyses epigenetic changes across the entire DNA strand, such as histone protein modifications or methylations at C-G "islands"

Transcriptomics analyses expression of a gene by sequencing free-floating messenger RNA strands

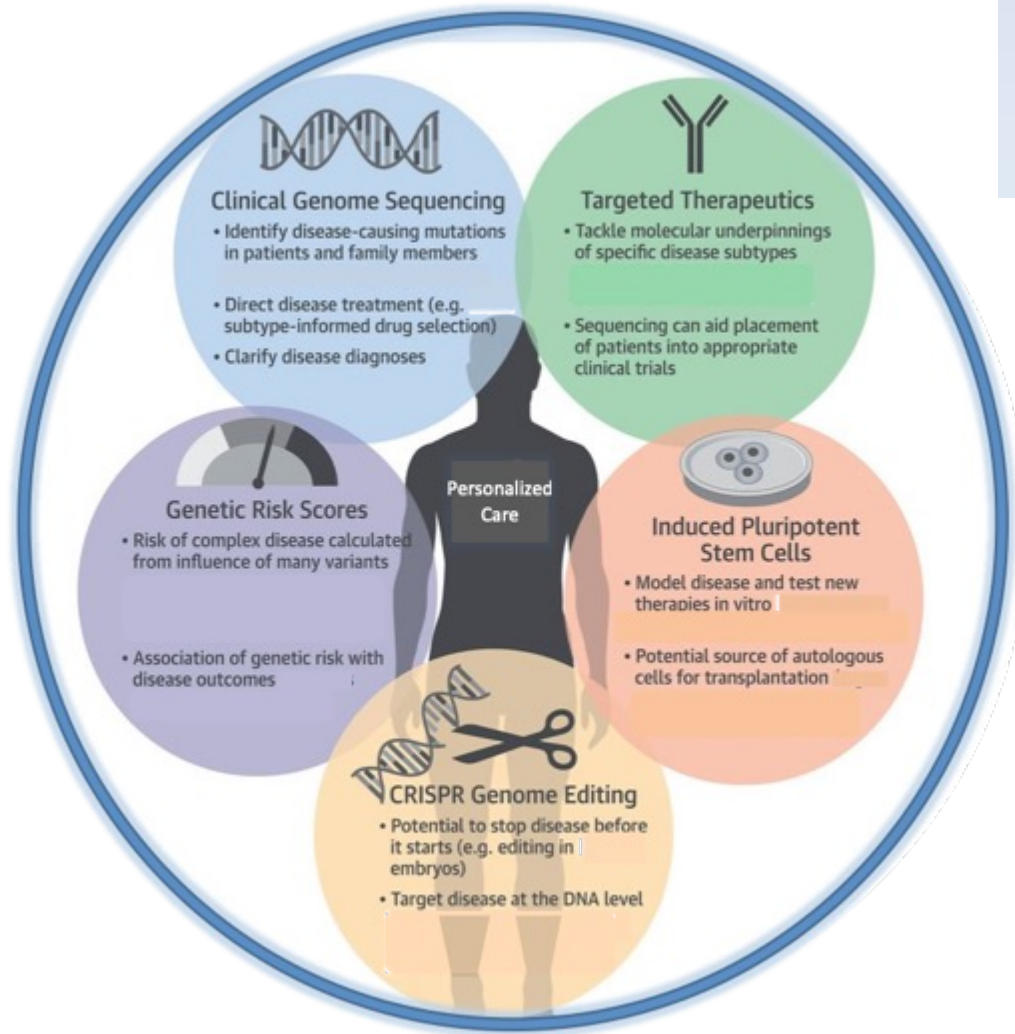
Proteomics analyses expression of a gene by identifying & quantifying the circulating proteins made by that gene

Metabolomics measures all low-molecular-weight molecules that are the end-products of cellular activities and metabolic pathways governed by the genome

Epigenomics: Key Pathway to Health & Healing



Genomic Medicine



Genomic medicine:

An emerging healthcare discipline that uses an individual's genomic data to support the prevention, diagnosis and treatment of medical conditions.

- Genetic risk assessment
- Early detection
- Diagnosis, including subtype
- Prognosis
- Treatments
 - Pharmacogenomics
 - Stem cell therapies
 - Genome editing

AYURVEDA :

5000 years of personalized, holistic healthcare

Conventional Care

“One size fits all”



+



Treatments



Effect



No effect



Adverse effects

Personalized (Ayurvedic) Care



Profile A



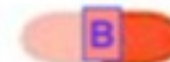
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Profile B



+



Profile C



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Effect



Effect



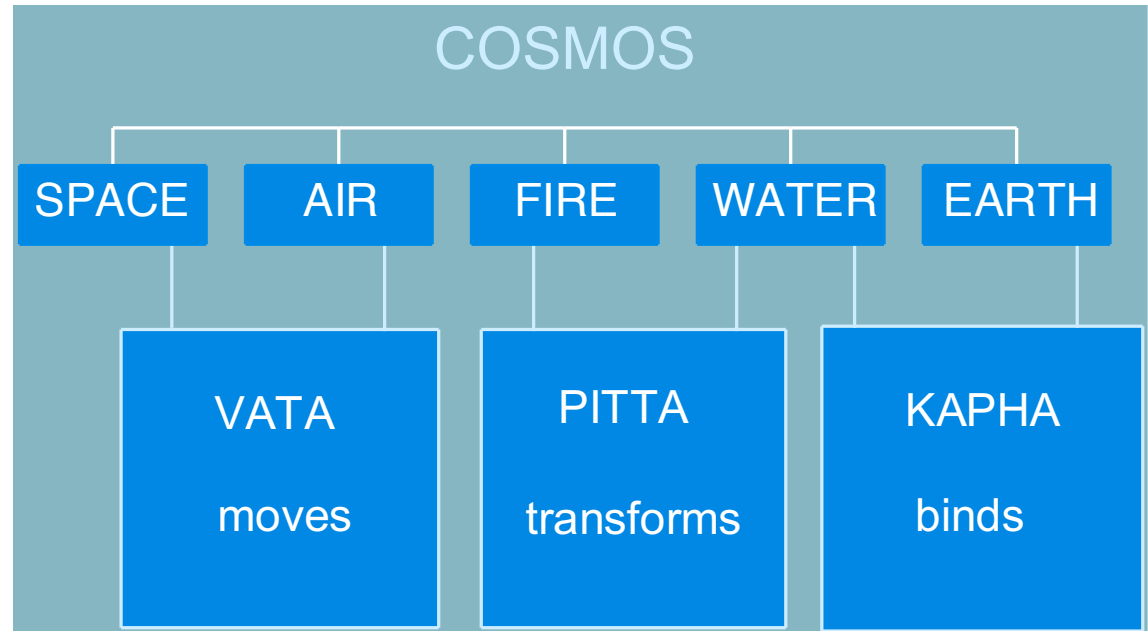
Effect



5 GREAT ELEMENTS

3 GREAT DOSHAS

AYURVEDA: WISDOM OF LIVING

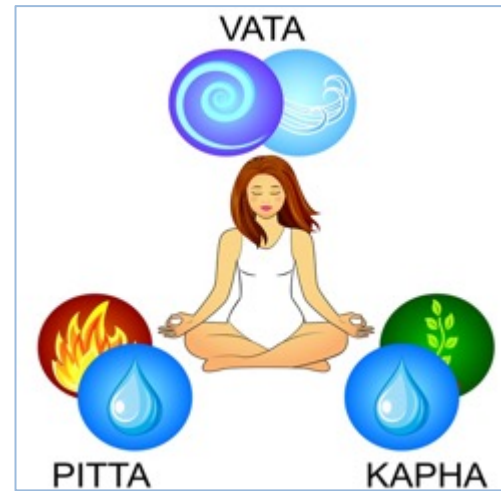


Each dosha is essential to life and is present in every person,
with specific expression at every level of being: body, mind, subtle energy

AYURVEDA: IMPORTANCE OF INDIVIDUAL CONSTITUTION

Each person has unique constitution of 3 doshas

Constitution ascertained via careful history & exam



* Image Source: Dreamstime

- ❖ Pulse
- ❖ Body Build & Weight
- ❖ Tongue, Skin, Hair, Nails
- ❖ Circulation
- ❖ Climate Tolerance

- ❖ Speech / Motor Activity
- ❖ Emotional Tendencies
- ❖ Memory & Cognition
- ❖ Eating / Elimination Patterns
- ❖ Sleeping Patterns

AYURVEDIC CONSTITUTIONAL TYPES



VATA

Lean, bony build
Rapid walk and talk
Erratic appetite & stamina
Sensitive to wind & cold

Quick, flexible mind
Learn fast, forget fast
Creative, enthusiastic
With stress: anxious, unsettled

Prone to lung disease, GI motility problems/gas, joint space disorders, neuropsych disorders, tinnitus, tics

Functions best with:
Regular, long sleep
Frequent meals: warm & rich
Warm, moist climate



PITTA

Muscular, moderate build
Forceful walk & talk
Strong appetite & stamina
Sensitive to heat

Sharp, penetrating mind
Focused learning & memory
Great willpower, leadership
With stress: irritable, jealous

Prone to bleeding disorders, stress ulcers, GI reflux, hypertension, angina, rashes, inflammation

Functions best with:
Moderate sleep
Regular meals: cool & sweet
Cool climate



KAPHA

Large, hefty build
Slow walk and talk
Steady appetite & stamina
Sensitive to fog & cold

Deliberate, calm mind
Learn slowly, good memory
Loyal, caring, forgiving
With stress: depressed, numb

Prone to obesity, diabetes, metabolic syndrome, pulm edema, congestive heart disease

Functions best with:
Less sleep
Fewer meals: light & spicy
Warm, dry climate

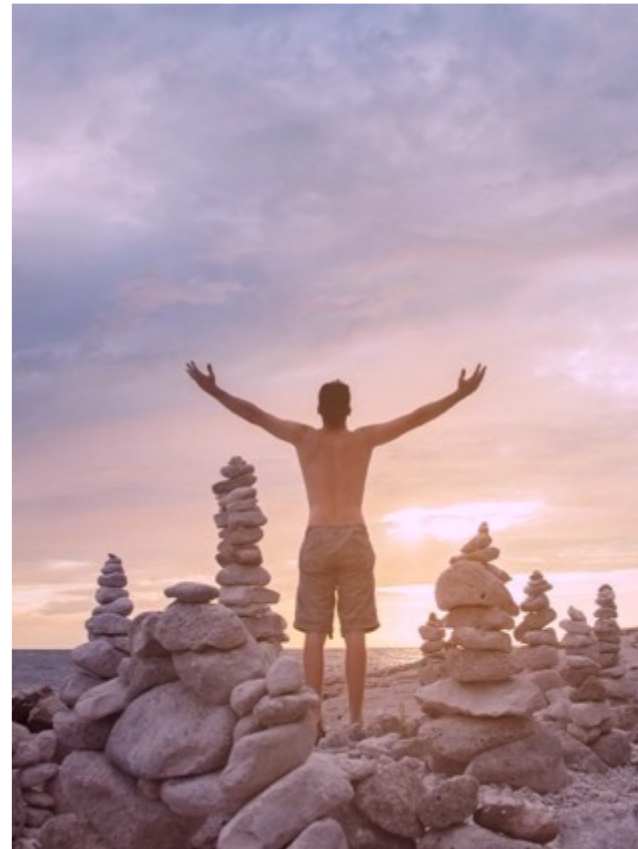
AYURVEDA: HEALTH AS HARMONIOUS LIVING

Health:

living in balance
with basic constitution

Illness:

living out of balance
with basic constitution



AYURVEDA: REMEDIES FOR DOSHA IMBALANCE

Remedies to re-balance dosha may be applied at any dimension, not just dimension where symptoms manifest

Attention to Nature

- ❖ Circadian/Seasonal Rhythms
- ❖ Climate
- ❖ Environment

Sensory Experiences

Social Experiences

Food & Spices

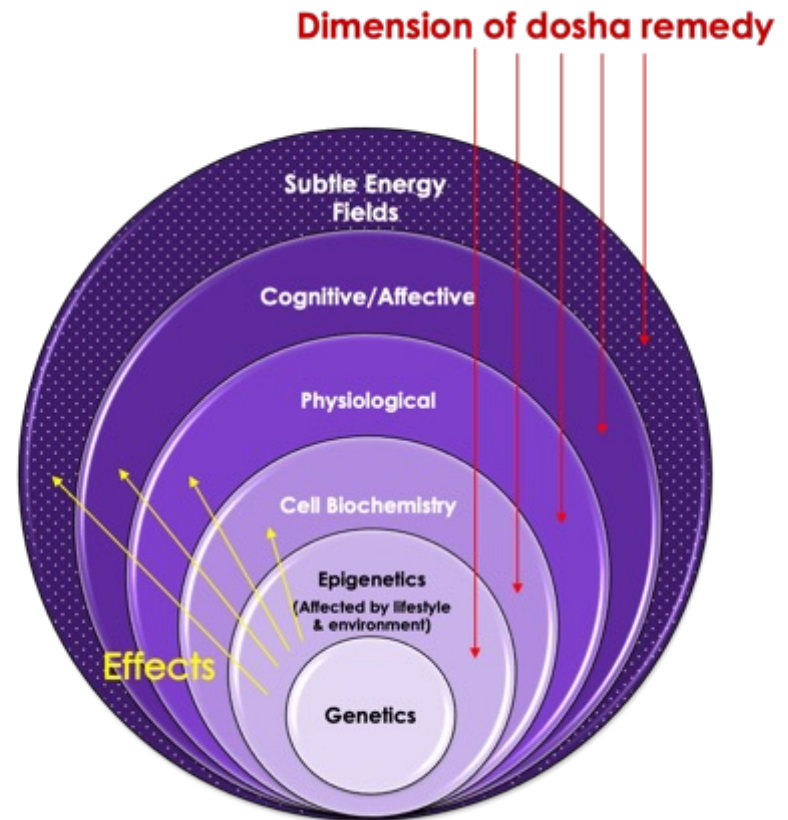
Detoxification Procedures

Herbal Medicine

Yoga Asanas & Exercise

Pranayama

Meditation



Ayurvedic Constitution: Validation of Assessment Tools



First validation of quantitative measure of tridosha (Joshi 2004)

- N=280 participants had constitution established by traditional clinical evaluation
- For each participant, phenotype attributes noted in machine-scannable format in relation to 28 mind-body domains identified by Ayurvedic expert panel as salient to dosha
- Tridosha quantified in each participant via regression modeling of weighted attributes
- Computer-derived constitution had high concordance with clinician-derived constitution
- Statistically validated with > 90% confidence level

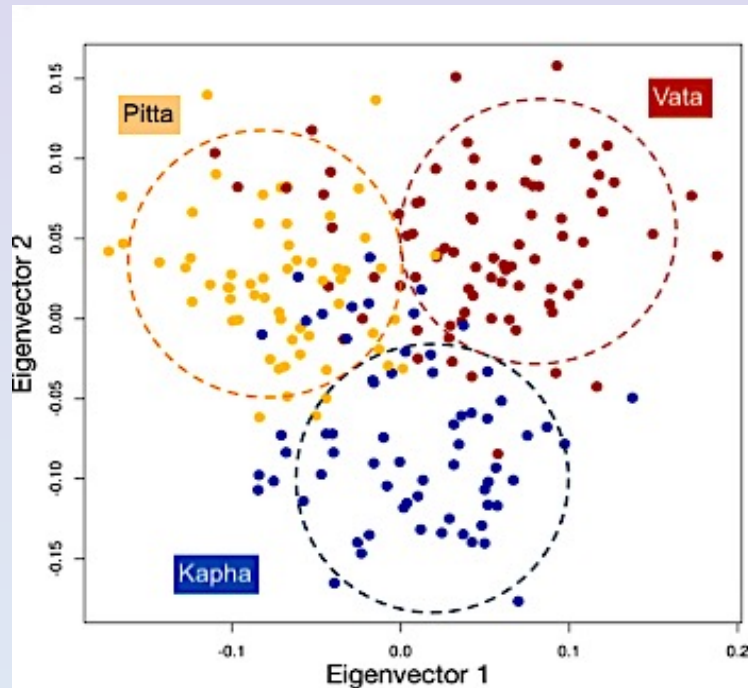
AyuSoft (Govt of India Centre for Development of Advanced Computing & Univ of Pune, 2006)

- Software app for standardized analysis of Ayurvedic constitution
- Translates knowledge from classical Ayurvedic texts to quantify tridosha via 85 features pertaining to anatomy, physiology, and psychology
- Used widely and now validated in many Ayurveda research studies (including Rotti 2014)
- Software can also access vast repository of other information from classical Sanskrit texts, including Ayurvedic diagnostics and treatment

Recapitulation of constitution by computer clustering of phenotype attributes (Tiwari et al, 2017)

- N=147 participants found by clinical eval to represent extreme V, P, K constitutions
- For each participant, phenotype attributes were noted in machine-scannable format in relation to 25 mind-body domains identified by classical Ayurvedic texts as salient to dosha
- Unsupervised random forests clustering of phenotype attributes of all participants yielded 3 clusters that corresponded well to the classical descriptions of V, P, K constitutions
- Silhouette analysis confirmed that the best number of clusters was 3

Ayurvedic Constitution: Genomic Studies



Correlation of SNPs and dosha type (Govindaraj 2015: Nature, Scientific Reports)

- Conducted genome-wide SNP analysis on 262 men belonging to three dosha-types
- Found 52 SNPs that were significantly different between dosha types ($p \leq 0.00001$)
- Principal component analysis (PCA) of these 52 SNPs successfully classified subjects into respective dosha types
- Validation in second sample: PCA analysis using same 52 SNPs classified a new set of 297 men into their respective dosha groups

- Genome-wide epigenetic analysis: dosha-related DNA methylation (Rotti 2015)
- Exome sequencing: dosha-related diff in 28 SNPs of 11 FDA genes (Prasher 2017)
- DNA sequencing of gut microbiome: dosha-related signature taxa (Chauhan 2018)

Ayurvedic Constitution: Genotype Studies

Dosha type may correlate with specific genotype:



HLA gene polymorphism (Patwardhan 2005)

- absence of the HLA DRB1*02 allele in Vata types
- absence of HLA DRB1*13 in Kapha types.

EGLN1 gene and hypoxia adaptation (Aggarwal 2010)

- TT genotype more frequent in Kapha types, correlated with higher expression of EGLN1 and tendency toward pulm edema
- TT genotype significantly less frequent in Pitta, and nearly absent in natives of high altitude Pitta types

CYP2C19 gene and drug metabolism (Godke 2011)

- up-regulated in Pitta types
- down regulated in Kapha types

Ayurvedic Chronobiology

- ❖ Doshas rise and fall in succession over day, year and lifecycle
- ❖ Health is optimized by attuning our activities to these rhythms of nature, keeping in mind one's unique constitution
- ❖ Verma et al 2018:
 - Summary of classical ayurvedic descriptions of diurnal & seasonal dosha fluctuations
 - Summary of research studies correlating variation in physiologic parameters to diurnal & seasonal dosha fluctuations

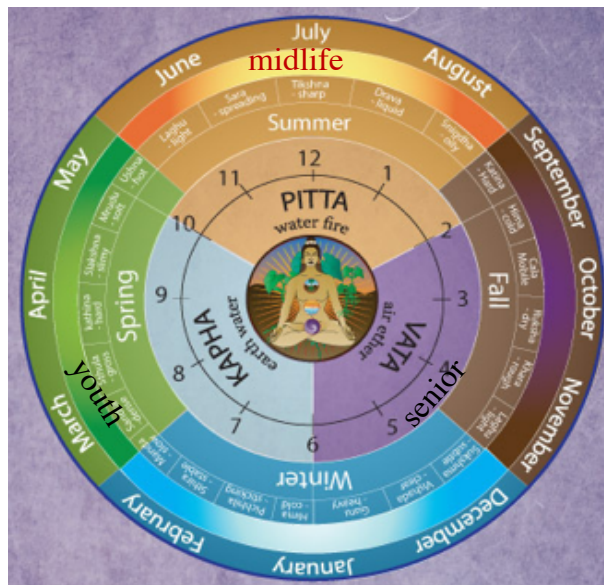
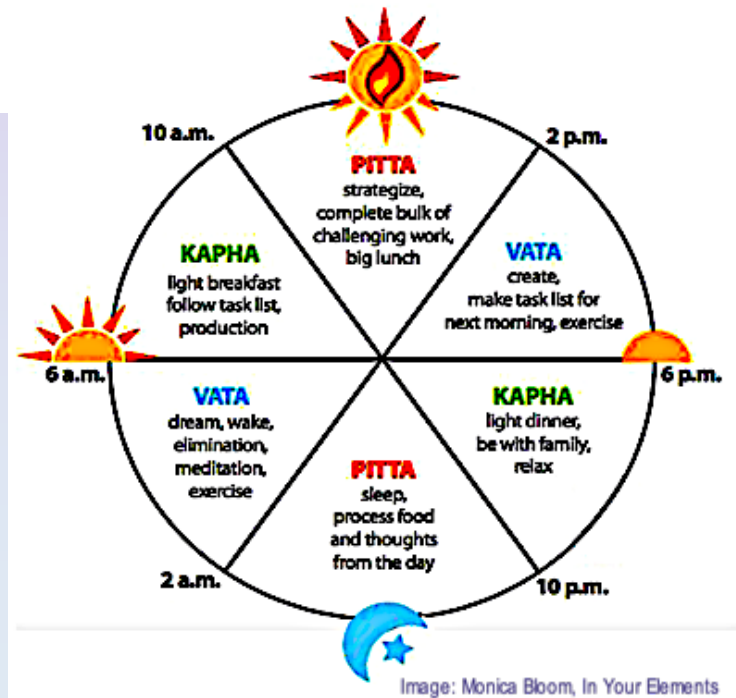


Image adapted from Aaron Staengl Copyright © 2009

- ❖ 2017 Nobel Prize in Medicine: biological “clock genes”
- ❖ Chang et al 2019:
 - Chronotype variant in PER2 gene associated with intrinsic circadian period in humans
- ❖ Jones et al 2019:
 - Genome-wide study of 697,828 people of European ancestry: 351 genetic loci for morning chronotype
- ❖ Parkar et al 2019
 - Disrupted sleep/eating patterns linked to health probs: metabolic syndrome, cancer, CV disease
 - Disrupted sleeping/eating affects gut microbiome → further dysregulates circadian rhythms

Ayurvedic Nutrition



Image: Banyan Botanicals

❖ Nutrigenomics: studies how dietary regimes & bioactive substances in food interact with the genome at the molecular level & affect health

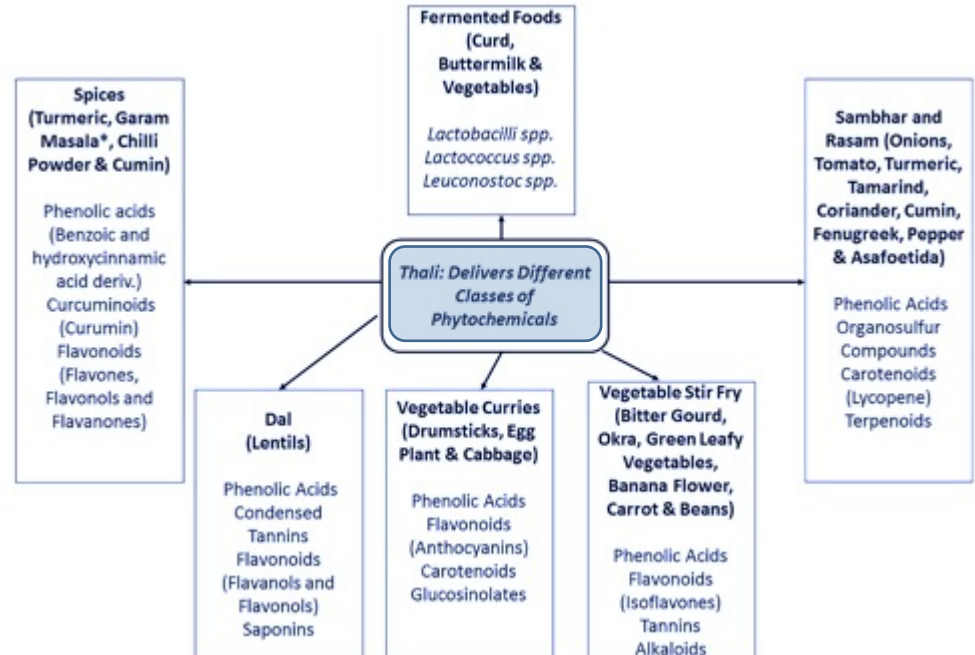
❖ Bhupathiraju et al 2018:

- Examined diet patterns & metabolomic profiles of 145 Asian Indians in USA
- Western/nonveg diet had metabolomic profile linked to cardiometabolic disease
- Authors recommend healthy plant-based diet with vegetables from all subgroups, whole grains, low-fat dairy, variety of legumes & other plant proteins (resembles traditional veg thali)

- ❖ Food is medicine and should fit constitution
- ❖ Six tastes of food, often presented in thali meal:
 - Vata-blanacing: sweet, salty, sour
 - Pitta-balancing: sweet, bitter, astringent
 - Kapha-blancing: pungent, bitter, astringent

❖ Shondelmyer et al 2018:

- Rise of chronic diseases in West correlates with loss of beneficial gut bacteria & microbial diversity
- Indian thali provides pre-biotics, probiotics & phytochemicals to restore diversity in gut flora
- Preclinical studies → potential of thali to prevent or reverse colon cancer, type 2 diabetes, other chronic metabolic disease linked to inflammation



Ayurvedic Detoxification



Stomach	(via emesis)
Upper GI	(via purgatives)
Lower GI	(via enema)
Nose/Sinuses	(via nasal irrigation)
Blood	(via herbs)

Health benefits of panchakarma may include:

- ❖ Balancing of doshas
- ❖ Boosting immunity
- ❖ Elimination of toxins
- ❖ Slowing ageing
- ❖ Restoring metabolic fire

Fagan and Herron, 2002

Pair of studies to evaluate 2-wk panchakarma as method to reduce toxic serum agrochemicals:

- Longitudinal 6 month: n=15; pre/post design
- Cross-sectional: n=48 panchakarma; n=40 controls

Gas chromatographic analysis in both studies:
significant ↓ of toxins/metabolites with panchakarma

Peterson et al 2016:

- Aimed to identify possible alterations in metabolomic profiles after panchakarma
- N=119; 54 in control group; 65 in 6-day panchakarma intervention including herbs, veg diet, meditation, yoga & massage.
- Metabolomics eval: Panchakarma linked to statistically signif changes in plasma levels of phosphatidylcholines, sphingomyelins
- Forthcoming studies to integrate panchakarma metabolomics with genomic, microbiome and physiological parameters

Ayurvedic Herbs

Bacopa Monniera



Brahmi

Centella asiatica



Mandukaparni

Anxiolytic & Nootropic

- Centella*
- Withania*
- Convolvulus
- Bacopa *

Antidepressant

- Withania*
- Convolvulus

(* RCTs)



Ashwagandha



Shankapushpi

Withania somnifera

Convolvulus pluricaulis

❖ Shukla et al 2016

- Examined 4 herbs in 3 dosha-balancing groups to assess for any similarity in cDNA transcripts
- cDNA AFLP analyses: in each dosha group, fraction of transcripts was monomorphic in active tissues
- EST subtractive analyses: yielded 150 unigenes in active tissues across the 12 plants

❖ Peterson et al 2019

- Fecal cultures from 12 healthy vegetarian donors
- Cultures supplemented with Kapikacchu, Gotu Kola, Brahmi, Shankhapushpi, Boswellia, Jatamansi, Bhringaraj, Guduchi, Ashwagandha or Shatavari to see if herbs modulate gut microbiota
- 16S rRNA sequencing showed one-third of the 243 species was altered by all herbs. Additional species were impacted in an herb-specific manner.
- Bacterial metabolites produced by herb-selected communities may alter gut/systemic immunity

Yoga Practices

- ❖ Yoga & Ayurveda: sister sciences
- ❖ Yoga includes asanas, pranayama, meditation
- ❖ Ayurveda tailors yoga practice to constitution



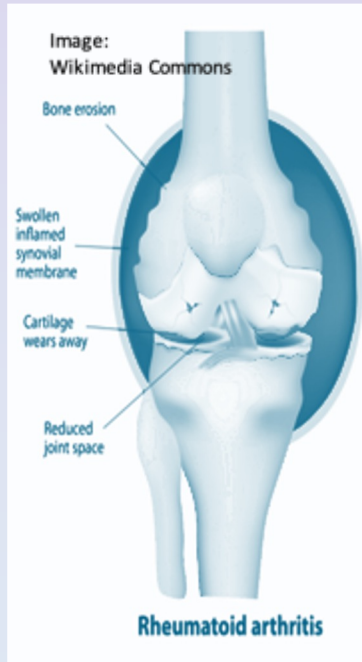
❖ Buric et al 2017

- Review of 18 studies of yoga & other MBIs, highlighting gene expression changes that may underlie health benefits of MBIs
- Practice of MBIs linked to downregulation of nuclear factor kappa B (NF- κ B) pathway
- Downregulation of NF- κ B pathway signals reduced stress and inflammatory response
- Acute inflammation may be adaptive in fighting injury or infection via activation of immune system, but chronic inflammation is maladaptive and poses health risks

❖ Bhasin et al 2018

- Examined transcriptomes in n=24 w/ Stage I essential hypertension who finished 8-wk training in Relaxation Response (RR)
- Transcriptome analysis identified 1771 genes regulated by RR
- Enrichment of anti-inflammatory M2 subtype of macrophages
- interactive network analysis: NF- κ B, vascular endothelial GF & insulin critical molecules

Potential of Ayur-genomics Approach in Complex Trait Research: Leads from a Pilot Study on Rheumatoid Arthritis



Juyal et al , PLOS ONE Sept 2012

Hypothesis:

- Dosha-based subgrouping of participants in genetic study of RA may identify individuals prone to specific disease sub-types with different etiologic and treatment pathways

Methods:

- N=681: 325 RA cases grouped by dosha + 356 controls grouped by dosha
- Tested for 15 SNPs from 7 inflammatory pathway genes and 6 SNPs from 4 oxidative stress pathway genes
- Association between dosha type and clinical variables including 21 SNPs was tested via regression analysis
- Severity of disease assessed in RA cases

Results:

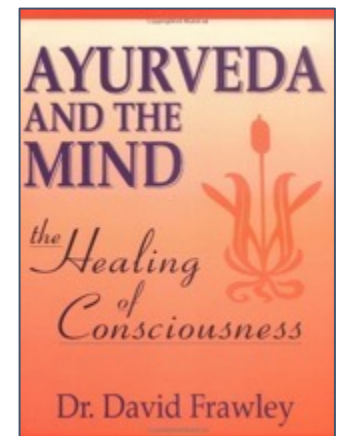
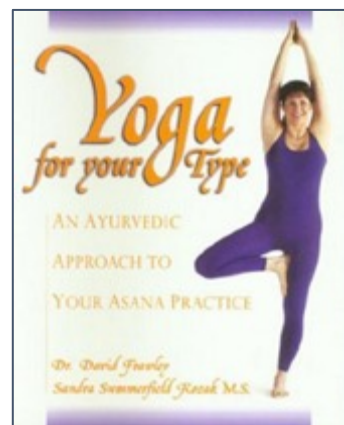
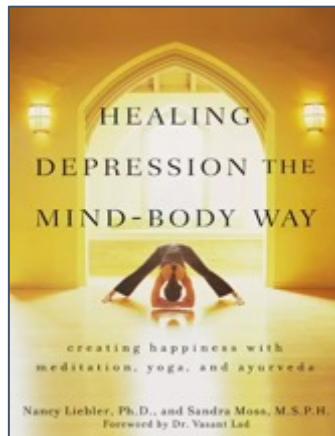
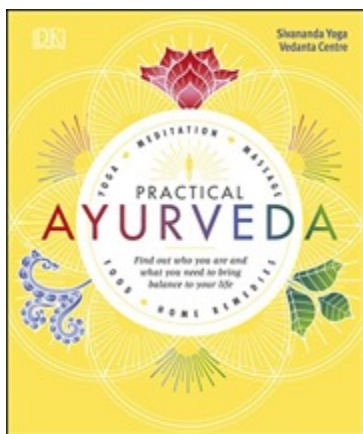
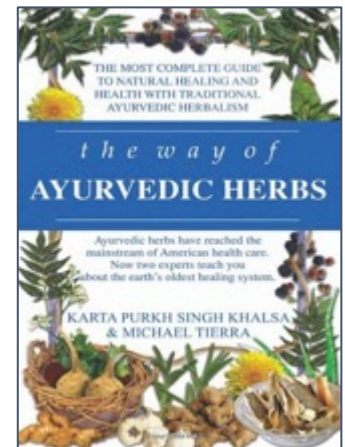
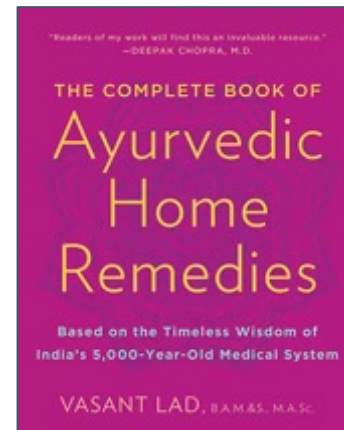
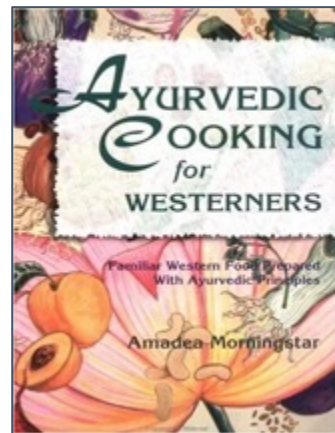
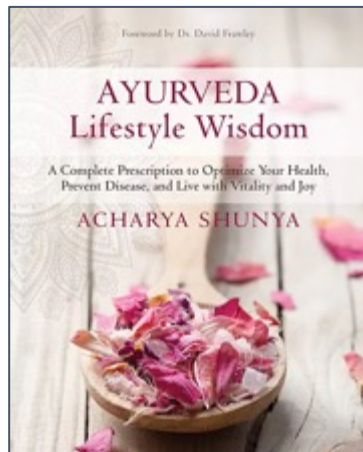
- Vata : associated with inflammatory pathway genes, CD40, ↓BMI, ↑ disease severity
- Pitta : associated with oxidative stress pathway genes
- Kapha: associated with oxidative stress pathway genes, ↑BMI

Ayurvedic Phenotypes : Potential Contributions to Personalized BioMedicine

- ❖ Facilitate discovery of biomarkers and potential sub-types in complex diseases
- ❖ Improve hypothesis generation in genome-wide studies by stratifying non-clinical populations by dosha to help locate genes and epigenomic tags of interest
- ❖ In clinical trials, underperforming therapy may be salvaged by identifying dosha sub-groups who show benefit despite lack of discernible benefit in total sample
- ❖ Offer testable preventive health strategies for those predicted by Ayurveda to be at higher risk for certain health problems
- ❖ If robust genetic/genomic correlates to dosha are identified, may offer cost-effective ways to screen for and treat some health conditions, especially in remote or resource-constrained regions



Resources: Ayurveda Practices





Every individual is different from another.

Infinite variation is seen in the universe,
And so too in human beings.

~ Charaka Samhita
200 BCE