



Predictive, Preventive and Personalized Medicine: Leads From Ayurvedic Concept of Prakriti (Human Constitution)

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Abstract

Purpose of Review Genomics has ushered in a phase of predictive, preventive and personalized medicine (PM), and several attempts are being made to detect genetic variations that are responsible for susceptibility to diseases and varied response to medications, however, have met with only a limited success. Ancient Indian system of medicine, Ayurveda, strongly emphasize on personalized patient care under the concept of *Prakriti* (phenotype-based human constitution). We would therefore like to put forward a new dimension of PM—the ‘*Prakriti*-based medicine’ bearing testable molecular and genetic correlates.

Recent Findings Current investigations in the field of genomics, PM and Ayurveda have inspired many researchers and started in-depth deliberation on how *Prakriti* (phenotype-based Ayurveda constitution) is associated with the field of genomics, biochemistry, psychology, physiology and therapeutics. Various genotypes have also been correlated with *Prakriti*. Studies have shown wide range of utilities of *Prakriti* assessment in therapeutics, i.e. from predicting disease susceptibility of an individual, prevention of impending diseases, early diagnosis through screening of the high risk, rational drug designing, customization of therapy (drug, diet and lifestyle) and health maintenance.

Summary Ayurvedic *Prakriti*-based treatment resonates with PM and pharmacogenomics and holds potential and promise for future predictive or preventive medicine. Further studies are warranted towards integrating or complementing genomics and contemporary medical science with *Prakriti* and explore the future possibilities.

Keywords Ayurveda · Traditional Indian medicine · Pharmacogenomics · Personalized medicine · Prakriti · Tridosha

Introduction

Decrypting human genome has steered current biomedical science towards a hope of revivifying contemporary symptomatic treatment approaches into personalized and predictive therapies depending upon an individual’s genetic makeup. Investigations in the past decade aptly introduced and mandated in-depth deliberation on how ‘personalized medicine

(PM)’ is providing an impetus in shaping the future of medicine. PM or individualized medicine is a rapidly advancing therapeutic approach owing to its potential to transform and strengthen the healthcare system. The basic principle of PM is to tailor the treatment strategies based on each individual’s clinical, genomic, epigenomic, proteomic and environmental profile [1]. Though the PM is gaining popularity in the past decade, the concept is not new as it bears resemblance with the time-tested ancient medical systems, viz. Ayurveda, traditional Chinese medicine and traditional Iranian medicine. These medical systems follow individualized treatment approach as per the human constitutional types defined as per their own well-defined wisdoms [2].

The concept of PM or predictive medicine has its roots date back to 1500 BCE in age-old traditional Indian medicine, Ayurveda, which has a stratified approach as its basic doctrine for personalizing the treatment under *Purusham Purusham Vikshya* (an individualized approach) principle [3]. The seeds of predictive and personalized medicine were sown by an ancient Ayurveda treatise—Charaka Samhita, which quotes that: ‘Every individual is distinct from another and hence

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should be treated as a different entity. As many variations are there in the universe, all are seen in human beings' [4]. *Prakriti* is the fundamental constitution of a person, formed at the time of birth, differentiates variations according to the *Beeja* (genetic) and three *doshas* or *Tridosha* (body humours, viz. *Vata* (kinetic), *Pitta* (metabolic) and *Kapha* (potential)), influence into three extreme geno-psycho-somatotypes or birth constitutions or body types, i.e. *Vata Prakriti*, *Pitta Prakriti* and *Kapha Prakriti*, and remains invariant throughout lifetime [4]. Some scholars have roughly related these *Vata*, *Pitta* and *Kapha* body constitutions with Sheldon somatotypes of twentieth century, i.e. ectomorphic, mesomorphic and endomorphic body types respectively [5].

Prakriti, the notable basic construct of Ayurvedic epistemology, elucidates the biological variability (at cellular and genomic level) that is observed in different individuals. *Prakriti* of each person determines the response differently when exposed to the same stimuli and makes every individual a distinct entity [6•]. Modern medicine classifies the human population based on geographical origin, ethnicity, race and other factors, while *Prakriti* classification distinguishes and characterizes a person apart from others based on morphological, physiological or psychological traits and is independent of racial, ethnic or geographical factors. The *Tridosha* work in harmony and regulate each other to maintain homeostasis, equilibrium, healthy body and mind. Any imbalance of *Tridosha* can lead to disorders as per the *Prakriti* of an individual. For instance, *Pitta Prakriti* persons are mentioned to be more susceptible to peptic ulcers, high blood pressure and skin disorders; a *Vata Prakriti* person to backache, joint aches and crackling joints; while individuals with *Kapha Prakriti* are more likely to develop obesity, diabetes and atherosclerosis. Various common health disorders and the susceptibility of different *Prakriti* types are stipulated in Table 1. Development and advancement of different health ailments with their subtypes are mentioned to be depending upon the derivation and manner of perturbation of *Tridosha*, and the treatment is aimed to maintain the *Tridosha* in homeostasis [3, 7]. Likewise, modern systems biology exemplified by translational P4 medicine surmises the convergence of multi-scalar genetic, cellular, physiological and environmental networks to speculate phenotypic outcomes of perturbations [8].

Present review provides comprehensive understanding on PM from evidence-based Ayurvedic perspective and how *Prakriti* (phenotype-based human constitution) is associated with the field of genomics, biochemistry, physiology and therapeutics.

Assessment of *Prakriti*

Over 150 anatomical and physical activity-related characteristic features are examined for *Prakriti* assessment, where physiological and psychological parameters are extrapolated

based on the responses of a person and past history [9•]. As per Ayurvedic classical texts, the distinct characters of three basic *Prakriti* types and their predisposition to diseases are stipulated in Fig. 1.

In order to avert misinterpretation of the clinical features during examination, recent and infrequent change of internal or external environment is also taken into consideration. It is an intricate task to infer *Prakriti* from such enormous range of features. Though clinical evaluation of *Prakriti* is non-empirical, it can be assessed and substantiated through advanced machine learning techniques, which may ease precise *Prakriti* prediction [10•]. For determination of *Prakriti*, along with classical Ayurvedic methods such as pulse detection and standard questionnaires (to identify characteristic features of individual's *Prakriti*), software like AyuSoft (mainly for *Prakriti* of adults) and PRS-IPA (mainly for *Prakriti* of children) are also being developed [11, 12]. Based on the assessment of *Prakriti*, therapy is planned in Ayurveda clinical practice. Ayurvedic mode of personalized treatment approach based on three *Prakriti* types is different from modern medical system and the same is portrayed in Fig. 2.

Pharmacogenomics Vis-à-Vis Ayurgenomics

Pharmacogenomics, a subset of *Prakriti*-based medicine, deals with genetic interactions with drugs, explains the inter-individual variations in drug responses (by correlating gene expression or single nucleotide polymorphism (SNP)) and helps PM approach to optimize rational drug therapy thereby ensures maximum efficacy with minimal adverse effects [13].

The variations in response to drug therapy due to differences in acetylation of drugs are well-known exemplar of genetic polymorphism. These demographic and ethnic differences affecting the phenotypic variability may be related to Ayurvedic concept of factors responsible for *Prakriti*, which include *Jati Prasakta*, *Kula Prasakta* and *Deshanupatini* types of *Prakriti* [4]. Ayurgenomics is an integrative approach utilizing genomics and principles of Ayurveda, aiming at discovery of predictive markers for preventive and PM by establishing the correlation between DNA and *Prakriti*. Better understanding of human genome and SNP has aided to understand the scientific basis of individual variation, which appear analogous with the concept of *Prakriti*-based medicine, i.e. Ayurgenomics [14•]. This Ayurvedic approach of phenotypic classification of three constitutional types seems to bear similarities with pharmacogenomics.

Genomic Counterparts of *Prakriti*

The correlation of the concept of *Prakriti* with genomics was hypothesized over a decade ago [14•]. To substantiate the

Table 1 Common health disorders and the susceptibility of different *Prakriti* types

Sr no.	Health disorder	Biomedical approximation with condition in Ayurveda	More susceptible Prakriti type
1.	Bleeding disorders	<i>Raktapitta</i>	Pitta
2.	Hypertension	<i>Raktagatavata</i>	Vata
3.	Peptic/gastric ulcer	<i>Annadrava shool, Parinama shool</i>	Pitta, Vata
4.	Atherosclerosis	<i>Dhamani Praticaya</i>	Kapha
5.	Alzheimer’s disease	<i>Smriti Bhransha</i>	Vata, Kapha
6.	Some specific cancers	<i>Granthi, Arbuda</i>	Kapha
7.	Arrhythmia	<i>Hridrava</i>	Vata
8.	Asthma	<i>Shwasa</i>	Kapha
9.	Liver cirrhosis	<i>Yakrita Vikara</i>	Vata, Pitta
10.	Type 2 diabetes	<i>Prameha</i>	Kapha, Vata
11.	Chronic obstructive pulmonary disease	<i>Shwasa Roga</i>	Kapha
12.	Metabolic syndrome	<i>Medavaha srotodusti lakshana, Apathyanimittaja prameha, Updrava of Avaran</i>	Kapha, Pitta
13.	Chronic renal failure	<i>Mutra Vikara</i>	Kapha, Vata
14.	Osteoporosis	<i>Asthisushirata</i>	Vata, Pitta
15.	Obesity	<i>Sthoulya</i>	Kapha
16.	Rheumatoid arthritis	<i>Amavata</i>	Vata
17.	Depression	<i>Avasada</i>	Vata, Pitta
18.	Dementia	<i>Smritibuddhihrass</i>	Vata

genetic and molecular basis of *Prakriti*, several dedicated attempts correlate *Prakriti* classification with genetic information and association of SNPs. Recent report has found

differential DNA methylation signatures in three distinct *Prakriti* types, thus, demonstrated the epigenetic basis of Ayurvedic human classification [15••]. Genetic connotation

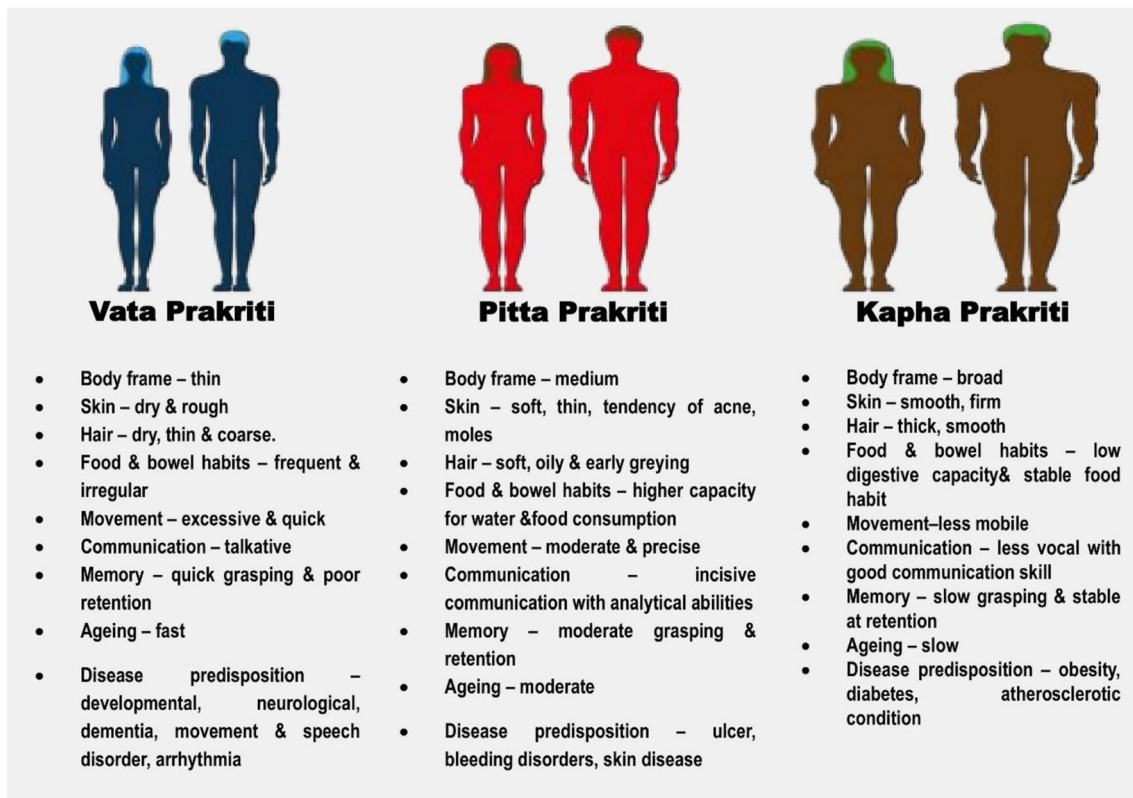


Fig. 1 Discriminate attribute of individuals of three contrasting feature of *Prakriti* types as described in original texts

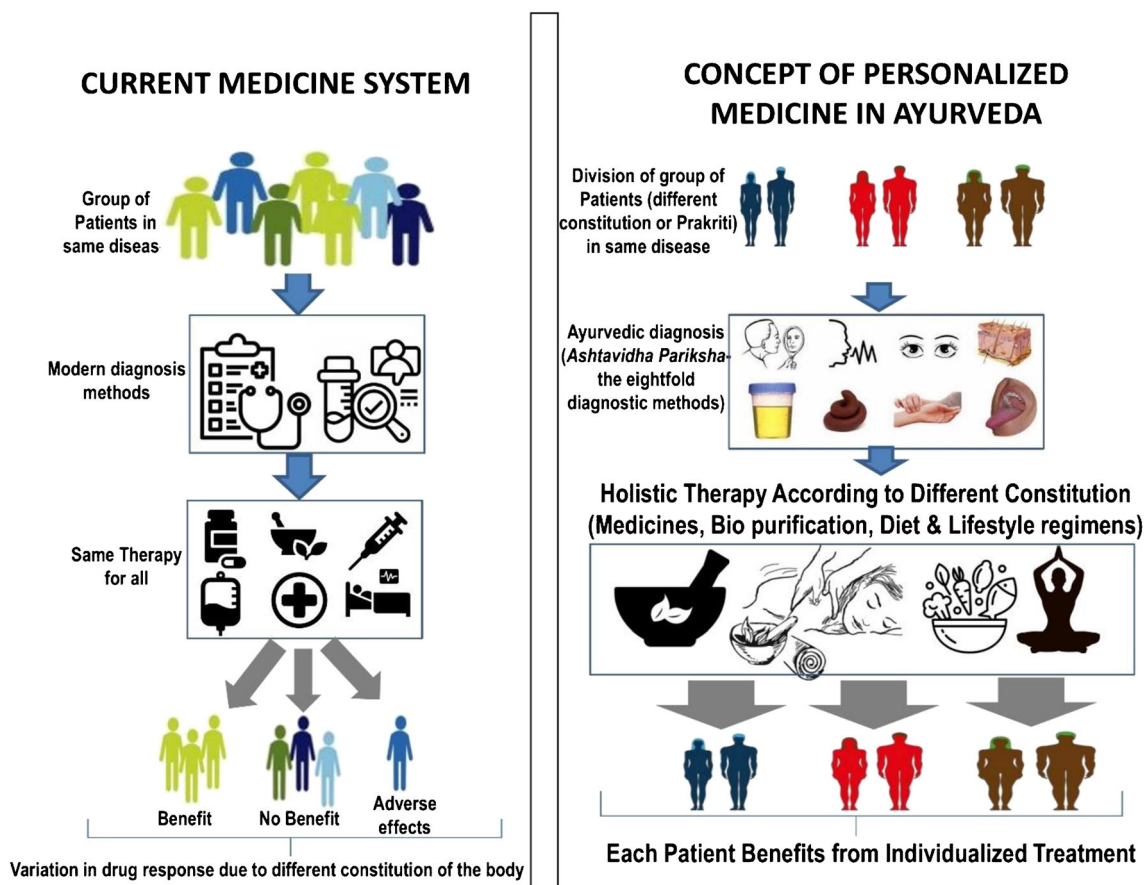


Fig. 2 Treatment approaches of modern medicine and traditional Ayurveda medical systems

of *Prakriti* demonstrated a link between Human Leukocyte Antigen (HLA) alleles and *Prakriti* type, ascertaining a rationale and preliminary experimental support for the hypothesis of a linkage between HLA alleles and *Tridosha* theory of human *Prakriti* types [16]. A study detected reasonable connection between HLA type and *Prakriti* type. It affirmed complete absence of the HLA DRB1*02 allele in the *Vata Prakriti* and of HLA DRB1*13 in the *Kapha* type, and higher allele frequency of HLA DRB1*10 in the *Kapha* than in the *Pitta* and *Vata* types [6••]. A study has reported a significant correlation between CYP2C19 genotype and *Pitta Prakriti*. [17]. A study reported a link of EGLN1 gene partaking in high altitude adaptation, which was explored through genetic analysis of three *Prakritis*. The TT genotype of rs479200 which was more frequent in *Kapha Prakriti* and correlated with higher expression of EGLN1 was linked with patients suffering from high-altitude pulmonary edema, while it was less frequent in *Pitta* and nearly absent in residents of high altitude [18].

A recent study pointed out linkage of both specific genes and genomic variations with the diverse phenotypes representative of distinct *Prakriti* types. They classified three *Prakritis* and substantiated the classification by using genome-wide SNP markers. The study conducted genome-wide SNP

analysis (Affymetrix, 6.0) of 262 well-classified individuals of three *Prakritis*. After 106 permutations, significant variation was found in 52 SNPs ($p \leq 1 \times 10^{-5}$) amongst *Prakritis* with no any stratification-related confounding effect. Principal component analysis (PCA) of these SNPs classified 262 individuals into *Vata*, *Pitta* and *Kapha* groups irrespective of their ancestry. The finding was further validated with 297 Indian people samples with known ancestry and noticed that PGM1 correlates with phenotype of *Pitta* as quoted in the *Charaka Samhita* suggesting the genetic basis of *Prakriti* [19••]. Thus, several researchers made attempts to correlate the genomes with Ayurvedic *Prakriti* concept and the same is highlighted in Fig. 3.

Drug Administration, Drug Safety and *Prakriti*

Ayurveda strongly emphasize that prior prescribing medication several factors should be analysed to avoid drug-related adverse effects, such as age, season and time of administration, pathological stage of disease, digestive power, individual humours (*dosha*) and individual constituent (*Prakriti*) [20]. Idiosyncratic drug reactions are aberrant or bizarre or

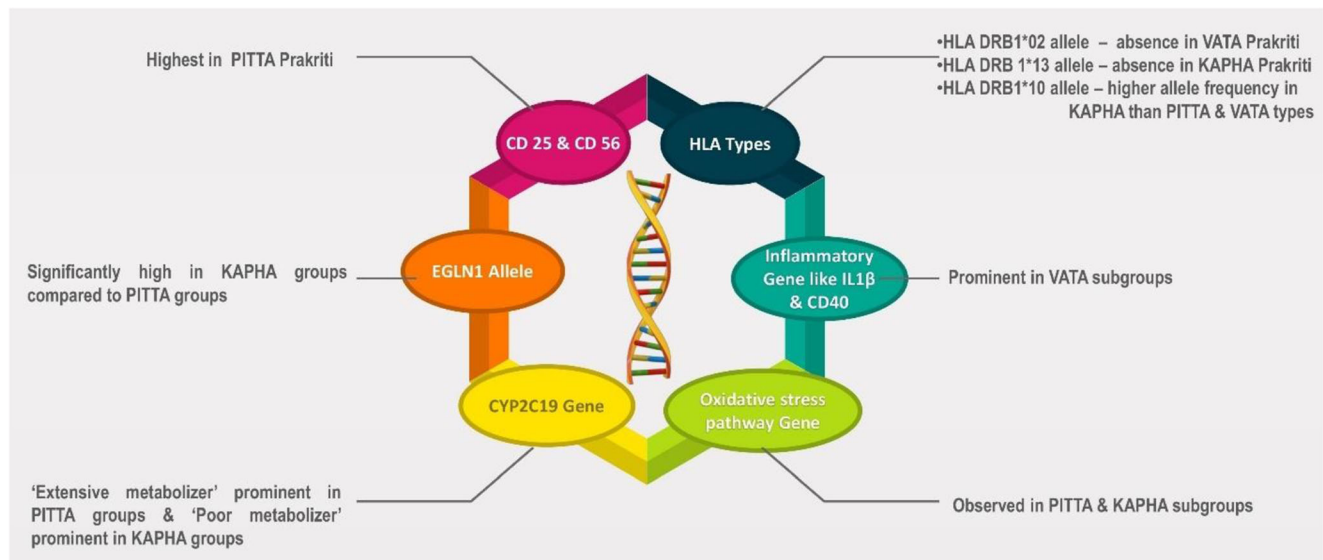


Fig. 3 Different genotypes correlated with *Prakriti*—based on published researches

hypersensitivity response of a person to a drug that is unrelated to the pharmacological effect of a drug and many a times the cause is unknown [21]. As per ‘Host vulnerability theory’, the effects of a drug vary from person to person [22]. The same concept has been explicated in Ayurveda as *Prakriti* or human constitution.

Studies also reveal that the different *Prakriti* persons may have dissimilar rates of drug metabolism which relates to drug metabolizing enzyme (DME) polymorphism as well. *CYP* gene polymorphisms are known to regulate drug tolerance and metabolism [23]. Researchers have correlated metabolic variability with *CYP2C19* genetic variability and HLA gene polymorphism to explicate the pharmacogenomics concept with distinct *Prakritis* [6•, 17]. In this interesting correlation between *CYP2C19* genotypes and *Prakriti*, Extensive Metabolizer genotype was present in *Pitta Prakriti* and Slow Metabolizer genotype was found in *Kapha Prakriti*. This validates the Ayurvedic concepts that *Kapha Prakriti* individuals are more prone to metabolic and cardiovascular disorders; accordingly, ancient scholars of Ayurveda advocate moderate exercise to *Kapha Prakriti* individuals to maintain *Kapha* in equilibrium and reduce the tendencies to develop diabetes and obesity [24, 25].

Several reports of adverse reaction of drugs and non-responsiveness to certain drugs are being witnessed [26–28]. Phenotypic classification of individuals as per *Prakriti* is also important in decreasing drug safety. In several examples, specific drugs are contraindicated in particular *Prakriti* type, e.g. Bhallataka (*Semecarpus anacardium*) and Hingu (*Ferula narthex*) are having hot potency and *Pitta* vitiating property therefore contraindicated in *Pitta* constitution individuals or *Pitta* dominant diseases [29]. Similarly, Dhatura (*Datura metel*) is having *Vata* vitiating potency, hence not advised in

Vata constitution persons or *Vata* dominant diseases [30]. Certain formulations are suitable for individuals of specific constitution, e.g. Ksheerbala Taila is indicated for *Vata Prakriti*, Kushmandavleha is indicated for *Pitta Prakriti* and Amrit Bhallataka is suitable for *Kapha Prakriti* individuals. Also, certain dosage forms are advised to certain *Prakriti* persons, e.g. Taila Kalpana (medicated oils) are usually indicated in *Vata Prakriti*, Ksheerpaka (medicated milk) and Hima Kalpana (cold infusions) in *Pitta Prakriti* and Asava-Arishta (fermented extracts) are advised in *Kapha Prakriti* individuals [31]. These examples clearly suggest that, consideration of Ayurvedic individualistic or constitution-based treatment approach while drug administration have effective role with respect to safety and efficacy.

Further exploration of Ayurvedic concept of constitution-based distinctive treatment plan could provide new directions for detecting the causal metabolic variability responsible for variations in drug response. These variations can be embraced under idiosyncrasy. Accordingly, rational drug designing should also emphasize on individual patients and sub-groups of patients.

Biochemical and Clinical Basis of *Prakriti*

The recent past has witnessed an extensive exploration on *Prakriti* apropos its genomic and biochemical correlations and subsequent clinical applications. The concept is claimed to have wide range of utilities in therapeutics, i.e. from predicting disease susceptibility of an individual, diagnosis, therapy and health maintenance (Fig. 4) [5, 16, 18, 32••].

Interestingly, in genome wide association studies (GWAS), over 2000 SNPs have been identified to be associated with

disease susceptibility. Understanding of *Prakriti* can help to surmount the current limitation of clinical heterogeneity in molecular genetic analysis of complex traits. A single extensive study conducted under Council of Scientific and Industrial Research (CSIR) led Indian Genome Variation (IGV) consortium project explored the genetic landscape of IGV related to disease and response to drugs [33, 34]. Individuals with three contrasting *Prakritis* showed strong contrast with respect to haematological parameters, body mass index (BMI), blood groups and at genome-wide expression levels [19••].

In a microarray profiling study, functional classes of genomes exhibiting differential expression amongst three *Prakritis* were found to be markedly involved with the bioprocesses like transport, regulating the protein kinase activity, immune responses and regulating the blood coagulation [32••]. A strong over-expression of genes was found in genes regulating cellular division and nucleocytoplasmic transport in *Vata Prakriti*, genes regulating immune surveillance in *Pitta Prakriti* and genes regulating anabolism in *Kapha Prakriti* individuals. It was interesting to note that 31% of the differentially expressed genes in these *Prakriti* types showed association with complex and monogenic diseases (in Online Mendelian Inheritance in Man (OMIM) and Genetic Association Database (GAD)) [32••].

Efforts have also been made to relate different *Prakriti* and their biochemical and transcriptomic profiles [35]. A study suggested discrete causal pathways for rheumatoid arthritis aetiology in *Prakriti*-based subgroups, thus supporting the Ayurvedic doctrines of *Prakriti* and PM. It related *Prakriti*

classification with inflammatory and oxidative stress-related genes, e.g. inflammation-regulating genes like IL1 β (C-C-C haplotype, $p = 0.0005$, OR = 3.09) and CD40 (rs4810485 allelic, $p = 0.04$, OR = 2.27) were found to be the determinants in *Vata* subgroup, while oxidative stress pathway genes in *Pitta* (SOD3 rs699473, $p = 0.004$, OR = 1.83; rs2536512 $p = 0.005$; OR = 1.88 and PON1 rs662, $p = 0.04$, OR = 1.53) and *Kapha* (SOD3 rs2536512, genotypic, $p = 0.02$, OR = 2.39) subgroups. Thus, Ayurgenomics viewpoint may have promising role in biomarker discovery for complex diseases [36]. *Prakriti*-based immunophenotyping of normal persons demonstrated striking dissimilarity in CD14, CD25 and CD56 marker expressions amongst *Prakriti* types. Increased CD25 and CD56 levels in *Kapha Prakriti* may signify better potential to exhibit immune response, which concord with the classical description in Ayurveda [37]. Serotonergic receptor gene 5HTR 2A showed a significantly high allele frequency in *Kapha Prakriti*. HLA genes are known to have profound role in defence response to infections and on immunogenic tendency to various diseases, and its high frequency was found in *Kapha Prakriti* [4].

Adenosine diphosphate (ADP)-induced maximal platelet aggregation (MPA) was found higher in *Vata-Pitta Prakriti* individuals and they responded better to lower dose of aspirin compared with other *Prakriti* types, which is suggestive of role of *Prakriti* identification in individualizing treatment or predicting disease susceptibility [38•]. Another study found the lesser intelligent quotient (IQ) of *Vata Prakriti* individuals in comparison with *Pitta Prakriti* and lesser IQ of *Pitta Prakriti* than *Kapha Prakriti*. Therefore, *Prakriti* assessment can offer decisive guidelines in direction of career selection

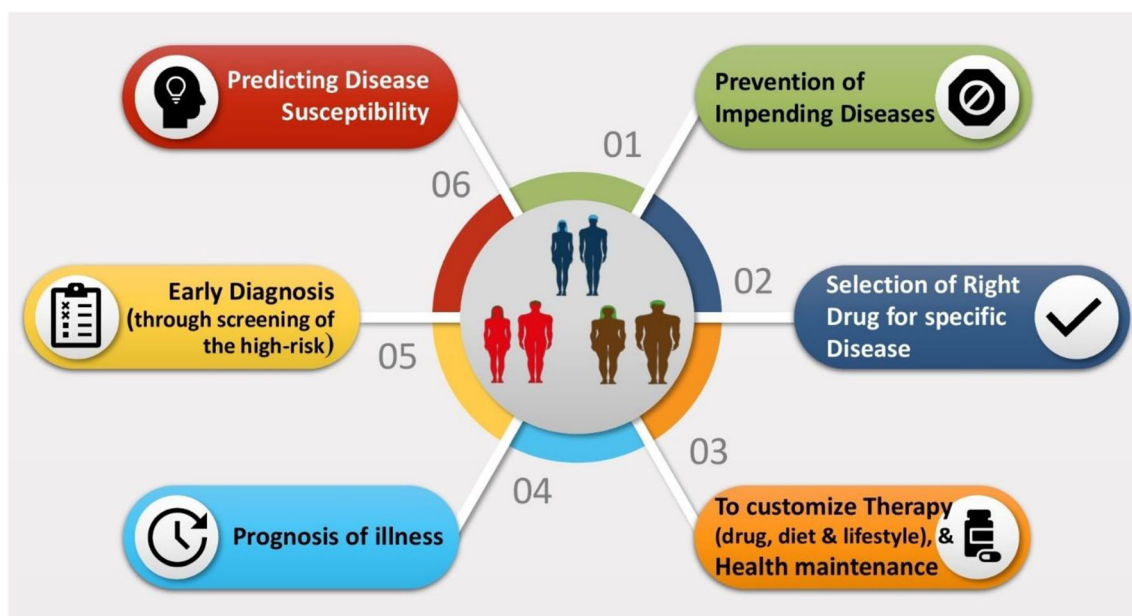


Fig. 4 Various utilities of *Prakriti* assessment in therapeutics

[39]. In a work, *Prakriti* was assessed in patients with established Parkinson's disease and the findings showed that the incidence of Parkinson's was higher in those with *Vata Prakriti* [40].

Another study investigated how walking (aerobic isotonic exercise) affected the physiological variants in diabetics as per *Prakriti* and found a strong association between blood pressure, pulse pressure, respiratory rate and certain biochemical parameters with the *Prakriti* of an individual at certain physiological conditions [41].

A study showed that the levels of serum uric acid, serum zinc, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and the common risk factors for cardiovascular disorders such as triglycerides (TG), low density lipid (LDL), very low density lipid (VLDL), low density lipid/high density lipid (LDL/HDL) ratio were significantly higher, whereas HDL level significantly lower in *Kapha Prakriti* individuals in comparison with other *Prakriti* type. They also found higher serum prolactin and prothrombin time levels in *Vata Prakriti*, and higher level of haematological parameters, viz. haemoglobin, packed cell volume (PCV) and red blood cells (RBC) in *Pitta Prakriti* individuals in comparison with other *Prakriti* [32••]. These observations were also supported by several studies, where *Kapha* dominant *Prakriti* subjects show a higher prevalence/susceptibility to obesity, type 2 diabetes, hyperuricemia, higher lipid profile and BMI values, cardiovascular risks and atherosclerosis as compared with *Vata* and *Pitta* dominant *Prakriti* [13, 42, 43]. Another study found significantly higher level of TG, VLDL and LDL and significantly lower HDL in *Vata-Kapha Prakriti* in comparison with other body constitutions [42].

One study reported *Kapha-Pitta Prakriti* individuals to be more susceptible to developing dyslipidaemia and related comorbidities [44]. In such *Prakriti* individuals, timely and effective lifestyle interventions can be planned to prevent lipid-related disorders. Another study assessed effect of aerobic exercise on obese type-2 diabetics and found more decline in serum insulin level and homeostatic model assessment of insulin resistance (HOMA-IR) in *Kapha Prakriti* than *Pitta* types; additionally, the increase in insulin sensitivity (HOMA-%S) was more in *Kapha Prakriti* individuals than *Pitta* type [45].

A multicenter study on healthy subjects found that *Kapha Prakriti* individuals were having higher BMI as opposed to *Vata Prakriti* [46]. A anthropometric study on infants found that *Vata Prakriti* infants were having lower weight, lean and thin (lower head circumference and chest circumference), and short stature (lower crown heel length), while it was maximum in *Kapha Prakriti* infants [47]. Researchers also studied correlation of different *Prakriti* types and blood groups of infants and found maximum occurrence of *Vata Prakriti* individuals in A⁺ blood group, *Pitta* type in O⁺ blood group, *Kapha* type

in B⁺ blood group and *Vata-Kapha Prakriti* in AB⁺ blood group [48].

A recent cross-sectional study analysed milk (for fats, solid non-fats, density, proteins, lactose, freezing-point, conductivity and pH) of lactating mothers as per *Prakriti* and found that the milk composition varied according to different *Prakriti* [49]. Several works have identified association of patterns of gut microbiota with host variables, viz. geography, age, dietary habits and *Prakriti* phenotypes.

An interesting study investigated healthy human gut microbiome structure within three distinct *Prakriti* groups from a genetically homogenous cohort and discovered differentially abundant taxa. 16S rRNA gene-based microbial community profiling was carried out. Despite overall uniform composition of gut microbial community, healthy individuals of distinct *Prakriti* types exhibited enrichment of specific bacteria. Bacteroidetes and Firmicutes (gut microbial components) showed differential abundance within *Prakriti* types [50•]. A recent report also suggested significance of *Prakriti* types as a potential stratifier of the gut microbiome [51].

A study through Ayurgenomics approach established a genetic link between EGLN1 and VWF in a constitution-specific manner which could modulate thrombosis/bleeding susceptibility and outcomes of hypoxia. A combination of derived EGLN1 allele (high altitude pulmonary edema (HAPE) associated) and ancestral VWF allele (thrombosis associated) was significantly high in *Kapha Prakriti* individuals as compared with *Pitta Prakriti* [52•].

Ageing is a relentless and unidirectional phenomenon of life [53]. In *Pitta Prakriti* person, aggravated functions of *Pitta* can be observed such as increased metabolism/basal metabolic rate (BMR), biotransformation and physiological functions, which may change the related physiology following which the anatomical structures are also affected with regard to decay and degeneration. It is thus suggested that *Pitta Prakriti* persons are prone to untimely or premature manifestations of ageing like graying of hairs, skin wrinkles and hair fall [54]. Though, scientific investigations are warranted to validate these concepts.

Thus, considering all these evidences, it can be inferred that the principles of Ayurgenomics have plausible impact on phenotype-genotype correlation, drug-discovery, pharmacogenomics and PM [16, 17].

Perspectives and Future Directions

In Ayurvedic therapeutics, focus is given to individualize the diet, lifestyle and medication as per different *Prakriti* classification to attain a healthy life. It is evident from this report that each specific disease poses as risk factor or show predominance to specific type of *Prakriti* individuals, thus said concept holds potential and promise for future predictive or

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