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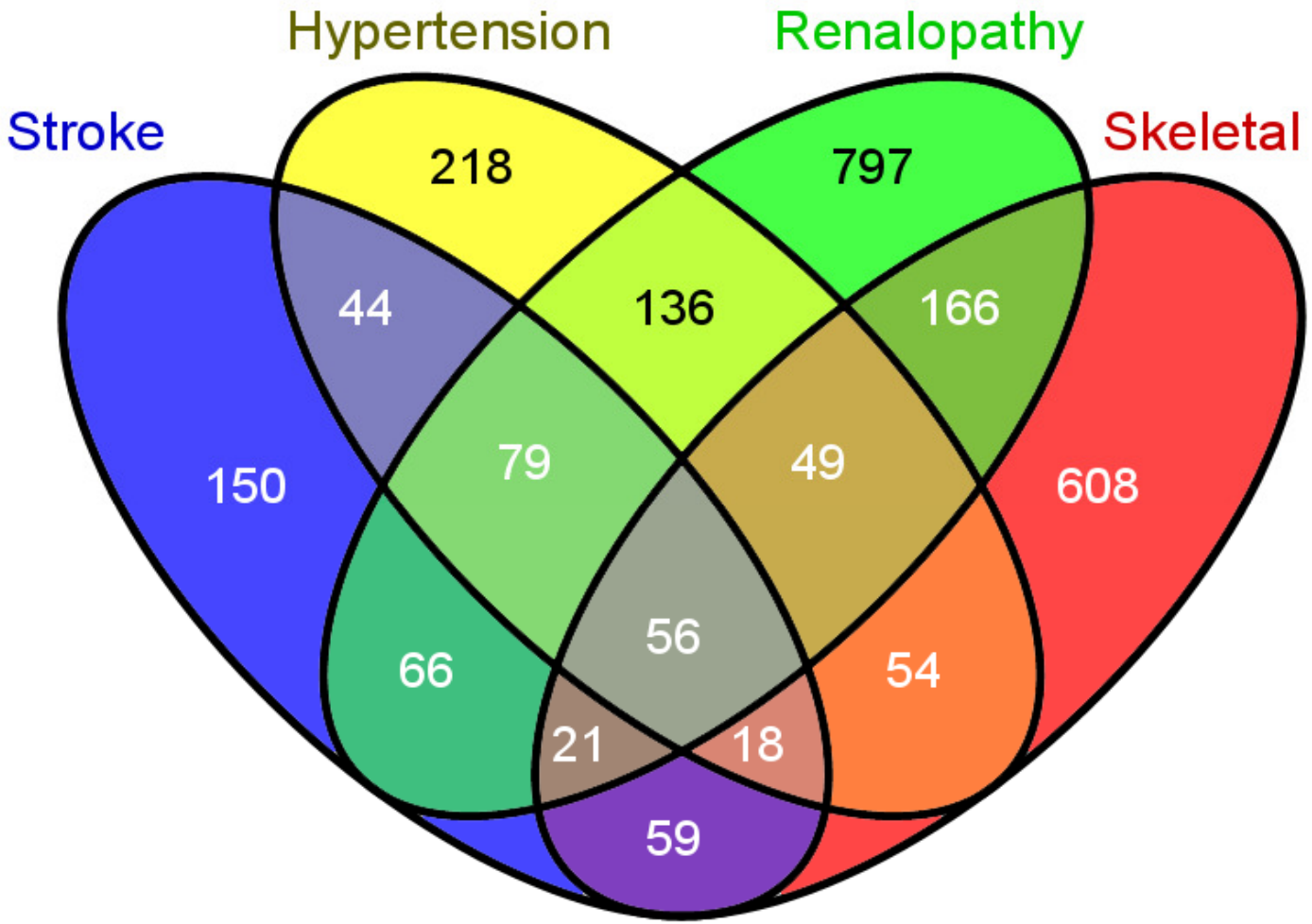
OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women.

Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

About OMICS Group Conferences

OMICS Group International is a pioneer and leading science even organizer, which publishes around 400 open access journals and conduct over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientifi conferences all over the globe annually with the support of more tha 1000 scientific associations and 30,000 editorial board members and 3. million followers to its credit

OMICS Group has organized 500 conferences, workshops and nationa symposiums across the major cities including San Francisco, Las Vegas, Sa Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bangalor and Mumbai.



NOS3, APOE, TNF, MTHFR, IL6, ACE, VEGFA, ESR1, ADIPOQ, MMP9, CRP, IL1B, PTGS2, TGFB1, TLR4, NPPB, IGF1, HIF1A, ITGB3, LEP, CXCL8, GSTM1, AGTR1, EDN1, CXCL12, CCL2, LPL, ADRB2, MAPK1, APOA1, SOD1, GHRL, RETN, INS, NOS2, TNFRSF11B, SOD2, HMGB1, FGF2, TNNT2, MIF, FTO, GH1, EPO, NOTCH3, TNNI3, HSPA1A, ENPP1, NOS1, SREBF1, PDGFRB, ANGPT1, KL, AQP4, SGK1, FABP4

Phenotype segregation network analysis (PSNA) identifies chronic complex disease triggers in substructured human groups

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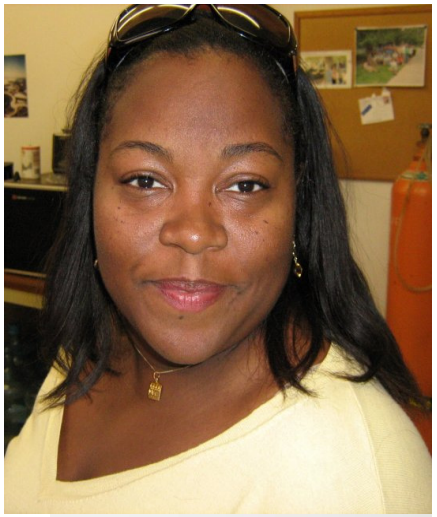

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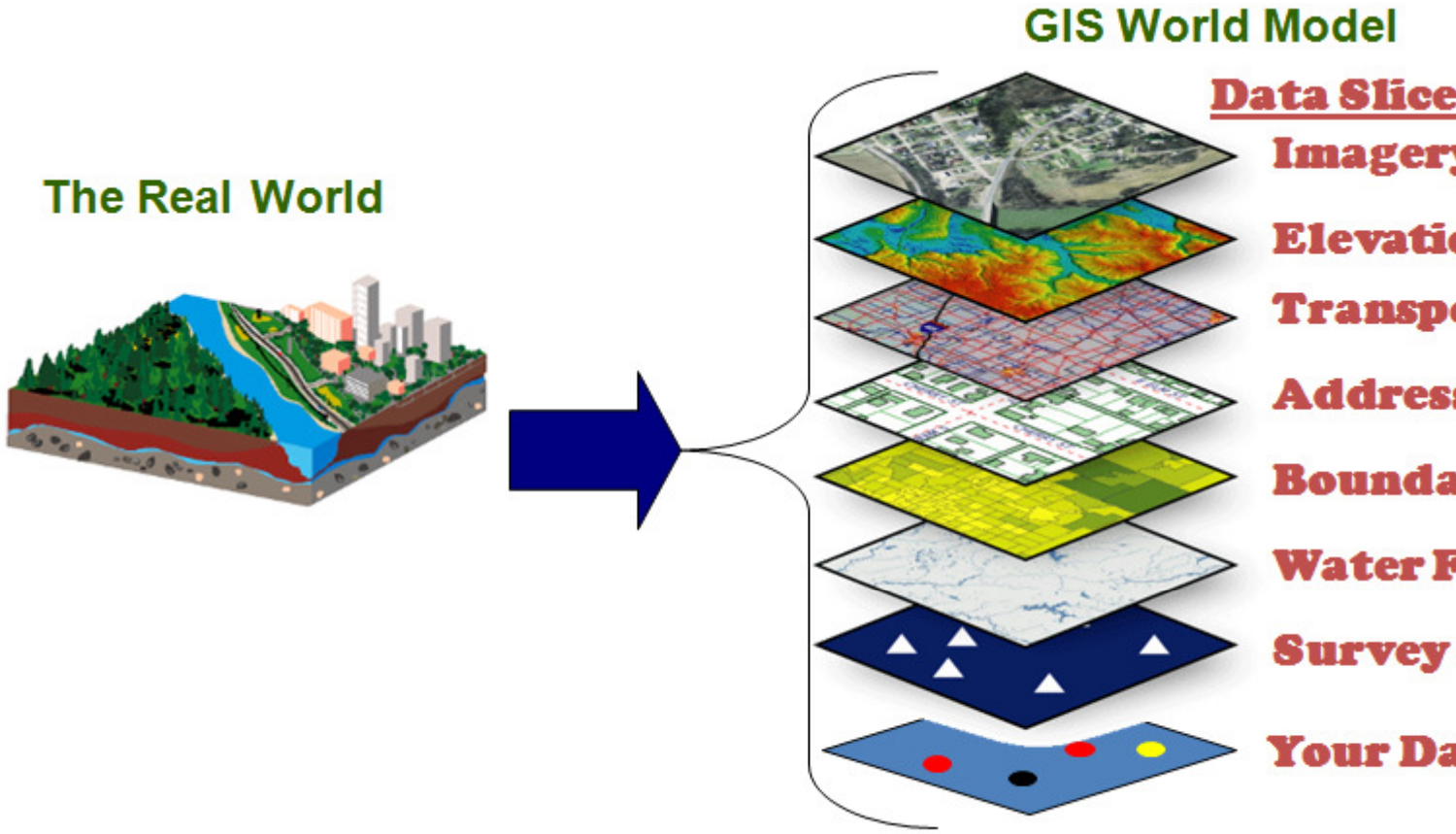
Complex chronic diseases

- 36,000,000 deaths by 2015
- 30% cardiovascular disease
- 13% cancer (especially breast, colon, prostate)
- 7% chronic respiratory disease
- 2% diabetes

- **Chronic kidney disease** (chronic kidney failure) describes the gradual loss of kidney function resulting in the build up of dangerous levels of fluid, electrolytes and toxins in the body.

ogenetic Layering

oethnic Groups



es:

2003 Ethnogenetic Layering: A Novel Approach to Determining Environmental Health Risk Potentials Among Children from Three US Regions. *Journal of Children's Health,* 1(3):369-386. ealthcare.com/doi/abs/10.3109/15417060390254355

04 Human genetic variation and health: Ethnogenetic layering as a way of detecting relevant population substructuring. *British Medical Bulletin*. 69:215-235. rdjournals.org/content/69/1/215.short

06 Illuminating cancer health disparities using ethnogenetic layering (EL) and phenotype segregation network analysis (PSNA). *J Cancer Education* 21(1):69-79. http://ukpmc.ac.uk/abstract/MED/1702

2008 Ethnogenetic Layering (EL): An alternative to the traditional race model in human variation and health disparity studies. *Annals of Human Biology* Mar-Apr 35(2):121-144. ealthcare.com/doi/pdf/10.1080/03014460801941752

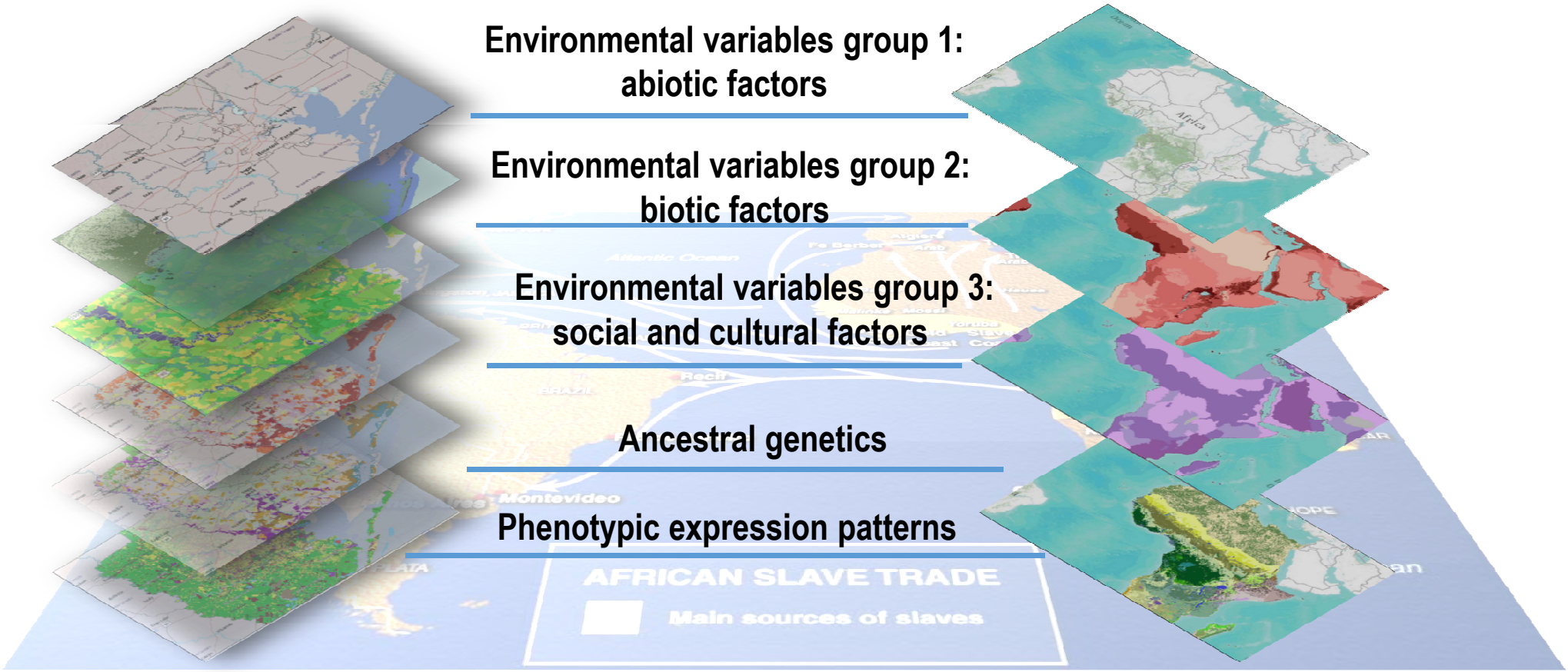
Ethnogenetic Layering General Methods

Collect and digitize measures; create geographic maps

Layer raster/vector maps; associate with research interest

Integrate ethnogenetic and other data

Calculate meta-data analysis for hypothesis testing



What is PSNA?

Phenotype **S**egregation **N**etwork **A**nalysis

Relies on high throughput assessments of MEGs by environmental variables and ancestral genetics and then by phenotypic traits.

Permits the representation (i.e., networks) of relationships between phenotypic traits and MEGs.

Serves as a “pointer” to identify which MEGs have the highest probability of revealing the underlying causes of specific disease-associated phenotypic correlations.

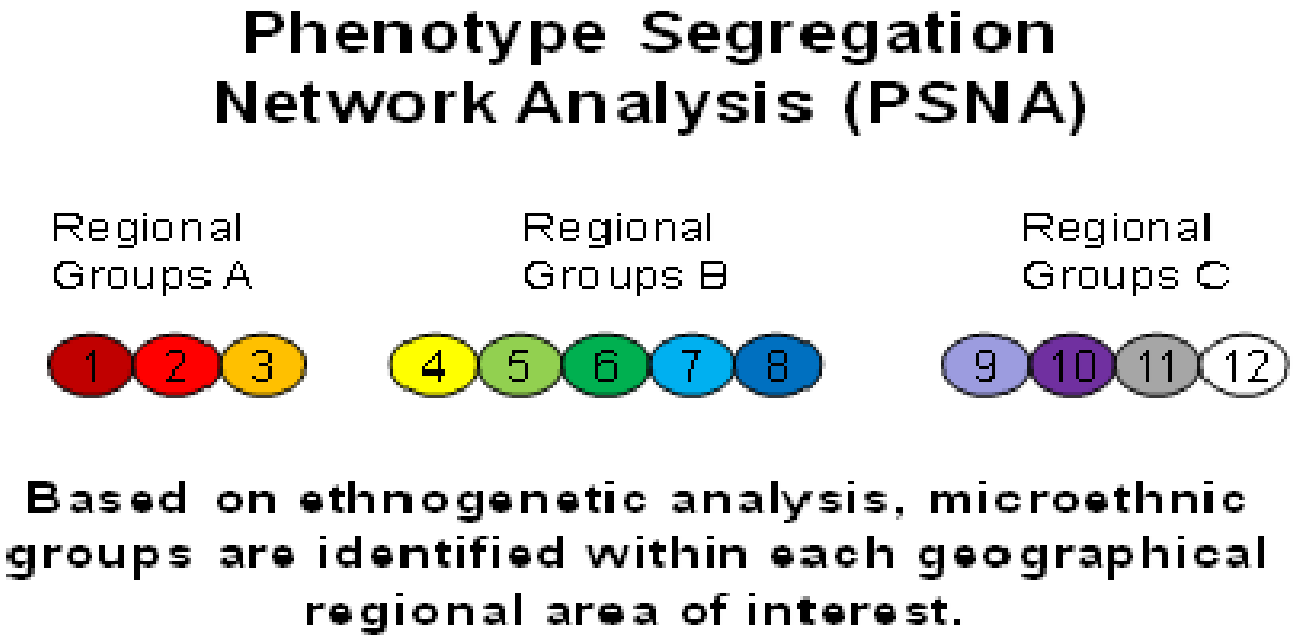
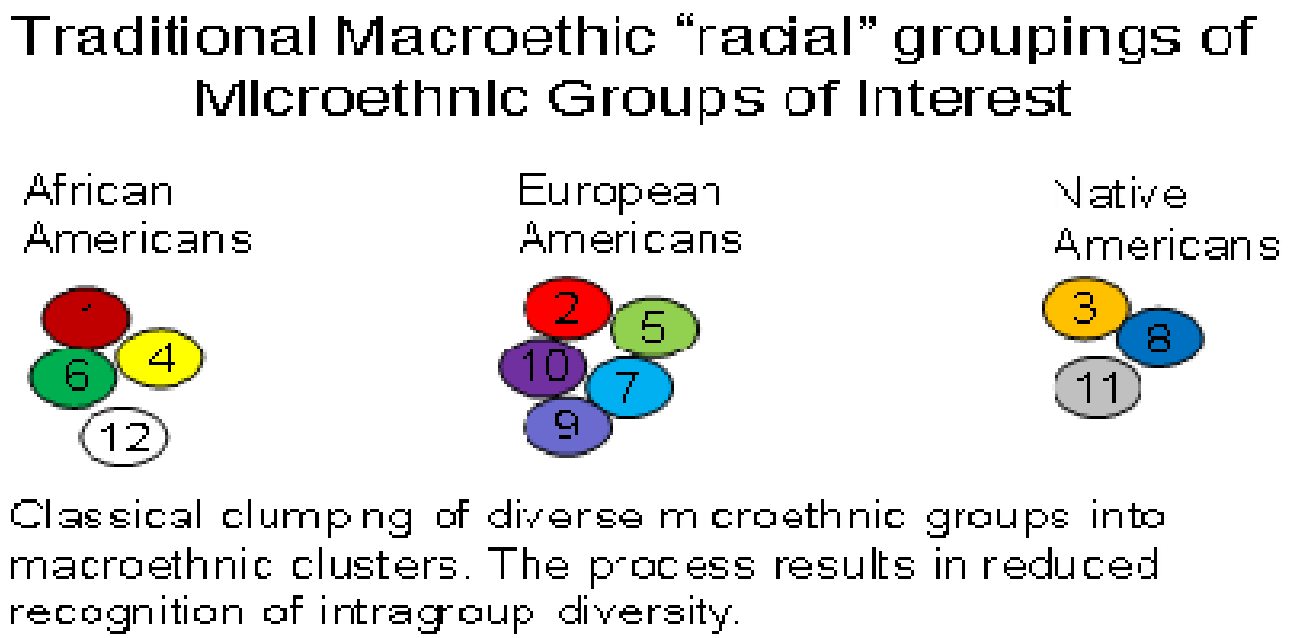
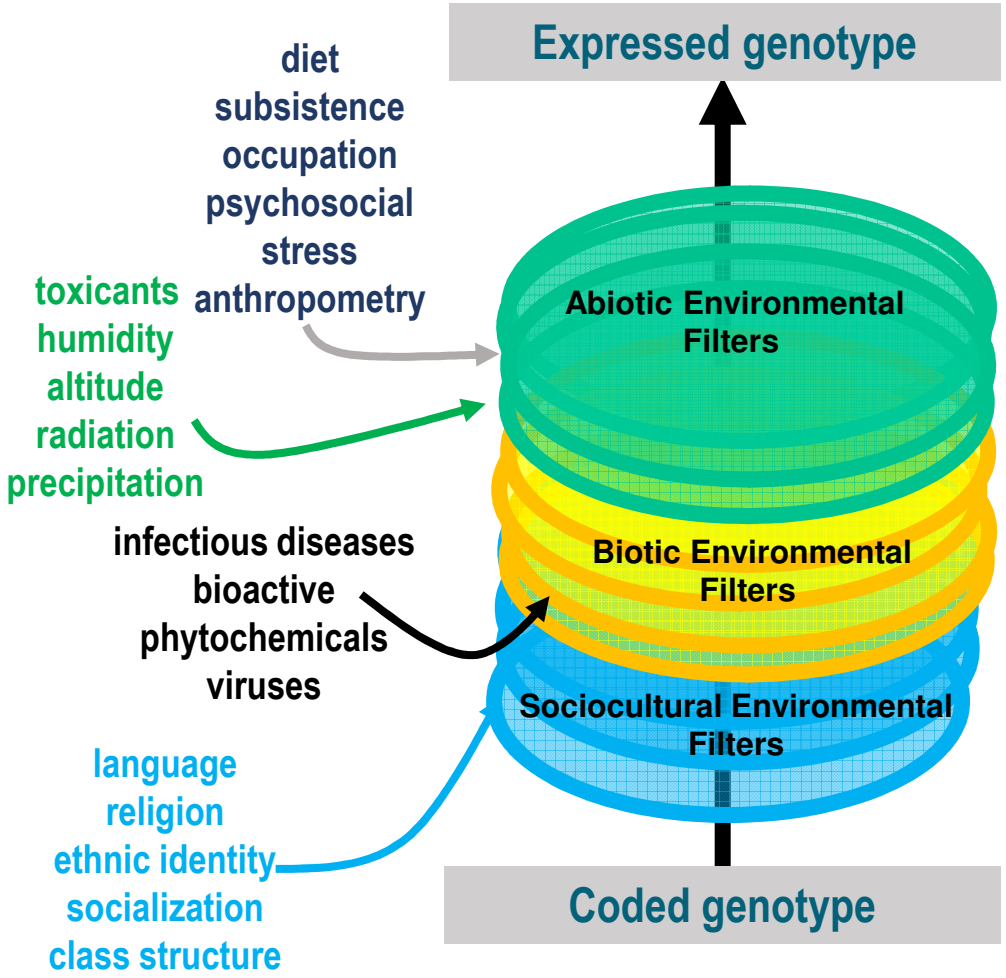


FIGURE 1. Ethnogenetic layering sorts a pool of MEGs by geographical region. This initial step can be contrasted with the traditional pattern of lumping MEGs into macroethnic or racial clusters across geographical space and ignoring both within-group substructure and between- group disease-relevant commonalities.



gure 2. Aggregated microethnic groups in the traditional racial model. When microethnic groups are umped based upon classic racial designations, "racial" groups are found in each geographical gion of interest but the nuanced analysis of local genetic, cultural, and environmental factors in sease causation is compromised.

Environmental Sources of Genotype-Phenotype Discontinuity



These factors provide additional sources of variation to the expressed genotype (the phenotype) and modify the coded genotypic message. While these factors are not genetic, they can behave in ways that influence gene expression over generations.

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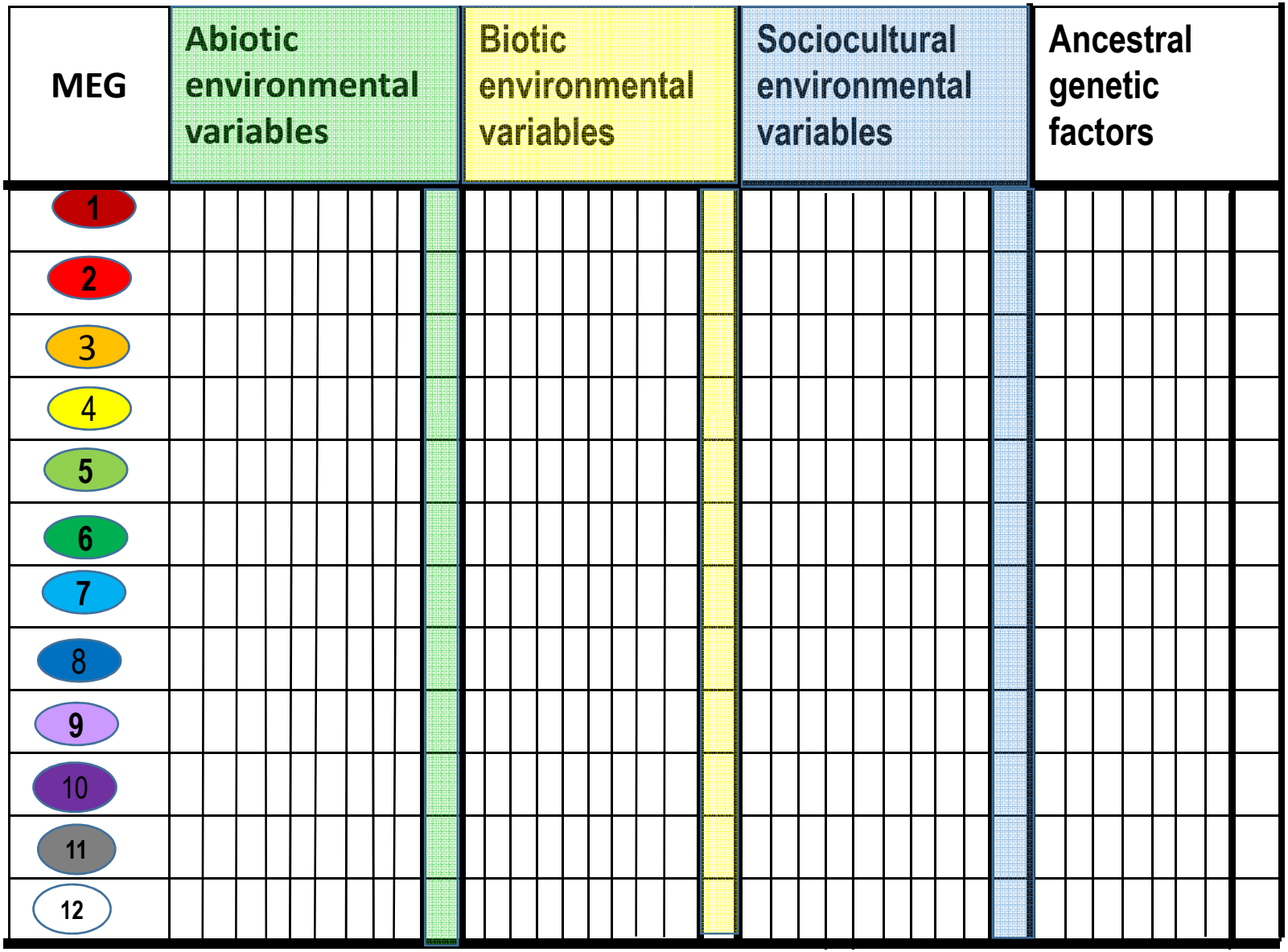
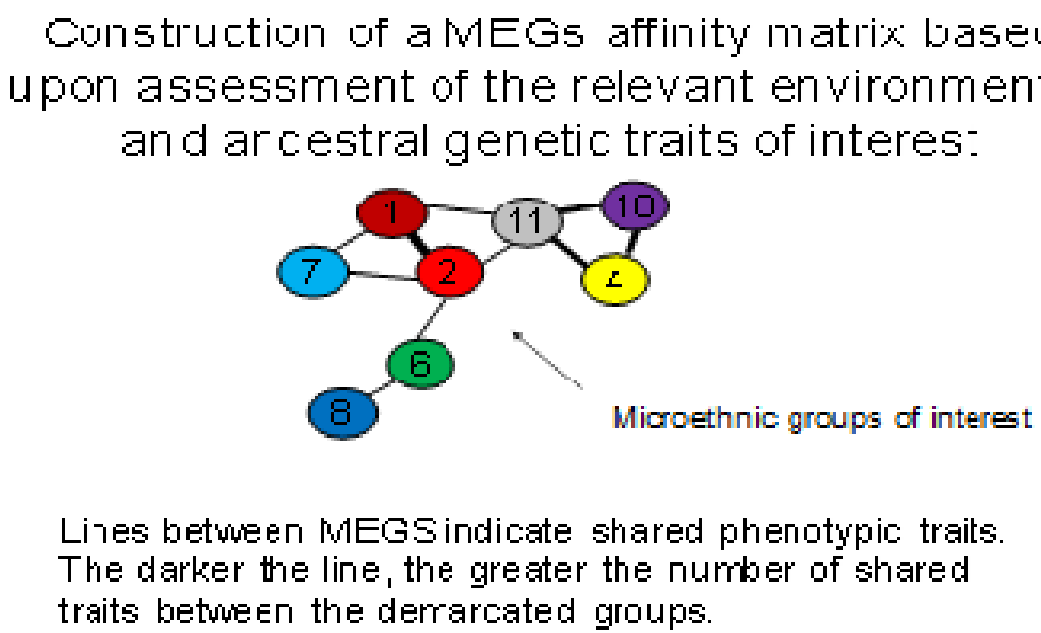
ble 1: Environmental variables and ancestral genetic factors used to sort MEGs.





igure 3. Affinity matrix of microethnic groups based upon presentation patterns of exposure to relevar nvironmental traits and ancestral genetic backgrounds. Heavy bars represent two or more traits in ommon while thin bars represent only one trait in common (based upon data presented in Table 1).

CKD- Associated Phenotypic Trait	Recent Reference

Tables 2.0 – 2.3 A subsample of 50 phenotypic traits associated with chronic renal disease for use in PSNA.

Table

-Associated Phenotypes for PSNA

abetes	Bjornstad et al 2014; Gosmanov et al 2014; Prakash 2013
gnitive impairment	Pulignano et al 2014; Seidel et al 2014; Miwa et al 2014
ne miRNA levels	Szeto 2014; Zununi Vahed et al 2014
nary proteome biomarkers	Gu et al 2014; Caliskan and Kiryluk 2014
omerular filtration rate (est.)	Rausch et al 2014; Ajayi et al 2014; Levey et al 2014
art failure	Segall et al 2014; Chawla et al 2014
pothyroidism	Paudel 2014; Prajapti et al 2013
-dihydroxyadeine urolittuasis	Ceballos-Picot et al 2014
late receptor alpha	Somers and O'Shannessy, 2014
spea and lung function	Palamidas et al 2014

Table 2

D-Associated Phenotypes for PSNA

Glycosylated hemoglobin A1c	Shipman et al 2014
Proteinuria	Cvitković et al 2014
Left atrial remodeling	Sciacqua et al 2014
Health literacy	Chow et al 2014; Roomizadeh et al 2014; Lopez-Vargas et al 2014; Burke et al 2014
Renal Anemia	Kelepouris and Kalantar-Zadeh 2014; Dousdampanis et al 2014
Vascular calcification	Knežević et al 2014
Urinary electrolytes/conductivity	Wang et al 2014; Blann 2014
Depression	Bantovich et al 2014; Knuth et al 2014; Schell et al 2014
Serum creatine	Proule et al 2014
Osteoporosis and osteopenia	Miller 2014; Gupta 2014; Salam et al 2014; Khan et al 2014
Cystatin C	Vigil et al 2014; Fox et al 2014; Jeon et al 2013; Li et al 2013
Renal Inflammation	Wu et al 2014; Kelepouris and Kalantar-Zadeh 2013
Atrial fibrillation	Buiten 2014
Dietary complements	Dori et al 2014; Hsieh et al 2014; Steiber 2014
Carotid artery stenting	AbuRahma et al 2014; Hakimi et al 2014

Table 2.

KD-Associated Phenotypes for PSNA

***APOL1* polymorphism**	Freedman et al 2014; Cooke Bailey et al 2014
Platelet reactivity	Mangiacapra et al 2014
Chronological age	Tonelli and Riella 2014; Nitta et al 2013
Serum complement C3	Molad et al 2014
Physical function and gait speed	Painter and Marcus 2013; Baumgaertel et al 2014
Albuminuria	Komenda et al 2014; Liu et al 2014; Abdelmalek et al 2014
Pleural effusion	Ray et al 2013
Peridontal disease	Mohangi et al 2013
Oxidative stress (mitochondria)	Daehn et al 2014
Auditory acuity	Lopez et al 2014; D'Andrea et al 2013
Nephrotoxic exogenous agents	Roxanas et al 2014; Ingrasciotta et al 2014; Akilesh et al 2014; Sánchez-González et al 2013
Cardiovascular disease	Cai et al 2013; Ahmadi et al 2014; Chawla et al 2014
Dyslipidemia	Omran et al 2013
Obesity	Park et al 2014

Table 2

KD-Associated Phenotypes for PSNA

	Insomnia and sleep apnea	Ahmed et al 2013
	Microvascular function	Imamura et al 2014
	Nutritional status	dos Santos et al 2013
	***WT1* or *TRIB3* polymorphisms**	Lipska et al 2014; Ding et al 2014
	Treatment resistant hypertension	Tanner et al 2014
	Renal histology	Wijetunge et al 2013; Tarnoki et al 2013
	Dopamine D2 receptor polymorphism	Jiang et al 2014
	Inflammatory myopathy	Couvrat-Desvergnes et al 2014
	FSGS and nephropathic biomarkers	Nafar et al 2014 ; Nkuipou-Kenfack et al 2014
	Diastolic function	Farshid et al 2013

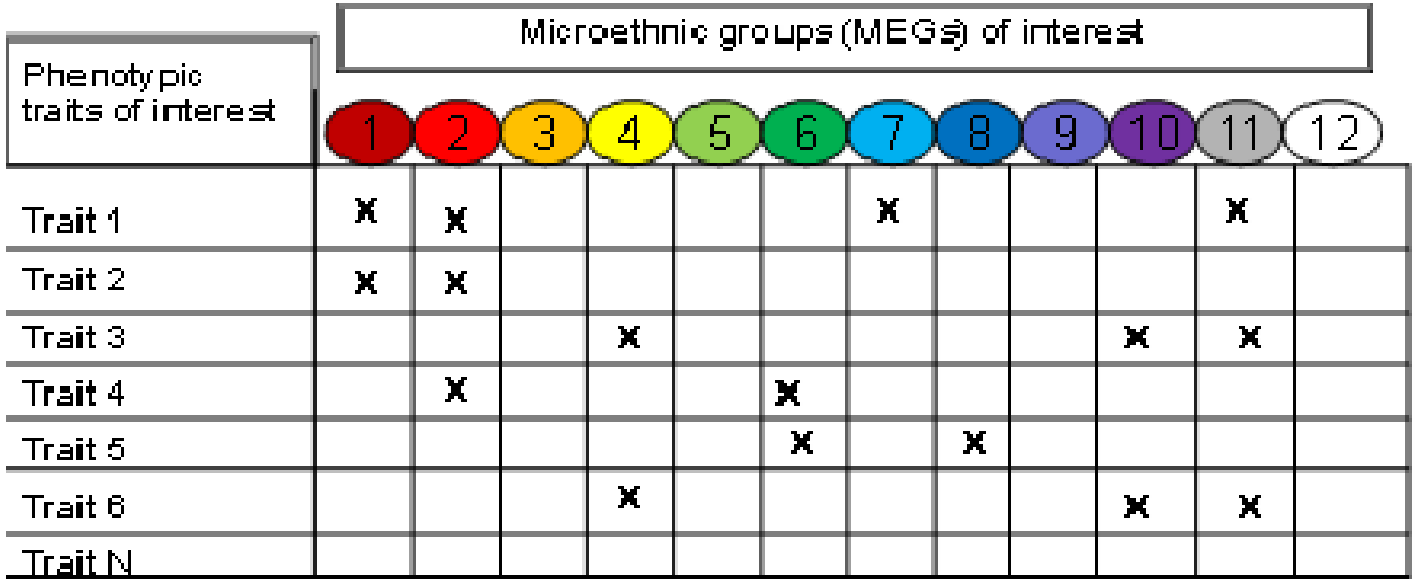
Production of a correlation matrix of the phenotypic trait interrelationships

Phenotypic traits without added rotating values	Phenotypic traits with added rotating values based upon Poisson or Gaussian distribution						
	Trait 1	Trait 2	Trait 3	Trait 4	Trait 5	Trait 6	Trait N
Trait 1	--	Z					
Trait 2	Z	--					
Trait 3			--			Z	
Trait 4				--	Z		
Trait 5				Z	--		
Trait 6			Z			--	
Trait N							--

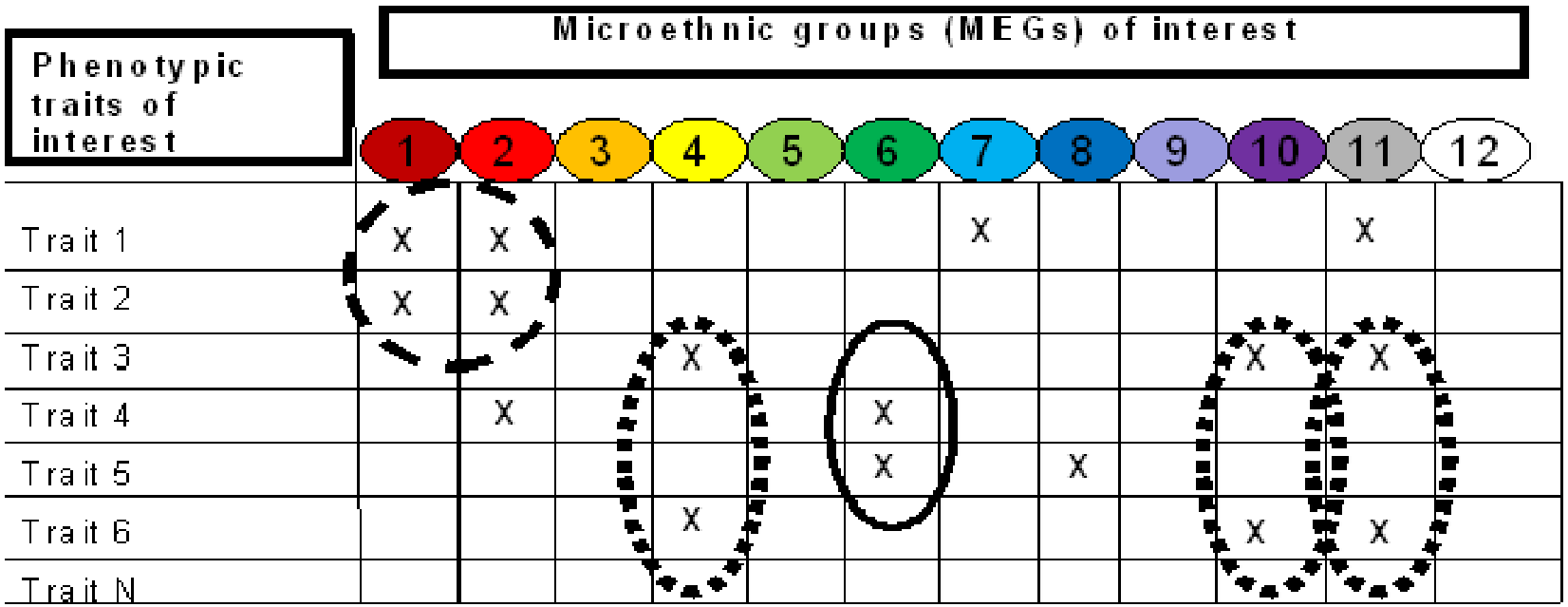
Z indicates presence of significant correlation between specific phenotypic traits in overall population studied.

Figure 4. A simplified version of the correlational matrix in PSNA for the traits listed in Tables 2.0-2.3 Z represents a statistically significant correlation between traits ($p<0.05$).

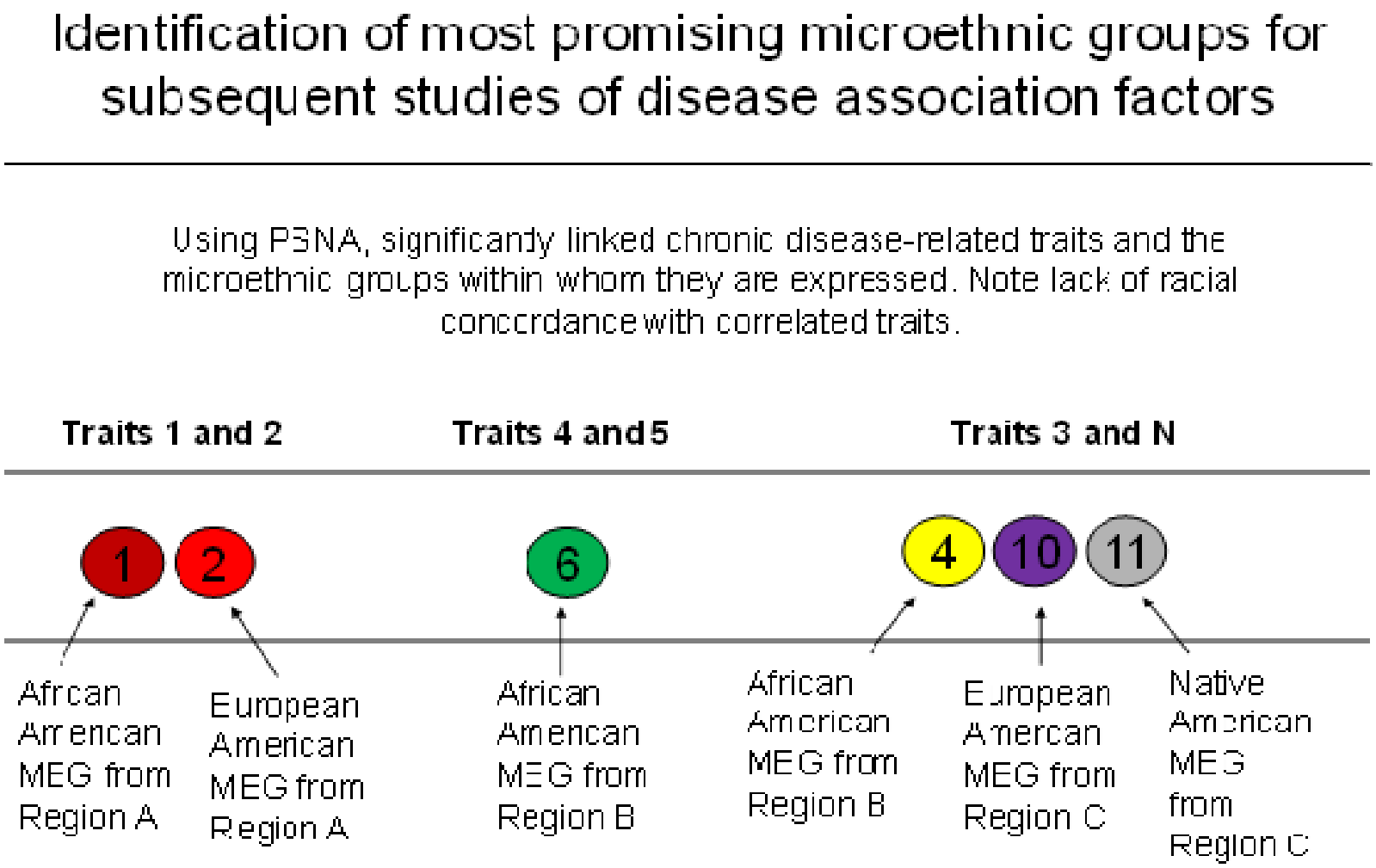
Identification of specific phenotypic traits of interest and evaluation of each microethnic group for these traits



gure 5. Validated phenotypic traits are evaluated in each MEG of interest and the results compared. X dicates the presentation of a specific phenotypic trait. MEGs with similar phenotypic presentations of e chronic disease of interest are studied further. Notice that MEGs 3, 5, 9, and 12 do not display any of e phenotypic traits under study.

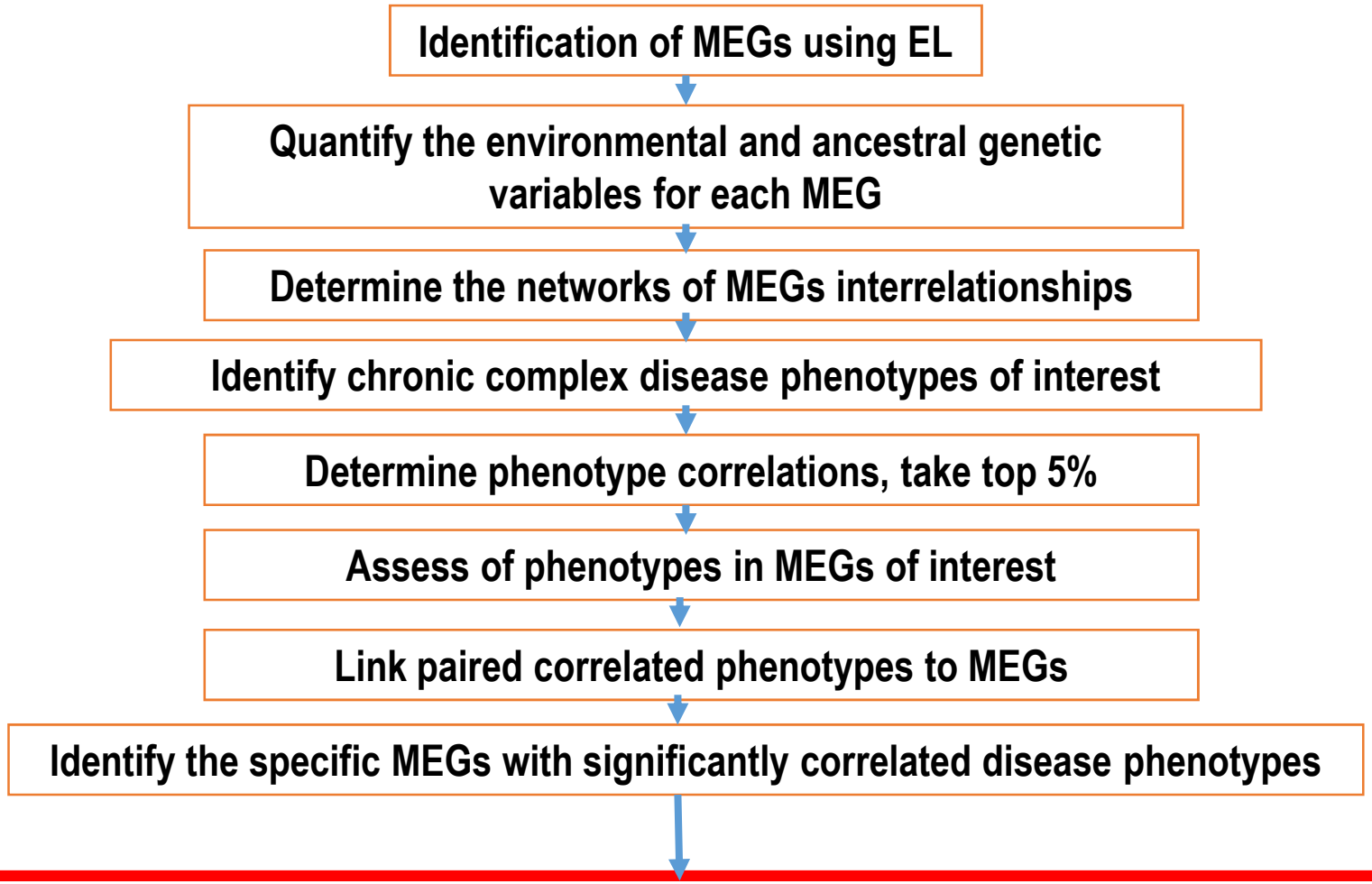


6. Identification of MEGs for subsequent genetic, cultural, and/or environmental analysis in chronic dis
on. In the case CKD-associated traits, microethnic groups 1 and 2 display linked phenotypic traits 1 an
hnic grous 4, 10, and 11 display linked phenotypic traits 3 and N and microethnic group 6 displays link
and 5.



7. Re-association of correlated traits with MEGs and "racial" identifications of identified MEGs. The lac greement (see Figure 4) with the traits suggests that regional genetic, cultural, and/or environmental ance may be playing more important roles than "race" *per se* in disease causation.

Step Algorithm for PSNA



Investigate the likely underlying causes of specific chronic disease associated phenotypic correlations by environmental and ancestral genetic variables

Applications of PSNA

PSNA should prove useful in a number of applications in the identification of risk factors in complex chronic diseases. For example, these include:

Ranking of classic diagnostic procedures and techniques for specific subgroups. In chronic disease studies, classic diagnosis and treatment procedures often find human biodiversity problematic. The recognition of substructure in macroethnic groups (=races) can, with PSNA, be used productively to provide more sensitive disease recognition strategies.

Improved specificity of treatment regimes for particular individuals and groups within targeted MEGs Unlike "individualized medicine" which does not integrate social, cultural, and environmental factors into diagnosis and treatment, or "race medicine" which ignores within group variability, PSNA focuses on the microethnic group level of analysis. This means that chronic disease intervention strategies can be localized to the specific social, cultural, environmental, and ancestral dynamics of regional MEGs.

Increased resolution of roles of social, cultural, and biological contributors to existing disparities. Integrative biology is particularly well poised to quantify the contributions of social, biological, and biocultural contributors to complex chronic disease health disparities. PSNA reduces some of the ambiguity in these quantifications by identifying the MEGs most likely to express specific correlated phenotypes. This makes association studies much less of a "shot in the dark". Our procedure also makes for more informed design in clinical trials/medical research.

Integration of sophisticated genetic, sociocultural, and environmental data in disease assessments. Finally the data on disease assessment must be meaningfully integrated for incorporation into local models o chronic disease. PSNA provides the context for these integrations and reduces the tendency in race-based studies to overextend research results to other MEGs with little more in common with the study group than a remote shared past.

Limitations of PSNA

Important independent phenotypic traits that are not linked to other phenotypic traits could be missed in our PSNA calculations.

Causation is not specifically implied by our analysis; PSNA simply points to statistical matches in the phenotypes examined and identifies the MEGs harboring those phenotypes. Causation requires additional analyses.

It is possible that in some cases, no MEGs will correspond with statistically correlated traits. However, our technique still recognizes geographic ‘clusters’ of people of equal public health significance.

Once the list of 100 phenotypic traits is finalized, the discovery of new phenotypic traits would require that the number correlations performed would have to be increased to include these in the analyses. On the other hand, if some of the studied phenotypic traits from the finalized list are subsequently discounted, the number of correlations undertaken would have to be decreased.

MEGs have to be periodically revisited since these are dynamic groups and all aspects of their composition are potentially undergoing change, particularly given the magnitude of recent immigration and ongoing assimilation.

PSNA is based on a nonreductionist, integrative platform. As such, its statistical analysis and application includes many different kinds of data, for example, behavioral, demographic, toxicological, pharmacologic, genetic, dietary, historical, etc.

Why is this research important?

Geneticists have been handicapped by (unknown) population substructure in the search for robust and consistent disease-associated genes.

Many of our GWAS results are of little clinical significance across population groups.

As health disparities grow, we need computation-assisted methods to sort through the high degree of variability in heterogeneous human groups to accurately identify the biological bases for these inequities.

Thank you for your attention.

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