
بسم الله الرحمن الرحیم

Symposium 9
Precision Medicine

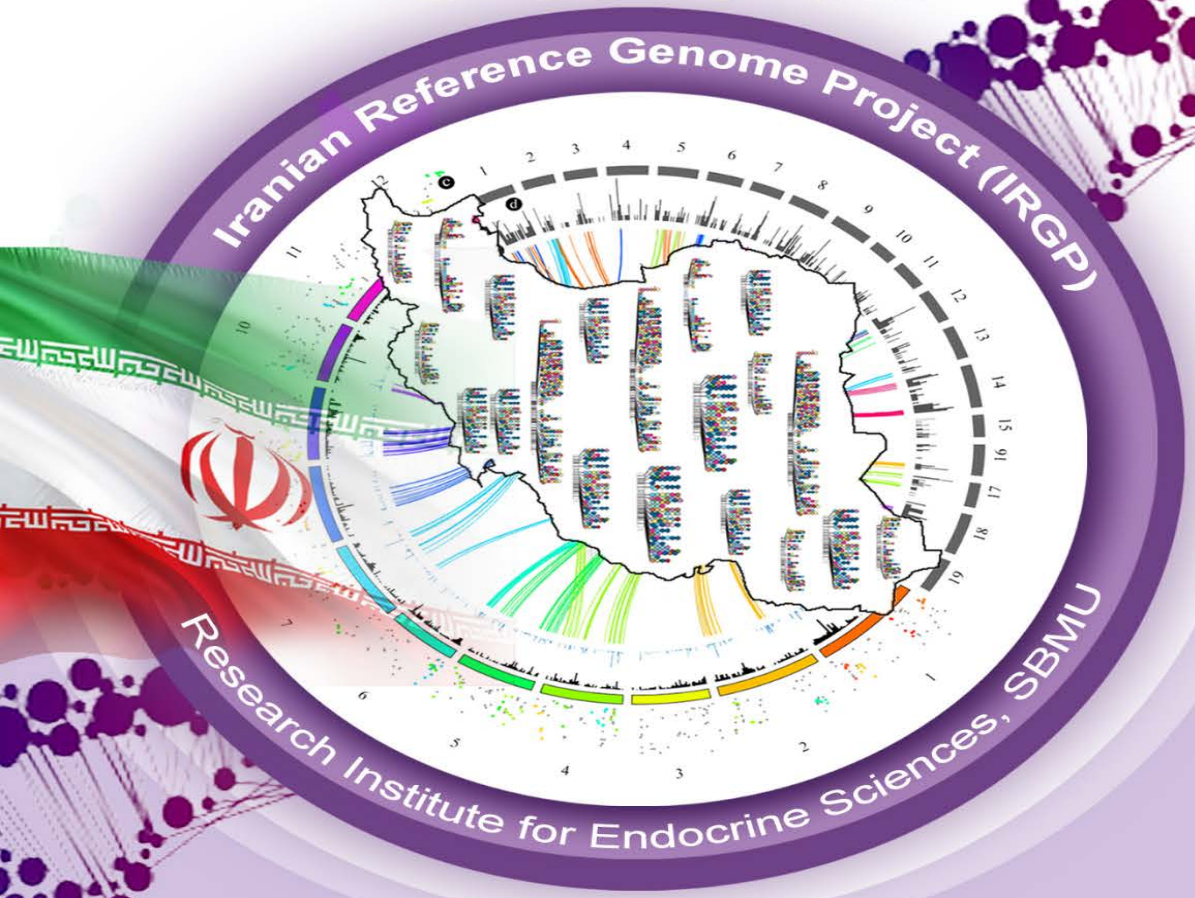
Iran Endocrine Society | Research Insititute for Endocrine Sciences | Shahid Beheshti University of Medical Sciences

چهاردهمین کنگره بین المللی
بیماری‌های غدد درون ریز و متابولیسم
THE 14th INTERNATIONAL CONGRESS OF
ENDOCRINE DISORDERS

Time	Title	Speaker
15:00-15:30	Precision medicine in Iran: Diabetes as an example	Dr. Maryam Daneshpour Medical geneticist
15:30-15:45	Genetic of Maturity onset diabetes mellitus in young (MODY) in TCGS	Dr. Sara Asgarian MD
15:45-16:00	The Genetic risk score of type 1 diabetes in TCGS	Dr. Maryam Moazam Molecular geneticist
16:00-16:30	Genome-wide association of type 2 diabetes in TCGS	Dr. Mahdi Akbarzadeh Statistical geneticist
16:30-17:00	The Role of Artificial intelligence in precision medicine	Dr. Hossein Lanjanian Bioinformatics

ژنوم مرجع ایرانیان

ژمیران



Precision medicine in Iran: Diabetes as an example

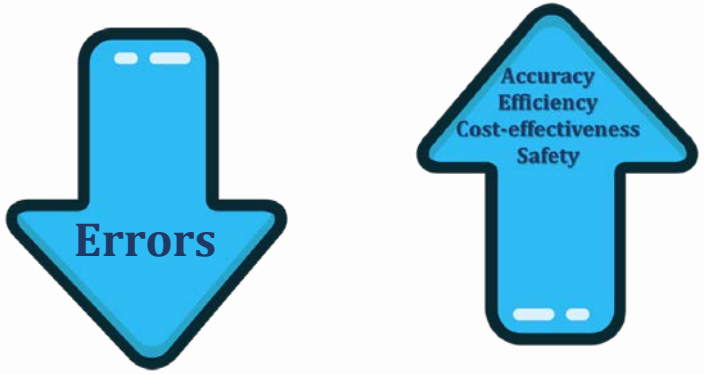
Outlines

- Precision vs Personalized
- History
- Definition
- TCGS
- Diabetes

3 era of Medicine

- Intuitive Medicine 1950s-80s
  - Common symptoms General therapy
- Evidence-Based Medicine 1980s-2000s
  - Best research evidence
  - Clinical expertise
  - Patient preferences and wants
- Precision Medicine 2010s-Present

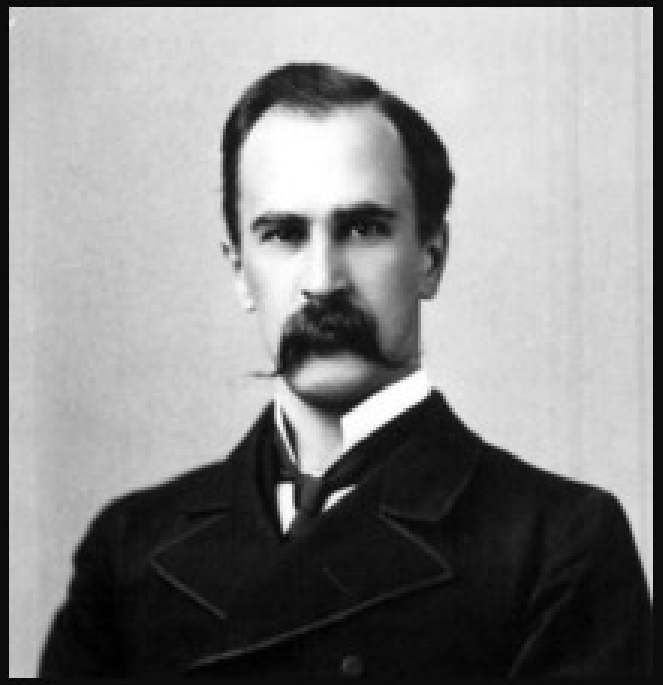
Precision vs Individualized



Medical decisions and health recommendations

Person's own data

William Osler



It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.

Mendel publishes his theory on the transmission of hereditary characters

1855

Wilhelm Johannsen coined the term **GENE**

1905

Bateson uses the word **GENETICS** for the first time

1909

James Watson and Francis Crick define their structural model of **DNA as a double helix**

1944

Avery, MacLeod, McCarty identify **DNA** as responsible for carrying **genetic charge**

1953

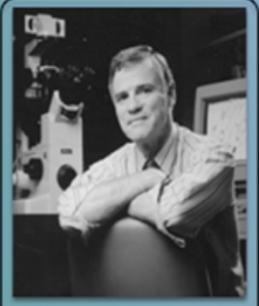
Frederick Sanger develops **DNA sequencing** techinques

1965

Marshal Nirenberg and Har Gobind Khorana define the **GENETIC CODE**

1977

1986



Leroy Hood automates DNA sequencing

1990

The **HUMAN GENOME** project begins led by J. Watson

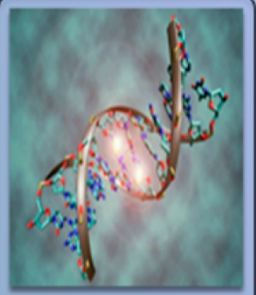
1995

Craig Venter begins the **massive DNA sequencing** era

2001

The **first draft** of the **HUMAN GENOME** is presented

2008

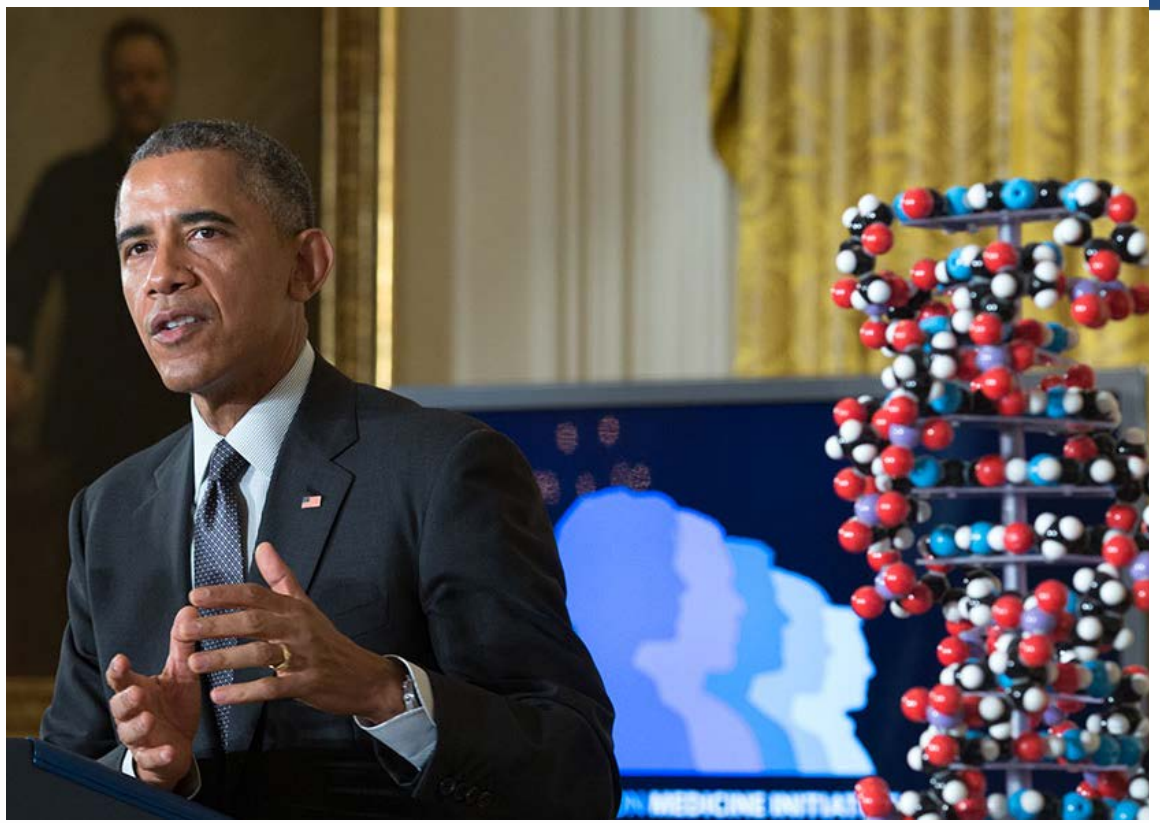


The GENOME of a type of **CANCER is first sequenced**

2012

Iont Torrent announces that is capable of sequencing a Genome for less than 1000 dollars

Precision Medicine Initiative



"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

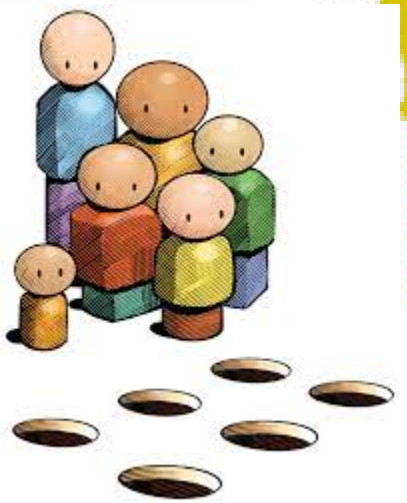
-President Barack Obama, State of the Union Address, January 20, 2015

Traditional „one size fits all“ approach

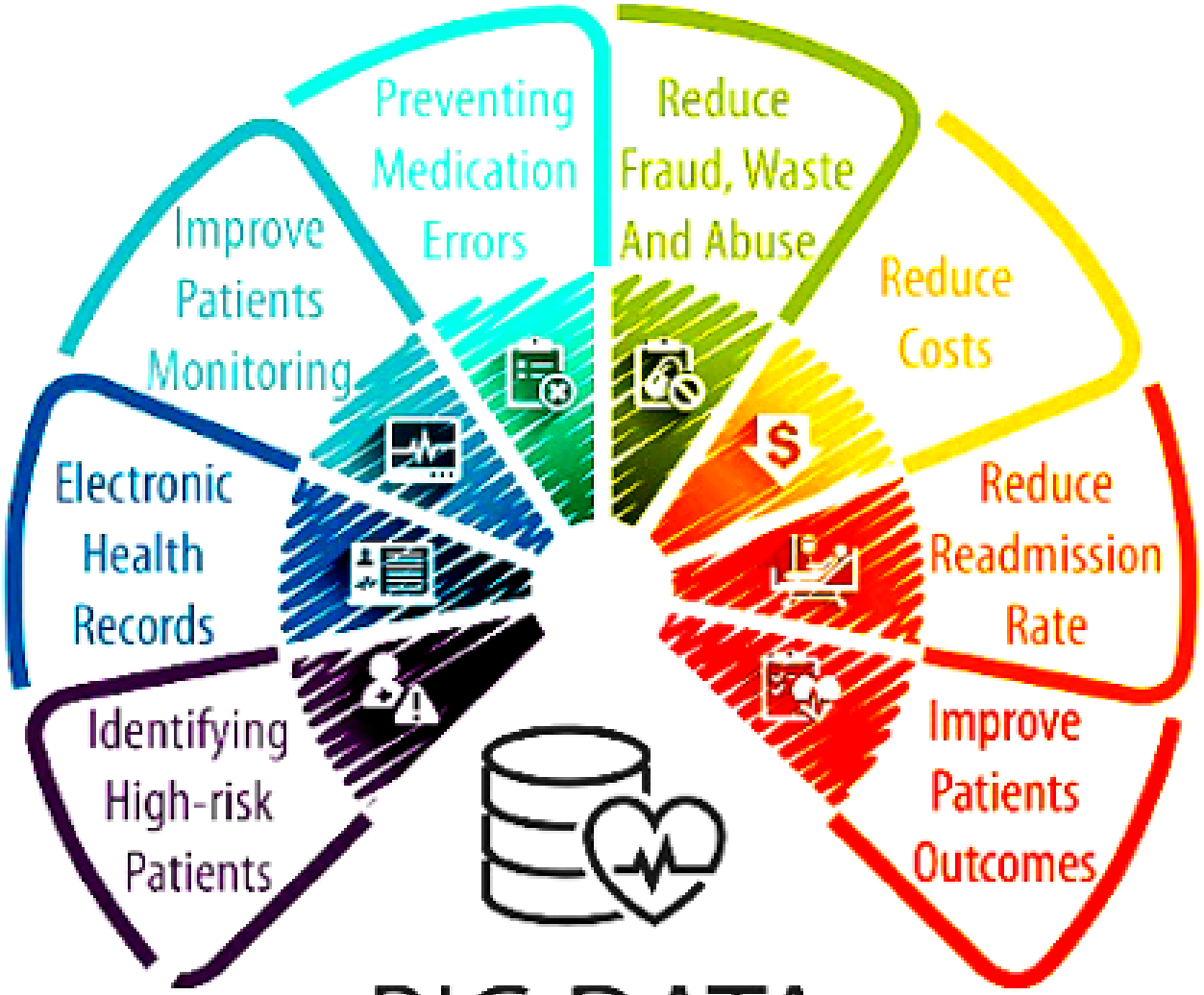
All patients with the same diagnosis receive same treatment

Personalized medicine approach

Treatment strategy based on patient´s unique genetic profile

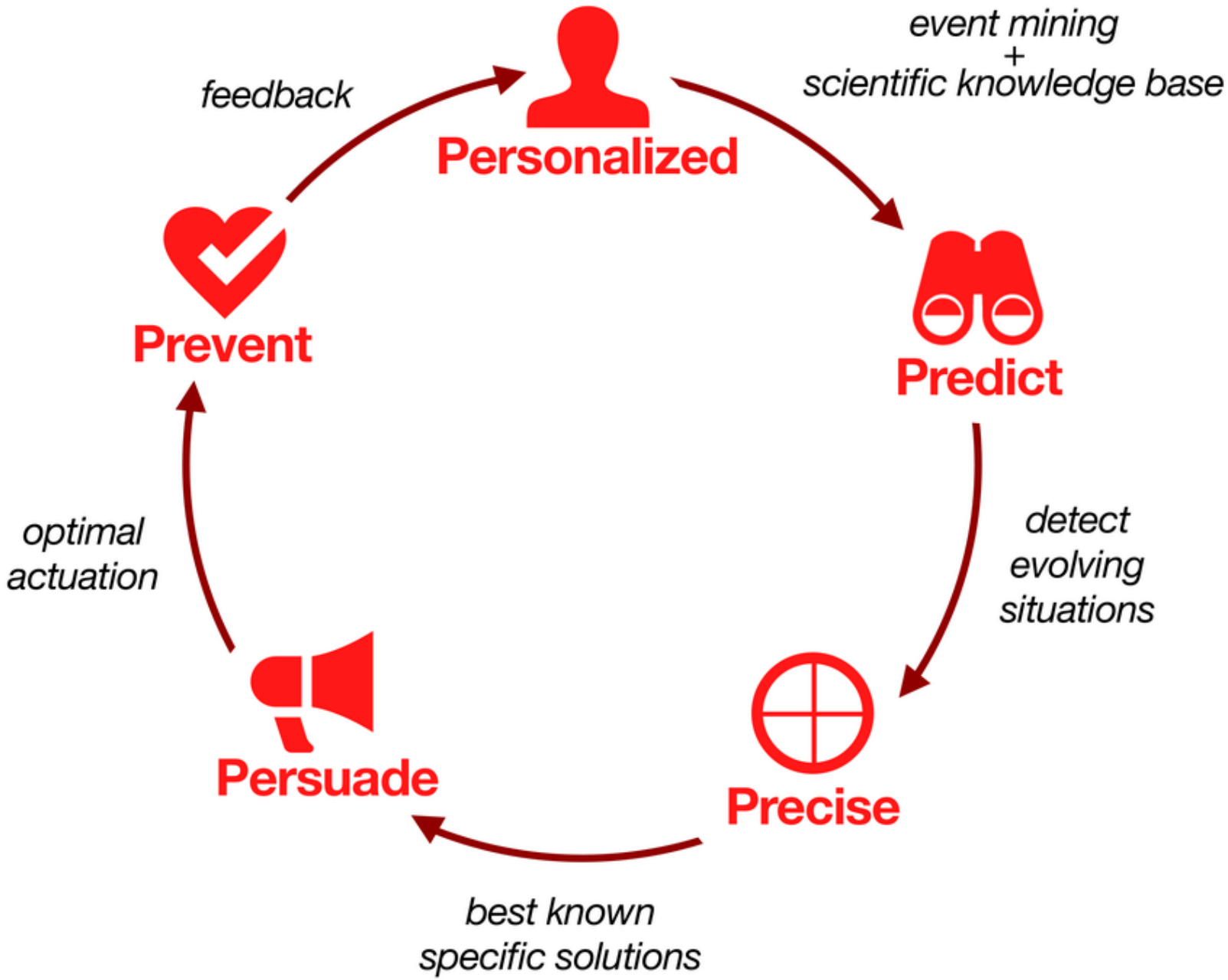


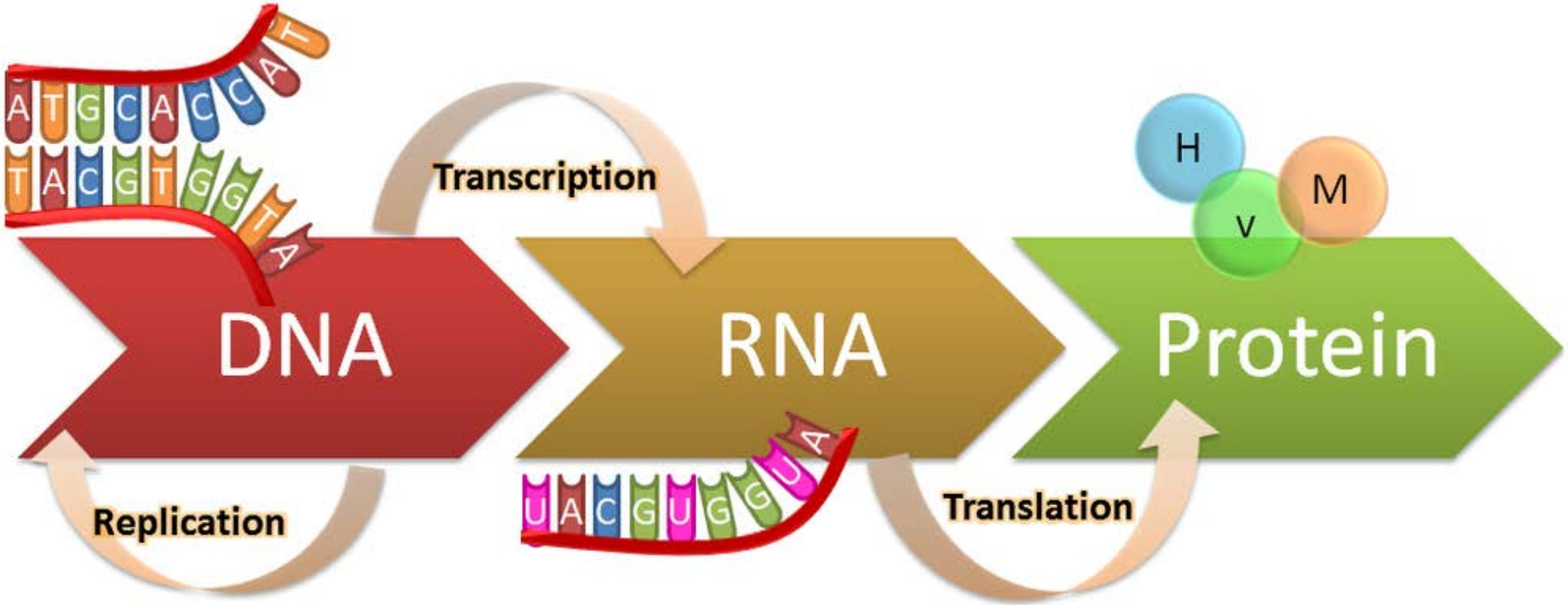
Genetic variations
Age; Gender; Race
Ethnicity; Addictions
Concomitant drugs
comorbidities
Environment

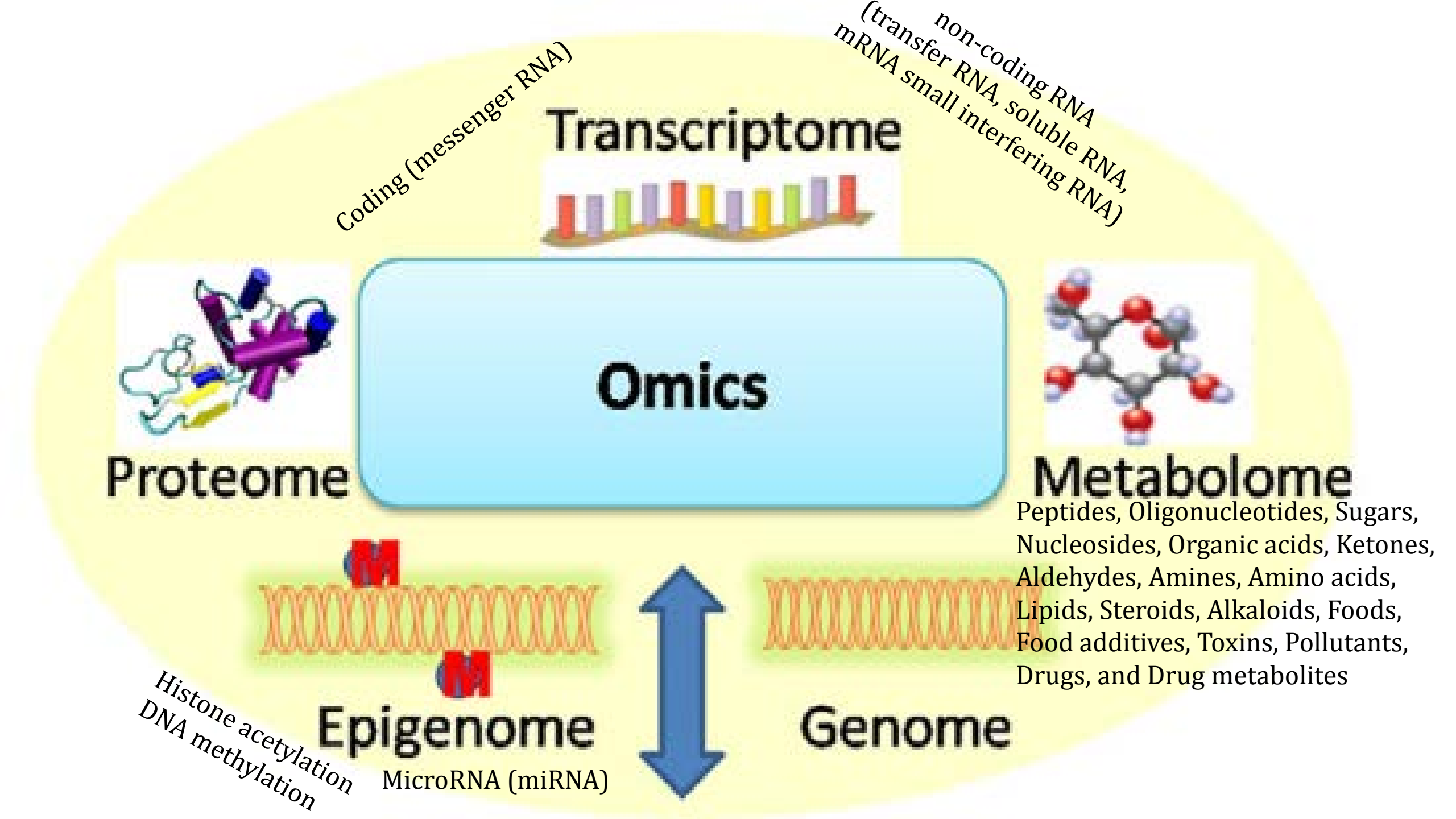


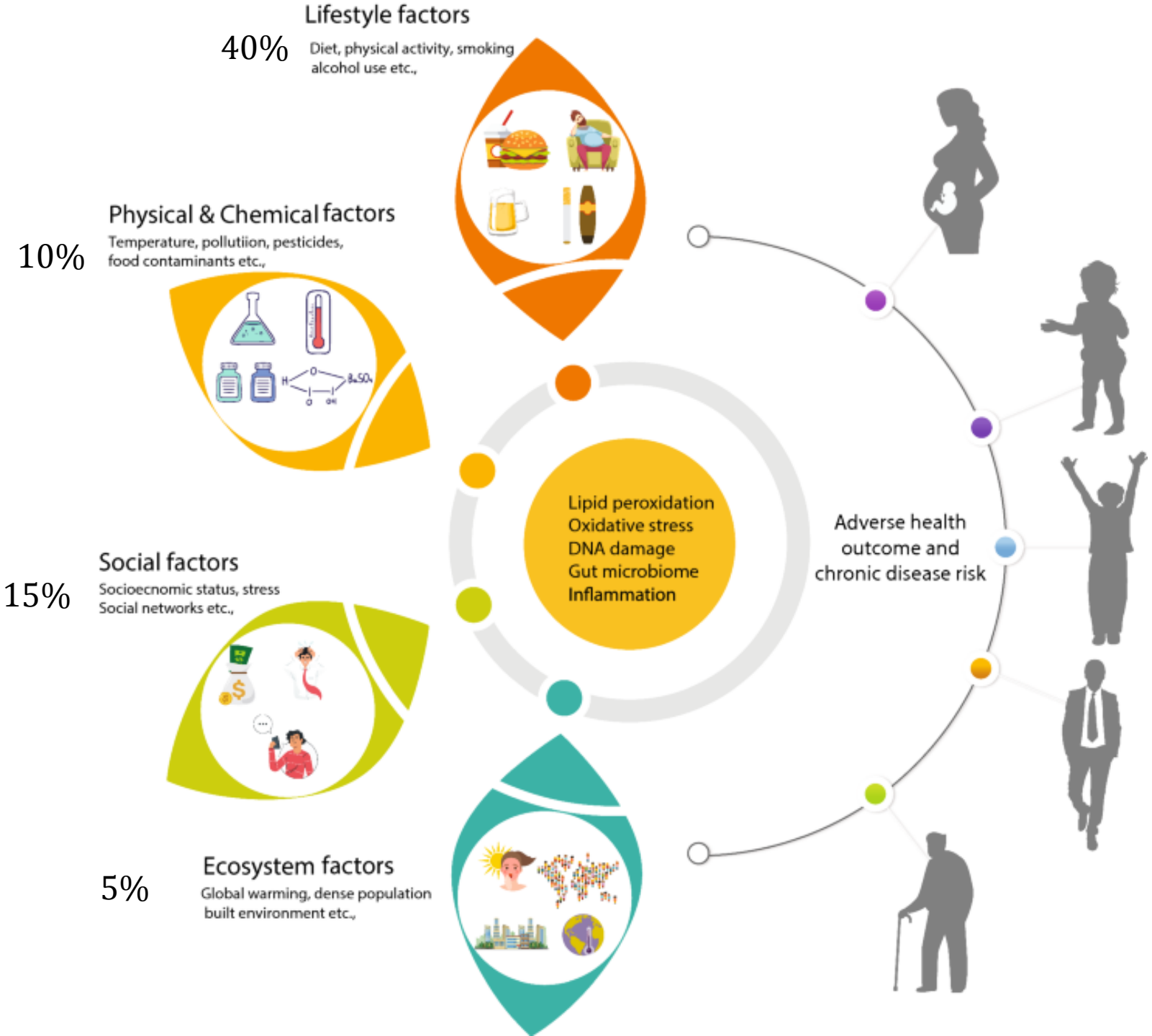
BIG DATA IN HEALTHCARE

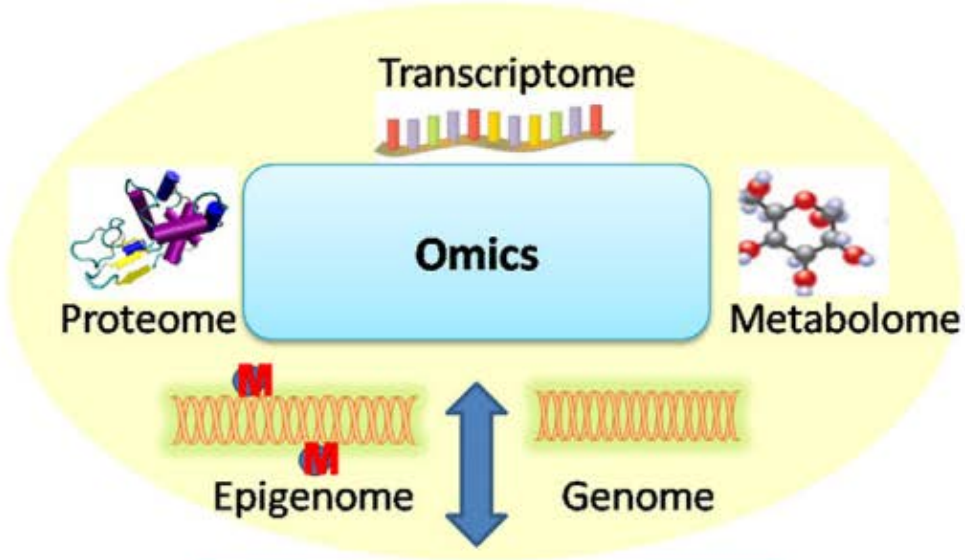
P^5 Cybernetic Health




Transcription
DNA
RNA
Protein
Replication
Translation
H
M
V


Coding (messenger RNA)
non-coding RNA
(transfer RNA, soluble RNA,
mRNA small interfering RNA)
Transcriptome
Proteome
Omics
Metabolome
Peptides, Oligonucleotides, Sugars,
Nucleosides, Organic acids, Ketones,
Aldehydes, Amines, Amino acids,
Lipids, Steroids, Alkaloids, Foods,
Food additives, Toxins, Pollutants,
Drugs, and Drug metabolites
Histone acetylation
DNA methylation
Epigenome
MicroRNA (miRNA)
Genome

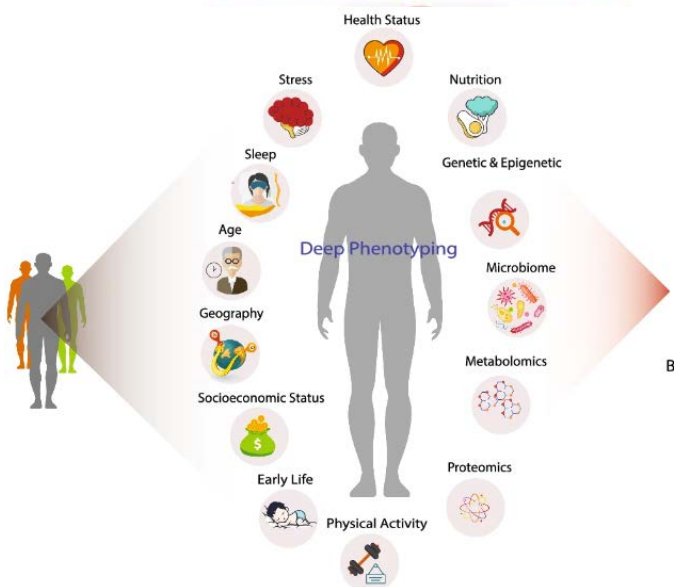

Lifestyle factors
40%
Diet, physical activity, smoking
alcohol use etc.,
Physical & Chemical factors
10%
Temperature, pollutiion, pesticides,
food contaminants etc.,
Social factors
15%
Socioecnomic status, stress
Social networks etc.,
Ecosystem factors
5%
Global warming, dense population
built environment etc.,
Lipid peroxidation
Oxidative stress
DNA damage
Gut microbiome
Inflammation
Adverse health
outcome and
chronic disease risk



Social & Behavioural Data

Big Data Analytics
Systems Bioinformatics
AI Algorithms

Environmental Impact



Digital Health

Tehran Cardiometabolic Genetic Study

ژنوم مرجع ایرانیان

The only longitudinal infrastructure for PM in Iran

Tehran Lipid and Glucose study

Demographic, Nutritional habits, Personality, Physical activity, Drug use, Medical history

Biochemical measurement, DNA extraction, WBC

Ethic forms
Questionnaires
Blood
Urine

Population selection 1998
Distinct 13 Tehran
6254 family

Intervention
Decreasing the incidence of type 2 diabetes
Diminishing the prevalence of metabolic syndrome and its components

Outcome follow-up
annually by telephone
Call and hospital report

Result
Analysis and published

World Health Organization
Trials
Journal of Human Hypertension
International Journal of Obesity
Europe PMC
DIABETES RESEARCH AND CLINICAL PRACTICE
nature
nature genetics

1999 Initial Recruitment and Survey
2002 3 Year Follow-up
2005 6 Year Follow-up
2008 9 Year Follow-up
2011 12 Year Follow-up
2014 15 Year Follow-up
2017 18 Year Follow-up
2021 22 Year Follow-up

Chip Typing
Sequencing
ICD11 Coding

Tehran Cardiometabolic Genetic Study

23676 person in 4497 family

More than 1200 phenotypes in 25 years and 7 phases

14000

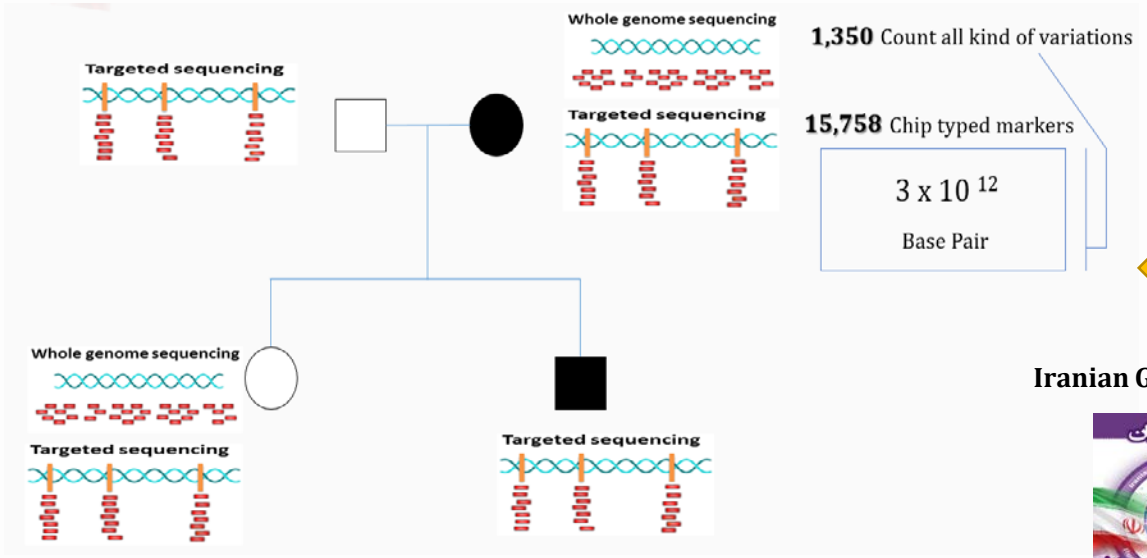
More than 600000 marker in genome

Quality control and familial relationship assessment

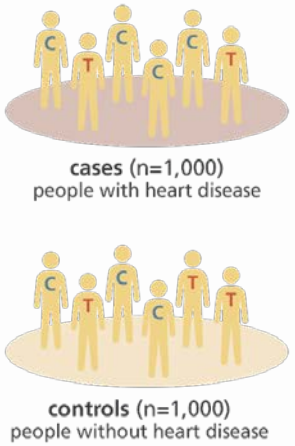
22801 person in 3098 family and 875 unrelated person

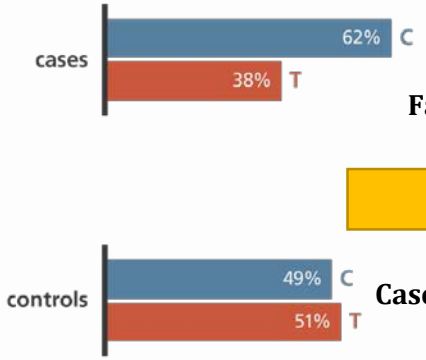
Imputation

Reference	Observation	Prediction
AA AT TT GG AG TG	A/G	AG
AA AT TT GG AA TT	A/A	AT
AA AG GG GG AA TG	./.	TG
GA GT TT GG AA TG	./.	GG
GA GT TT GG AA TT	A/A	AT
GA GT TG GG AT TC	T/T	TG
GA GT TG GG AT TC	C/G	CG



Iranian Genome Project



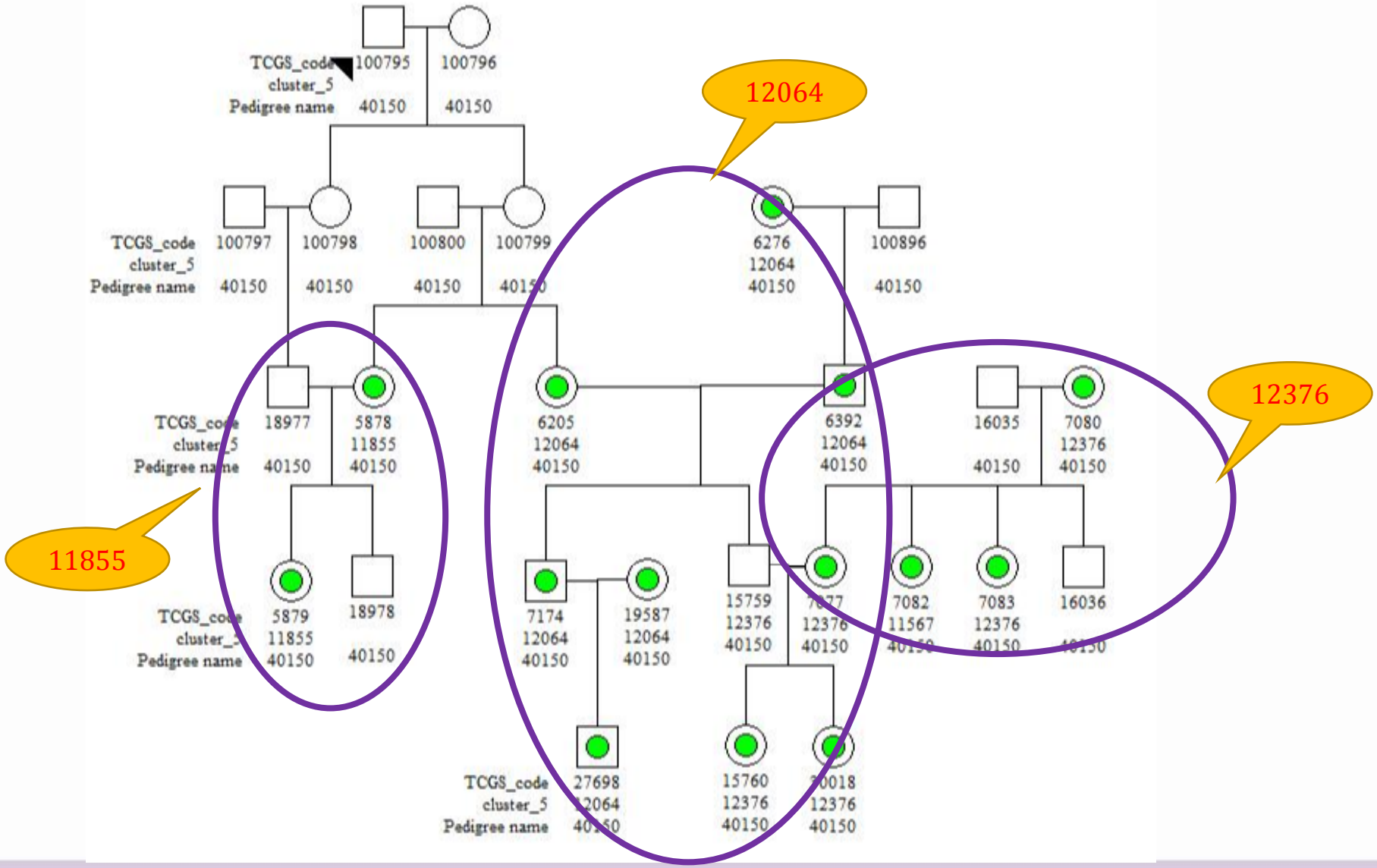


Familial

Association analysis

Case-Control

Family correction after genotyping



Longitudinal Family Based Studies

Aim: follow-up major incident & prevalence of cardio-metabolic-related health events

Traits: More than 1000 phenotypes in 22 years and 7 phases

TLGS

Tehran Lipid and Glucose Study

Cohort study

Start: 1999, Ongoing

N: 23265 (Female 49.6%)

Pedigrees: 3758 (Max:74)

N: 19118
Chip:13346
(WGS: 1023)

Aim: Evaluating and comparing several surgical bariatric procedures

Traits: More than 300 phenotypes in 9 years

TOTS

Tehran Obesity Treatment Study

Cohort

Start: 2013, Ongoing

N: 5500 (Female 79.7%)

Pedigrees: 376 (Max:8)

N:469
Chip: 457

Aim: Genetic investigation of Thyroid cancer

Traits: More than 10 phenotypes in 20 years

TCP

Thyroid Cancer Project

Clinical registry

Start: ۲۰۰۱, Ongoing

N: 452 (Female 56.9%)

Pedigrees: 169 (Max:16)

N: 452
Chip: 416

Aim: Genetic investigation of inherited genetic disease

Traits: More than 50 phenotypes in 11 years

CFP

Clinical Follow-up Project

Clinical registry

Start: 2011, Ongoing

N: 328 (Female 51.8%)

Pedigrees: 148 (Max:6)

N:328
Chip: 320
(WGS: 258)

Tehran Cardiometabolic genetic study (TCGS)

Aim: within a longitudinal family-based cohort in response to the lack of fundamental knowledge of the genetic variation diversity pattern in the Iranian population, concentrating on evaluating the genetic basis of Cardiometabolic risk factors.

Data: N:20367 (Female 51.8%); Pedigree: 4451 (Max:74), Chip:14539; WGS: 1281; Genetic Markers (SNP, Indel): ~62 M

Variables: Physical examination, Biochemical markers, Medical history

Start: 2012; Ongoing

European Journal of Epidemiology
https://doi.org/10.1007/s10654-023-01008-1

COHORT UPDATE

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Cohort profile update: Tehran cardiometabolic genetic study

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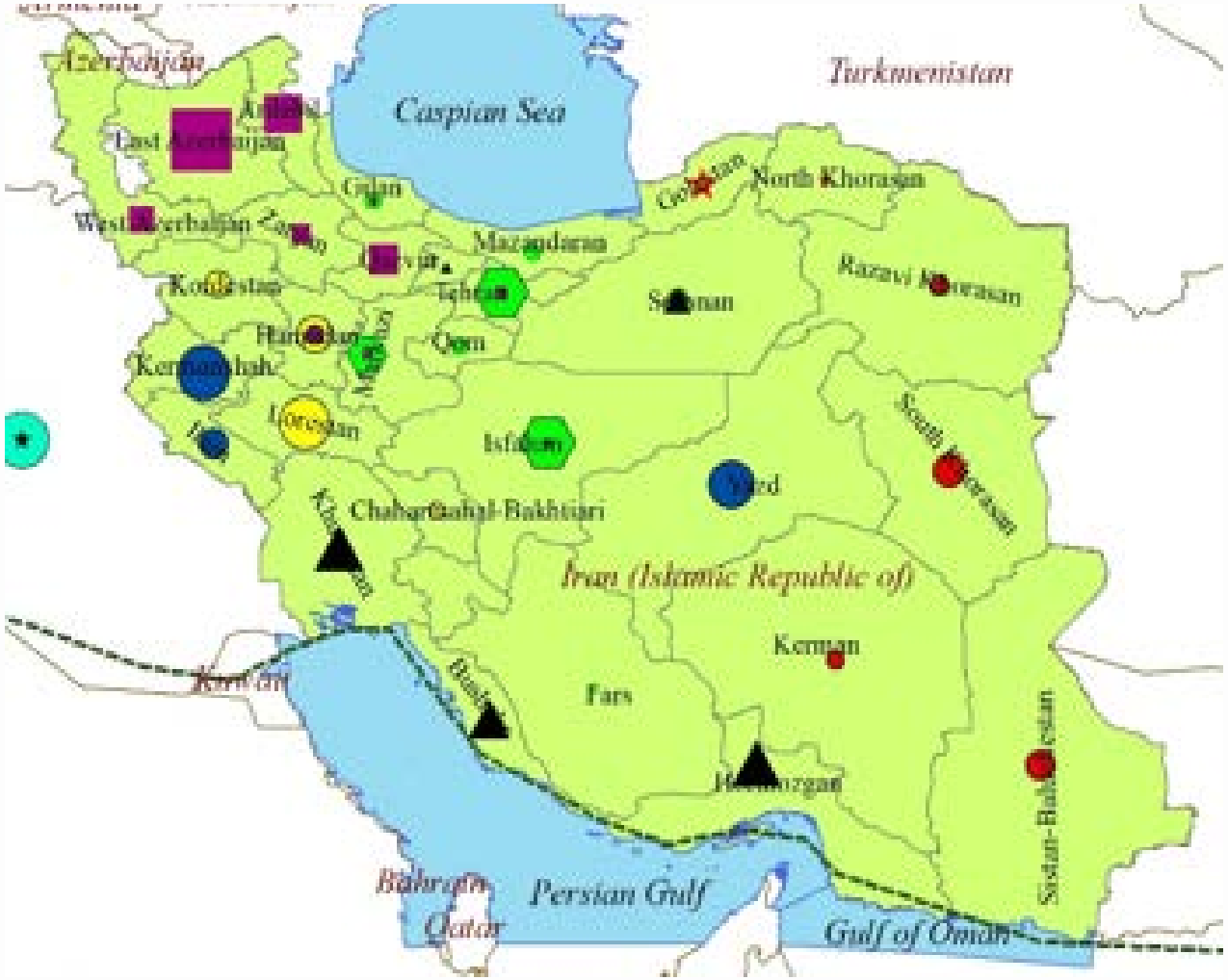
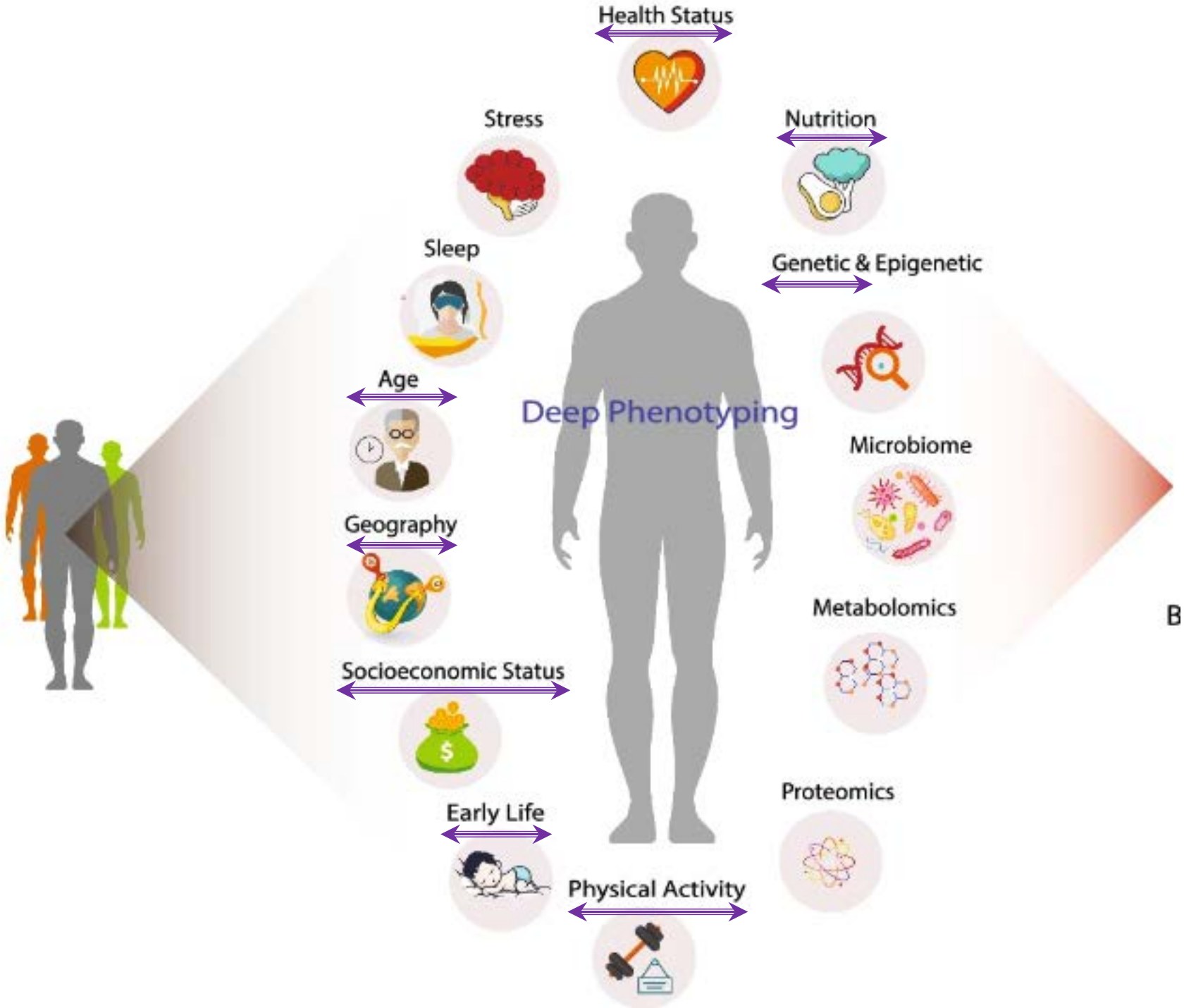
Population diversity

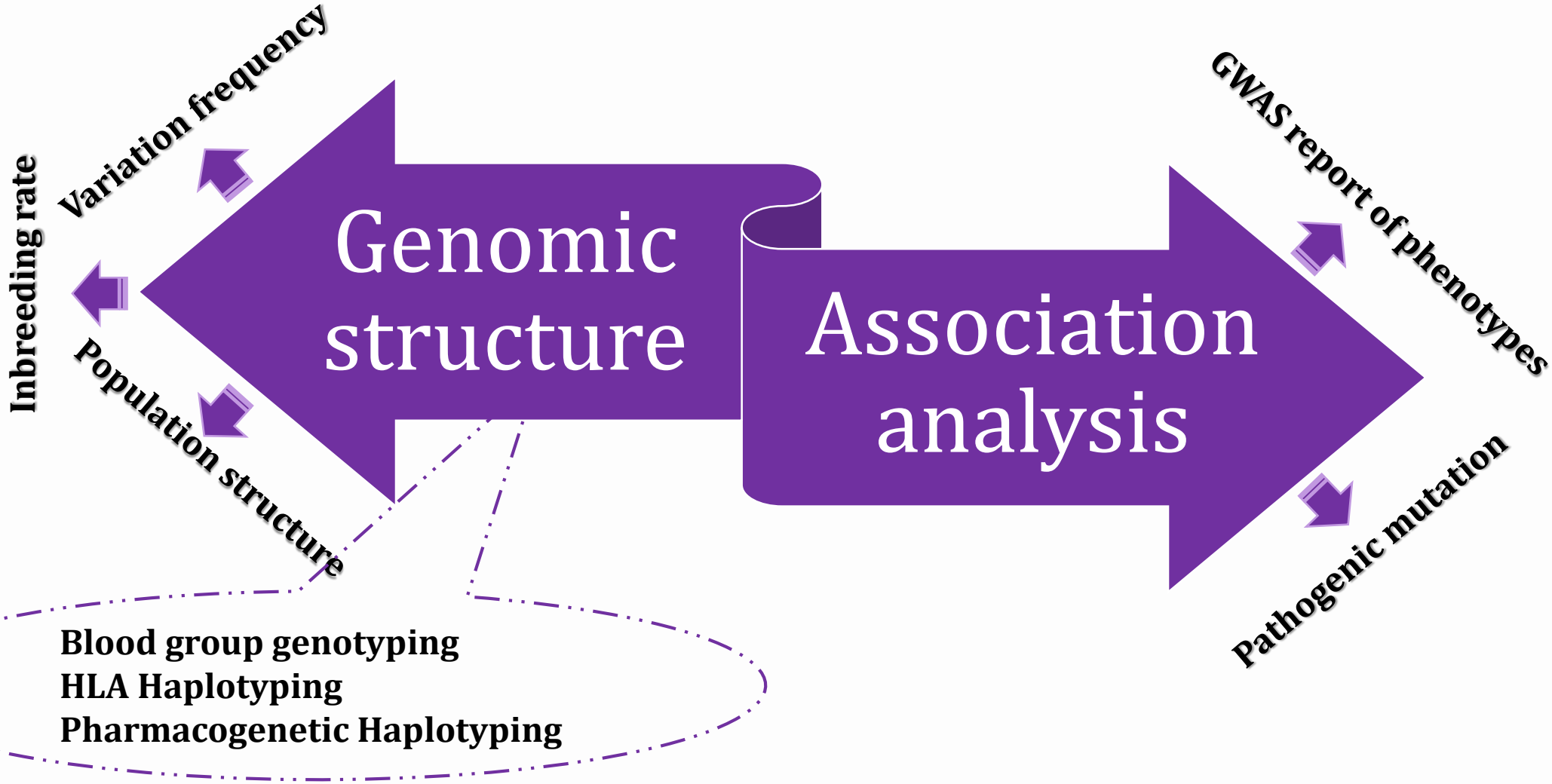
Participants, n*	20,367	
Female, n (%)	10,558 (51.8)	
Age at baseline mean (s.d.)	46.86 (21.53)	
Iranian ethnicity, n	Persian, n	4729
	Turk, n	746
	Gilak, n	255
	Lur, n	133
	Arab, n	84
	Kurd, n	69
	Balouch, n	28
	Turkman, n	14
	Tat, n	13
	Qashqai, n	3
	Mixed, n	103



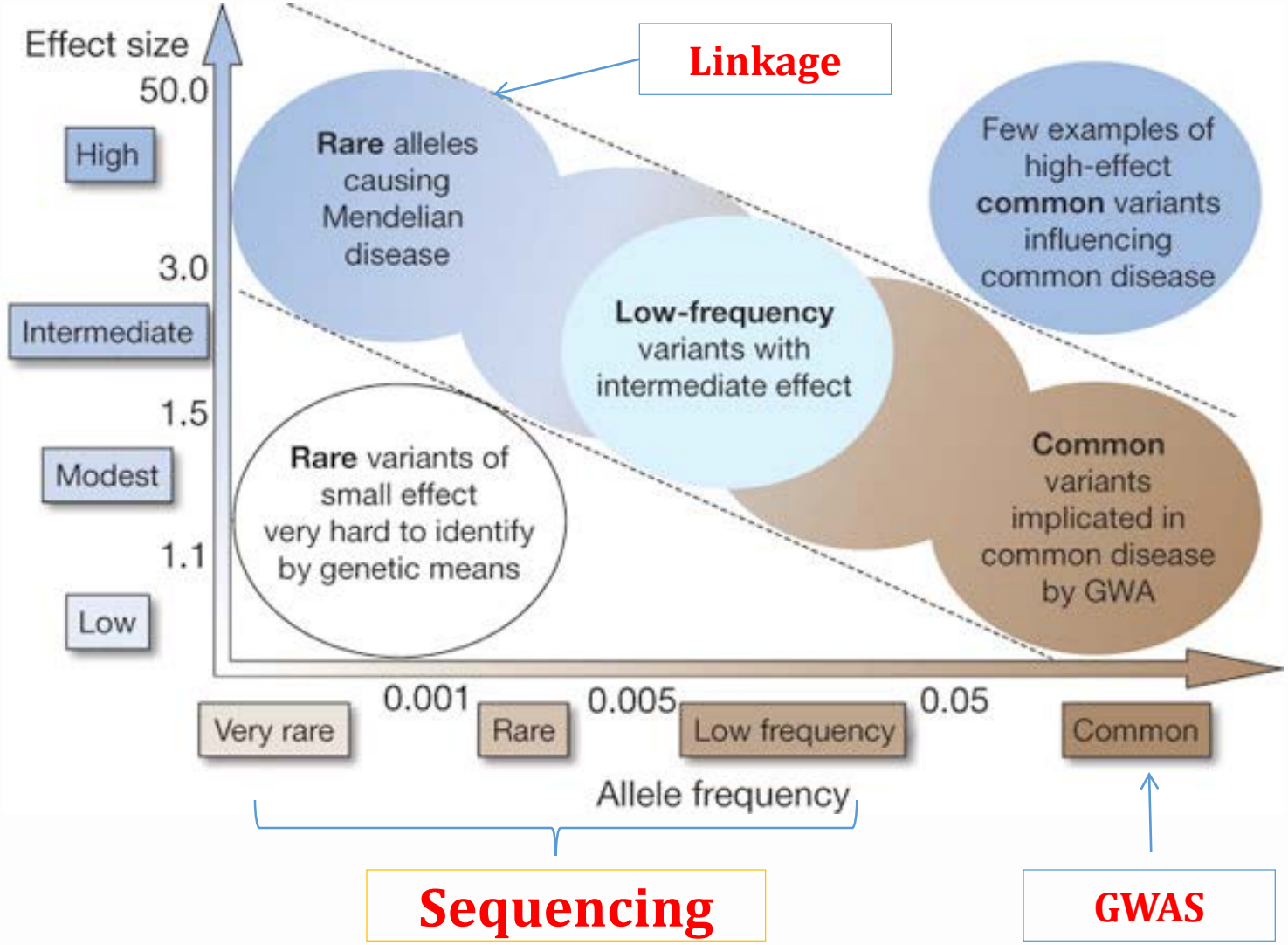
Laboratory Blood Test	Basic metabolic panel (n=11)
	Lipid panel (n=4)
	Advanced Lipid Panel (n=4)
	Inflammatory panel (n=4)
	Thyroid Function Test (n=9)
	Liver Function Test (n=5)
	Hormones (n=4)
	Others (n=4)
Self-Reported Questionary	Demographic information (n=8)
	Ethnicity (n=7)
	Past Medical History (n=47)
	Adoloscents Smoking (n=15)
	Adults Smoking (n=40)
	Adolescents Physical Activity (n=8)
	Adults Physical Activity (n=17)
	Obstetric and Gynecology (n=73)
	Dietary intake (n=221)
	Follow up (n=58)
	Health-related quality of life (HRQoL) (n=75)

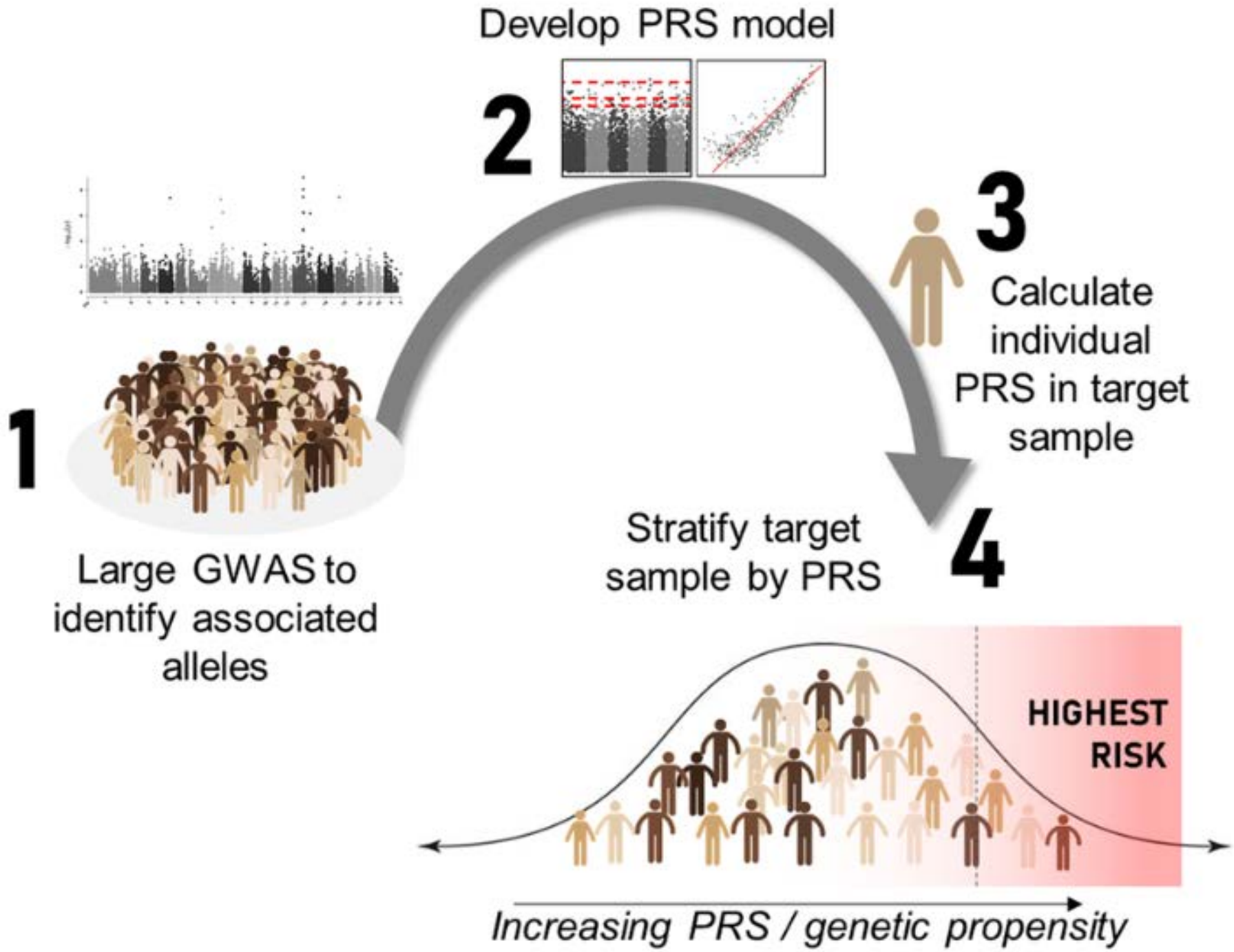
Medical condition	1-Certain infectious or parasitic diseases (n= 47)
	2-Neoplasms (n= 68)
	3-Diseases of the blood or blood forming organs (n= 14)
	4-Diseases of the immune system (n= 11)
	5-Endocrine nutritional or metabolic diseases (n= 49)
	6-Mental behavioural or neurodevelopmental disorders (n= 25)
	7-Sleep wake disorders (n= 2)
	8-Diseases of the nervous system (n= 34)
	9-Diseases of the visual system (n= 31)
	10-Diseases of the ear or mastoid process (n= 14)
	11-Diseases of the circulatory system (n= 43)
	12-Diseases of the respiratory system (n= 37)
	13-Diseases of the digestive system (n= 52)
	14-Diseases of the skin (n=27)
	15-Diseases of the musculoskeletal system or connective tissue (n= 43)
	16-Diseases of the genitourinary system (n= 66)
	17-Conditions related to sexual health (n= 1)
	18-Pregnancy child birth or the puerperium (n= 22)
	19-Certain conditions originating in the perinatal period (n= 12)
	20-Developmental anomalies (n= 28)
	21-Symptoms signs or clinical findings not elsewhere classified (n= 84)
	22-Injury poisoning or certain other consequences of external causes (n= 75)
	23-External causes of morbidity or mortality (n= 19)
	24-Factors influencing health status or contact with health services (n= 27)

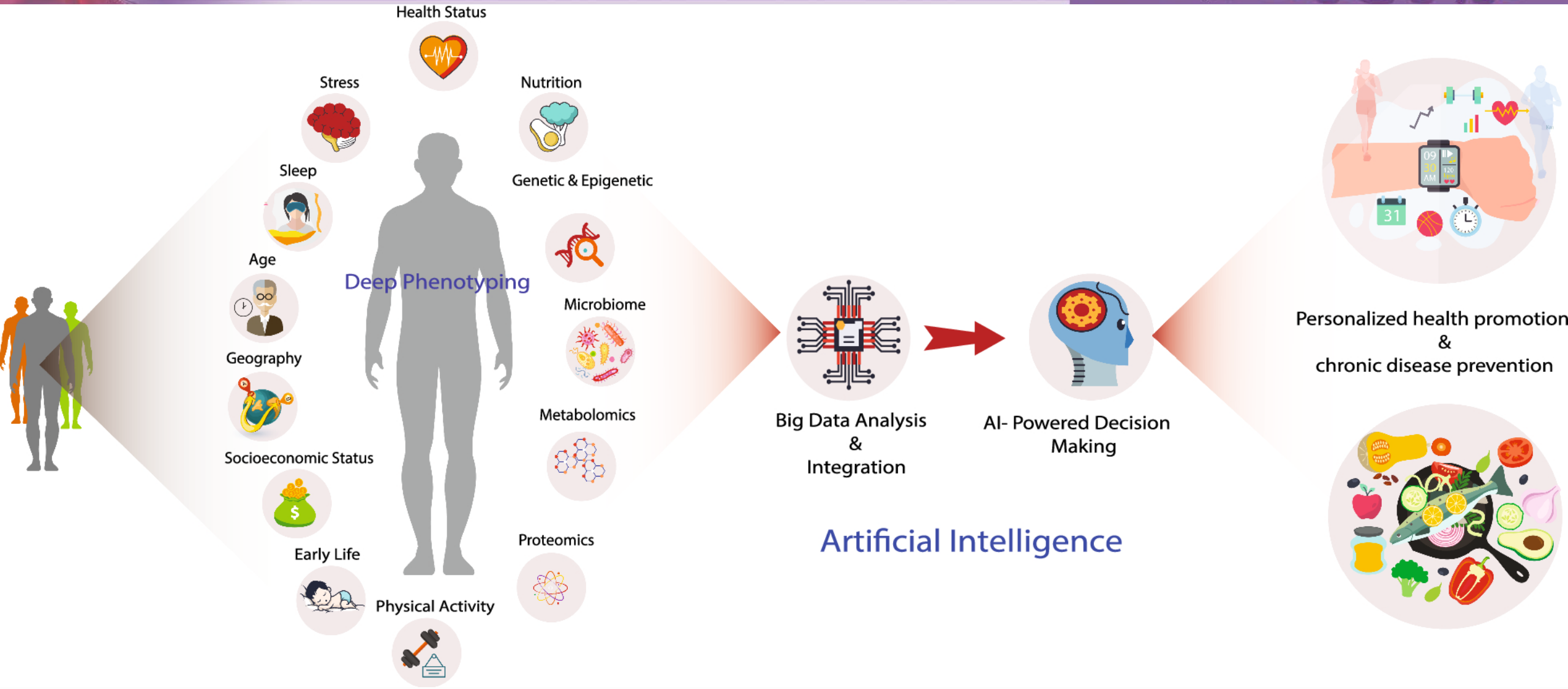

Health Status
Stress
Nutrition
Sleep
Genetic & Epigenetic
Age
Deep Phenotyping
Microbiome
Geography
Metabolomics
Socioeconomic Status
Proteomics
Early Life
Physical Activity
B


Genomic structure
Association analysis
Variation frequency
Inbreeding rate
Population structure
GWAS report of phenotypes
Pathogenic mutation
Blood group genotyping
HLA Haplotyping
Pharmacogenetic Haplotyping

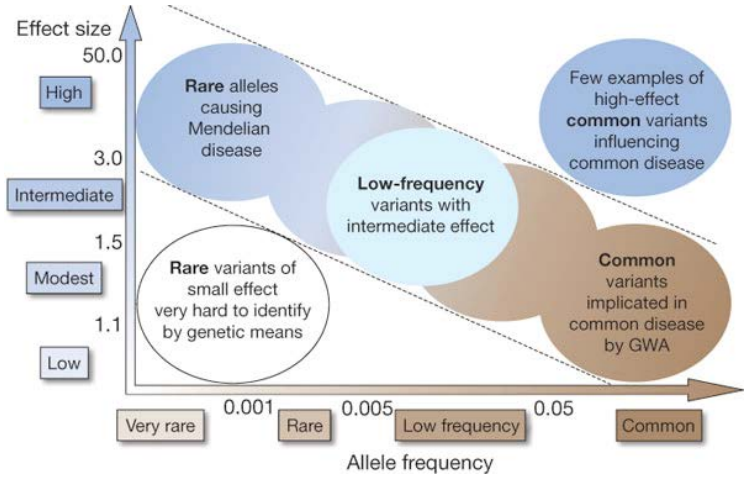
Genetic Spectrum of Complex Diseases




Develop PRS model
2
3
Calculate individual PRS in target sample
1
Large GWAS to identify associated alleles
Stratify target sample by PRS
4
HIGHEST RISK
Increasing PRS / genetic propensity


Health Status
Stress
Nutrition
Sleep
Genetic & Epigenetic
Age
Deep Phenotyping
Microbiome
Geography
Metabolomics
Socioeconomic Status
Early Life
Proteomics
Physical Activity
Big Data Analysis
&
Integration
AI- Powered Decision
Making
Artificial Intelligence
Personalized health promotion
&
chronic disease prevention

Diabetes and Precision Medicine


Effect size
50.0
High
3.0
Intermediate
1.5
Modest
1.1
Low
Rare alleles causing Mendelian disease
Few examples of high-effect common variants influencing common disease
Low-frequency variants with intermediate effect
Rare variants of small effect very hard to identify by genetic means
Common variants implicated in common disease by GWA
0.001
0.005
0.05
Very rare
Rare
Low frequency
Common
Allele frequency

Thank you for your attention