Cambridge Prisms: Precision Medicine

www.cambridge.org/pcm

Ayurgenomics-based frameworks in precision and integrative medicine: Translational opportunities

Mitali Mukerji

Department of Bioscience and Bioengineering, Indian Institute of Technology Jodhpur, Karwar, India and School of Artificial Intelligence and Data Science (AIDE), Indian Institute of Technology Jodhpur, Karwar, India

Review

Cite this article: Mukerji M (2023). Ayurgenomics-based frameworks in precision and integrative medicine: Translational opportunities. *Cambridge Prisms: Precision Medicine*, **1**, e29, 1–14
https://doi.org/10.1017/pcm.2023.15

Received: 19 October 2022
Revised: 22 May 2023
Accepted: 11 June 2023

Keywords:
drug repurposing; genomics; precision medicine; therapeutic innovations; preventive medicine; Prakriti

Corresponding author:
Mitali Mukerji;
Email: mitali@iitj.ac.in

Abstract

In today's globalized and flat world, a patient can access and seek multiple health and disease management options. A digitally enabled participatory framework that allows an evidence-based informed choice is likely to assume an immense importance in the future. In India, traditional knowledge systems, like Ayurveda, coexist with modern medicine. However, due to limited crosstalk between the clinicians of both disciplines, a patient attempts integrative medicine by seeking both options independently with limited understanding and evidence. There is a need for an integrative medicine platform with a formalized approach, which allows practitioners from the two diverse systems to crosstalk, coexist, and coevolve for an informed cross-referral that benefits the patients. To be successful, this needs frameworks that enable the bridging of disciplines through a common interface with shared ontologies. Ayurgenomics is an emerging discipline that explores the principles and practices of Ayurveda combined with genomics approaches for mainstream integration. The present review highlights how in conjunction with different disciplines and technologies this has provided frameworks for (1) the discovery of molecular correlates to build ontological links between the two systems, (2) the discovery of biomarkers and targets for early actionable interventions, (3) understanding molecular mechanisms of drug action from its usage perspective in Ayurveda with applications in repurposing, (4) understanding the network and P4 medicine perspective of Ayurveda through a common organizing principle, (5) non-invasive stratification of healthy and diseased individuals using a compendium of system-level phenotypes, and (6) developing evidence-based solutions for practice in integrative medicine settings. The concordance between the two contrasting streams has been built through extensive explorations and iterations of the concepts of Ayurveda and genomic observations using state-of-the-art technologies, computational approaches, and model system studies. These highlight the enormous potential of a trans-disciplinary approach in evolving solutions for personalized interventions in integrative medicine settings.

Impact statement

Globally, there has been a significant shift in healthcare from a reactive to a proactive approach with an emphasis on P4 (Preventive, Predictive, Personalized, and Participatory) and precision medicine. Ayurveda, an ancient system of medicine, has been practicing this approach for thousands of years, but its integration with modern medicine in clinical settings is still limited. Currently, individuals who want to avail of both systems do so independently without an evidence-based informed choice. The two medical streams have different approaches to diagnosis, treatment, and therapy. Modern medicine focuses on treating diseases in an organ-specific manner, while Ayurveda takes a holistic perspective, treating the individual in a personalized manner based on their inherent constitution type "Prakriti." Ayurvedic medicines consist of complex herbal formulations, different from modern medicine drugs that often prioritize active principles. Both systems have their merits, but they currently do not have much cross-communication or collaboration. A dialogue between Ayurveda and modern medicine can offer patients more options for managing their health. The emerging field of Ayurgenomics shows promise in bridging the two contrasting disciplines of medicine. Research in this area over the last two decades has provided a unifying ontological framework to explore the molecular basis of principles and practices. These have provided (a) a molecular basis of inter-individual differences between *Prakriti* that govern their differential health and disease trajectories, (b) methods for phenotype-based non-invasive methods of stratification of healthy individuals, (c) biomarkers and targets for early actionable interventions, and (d) platforms for evidence-based usage of Ayurvedic medicines. By combining the strengths of Ayurveda and modern medicine through Ayurgenomics, there is potential to enhance patient care and promote a more precise, integrative, and effective healthcare system that embraces preventive, predictive, personalized, and participatory aspects.

Introduction

Enormous inter-individual variability in susceptibility to common and complex diseases, as well as response to geo-climatic conditions, therapy, diet, and lifestyle exists in worldwide populations. This has been acknowledged even more as we battled the COVID-19 pandemic, where the same strain evoked a highly variable infectivity and response, hypoxic and inflammatory consequences, and even morbidity. This difference was seen even amongst closely related family members. Also, as the virus and the disease evolved within an individual, variable complication of "long COVID" beyond a year of infection were reported. During the COVID-19 pandemic, we also witnessed an accelerated pace of drug discovery, primarily through drug repurposing. Since the timelines for evolving therapeutic solutions were impossible, there were many trials and errors, some with grave consequences. In many populations, alternative options from traditional knowledge-based systems were also sourced. In this backdrop, all the diverse arms of P4 (Predictive, Preventive, Personalized, and Participatory) medicine that aims to evolve solutions for the management of health and disease in a stratified manner in population and precisely in individuals assumed an immense importance (Hood and Friend, 2011; Hood and Flores, 2012; Tian et al., 2012). P4 medicine resonates with the principles of Ayurveda that dates back to thousands of years and are still practiced widely (Prasher et al., 2016; Lemonnier et al., 2017). Ayurvedic Market size was valued at USD 6.50 Billion in 2020 and is projected to reach USD 21.12 Billion by 2028, growing at a CAGR of 15.63% from 2021 to 2028 according to a recent verified market report (https://www.verifiedmarketresearch.com/product/ayurvedic-market/).

In Ayurveda, the concepts of individuality that govern the baselines of health, response to environment, and disease trajectories and form the basis for personalized and precision interventions is extensively documented (Prasher et al., 2016). Much to the surprise of many, an Ayurveda clinician of today refers to the same ancient documentation for evolving therapies for diseases that seemingly are of recent origin (Sharma, 1981, 1999). These could be for any complex syndrome that is precipitated by lifestyle factors of today, for example, obesity, asthma, and diabetes, or the newly emergent diseases such as COVID-19. It is a matter of curiosity as to how they deconvolute modern diseases and descriptions, make ontological links with ancient texts, and also repurpose medications for a present-day ailment.

The medicines in Ayurveda are often mixed and complex formulations derived from different herbs; many a times the same herb is used in the treatment of diverse diseases. This is in stark contrast to contemporary practices, where despite an appreciation of shared aetiologies, individuality, as well as polypill needs, a system's perspective is rarely taken into account. A patient with multiple ailments is treated by different specialists and rarely a holistic as well as integrative approach is followed. For an integrative medicine to be delivered in practice there needs to be a shared vocabulary with unifying ontologies that enables interpretation by experts of either disciplines, sharing of the information and also evidence-based health management options from both within and between the streams. Ayurgenomics provides a genomics-based interface to explore the ontological links between the two streams. This field is gradually gaining recognition (Patwardhan and Bodeker, 2008; Patwardhan, 2014; Gupta, 2015; Mukerji and Prasher, 2015; Prasher et al., 2016; Sreedevi et al., 2016; Lemonnier et al., 2017; R.T and Kalaichevan, 2020; Wallace, 2020; Venkanna Rao, 2022).

Human genetic individuality, health baselines, and disease trajectory: Modern medicine versus Ayurveda

Genomic advancements are blurring the boundaries between the specialties of modern medicine and emphasis has now shifted to a system-based network medicine (Loscalzo et al., 2007; Loscalzo and Barabasi, 2011; Chen and Snyder, 2012; Noell et al., 2018). This has primarily been propelled by the large-scale genome and phenome-wide association studies (GWAS and PHEWAS) that have revealed extensive pleiotropy, as well as overlap of genes and networks between disparate diseases. Shared intermediate patho-phenotypes are observed between diseases and different endophenotypes within the same disease sometimes govern differential outcomes (Loscalzo et al., 2007). The endophenotypes include inflammation, fibrosis, wound healing, immune response, cell proliferation, and apopotosis/necrosis that govern outcomes, such as stroke, hemolytic crisis, pain, and so on. The specificity for a disease could thus be a cumulative consequence of innate predisposition, modifier genes, and local environment. For example, in sickle cell anemia, with the same primary mutations a patient can have pain, hemolytic crisis, or thrombosis due to variability in modifier genes and environment such as dehydration, hypoxia, and infection and presently it is difficult to predict trajectories from primary mutations.

Evidence of extensive inter-individual variability is also apparent from observations of the numbers needed to treat (NNT) and numbers needed to harm (NNH) from a large number of randomized control trials (https://www.thennt.com/). This has clearly highlighted the need for stratification of population for most effective outcomes (Cook and Sackett, 1995). A large-scale study on millions of patients on three common diseases, diabetes, hypertension, and depression, have reported extensive heterogeneity in treatment practices of drugs with a trial-and-error approach (Hripcsak et al., 2016). These are changing the clinical trial design paradigm from conventional randomized controlled trials (RCTs) to n-of-1 trials wherein interventions are planned through a double-blinded randomized crossover trial conducted in a single patient (Lillie et al., 2011).

A few aspects are now being appreciated in recent times (1) There is an enormous inter-individual variability that governs variable outcomes in health, disease as well as during management and we need to evolve methods for risk stratification (Khera et al., 2018; Gibson, 2019a, 2019b; Nagpal et al., 2022). (2) Health cannot be defined by an absence of disease state and we need to evolve measures for defining health and individuality (Olson, 2012; Topol, 2019). (3) Yield of biomarker discovery and association studies could increase if there were methods to reduce phenotypic heterogeneity in reference controls (Olson, 2012; Prasher et al., 2016; Noell et al., 2018; Juyal et al., 2022).

Ayurveda, in contrast, has a clear definition of health baselines that determines individuality, is scale-free (like waist to hip ratio), and govern inter-individual differences in response, susceptibility as well as disease and therapeutic outcomes (extensively reviewed in Prasher et al., 2016). Individuals in any population can be stratified to seven broad constitution groups "*Prakriti*" that are fixed very early in life, remain invariant throughout lifetime (Sharma, 1981, 1999). These differences arise from a unifying organizing principle that determines an individual's thresholds in health and perturbations during disease, predict risks for different diseases and allows optimization of therapy. Drugs or therapy are mapped to specific imbalances to restore homeostasis. All this is contextualized in the geo-spatio-temporal context keeping ethnicity and heritability into

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

Box 1. Explanation of some terminologies.

Tridoshas as organizing principle: These are the three "*tri*" physiological entities "*doshas*" that govern homeostasis in the system. The three entities are called *Vata (V)*, *Pitta (P)*, and *Kapha (K)* that govern the kinetic, metabolic, and potential axes of the systems respectively. Functions attributed to *Vata* – are transport, signaling, communication, networking, and so on; *Pitta* -metabolism, digestion, thermoregulation, immunity, inflammation, and so on; and *Kapha* – structure, strength, stability, lubrication, and so on to the system.

Prakriti: An individual has all three *doshas* but in varying proportions. This is determined at the time of fertilization. The relative proportions of *doshas* define seven broad homeostatic states "*Prakriti*" of the system; predominant – V, P, K, and mixed VP, PK, VK, and VPK. Homeostatic/baselines proportions of doshas are dynamic and fluctuate with respect to temporal spatial and environmental cues but within threshold ranges. For example, in humans, there are specific hours of the day in morning and evening where the specific doshas peak (6-10-K; 10-2-P, and 2-6-V). Dry weather/locations elevate V and hot weather P.

Prakriti assessment: System-level attributes, namely, anatomical, physiological, response, and behavioral are assessed to assign Prakriti in healthy individuals. Prakriti is assigned to an individual keeping in context inheritance (*shukra, shonita*) and prenatal exposures (*matur ahar, vihar*), ethnicity (*Jatiprasakta*), heritability (*Kulprasakta*), geography (*Desh-anupatini*), age (*Vaya-anupatini*), and seasons (*Kala-anuapatini*). *Prakriti* of an individual remains invariant throughout lifetime as this is assessed keeping in context the proportions of doshas and their dynamics due to the above-influencing factors and response attributes of the doshas.

Vikriti: Imbalance of proportions of doshas from their homeostatic state is termed as *Vikriti*. Individuals could have imbalance of dosha in any of the three axes but they are differentially susceptible due to their varying thresholds. Thus the homeostatic thresholds for V in *Vata* individual might be an imbalance for *Pitta* individuals and vice versa. Diseases are diagnosed on the basis of manifestation of aberrant doshas at the system level. The goal of Ayurveda is to restore baseline doshas keeping in a Prakriti-specific manner.

Trisutra: The drugs, diet, and lifestyle regimes are classified on the basis of their actions on specific doshas. The understanding of the linkage between the three aspects "*trisutra*" of cause (*hetu*), features (*linga*), and therapy (*aushadha*) through the common organizing principle of *tridosha* forms the basis of its translation from principle to practice in an individualized perspective.

perspective. The understanding of the linkage between cause, features, and therapy through the common organizing principle forms the basis of its translation from principle to practice in an individualized perspective. This resonates with the current approach of precision and networked medicine (Prasher et al., 2016) (see Box 1).

Ayurgenomics: A framework for probing ontological links between modern medicine and Ayurveda

Ayurgenomics is an emerging discipline that seeks to bridge and build an operational framework for integrating the principles of Ayurveda with modern medicine for translational applications (Mukerji and Prasher, 2011; Sethi et al., 2011; Sreedevi et al., 2016; Prasher et al., 2017; Singh et al., 2019; Wallace, 2020; Venkanna Rao, 2022). This uses the tools of genomic and related omics to explore and elucidate the molecular correlates of "*tridosha*," the common organizing principle in Ayurveda.

Amongst the seven broad *Prakriti types* the extreme/predominant *Vata*, *Pitta*, *Kapha* are most readily distinguishable (Hankey, 2005; Prasher et al., 2016). These display contrasting phenotyping attributes comprise 10% of the population and have predominance of either of *doshas*. *Prakriti* of individuals is assessed using a compendium of composite phenotypes that encompass anatomical, physiological, response, and activity-associated attributes. Nearly two decades of exploratory research carried out by different groups have provided molecular correlates of *Prakriti* from different functional hierarchies – phenomic, genetic, genomic, epigenomic, transcriptomic, metagenomic as well as at biochemical, immunological, and cellular levels, and most recently, at the physiological level (Bhushan et al., 2005; Prasher et al., 2008; Aggarwal et al., 2010, 2015; Joshi et al., 2011; Rotti et al., 2014, 2015; Satyamoorthy et al., 2014; Govindaraj et al., 2015; Tiwari et al., 2017; Chauhan et al., 2018; Chaudhari et al., 2019; Abbas et al., 2020, 2022; Mobeen et al., 2020; Chakraborty et al., 2021; Shalini et al., 2021; Rani et al., 2022). These studies have been primarily conducted on healthy individuals of extreme and contrasting constitution types that are most easily discernible at the level of composite phenotypes, and who also have contrasting responses and vulnerability (Prasher et al., 2017). There have been novel discoveries, iterative developments and insights as well as opportunities for translation into integrative medicine settings (Ahmad et al., 2012; Juyal et al., 2012, 2022; Gheware et al., 2021a, 2021b; Haider et al., 2021, 2022; Table 1).

Ayurgenomics-based studies have provided the following insights for application (1) a compendium of composite system-level non-invasive phenotypes that could be assessed in healthy individuals to predict inherent risk for different diseases, exposures, and also for monitoring health trajectories, (2) molecular correlates of "dosha" mapping to intermediate patho-phenotypes that could enable setting of individualized baselines in health, (3) a method to enrich for informative variations and molecular axes that could enable development of marker panels as well as be useful for computation of individual risk scores for early and stratified interventions, (4) development of preclinical disease models for molecular delineation of dosha specific interventions, (5) operational frameworks for network medicine based on *trisutra* principles and leads, and (6) Evidence-based solutions for Ayurveda drug usage, actionable targets and novel molecules for drug development and repurposing. The application space of Ayurgenomics and the existing needs for technology developments is illustrated with specific examples in the subsequent sections (Figure 1).

Molecular correlates from studies on extreme *Prakriti* types could help define baselines of health

There is a common underlying theme to all diseases. In response to diverse environmental triggers that could include heat, hypoxia, Ultraviolet, infection, and dehydration, individuals are either resilient or could present with variable outcomes, such as thrombosis, bleeding, fibrosis, and pain, which are mainly restricted to a specific organ (Loscalzo et al., 2007; Noell et al., 2018). These diseases manifest through intermediate endophenotypes, such as immune response, inflammation, cell adhesion, cell proliferation, apoptosis, necrosis, and so on. A disease in an individual is thus a cumulative effect of rare and common variations in highly penetrant, as well as, modifier genes along with epigenetic effects. Threading the genotypes to variable phenotypic outcome through the different levels of functional hierarchy in an individualized manner is a major aim of precision medicine.

There has been a massive deluge of variation data from whole genome and exome sequencing, as well as genome-wide association studies from diverse populations. Methods are now being evolved to develop polygenic risk scores (PRS) that take into account the cumulative involvement of risk/protective alleles for more effective stratification in precision medicine (Khera et al., 2018; Gibson, 2019b; Nagpal et al., 2022). Genome-wide expression studies on

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

Table 1. Studies of predominant *Prakriti* types in healthy individuals at different omic levels

Omics study	Approach	Differences amongst predominant *Prakriti* types
Biochemical and transcriptome *Subjects*: 96 healthy individuals of predominant *Prakriti* screened out of 850 subjects from a genetically homogeneous population from North India (NI) of both genders V-39, P-29, K-28 (Prasher et al., 2008)	*Assay system* Transcriptomic – 19Kv8cDNA array (8,416 genes)	*251 differentially expressed transcripts, for example,* *Vata*: up – nucleocytoplasmic transport, cell cycle, DNA repair and recombination, dn – inflammatory and biotic response *Pitta*: up – response to biotic stimulus, dn – olfactory transduction *Kapha*: up – cellular biosynthesis, cofactor and purine salvage dn – complement activation
	Biochemical – 33 parameters with permutation tests	Biochemical – gender-specific differences in Baseline levels of intermediate patho-phenotypes *Vata*: up – serum prolactin and PTT *Pitta*: up – hematological parameters *Kapha*: up – lipid profiles, serum uric acid, GGPT, SGPT, Zinc
High-throughput genotyping *Subjects*: *Discovery cohort* Differentially expressed genes from above cohort (NI) with 92 matched background controls *Validation cohort* HAPE subjects – 92 (Aggarwal et al., 2010)	*Assay system* Illumina custom golden gate array141 tag SNPs from 30 representative genes of 251 differentially expressed genes of NI EGLN1 variation from 32 populations in HGDP panel and 552 samples 24 populations in IGV panel SNAPSHOT assay for EGLN1 genotyping of EGLN1	Differentially expressed genes amongst *Prakriti* associated with SNP frequency differences (eQTL) 14 SNPs significant in AKT3, EGLN1, FAS, FBN2, RAD51 genes *Pitta* allele – dn – *EGLN1* expression and adaptation to high altitudes in IGV and HGDP population *Kapha* allele correlated with up – *EGLN1* expression is associated with susceptibility to HAPE *EGLN1* SNPS (rs479200,rs480902) contribute to expression difference in hypoxia
Custom array based High-throughput genotyping *Subjects*: 96 samples from NI cohort and 552 samples from 24 Indian populations (IGV) (Aggarwal et al., 2015)	*Assay system* Illumina custom golden gate array 2,800 SNPs from 776 disease-candidate genes Validation study in mouse model	Allelic differences in *SPTA1, VWF, OLR1, UCP2, OR6K3, LEPR, OR10Z1* – hemostasis, olfaction, lipid metabolism, and so on Genetic interaction between EGLN1 (rs480902) and VWF (rs 1,063,856) predict *Pitta* with bleeding and *Kapha* with thrombosis outcomes in hypoxia
GWAS array-based genotyping *Subjects*: 262 well-classified predominant *Prakriti* males individuals from diverse ethnicity V-94, P-75, and K-93 (Govindaraj et al., 2015)	*Assay system* Affymetrix, 6.0 microarray platform Validation – targeted sequencing of PGM1	52 *Prakriti* differentiating SNPs without any confounding effect of stratification *PGM1* (metabolism-associated genes) variants differentiate *Pitta* and correlates with metabolic phenotype described in Ayurveda
Pharmacogenes from Exome sequencing *Subjects* 72 subjects of Predominant *Prakriti* (18 of each) as well as controls from NI cohort (Prasher et al., 2017)	*Assay system* Illumina Next Generation Sequencing platform (NGS) Hiseq2000 platform 47 genes that are US-FDA-approved pharmacogenomic biomarkers	28 SNPs of 11 FDA-approved genes – CYP2C19, CYP2B6, ESR1, F2, PGR, HLA-B, HLA-DQA1, HLA-DRB1, LDLR, CFTR, CPS1 differ between *Prakriti* – relevant in antiepileptic, antithrombotic, antipsychotic, antiviral, lipid lowering, cancer, diuretic, and so on Novel – A nonsynonymous exonic variation (rs1137101) in the LEPR gene associated with bodyweight gain due to antiepileptic drug (valproic acid) higher in *Kapha* compare to *Pitta*
Exome sequencing *Subjects* 108 healthy individuals 54 each from NI and VADU cohorts of North and Western India, respectively V/P/K and background population – 18 samples in each group (Abbas et al., 2020, 2022)	*Assay system* Illumina Next Generation Sequencing platform (NGS) Hiseq2000 platform Comparisons between cohorts and with background controls Fisher's test with permutation tests (80,000 iterations)	1,181 overlapping genes with 115 SNPS (91 eQTLS) replicated across both cohorts GO enrichments – *P versus K*: interferon and IFNG, biological adhesion, hemostasis *V versus K* – synapse activity, cell development, anatomical structure development *V versus P* – neurogenesis, + regulation of nucleocytoplasmic transport, cAMP, and carbohydrate derivative synthesis *GWAS*: 6 replicated GWAS SNPs associated with anthropometric traits, obesity, WHR, skin pigmentation, circadian rhythm, sleep, and sensory functions
Epigenomics *Subjects:* 147 male subjects of predominant *Prakriti* (20-30 years) out of screening of 3,416 subjects across diverse ethnic and linguistic groups, and geography K-52, P-48, V-47 (Rotti et al., 2014)	*Assay system* Methylated DNA immunoprecipitation (MEDIP) and microarray analysis on illumina platform Validation through bisulfite DNA sequencing	Global methylation difference specific to *Prakriti* types and at sites associated with diseases *Kapha*: up – promoter, obesity, cell growth, cellular adhesion, and maintenance of cellular integrity, *for example*, *CDH22* *Pitta*: up – gene body, metabolism, hormone secretion nucleic acid metabolism, *for example*, *UNBA, SK1, TP73,*

(*Continued*)

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

Table 1. (*Continued*)

Omics study	Approach	Differences amongst predominant *Prakriti* types
		RUNX3, SOX11 *Vata* – up – cell communication, transcription, signal transduction, development, *for example*, *HOXB1, LMX1B, LHX1, EN2*
Gut metagenomics *Subjects*: 135 healthy individuals of predominant *Prakriti* from 528 individuals of VADU cohort both genders V-48, P-35, K-52 (Chauhan et al., 2018)	*Assay system* 16S rRNA sequencing of gut metagenome with V2-V6 on Roche FLX platform	Sharing of core microbiome amongst *Prakriti. Prakriti* specific signatures more specifically in females whose dysbiosis is associated with health and disease states – *for example*, *Pitta* – butyrate-producing microbes (protective against inflammation, IBS) *Kapha* – *Prevotella copri* (correlated with inflammation and known to induce insulin resistance) *Vata* females – *E. Rectale* and *R. Hominis* that are butyrate producers
Computational functional metagenomics Functional profiling of gut metagenome of Vadu cohort from the above study (Mobeen et al., 2020)	*Assay system* Imputed metagenomics approach with predicted functional profiles from KEGG	*Kapha* – amino acid metabolism and biosynthesis pathway, replication, translational repair and stress response, high abundance of potential pathogen *Pitta* – biosynthesis of amino acids, up – metabolism-related pathways cholrakane, chloralkene, nitrotolouene, nitrogen metabolism *Vata* – Butyrate producers (lean body)
Gut and stool metagenomics Healthy individuals of Predominant *Prakriti* of both genders from cosmopolitan population of South India *Gut* *Males* – K-46, 52-P, 35-V; *Females* – 35-K, 12-P, 29-V *Buccal* *Males* – 41-K, 48-P, 34-V; *Females* – 36-K, 10-P, 31-V (Shalini et al., 2021)	*Assay system* Illumina Miseq platform 16srRNA sequencing with primers for V3 and V4 regions	Large sharing of microbes amongst *Prakriti* Gut signature microbes resonate with Ayurveda description, *for example*, *Kapha* – Butyricicoccus that is known to suppress inflammation *Pitta* – Turicibacter linked to host immunity and associated with inflammation *Vata* – Paraprevotellais usually found to be negatively correlated with BMI, percentage body fat, adiposity index, and estimated visceral fat *Oral* – the proportion of pathogenic bacteria was least in *Pitta*
* *Candidate genes* HLA-DRB1 variants in 76 subjects: 32 P, 34 K, 10 V (Bhushan et al., 2005)	Polymorphism assay by PCR	Frequency of HLADRB1*13 associated with protection against dementia and autoimmune lower in Vata
* *Candidate genes* CYP2C19 *1*2*3 polymorphism 167 predominant *Prakriti* (26 V, 43 P, and 63 K) from a screening of 489 subjects (Joshi et al., 2011)	PCR-RFLP method	Fast metaboliser in P Poor Metabolizer in K

Note: These studies have been carried out on healthy individuals of predominant and contrasting *Prakriti* types – *Vata* (V), *Pitta* (P), and Kapha (K) from diverse cohorts. The number of subjects, population details, and gender information are included. A brief summary of key results with few examples in each of the studies has been highlighted. The references for the studies are also included. *A few candidate gene-based studies are included. eQTL, expression quantitative trait loci; HAPE, high altitude pulmonary edema; HGDP, human genome diversity panel; IGV, Indian Genome Variation Consortium Project. Up and dn indicates the direction of expression/levels towards positive and negative, respectively.

healthy individuals have also revealed high inter-individual variance within a population (Montgomery and Dermitzakis, 2011; Martin et al., 2014). A major challenge, however, is threading genotypes to phenotypes through enormous genetic heterogeneity within populations. The effect of common genetic variants associated with many diverse diseases in GWAS studies is often masked in this heterogeneity as there are no adequate methods to comprehensively define and distinguish healthy individuals within a population (Manolio et al., 2009; Eichler et al., 2010). Using millions of electronic health records that are available in cohorts on whom genome-wide association studies have been conducted for specific traits, phenotype–phenotype associations are being derived through phenome-wide association studies (Denny et al., 2010). The presence of overlapping phenotypes that are captured in health records has enabled the discovery of pleiotropic variants that connect different diseases and phenotypes through shared variants.

Genome-wide expression, genetic variation (microarray based as well as exome), and epigenome (global methylation and array based) studies on extreme *Prakriti* healthy individuals that have predominance of one of the *dosha*s, have provided molecular correlates of *tridosha* (Prasher et al., 2008; Govindaraj et al., 2015; Rotti et al., 2015; Abbas et al., 2020, 2022). Some of the highlights of these studies have been provided in Table 1. Contrasting *dosha*s exhibit differences with respect to gene-ontology enrichments. In the first of such studies carried out on healthy individuals the authors reported ontological differences between the individuals of contrasting constitution types at genome-wide expression and biochemical levels (Prasher et al., 2008). Corroborating observations of differences in ontological enrichments between different constitution types have been reported from multiple studies that have been carried out at different functional hierarchies and in different population cohorts. For instance cell proliferation and DNA damage response differentiates *Vata Prakriti*, T-cell mediated

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

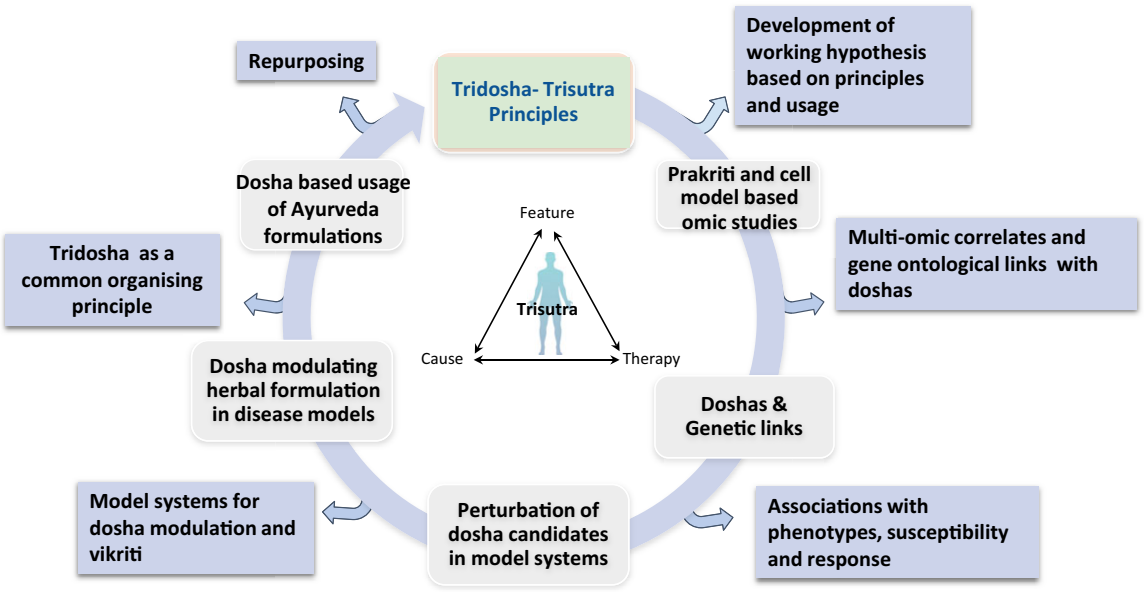

Figure 1. Summary of research highlights and potential of Ayurgenomics. Molecular correlates of *Tridosha*, the common organizing principle in Ayurveda have been explored through studies on healthy individual of three extreme *Prakriti* constitution types that have predominance of either *Vata, Pitta*, or *Kapha doshas* as well as have been validated in model systems. These have been studied at various levels of functional hierarchy from molecular (genetic and epigenetic) to expression and response at cellular (transcriptomic, metagenomic, biochemical) and organ – physiome level and also with respect to multisystem phenotypic attributes in diverse populations. These have been validated through cell-based studies, in LCL and disease models (cell-based and mouse), and machine learning approaches. The studies have highlighted the application of Ayurgenomics for elucidating PhenotypetoPhenotype linkages in an individual, understanding the genetic and phenotypic basis of human individuality, identification of different baselines of intermediate patho-phenotypes that govern outcomes in health, genetic variations, and biomarkers for risk and response stratification in healthy individuals, novel therapeutic targets, systems' understanding and drug repurposing through *trisutra* framework. These could be useful for noninvasive risk stratification of healthy individual, endophenotype identification in diseases, evolving polygenic risk scores from GWAS studies for more effective risk stratification, identification of actionable targets and genes with pleiotropic effects from PHEWAS cohorts, development of preclinical models for exploring and generating evidence-based usage Ayurveda formulations and in developing endophenotype based precision and networked medicine.

immunity, elevated metabolism and inflammation in *Pitta Prakriti*, and lipid profiles and BMI-associated correlates differentiate *Kapha* have been observed from expression, epigenetic as well as genetic studies (Prasher et al., 2008; Rotti et al., 2015; Abbas et al., 2020, 2022). Besides these, there are differences in different cellular and physiological axes that are associated with development, cell adhesion, signaling, and transport functions as well as processes that govern circadian rhythm, olfaction, and so on. Differences in gut microbiome that are correlated with many disease predispositions have also been reported amongst *Prakriti* type (Chauhan et al., 2018; Chaudhari et al., 2019; Mobeen et al., 2020; Shalini et al., 2021). Recently a study on two cohorts has also reported physiological difference in response to orthostatic stress that was evaluated by heart rate variability (Rani et al., 2022). All these studies substantiate that the assessment of extreme *Prakriti* can be used to assess the proportions of different "*dosha*s," their dynamics in a healthy individual, and predict the associated risk and trajectories. Noteworthy, the healthy individuals displayed baseline differences in the processes linked to intermediate patho-phenotypes that are often perturbed in diseases (Prasher et al., 2008).

It seems probable that differences in baselines of intermediate phenotypes of healthy individuals could be governed by a need to maintain a homeostatic state in an individual and subvert the deleterious consequences of an epistatic variant. For example, in one of our studies, we demonstrated that the elevated bleeding risk in *Pitta* could be a protective phenotype to subvert the epistatic effect of a variation in oxygen sensor gene EGLN1 that contributes to higher baseline levels of hypoxia responsiveness (Aggarwal et al., 2010, 2015). Hypoxic conditions lead to increase in angiogenesis and enhanced formation of platelet glycoprotein as a protective phenotype. However, in a chronic state of hypoxia this could put an individual to enhanced risk of thrombosis. In individuals where baseline levels of hypoxia are higher, a bleeding-linked state could thus be physiologically favorable. In another study, we demonstrate how elevated baseline levels of cell proliferation *Vata Prakriti* could be advantageous if the individuals have an inherent sensitivity to DNA-damaging conditions (Chakraborty et al., 2021). An inherent susceptibility to DNA-damaging agents at the embryonic stage might have led to a genetic rewiring that ensures higher baseline states of cell proliferation for more effective recovery. This, however, later in life might contribute to differences in outcomes due to the involvement of the cell proliferation axes.

The above observations suggest if interventions are targeted toward elevated levels of intermediate patho-phenotypes without taking cognizance of an individual's baselines, this could lead to ineffective outcomes in diseases or even drastic consequences. For instance, ischemic consequences in hypoxia might differ amongst individuals based on their constitution types and would have different treatment and dose calibration requirements. Also, DNA-damaging agents in cancer conditions, if calibrated on the basis of thresholds of DNA damage sensitivity of cancerous tissues without a cognizance of inherently baseline proliferation rates in response to such conditions, could result in higher recurrence in some individuals. Could different constitution types govern such differences? Interestingly, according to textual descriptions there are many intermediate pathophenotype that are described to be *Prakriti* specific. For instance, amongst many distinguishing features, pain-related outcomes are more prevalent in individuals

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

Table 2. *Prakriti* (dosha) associated differential functional outcomes in baseline physiology, stress response, and diseases

Baseline differences in LCL lines of Predominant Prakriti 8 Lymphoblastoid cell lines of predominant *Prakriti* (V-3, P-2, K-3) from males of VADU cohort (Chakraborty et al., 2021)	Growth characteristics of LCLs Cell proliferation and cell death in response to UV	Significant differences in cell proliferation *Kapha:* slower than *Vata* and *Pitta.* *Vata:* up ($p < 0.001$) – cell death in response to UV, but recovers its numbers due to an inherent higher rates of proliferation
Variability in aggregation response amongst Prakriti Subjects: VK-4; VP-16; PK-65; PV-12; KV-4; KP-36 (Bhalerao et al., 2012)	Platelet aggregatory response after treatment with aspirin (2.5 and 5 uM) using the turbidometric method on a Chronolog platelet aggregocorder	Largest response-VP > KV > PV Slow response in PK at 2.5 uM
Immunophenotypes of predominant Prakriti *Subjects*: 222 Males from diverse ethnicity of predominant *Prakriti* male individuals – V-70, P-57, and K-95 (Satyamoorthy et al., 2014)	Immunophenotyping using fluorochrome labeled antibodies using FACs analysis – CD3, CD4, CD8, CD14, CD25, CD56, CD 69, CD71, and HLADR	*Pitta*: positive corelation with CD14 associated with hypersensitivity reaction *Kapha*: positive corelation with CD 25 and CD56 associated with cell adhesion and better immune response *Vata*: negative corelation with CD 25 is associated with recurrent infections and CD56 poor immune response
Physiological response to orthostatic stress Subjects: 379 subjects from North (NI) and Vadu Cohorts V-97, P-68, and K-68 K and 146 mixed (Rani et al., 2022)	Assessment of Differential response by Head Up Tilt (HUT) test using heart rate variability (HRV)	*Kapha* lower baseline HRV and significantly lower change in HRV parameters in response to HUT *Vata* – maximum drop in parasympathetic activity in HUT suggestive of early autonomic dysfunctions
Response to stress in diabetics of different Prakriti *Subjects* – 60 individuals from three predominant Prakriti, each consisting of 10 diabetic patients and 10 healthy individuals (Banerjee et al., 2021)	Cell-based assay for Reactive oxygen species (ROS) generation, blood DNA content, DNA damage, apoptosis of blood cells, and interaction of DNA with various carcinogens in patient samples	*Vata*: Significantly lower ROS and total cell damage ($p < 0.001$); more prone to lead and arsenic and reduced – DNA content and more DNA damage in T2DM
Endophenotypes of Rheumatoid arthritis in predominant Prakriti *Subjects*: 325 controls of RA (V-39, P-207, K-99) and 356 cases (V-48, P-186, K-78) 18–50 years both genders (Juyal et al., 2012)	12 Candidate gene of inflammatory and oxidative stress pathway in a case-control study in total versus three subgroups of rheumatoid arthritis using the PCR-RFLP method	Excess of RA patients with *Pitta* predominant *prakriti* Severity more pronounced in Vata with high anti-CCP antibody titer, ESR and RA factors, and low Hb and age *Vata* – inflammatory pathway; ESR, *TNFα* SNP (rs1800629) and *CD40* (rs4810485) *Pitta* – oxidative stress, BMI, ESR, and *SOD3* (rs2536512) *Kapha* – Age, Hb, and *tnfα* (rs1800630)
Prakriti based GWAS in RA in north India cohort *Subjects*: 293 controls (33 V, 175 P, 85 K) and 244 RA cases (49 V, 117 P, 78 K) Age (18–50 years) (Juyal et al., 2022)	High-throughput genotyping using illumina Human 660 W Quad BeadChip v1.C (655 216 markers)	Novel SNPs with suggestive *p*-value 1 E-05 were associated with the three RA subgroups *Vata*: RP11-536O18.1; CTC-498 M16.4 *Pitta*: TXNDC16, PCDH8, KLHL25, NTF3, RP11-93I21.3 and SERTM1 *Kapha*: ZBTB34, ITGB8, and GPR12 (rs9512378)

with heightened *Vata*, bleeding in *Pitta*, and thrombosis in *Kapha Prakriti.* Of interest, there are also textual descriptions that describe certain biological processes being enriched in particular *dosha*s, for example, enhanced cell proliferation in *Vata* and inflammation in *Pitta* and adhesion in *Kapha*. Many of the molecular observations resonate with descriptions of Ayurveda (Tables 1 and 2).

Since we observe hypoxia responsiveness as an axis that differs between *Pitta* and *Kapha* and also govern differences in bleeding versus thrombotic risks, it is testable whether we might be able to predict trajectories of sickle cell patients based on their *Prakriti* types. There are a number of modalities through lifestyle, dietary as well as drugs through which doshic imbalances are managed. It might therefore be possible to manage the quality of life through *dosha* modulating formulations once the *Prakriti* phenotypes are assessed, and is testable in retrospective cohorts. The relevance of this is borne out by the most recent observations across the world where there was a wide variability in hypoxia response and inflammatory consequences even between related family members. Could these be governed by constitutional types?

Extreme *Prakriti* genomics enables the enrichment of genetic markers associated with pleiotropic effects, differential susceptibilities, drug, and environmental response

Exome sequencing of healthy individuals of extreme *Prakriti* types has provided some interesting insights (Abbas et al., 2020, 2022). Extreme *Prakriti* types in a population are rare and are often the most vulnerable to specific types of diseases. Genetic, genome-wide arrays and sequencing have revealed the enrichment of biological processes in *Prakriti* specific manner (Table 1). Variations that govern differences in expression (eQTLs) were also enriched in *Prakriti* specific manner amongst healthy individuals and govern

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

differences with respect to environmental triggers for example hypoxia, UV, DNA damage, and so on. Also, a significant fraction of GWAS-associated variants (that are normally identified from disease associations) differ in frequency between the *Prakriti* groups. When the *Prakriti* groups are pooled their frequency gets averaged and assumed to be a similar frequency as the background population. Since variations associated with GWAS traits are common in the population, extreme *Prakriti* could be individuals who are most predisposed, thus, this method of phenotyping might allow identification of predisposed individuals and associated genes (Table 2). Many of these variants are also reported to have pleiotropic effects as evidenced from their overlap with reported variants in PHEWAS studies and also drug targets. This shows it is possible to identify actionable variations and associated composite phenotypes based on *Prakriti* for risk stratification. Similar to genome-wide expression, exome sequencing also revealed specific ontological enrichments in differentiating genes for specific *Prakriti* types. This approach could also be useful in pharmacogenomics settings as the variations that are linked to differences in drug metabolisms differ between *Prakriti* types (Joshi et al., 2011; Prasher et al., 2017). Some of the prominent examples include human leukocyte antigen (HLA) types as well as genes in whom variations have been approved by FDA for optimizing drug dosage, for example, clopidogrel, bupropion, warfarin, abacavir, and so on. Interestingly, some of the variations in genes such as VWF, F2, and SERPINA10 genes associated with specific risks, of bleeding and thrombosis were enriched in *Pitta* and *Kapha Prakriti* respectively. Such risks are described for these *Prakriti* groups in Ayurveda. Sequencing of phenotypic extremes is assuming immense importance in the identification of disease susceptible genes as well as drug targets (Harper et al., 2015; Heck et al., 2017). Such a sequencing strategy in Prakriti provides an added advantage of linkage with multisystem phenotypes.

Prakriti based noninvasive risk stratification in phenomics studies

Previous studies described emphasize that healthy individuals stratified on the basis of *Prakriti* type could be useful for early identification of at-risk individuals who might have different management needs. As described earlier, *Prakriti* types are distinguished on the basis of system-level composite phenotypes. Integration of knowledge of these composite phenotypes that are connected in an individual-specific manner could enable an affordable and noninvasive approach of stratification across large populations. Since *Prakriti* of an individual remains invariant throughout lifetime, a single assessment of an individual is highly affordable and can also be implemented in prospective cohorts (Juyal et al., 2012, 2022). Conjoint assessment with health and disease indications could be highly revealing. This may no longer seem incongruous to the modern audience as there is now ample evidence accumulating that demonstrates the association of non-invasive phenotypes with disease risk. For instance, the relatively innocuous measures, like the 2D/4D finger length ratio is highly informative in predicting many diverse outcomes, such as risk for cardiovascular diseases, Attention deficit hyperactivity disorder ADHD, and behavioral traits, and so on (Manning et al., 1998; Manning et al., 2001; Manning et al., 2007; Coates et al., 2009; Fischer Pedersen et al., 2021).

The composite nature of these phenotypes in an individual-specific manner has also been recapitulated by unsupervised machine learning and advanced statistics approaches in a study on two cohorts (Tiwari et al., 2017). This has enabled the development of predictive models and the identification of classifiers that distinguish individuals with contrasting doshic proportions. Evidence of phenotypes to phenotype connectivity is also being uncovered through phenome-wide association studies (PHEWAS). The EHR records in millions of subjects are used to create a picture of composite phenotype through a common genetic lead and associated overlapping phenotypes (Denny et al., 2010, 2013; Pendergrass and Ritchie, 2015; Liu and Crawford, 2022). Integration of assessment of composite phenotypes/*Prakriti* in these cohorts can accelerate the phenome assembly process by providing a phenotype scaffold in a manner analogous to genome sequence assemblies (Abbas et al., 2020, 2022). Just like in the absence of a scaffold, a de novo genome assembly requires millions of reads, PHEWAS studies require millions of health records for phenome assemblies.

Prakriti phenotyping in retrospective cohorts could be an alternative route, for the identification of endophenotypes that could govern differential outcomes (Table 2). The importance of *Prakriti* assessment in disease cohorts is borne out of two studies on rheumatoid arthritis that demonstrate conditioning disease groups with *Prakriti* labels allows identification of variants with higher effect sizes and also different endophenotypes (Juyal et al., 2012, 2022; Table 2). These are also supported by genetic and exome studies that demonstrate risk alleles that associate with different diseases are partitioned differently amongst the healthy individual of different constitutions. In a population, the frequency of these risk alleles is masked due to extensive phenotypic heterogeneity (Aggarwal et al., 2010; Abbas et al., 2022).

Although the composite phenotypes in individuals of extreme phenotypes are readily distinguishable and explainable, methods are needed to objectively define the dual types that comprise a major fraction of the population (~90%) and have mixture of different *doshic* proportions. Since the *dosha*s govern physiological entities, it is likely that some emergent phenotypes in the dual types could help distinguish and stratify these groups. Large-scale phenotyping using digital devices that can capture the compendium of phenotypes described for *Prakriti* in diverse settings could be of enormous utility. As a large number of combinatorial possibilities exist for dual *Prakriti*, the development of AI-based predictive models for objectively assigning *Prakriti* in large datasets is required. These could be attempted in large cohorts that are being developed by the government of India initiatives, which aim to integrate *Prakriti* information in health cards and involves phenotyping individuals across the country in AYUSH health and wellness centers using uniform protocols.

Molecular correlates in *Trisutra* framework: Platform for evidence-based usage of Ayurveda formulation and drug repurposing

Most often a herb that forms a constituent of a medicinal formulation in Ayurveda is used in drug discovery programs. However, the therapeutic approach in Ayurveda contrasts with the conventional pharmacological reductionist approach that is inspired from herbal formulations. In the latter, the focus is mostly to identify the active principle that could be further synthesized chemically, and then taken forth for further mechanistic and preclinical/clinical studies. This approach though has been useful for the discovery of many small molecules, has not been able to provide an

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

understanding of their mechanisms from a clinical and systems perspective. A drug in such a form (with only the active principle) cannot be prescribed in an Ayurveda setting. Drugs typically are discovered with a particular disease focus, but now with thousands of genome-wide association studies, it is becoming evident that there is an extensive disease gene network. Different diseases could have shared mutations and genes. In most complex diseases ultimately a patient has to have a polypill which could be either multiple medicines (modern) or a formulation with multiple active principles (Ayurveda). There is a large focus on research on drug repurposing to reduce the time and cost for drug discovery as has been evident throughout the COVID-19 pandemic.

In Ayurveda, a systemic understanding seems to be implicitly applied in practice as a single herb is most often used in multiple and diverse conditions, and a single clinician can treat multiple diseases (Patwardhan and Mashelkar, 2009). Also, the treatment strategies seem to consider emergent properties in terms of the disease, as well as diseased states within a spatio-temporal context. In today's precision medicine, this is the ultimate aim. The "*trisutra*" framework resonates with the network medicine concept where the features (phenotypes), causes (diseases), and therapy (drugs) are unified through a common organizing principle of *tridosha.* If *tridosha* has a molecular correlate then it is possible to query this network from any of the axes. The two following examples would demonstrate how this is testable and applicable for translation, where the query is initiated from the phenotype and the other from the drug perspective.

In the first example, a gene "EGLN1" that is an oxygen sensor and regulates the hypoxia responsiveness axis through HIF1 differed between two constitution types "*Pitta* and *Kapha*" amongst healthy individuals at the expression and genetic level (Aggarwal et al., 2010). This genetic difference contributes to either adaptation to high altitude or susceptibility to high altitude pulmonary edema. A small molecular inhibitor of EGLN1 in a mouse model of asthma revealed that modulation of hypoxia axis could lead to airway hyper-responsiveness, exacerbate inflammatory consequences and mitochondrial dysfunction and elicit steroid-resistant asthma features (Ahmad et al., 2012). A herbal formulation, Adathoda vasica, widely used to treat asthma and is described in Ayurveda to modulate perturbations of the *Pitta-Kapha* axis was further tested in the above model (Gheware et al., 2021b). The hypothesis was if in Ayurveda, medicines are selected on the basis of *doshic* imbalances, then the molecular correlates to the *doshic* imbalances would be actionable points. When used in the above model, Adathoda vasica alleviated all the above conditions including inflammation, restored mitochondrial dysfunction and was validated as a HIF1a inhibitor. The effect of the formulation in the hypoxia axis was also evident in the lung transcriptome, thus explaining why this medicine could work in other diseases where hypoxia is a cause or consequence, and could be repurposed in preclinical models of sepsis and COVID-19 (Gheware et al., 2021a). This entire framework provided EGLN1 as a biomarker, which is now been widely accepted to be a target a large number of diseases and associated genetic variations have been replicated in multiple studies and altitudes of the world (Simonson et al., 2010; Brutsaert et al., 2019). Differences in the wound healing axis between *Pitta* and *Kapha Prakriti* have been corroborated in genome-wide expression and exome studies (Prasher et al., 2008; Abbas et al., 2022). Adhathoda vasica has been extensively studied from the active principle perspective, but this is the first time that a complete formulation was demonstrated to work on the hypoxia axis. This provides a unifying link to its usage in multiple indications and in all instances hypoxia could be a primary determinant. Thus the *trisutra* framework for translation of concepts of ayurveda that is linkage between feature-cause-therapy could be established through a molecular correlate (EGLN1) of *tridosha* (the common organizing principle) (Figure 2).

A second way to probe the networked concept of *trisutra* could be from the therapy perspective. In Ayurveda, a drug can be used for multiple and seemingly diverse diseases. This could be because multiple molecules in a formulation are targeting different diseases, or that a shared pathway connects diverse diseases. Our group took an example drug, Cessamplous pareira (CIPA) that is widely used to treat fever-like conditions and hormonal disturbance in women to test this hypothesis. We tested this through a connectivity map (CMAP) framework. Connectivity maps provide a compendium of transcriptional signature profiles from millions of perturbations (small molecules, drugs, gene knock outs, over-expression) from

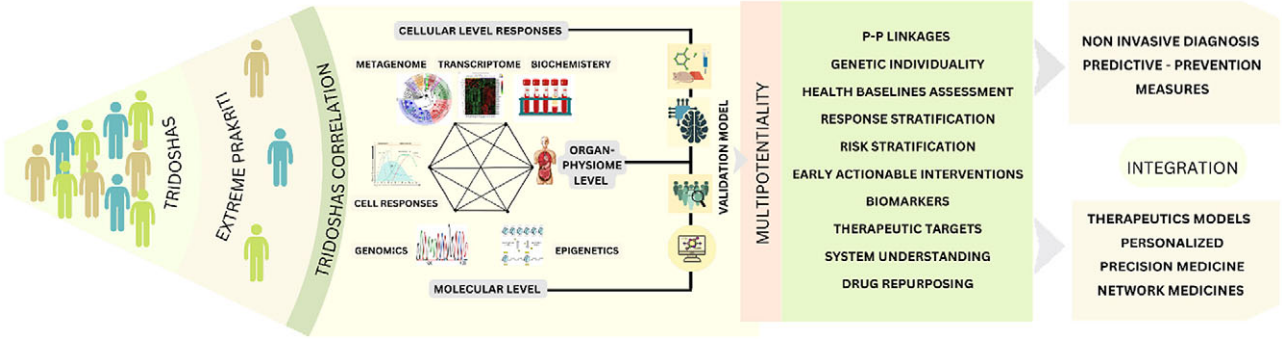

Figure 2. Iterative approach of Ayurgenomcs for the development of an operational framework of network medicine based on concepts of Ayurveda. In Ayurveda, the three axes of causes, features, and therapy (*trisutra*) are linked through a common organizing principle (*tridosha*) that govern three physiological entities described broadly by kinetic (*Vata*), metabolic (*Pitta*), and structural (*Kapha*) attributes respectively. *Tridosha* feature descriptions resonate with modern GO (gene ontology) descriptors. Relative proportion of *tridosha* governs human constitutions (*Prakriti*) with extreme types having predominance of one of the *dosha*s. The extreme individual *Prakriti* have contrasting phenotypes, responses and health trajectories and are more vulnerable to specific groups of diseases. Multiomic studies on extreme constitution reveal molecular correlate of *Tridosha* that have different GO and pathway enrichments and are associated with contrasting susceptibilities, environmental response, and drugs. Perturbation of the *dosha* associated genes in model systems provide molecular evidence for *dosha* involvement in disease states (*Vikriti*) through specific axis. This provides a test bed for exploring mechanism of action of herbal formulation used for modulation of specific disease and *dosha* perturbations. The above framework has been validated with respect to hypoxia axis through this iterative approach and is described in the text. It has also provided mechanism of action of Cessamplous pareira from its usage perspective and evidence for recommendation in COVID-19 both from its effect on host and pathogen.

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

different cell lines (Lamb et al., 2006; Subramanian et al., 2017). One can use a test drug and compare the signatures to infer possible modes of action of a novel compound or a mixed formulation. CMAP analysis of CIPA revealed that the molecules in this drug have matching signatures with protein synthesis inhibitors, many of which are antiviral, and this could work through ESR1 axis (Haider et al., 2021). These were validated in infection models of dengue in cell lines and also showed a repurposing possibility in SARS-CoV2 infection (Haider et al., 2022). Moreover, the complete formulation was more effective compared to single molecules in SARS-CoV2 inhibition. Transcriptome analysis and conjoint analysis with GSEA also revealed its involvement in the estrogen axis and possible usage in diseases where these need to be alleviated. Also docking studies revealed potential binding of a large number of molecules of CIPA to bind to ESR1 as also SARSCoV2. There is accumulating literature on the evidence of a link between the estrogen axis and viral inhibition. This study not only provides an evidence-based usage of Ayurveda formulation, but also provides new targets and molecules for therapeutic intervention. Noteworthy, both studies described above have integrated the principles and usage of the formulation from Ayurveda perspective in the study. Both drugs have been widely used and studied, but the above studies highlight the difference if traditional knowledge is integrated in these studies.

Therefore, the incorporation of principle and clinical usage in drug discovery programs that are sourced from herbs described in Ayurveda could provide interesting scaffold for discovering novel links, targets, and molecules. However, there is a need to develop, (1) experimental assays and models that can probe mechanisms in poly-pharmacological framework, (2) Patient-specific models that recapitulate the evolution of different stages of the diseases coupled with multi-omic (genomic, transcriptomic, proteomic, metabolomic) approaches for high-throughput and integrative screening of herbal formulations and discovery of targets, and (3) Poly-pharmacological based computational frameworks for docking, in silico identification of plausible therapeutic targets of the plant secondary metabolites as well as structure-guided discovery of molecules and targets. This should allow combinatorial synthesis of active constituents for the most effective outcomes. The route to such discoveries could be reduced if we are able to build an integrative platform that allows crosstalk between the two systems. Ayurgenomics-based approaches could have wide applications in defining the requirement for a platform for crosstalk and an interoperable framework in integrative medicine.

Ayurgenomics applications in integrative medicine settings

In the present times, patients are faced with multiple options for health and disease management, especially in India and Asian countries where traditional medicine is widely practiced. There is also an increased recognition for this in many populations of West. Besides, changing demographics that include a burgeoning younger population, an increase in mobility to nonnative environments, proportionately high aging population, and other cultural transitions, pose a major economic burden. Integrative medicine that combines principles and practices of traditional medicine, such as Ayurveda, could increase health and disease management options for individuals. This would also complement the current move toward digital, systemic, wholistic, and precise P4 (Predictive, Preventive, Personalized, Participatory) medicine of the contemporary times with an additional promotive component (Topol, 2014, 2019; Banerjee et al., 2015; Mukerji and Prasher, 2015; Lemonnier et al., 2017).

Ayurgenomics thus provides an operational framework and platform for integration of principles and practices of Ayurveda with modern medicine (Figure 2). Through an iterative approach, the utility of this framework in translation has been demonstrated. This platform can propel new knowledge and developments. It allows the discovery of molecular and multi-omic correlates of the common organizing principle *tridosha* that govern constitution types "*Prakriti*." These molecular correlates (1) differentiate healthy individuals, (2) exhibit different baselines of intermediate patho-phenotypes that are associated with disease predisposition, (3) provide genetic links to disease predisposition and environmental responsiveness, and (4) can provide new leads for early actionable interventions and therapeutic targets. We observed recurrent themes across studies wherein intermediate patho-phenotypic states differ amongst *Prakriti* at baselines (Table 1). This is relevant in predicting individualized health trajectories and calibrating interventions. The contemporary relevance of this framework is evident from its potential in situations like the COVID-19 pandemic. For example, the pathways discovered to differ between *Prakriti* govern differential outcomes in COVID-19, more specifically, the ability to cope with hypoxia or the susceptibility to inflammatory consequences. This highlights a scope for risk stratification and prioritization of informative markers using *Prakriti* methods. Secondly, the intervention points are actionable with Ayurveda medicines as has been demonstrated by both Adathoda vasica and Cessamplous pareira. This evidence-based approach can increase the acceptability of Ayurveda recommendations and also highlights herbal recommendations from Ayurveda are testable in an Ayurgenomics framework. Such studies can provide new biomarker targets, drug repurposing possibilities, and enables bioprospecting for new molecules.

Thus, Ayurgenomics provides molecular subtitles to Ayurveda concepts and enables ontological links with modern medicine through a shared genomics dictionary. In addition, the development of technology-enabled platforms that would makes this information interoperable with modern medicine could provide exciting opportunities for integrative medicine especially in precision medicine settings (Singh et al., 2018; Mukerji and Sagner, 2019). For example, predominant "*Vata*" individuals have higher cell proliferation rates in baseline and are also more prone to DNA-damaging agents. Inherent differences in cell proliferation have been demonstrated to govern variability in lithium response in cell lines derived from bipolar disorder patients (Paul et al., 2020). Also, analysis of predominant Prakriti in a cohort of diabetes has shown that *Vata* Prakriti individuals are not only more prone but also exhibit heightened response to DNA-damaging agents (Banerjee et al., 2021). Could *Prakriti* phenotyping provide an additional assistance in pharmacogenomic settings? *Prakriti* and cell proliferation rate assessment from healthy tissues might be additionally useful for in cancer management. Higher baseline of cell proliferation rates that have evolved to modulate response to DNA-damaging agents could confound calibration of dosage of DNA-damaging agents and promote recurrence. Genetic as well as exome analysis reveals differences in pharmacogenes as well as response to drugs amongst extreme constitution types (Joshi et al., 2011; Bhalerao et al., 2012; Prasher et al., 2017). Thus, the integration of Ayurveda-based phenotyping could be of use in pharmacological settings. A third aspect is the scope of Ayurgenomics in translation. Differences in probing the molecular pathways involved in poly-herbal formulation through this framework could not only provide molecular

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

links to its usage, but also allow development of novel drug discovery paradigms with a poly-pharmacological framework and inspire combinatorial synthesis of multiple molecules for network medicine.

Concluding remarks

"Integrative Medicine" formalized as another option for health management is urgently required. However, Ayurveda faces a disconnect with a modern audience. There is limited scientific evidence in contemporary language about the principles of systems' medicine and there are also challenges in understanding the heterogeneity in treatment modalities. There is a need for developing and evolving a common language and evidence-based technology solutions for its integration into mainstream and interoperability with other medicinal systems. Moving forward, these gap areas need to be addressed. A technology-enabled ecosystem for evolving harmonized protocol for integrative medicine is required. These would involve the integration of digital devices and IOT-based technologies that not only allow automated capture of large-scale data but also enable the development of AI-based recommendation engines that could assist the Ayurveda clinicians in objective decision-making. Big data analytics and natural language processing-based methods could enable integration of ontologies from modern and Ayurveda systems in an interoperable framework. Integration of multi-omic technologies, including electronics and sensors with devices, chemical, genomics, molecular as well as digital markers for calibrating therapy, evolving standardized protocols, as well as monitoring treatment and outcomes and uniform data sharing platforms and architecture could all be enablers for realizing "Evidence-based Ayurveda" solutions and a participatory framework for managing health. Besides integrative medicine, this could also increase outreach, access, and surveillance, as well as affordable solutions.

Open peer review. To view the open peer review materials for this article, please visit http://doi.org/10.1017/pcm.2023.15.

Acknowledgments. This review highlights the works of many groups across India and also the major consortium initiatives supported by CSIR, AYUSH, and DST to CSIR-IGIB. The present support from the Ministry of AYUSH (S/MOA/MTM/AA/20210105) and IIT Jodhpur to advance the science through a Centre of Excellence grant in Ayurtech for Integrative precision health and medicine by the Ministry of AYUSH to the School of Artificial Intelligence and Data Science (AIDE) School at IIT Jodhpur is duly acknowledged. The author thanks Dr. Atish Gheware and Prof. Greg Gibson from Georgia Tech in Atlanta for critical reading of the manuscript.

References

Abbas T, Chaturvedi G, Prakrithi P, Pathak AK, Kutum R, Dakle P, Narang A, Manchanda V, Patil R, Aggarwal D, Girase B, Srivastava A, Kapoor M, Gupta I, Pandey R, Juvekar S, Dash D, Mukerji M and Prasher B (2022) Whole exome sequencing in healthy individuals of extreme constitution types reveals differential disease risk: A novel approach towards predictive medicine. *Journal of Personalized Medicine* **12**, 489–497. https://doi.org/10.3390/jpm12030489.

Abbas T, Kutum R, Pandey R, Dakle P, Narang A, Manchanda V, Patil R, Aggarwal D, Bansal G, Sharma P, Chaturvedi G, Girase B, Srivastava A, Juvekar S, Dash D, Prasher B and Mukerji M (2020) Genetic differences between extreme and composite constitution types from whole exome sequences reveal actionable variations. *bioRxiv*.

Aggarwal S, Gheware A, Agrawal A, Ghosh S, Indian Genome Variation Consortium, Prasher B and Mukerji M (2015) Combined genetic effects of EGLN1 and VWF modulate thrombotic outcome in hypoxia revealed by Ayurgenomics approach. *Journal of Translational Medicine* **13**, 184–194. https://doi.org/10.1186/s12967-015-0542-9.

Aggarwal S, Negi S, Jha P, Singh PK, Stobdan T, Pasha MA, Ghosh S, Agrawal A, Indian Genome Variation Consortium, Prasher B and Mukerji M (2010) EGLN1 involvement in high-altitude adaptation revealed through genetic analysis of extreme constitution types defined in Ayurveda. *Proceedings of the National Academy of Sciences of the United States of America* **107** (3), 18961-18966. https://doi.org/10.1073/pnas.1006108107.

Ahmad T, Kumar M, Mabalirajan U, Pattnaik B, Aggarwal S, Singh R, Singh S, Mukerji M, Ghosh B and Agrawal A (2012) Hypoxia response in asthma: Differential modulation on inflammation and epithelial injury. *American Journal of Respiratory Cell and Molecular Biology* **47**, 1–10. https://doi.org/10.1165/rcmb.2011-0203OC.

Banerjee S, Biswas TK, Chattopadhyay K, Arzoo SH and Chattopadhyay B (2021) An approach to screen genotoxic-susceptible diabetic population of various *Prakriti* groups for personalized disease management. *Journal of Alternative and Complementary Medicine* **27**(1), 80–87. http://doi.org/10.1089/acm.2020.0001.

Banerjee S, Debnath P and Debnath PK (2015) Ayurnutrigenomics: Ayurveda-inspired personalized nutrition from inception to evidence. *Journal of Traditional and Complementary Medicine* **5**, 228–233.

Bhalerao S, Deshpande T and Thatte U (2012) *Prakriti* (Ayurvedic concept of constitution) and variations in platelet aggregation. *BMC Complementary and Alternative Medicine* **12**, 248–252. https://doi.org/10.1186/1472-6882-12-248.

Bhushan P, Kalpana J and Arvind C (2005) Classification of human population based on HLA gene polymorphism and the concept of *Prakriti* in Ayurveda. *Journal of Alternative and Complementary Medicine* **11**, 349–352. https://doi.org/10.1089/acm.2005.11.349.

Brutsaert TD, Kiyamu M, Revollendo GE, Isherwood JL, Lee FS, Rivera-Ch M, Leon-Velarde F, Ghosh S and Bigham AW (2019) Association of EGLN1 gene with high aerobic capacity of Peruvian Quechua at high altitude. *Proceedings of the National Academy of Sciences of the United States of America* **116**, 24006–24011. https://doi.org/10.1073/pnas.1906171116.

Chakraborty S, Singhmar S, Singh D, Maulik M, Patil R, Agrawal SK, Mishra A, Ghazi M, Vats A, Natarajan VT, Juvekar S, Prasher B and Mukerji M (2021) Baseline cell proliferation rates and response to UV differ in lymphoblastoid cell lines derived from healthy individuals of extreme constitution types. *Cell Cycle* **20**, 903–913. https://doi.org/10.1080/15384101.2021.1909884.

Chaudhari D, Dhotre D, Agarwal D, Gondhali A, Nagarkar A, Lad V, Patil U, Juvekar S, Sinkar V and Shouche Y (2019) Understanding the association between the human gut, oral and skin microbiome and the Ayurvedic concept of *prakriti*. *Journal of Biosciences* **44**, 112–119. https://doi.org/10.1007/s12038-019-9939-6.

Chauhan NS, Pandey R, Mondal AK, Gupta S, Verma MK, Jain S, Ahmed V, Patil R, Agarwal D, Girase B, Shrivastava A, Mobeen F, Sharma V, Srivastava TP, Juvekar SK, Prasher B, Mukerji M and Dash D (eds) (2018) Western Indian rural gut microbial diversity in extreme *Prakriti* endo-phenotypes reveals signature microbes. *Frontiers in Microbiology* **9**, 1–12. https://doi.org/10.3389/fmicb.2018.00118.

Chen R and Snyder M (2012) Systems biology: Personalized medicine for the future? *Current Opinion in Pharmacology* **12**, 623–628.

Coates JM, Gurnell M and Rustichini A (2009) Second-to-fourth digit ratio predicts success among high-frequency financial traders. *Proceedings of the National Academy of Sciences of the United States of America* **106**, 623–628. https://doi.org/10.1073/pnas.0810907106.

Cook RJ and Sackett DL (1995) The number needed to treat: A clinically useful measure of treatment effect. *BMJ* **310**, 452–454. https://doi.org/10.1136/bmj.310.6977.452.

Denny JC, Bastarache L, Ritchie MD, Carroll RJ, Zink R, Mosley JD, Field JR, Pulley JM, Ramirez AH, Bowton E, Basford MA, Carrell DS, Peissig PL, Kho AN, Pacheco JA, Rasmussen LV, Crosslin DR, Crane PK, Pathak J, Bielinski SJ, Pendergrass SA, Xu H, Hindorff LA, Li R, Manolio TA, Chute

CG, Chisholm RL, Larson EB, Jarvik GP, Brilliant MH, McCarty CA, Kullo IJ, Haines JL, Crawford DC, Masys DR and Roden DM (2013) Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nature Biotechnology* **31**, 1102–1111. https://doi.org/10.1038/nbt.2749.

Denny JC, Ritchie MD, Basford MA, Pulley JM, Bastarache L, Brown-Gentry K, Wang D, Masys DR, Roden DM and Crawford DC (2010) PheWAS: Demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics* **26**, 1205–1210. https://doi.org/10.1093/bioinformatics/btq126.

Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH and Nadeau JH (2010) Missing heritability and strategies for finding the underlying causes of complex disease. *Nature Reviews. Genetics* **11**, 445–450.

Fischer Pedersen JK, Klimek M, Galbarczyk A, Nenko I, Sobocki J, Christensen DL and Jasienska G (2021) Digit ratio (2D:4D) is not related to cardiovascular diseases or their risk factors in menopausal women. *American Journal of Human Biology* **33**. https://doi.org/10.1002/ajhb.23505.

Gheware A, Dholakia D, Kannan S, Panda L, Rani R, Pattnaik BR, Jain V, Parekh Y, Enayathullah MG, Bokara KK, Subramanian V, Mukerji M, Agrawal A and Prasher B (2021a) Adhatoda Vasica attenuates inflammatory and hypoxic responses in preclinical mouse models: Potential for repurposing in COVID-19-like conditions. *Respiratory Research* **22**, 99–113. https://doi.org/10.1186/s12931-021-01698-9.

Gheware A, Panda L, Khanna K, Bhatraju NK, Jain V, Sagar S, Kumar M, Singh VP, Kannan S, Subramanian V, Mukerji M, Agrawal A and Prasher B (2021b) Adhatoda vasica rescues the hypoxia-dependent severe asthma symptoms and mitochondrial dysfunction. *American Journal of Physiology. Lung Cellular and Molecular Physiology* **320**, L757-L769. https://doi.org/10.1152/ajplung.00511.2020.

Gibson G (2019a) Going to the negative: Genomics for optimized medical prescription. *Nature Reviews. Genetics* **20**, 1–2.

Gibson G (2019b) On the utilization of polygenic risk scores for therapeutic targeting. *PLoS Genetics* **15**. https://doi.org/10.1371/journal.pgen.1008060.

Govindaraj P, Nizamuddin S, Sharath A, Jyothi V, Rotti H, Raval R, Nayak J, Bhat BK, Prasanna BV, Shintre P, Sule M, Joshi KS, Dedge AP, Bharadwaj R, Gangadharan GG, Nair S, Gopinath PM, Patwardhan B, Kondaiah P, Satyamoorthy K, Valiathan MV and Thangaraj K (2015) Genome-wide analysis correlates Ayurveda *Prakriti*. *Scientific Reports* **5**, 1–12. https://doi.org/10.1038/srep15786.

Gupta PD (2015) Pharmacogenetics, pharmacogenomics and ayurgenomics for personalized medicine: A paradigm shift. *Indian Journal of Pharmaceutical Sciences* **77**, 135–141.

Haider M, Anand V, Enayathullah MG, Parekh Y, Ram S, Kumari S, Anmol PG, Shukla M, Dholakia D, Ray A, Bhattacharyya S, Sharma U, Bokara KK, Prasher B and Mukerji M (2022) Anti-SARS-CoV-2 potential of Cissampelos pareira L. identified by connectivity map-based analysis and in vitro studies. *BMC Complementary Medicine and Therapies* **22**, 114–123. https://doi.org/10.1186/s12906-022-03584-3.

Haider M, Dholakia D, Panwar A, Garg P, Gheware A, Singh D, Singhal K, Burse SA, Kumari S, Sharma A, Ray A, Medigeshi GR, Sharma U, Prasher B and Mukerji M (2021) Transcriptome analysis and connectivity mapping of Cissampelos pareira L. provides molecular links of ESR1 modulation to viral inhibition. *Scientific Reports* **11**, 20095–20103. https://doi.org/10.1038/s41598-021-99444-0.

Hankey A (2005) The scientific value of Ayurveda. *Journal of Alternative and Complementary Medicine* **11**, 221–225.

Harper AR, Nayee S and Topol EJ (2015) Protective alleles and modifier variants in human health and disease. *Nature Reviews. Genetics* **16**, 689–701.

Heck A, Milnik A, Vukojevic V, Petrovska J, Egli T, Singer J, Escobar P, Sengstag T, Coynel D, Freytag V, Fastenrath M, Demougin P, Loos E, Hartmann F, Schicktanz N, Bizzini BD, Vogler C, Kolassa I-T, Wilker S, Elbert T, Schwede T, Beisel C, Beerenwinkel N, de Quervain DJ-F and Papassotiropoulos A (2017) Exome sequencing of healthy phenotypic extremes links TROVE2 to emotional memory and PTSD. *Nature Human Behaviour* **1**, 1–10. https://doi.org/10.1038/s41562-017-0081.

Hood L and Flores M (2012) A personal view on systems medicine and the emergence of proactive P4 medicine: Predictive, preventive, personalized and participatory. *New Biotechnology* **29**, 613–624. https://doi.org/10.1016/j.nbt.2012.03.004.

Hood L and Friend SH (2011) Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nature Reviews. Clinical Oncology* **8**, 184–187. https://doi.org/10.1038/nrclinonc.2010.227.

Hripcsak G, Ryan PB, Duke JD, Shah NH, Park RW, Huser V, Suchard MA, Schuemie MJ, De Falco FJ, Perotte A, Banda JM, Reich CG, Schilling LM, Matheny ME, Meeker D, Pratt N and Madigan D (2016) Characterizing treatment pathways at scale using the OHDSI network. *Proceedings of the National Academy of Sciences of the United States of America* **113**, 7329–7336. https://doi.org/10.1073/pnas.1510502113.

Joshi K, Ghodke Y and Patwardhan B (2011) Traditional medicine to modern pharmacogenomics: Ayurveda *Prakriti* type and CYP2C19 gene polymorphism associated with the metabolic variability. *Evidence-based Complementary and Alternative Medicine* **2011**, 1–5. https://doi.org/10.1093/ecam/nep206.

Juyal RC, Negi S, Wakhode P, Bhat S, Bhat B and Thelma BK (2012) Potential of Ayurgenomics approach in complex trait research: Leads from a pilot study on rheumatoid arthritis. *PLoS One* **7**. https://doi.org/10.1371/journal.pone.0045752.

Juyal G, Pandey A, Garcia SL, Negi S, Gupta R, Kumar U, Bhat B, Juyal RC and Thelma BK (2022) Stratification of rheumatoid arthritis cohort using Ayurveda based deep phenotyping approach identifies novel genes in a GWAS. *Journal of Ayurveda and Integrative Medicine* **13**, 1–10. https://doi.org/10.1016/j.jaim.2022.100578.

Khera A, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT and Kathiresan S (2018) Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature Genetics* **50**, 1219–1224.

Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, Lerner J, Brunet JP, Subramanian A, Ross KN, Reich M, Hieronymus H, Wei G, Armstrong SA, Haggarty SJ, Clemons PA, Wei R, Carr SA, Lander ES and Golub TR (2006) The connectivity map: Using gene-expression signatures to connect small molecules, genes, and disease. *Science* **313**, 1929–1935. https://doi.org/10.1126/science.1132939.

Lemonnier N, Zhou G-B, Prasher B, Mukerji M, Chen Z, Brahmacharid SK, Nobleg D, Auffraya C and Sagnerh M (2017) Traditional knowledge-based medicine: A review of history, principles, and relevance in the present context of P4 systems medicine. *Progress in Preventive Medicine* **2**, 1–13. https://doi.org/10.1097/pp9.0000000000000011.

Lillie EO, Patay B, Diamant J, Issell B, Topol EJ and Schork NJ (2011) The n-of-1 clinical trial: The ultimate strategy for individualizing medicine? *Personalized Medicine* **8**, 161–173. https://doi.org/10.2217/pme.11.7.

Liu S and Crawford DC (2022) Maturation and application of phenome-wide association studies. *Trends in Genetics* **38**, 353–363.

Loscalzo J and Barabasi AL (2011) Systems biology and the future of medicine. *Wiley Interdisciplinary Reviews. Systems Biology and Medicine* **3**, 619–627. https://doi.org/10.1002/wsbm.144.

Loscalzo J, Kohane I and Barabasi AL (2007) Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. *Molecular Systems Biology* **3**, 1–11.

Manning JT, Baron-Cohen S, Wheelwright S and Sanders G (2001) The 2nd to 4th digit ratio and autism. *Developmental Medicine and Child Neurology* **43**, 160–164. https://doi.org/10.1111/j.1469-8749.2001.tb00181.x.

Manning JT, Morris L and Caswell N (2007) Endurance running and digit ratio (2D:4D): Implications for fetal testosterone effects on running speed and vascular health. *American Journal of Human Biology* **19**, 416–421. https://doi.org/10.1002/ajhb.20603.

Manning JT, Scutt D, Wilson J and Lewis-Jones DI (1998) The ratio of 2nd to 4th digit length: A predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. *Human Reproduction* **13**, 3000–3004. https://doi.org/10.1093/humrep/13.11.3000.

Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA and Visscher PM (2009) Finding the missing heritability of complex diseases. *Nature* **461**, 747–753.

Martin AR, Costa HA, Lappalainen T, Henn BM, Kidd JM, Yee MC, Grubert F, Cann HM, Snyder M, Montgomery SB and Bustamante CD (2014) Transcriptome sequencing from diverse human populations reveals differentiated regulatory architecture. *PLoS Genetics* **10**. https://doi.org/10.1371/journal.pgen.1004549.

Mobeen F, Sharma V and Prakash T (2020) Comparative gut microbiome analysis of the *Prakriti* and Sasang systems reveals functional level similarities in constitutionally similar classes. *3 Biotech* **10**. https://doi.org/10.1007/s13205-020-02376-1.

Montgomery SB and Dermitzakis ET (2011) From expression QTLs to personalized transcriptomics. *Nature Reviews. Genetics* **12**, 277–282. https://doi.org/10.1038/nrg2969.

Mukerji M and Prasher B (2011) Ayurgenomics: A new approach in personalized and preventive medicine. *Science and Culture* **77**.

Mukerji M and Prasher B (2015) Genomics and traditional Indian ayurvedic medicine. *Genomics and Society: Ethical, Legal, Cultural and Socioeconomic Implications* **2016**, 271–292.

Mukerji M and Sagner M (2019) Genomics and big data analytics in Ayurvedic medicine. *Progress in Preventive Medicine* **4**, 1–2. https://doi.org/10.1097/pp9.0000000000000021.

Nagpal S, Tandon R and Gibson G (2022) Canalization of the polygenic risk for common diseases and traits in the UK biobank cohort. *Molecular Biology and Evolution* **39**. https://doi.org/10.1093/molbev/msac053.

Noell G, Faner R and Agustí A (2018) From systems biology to p4 medicine: Applications in respiratory medicine. *European Respiratory Review* **27**, 1–15. https://doi.org/10.1183/16000617.0110-2017.

Olson M (2012) Human genetic individuality. *Annual Review of Genomics and Human Genetics* **13**, 1–7.

Patwardhan B (2014) Bridging Ayurveda with evidence-based scientific approaches in medicine. *EPMA Journal* **5**, 1–7.

Patwardhan B and Bodeker G (2008) Ayurvedic genomics: Establishing a genetic basis for mind-body typologies. *Journal of Alternative and Complementary Medicine* **14**, 571–576. https://doi.org/10.1089/acm.2007.0515.

Patwardhan B and Mashelkar RA (2009) Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show the way forward? *Drug Discovery Today* **14**, 804–811.

Paul P, Iyer S, Nadella RK, Nayak R, Chellappa AS, Ambardar S, Sud R, Sukumaran SK, Purushottam M, Jain S, ADBS Consortium and **Viswanath B** (2020) Lithium response in bipolar disorder correlates with improved cell viability of patient derived cell lines. *Scientific Reports* **10**, 1–10. https://doi.org/10.1038/s41598-020-64202-1.

Pendergrass SA and Ritchie MD (2015) Phenome-wide association studies: Leveraging comprehensive phenotypic and genotypic data for discovery. *Current Genetic Medicine Reports* **3**, 92–100. https://doi.org/10.1007/s40142-015-0067-9.

Prasher B, Aggarwal S, Mandal AK, Sethi TP, Deshmukh SR, Purohit SG, Sengupta S, Khanna S, Mohammad F, Garg G, Brahmachari SK, Indian Genome Variation Consortium and **Mukerji M** (2008) Whole genome expression and biochemical correlates of extreme constitutional types defined in Ayurveda. *Journal of Translational Medicine* **6**, 1–12. https://doi.org/10.1186/1479-5876-6-48.

Prasher B, Gibson G and Mukerji M (2016) Genomic insights into ayurvedic and western approaches to personalized medicine. *Journal of Genetics* **95**, 209–228.

Prasher B, Varma B, Kumar A, Khuntia BK, Pandey R, Narang A, Tiwari P, Kutum R, Guin D, Kukreti R, Dash D, TRISUTRA Ayurgenomics Consortium and **Mukerji M** (2017) Ayurgenomics for stratified medicine: TRISUTRA consortium initiative across ethnically and geographically diverse Indian populations. *Journal of Ethnopharmacology* **197**, 274–293.

R.T K and Kalaichevan A (2020) Molecular dynamics of Ayurgenomics. *Journal of Indian Studies* **10**, 31–37. https://doi.org/10.22452/jis.sp2013no1.7.

Rani R, Rengarajan P, Sethi T, Khuntia BK, Kumar A, Punera DS, Singh D, Girase B, Shrivastava A, Juvekar SK, Pesala B, Mukerji M, Deepak KK and Prasher B (2022) Heart rate variability during head-up tilt shows individual differences among healthy individuals of extreme *Prakriti* types. *Physiological Reports* **17**, 1–16.

Rotti H, Mallya S, Kabekkodu PS, Chakrabarty S, Bhale S, Bharadwaj R, Bhat BK, Dedge AP, Dhumal VR, Gangadharan GG, Gopinath PM, Govindaraj P, Joshi KS, Kondaiah P, Nair S, Nair SN, Nayak J, Prasanna BV, Shintre P, Sule M, Thangaraj K, Patwardhan B, Valiathan MV and Satyamoorthy K (2015) DNA methylation analysis of phenotype specific stratified Indian population. *Journal of Translational Medicine* **13**, 1–12. https://doi.org/10.1186/s12967-015-0506-0.

Rotti H, Raval R, Anchan S, Bellampalli R, Bhale S, Bharadwaj R, Bhat BK, Dedge AP, Dhumal VR, Gangadharan GG, Girijakumari TK, Gopinath PM, Govindaraj P, Halder S, Joshi KS, Kabekkodu SP, Kamath A, Kondaiah P, Kukreja H, Kumar KL, Nair S, Nair SN, Nayak J, Prasanna BV, Rashmishree M, Sharanprasad K, Thangaraj K, Patwardhan B, Satyamoorthy K and Valiathan MV (2014) Determinants of *prakriti*, the human constitution types of Indian traditional medicine and its correlation with contemporary science. *Journal of Ayurveda and Integrative Medicine* **5**, 167–175. https://doi.org/10.4103/0975-9476.140478.

Satyamoorthy K, Guruprasad K, Nayak J, Kabekkodu SP, Kukreja H, Mallya S, Nayak J, Bhradwaj RC, Gangadharan GG, Prasanna BV, Raval R, Kamath A, Gopinath PM, Kondaiah P and Satyamoorthy K (2014) Immunophenotyping of normal individuals classified on the basis of human dosha *prakriti*. *Journal of Ayurveda and Integrative Medicine* **5**, 43–49. https://doi.org/10.4103/0975-9476.128857.

Sethi TP, Prasher B and Mukerji M (2011) Ayurgenomics: A new way of threading molecular variability for stratified medicine. *ACS Chemical Biology* **6**, 875–880.

Shalini TV, Jnana A, Sriranjini SJ, Tanwar AS, Brand A, Murali TS, Satyamoorthy K and Gangadharan GG (2021) Exploring the signature gut and oral microbiome in individuals of specific Ayurveda *prakriti*. *Journal of Biosciences* **46**, 1–20. https://doi.org/10.1007/s12038-021-00182-2.

Sharma PV (1981) *Charaka Samhita: Text with English Translation*. Varanasi: Chaukambha Orientalia.

Sharma PV (1999) *Susruta-Samhita: With English Translation of Text and Dalhana's Commentary along with Critical Notes*. Varanasi: Chaukamba Vishwa Bharati.

Simonson TS, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, Bai Z, Lorenzo FR, Xing J, Jorde LB, Prchal JT and Ge R (2010) Genetic evidence for high-altitude adaptation in Tibet. *Science* **329**, 72–75. https://doi.org/10.1126/science.1189406.

Singh H, Bhargava S, Ganeshan S, Kaur R, Sethi T, Sharma M, Chauhan M, Chauhan N, Chauhan R, Chauhan P and Brahmachari S (2018) Big data analysis of traditional knowledge-based Ayurveda medicine. *Progress in Preventive Medicine* **3**. https://doi.org/10.1097/pp9.0000000000000020.

Singh S, Gehlot S and Agrawal NK (2019) Basis of disease manifestation: A molecular and Ayurvedic approach with an integrated concept of Ayurgenomics. *Journal of Natural Remedies* **19**, 99–113.

Sreedevi S, Sayed R, Harikumar KB and Tripathy RN (2016) Ayurgenomics: A novel approach in preventing congenital anomalies: A review. *International Journal of Research in Ayurveda and Pharmacy* **7**, 51–53.

Subramanian A, Narayan R, Corsello SM, Peck DD, Natoli TE, Lu X, Gould J, Davis JF, Tubelli AA, Asiedu JK, Lahr DL, Hirschman JE, Liu Z, Donahue M, Julian B, Khan M, Wadden D, Smith IC, Lam D, Liberzon A, Toder C, Bagul M, Orzechowski M, Enache OM, Piccioni F, Johnson SA, Lyons NJ, Berger AH, Shamji AF, Brooks AN, Vrcic A, Flynn C, Rosains J, Takeda DY, Hu R, Davison D, Lamb J, Ardlie K, Hogstrom L, Greenside P, Gray NS, Clemons PA, Silver S, Wu X, Zhao WN, Read-Button W, Wu X, Haggarty SJ, Ronco LV, Boehm JS, Schreiber SL, Doench JG, Bittker JA, Root DE, Wong B and Golub TR (2017) A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. *Cell* **171**, 1437–1452. https://doi.org/10.1016/j.cell.2017.10.049.

Tian Q, Price ND, Hood L (2012) Systems cancer medicine: Towards realization of predictive, preventive, personalized and participatory (P4) medicine. *Journal of Internal Medicine* **271**, 111–121.

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press

Tiwari P, **Kutum R**, **Sethi T**, **Shrivastava A**, **Girase B**, **Aggarwal S**, **Patil R**, **Agarwal D**, **Gautam P**, **Agrawal A**, **Dash D**, **Ghosh S**, **Juvekar S**, **Mukerji M and Prasher B** (2017) Recapitulation of Ayurveda constitution types by machine learning of phenotypic traits. *PLoS One* **12**. https://doi.org/10.1371/journal.pone.0185380.

Topol EJ (2014) Individualized medicine from prewomb to tomb. *Cell* **157**, 241–253.

Topol EJ (2019) High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine* **25**, 44–56.

Venkanna Rao B (2022) Personalized medicine: Ayurgenomics and modern medicine. *Indian Journal of Pharmacy Practice* **15**. https://doi.org/10.5530/ijopp.15.1.1.

Wallace RK (2020) Ayurgenomics and modern medicine. *Medicina (Lithuania)* **56**, 1–7.

https://doi.org/10.1017/pcm.2023.15 Published online by Cambridge University Press