
بسم الله الرحمن الرحیم

بسترهای پزشکی شخصی در ایران

Precision medicine in Iran

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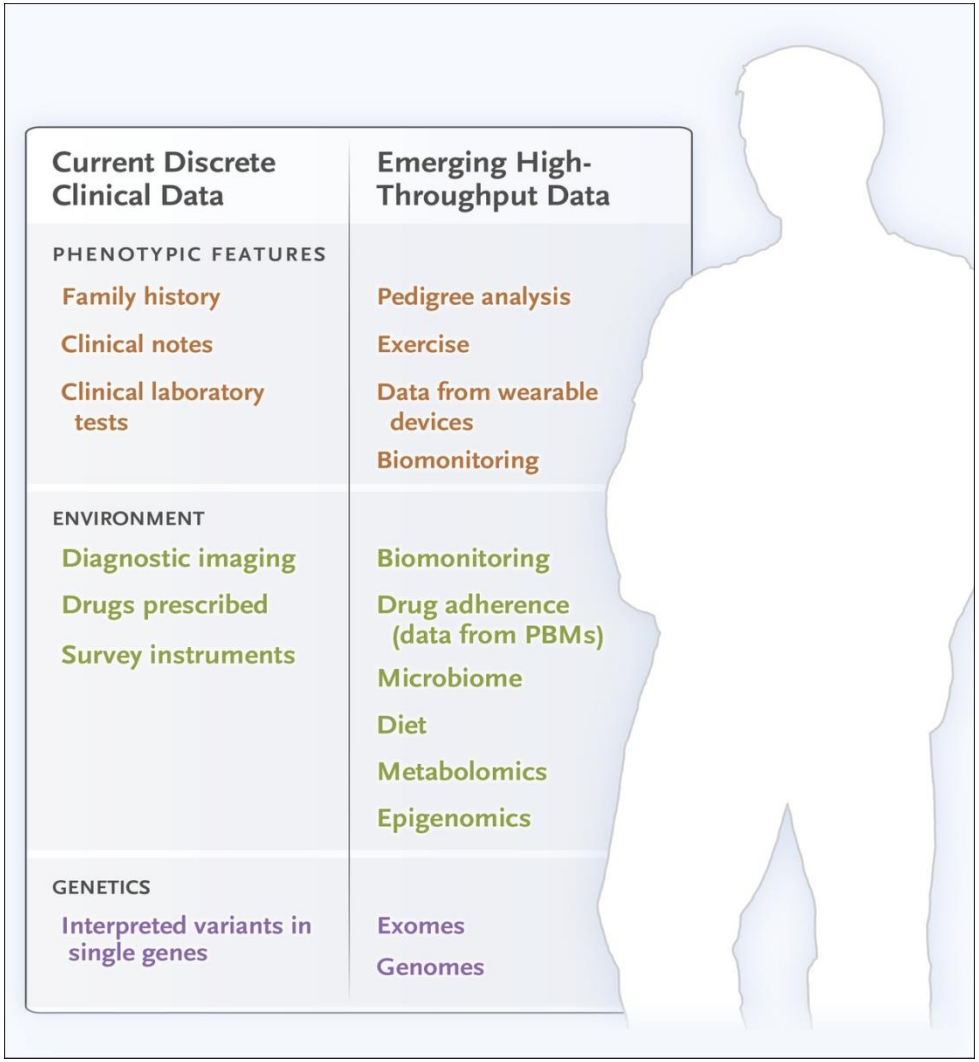
دانشگاه علوم پزشکی شهید بهشتی

۱۱مهر ماه ۱۴۰۳

Agenda

- Genomic driven precision medicine
- Practical application of precision medicine
- Precision medicine in diabetes
- Risk prediction of DM
- Pharmacogenetics of DM
- Precision medicine in Iran
- Tehran cardiometabolic genetic study
- Challenges and Conclusions

Multimodal Clinical and High-Throughput Data, Captured in Diverse Ways

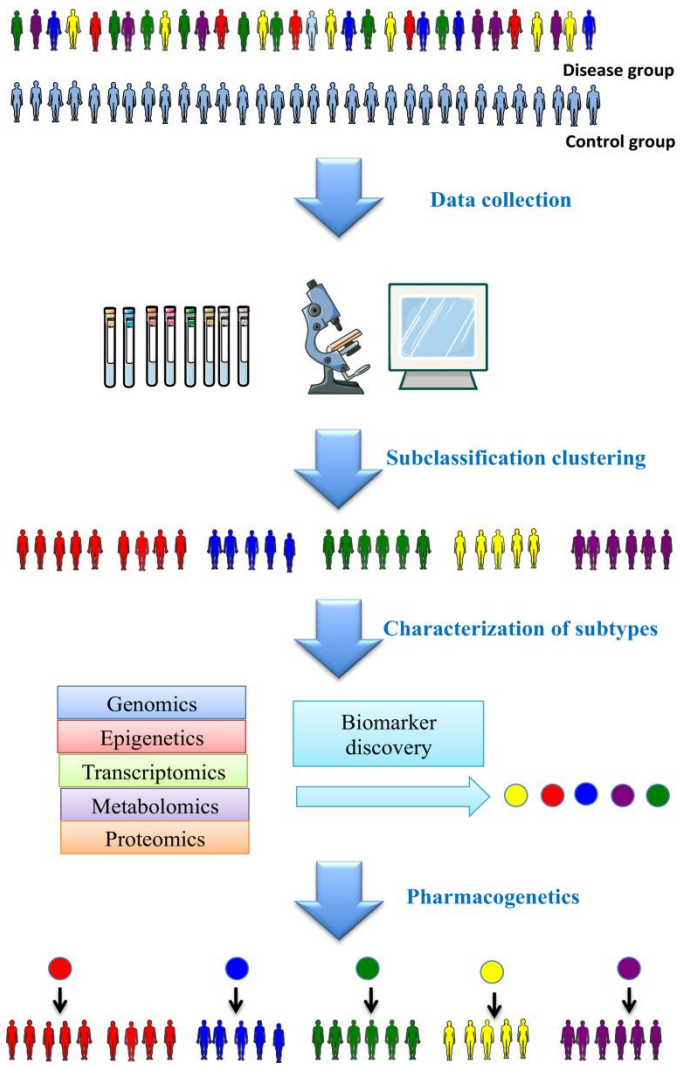


Haebdel MA, et al. N Engl J Med. 2018; 379: 1452

Precision Medicine: Definition

Personalized medicine is defined as a combination of molecular profiling and traditional diagnostic and therapeutic strategies precisely adapted to the individual requirements of patients.

An overview of precision medicine approaches



Prasad RB, J Intern Med. 2019 Jan;285(1):40-48

PRACTICAL APPLICATIONS for Precision Medicine

❖**Data sharing and regulatory science** **are critical components of precision medicine.**

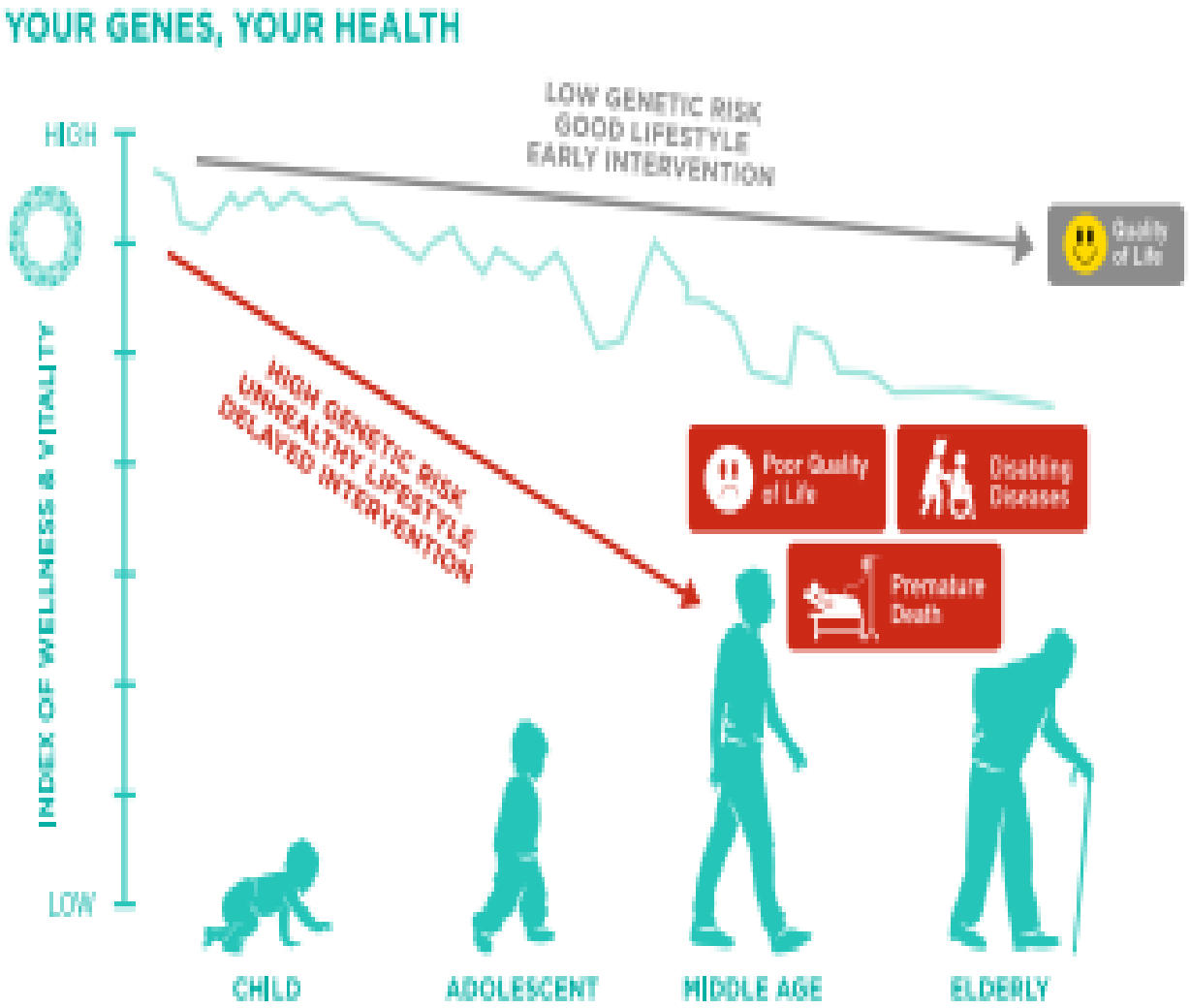
❖**Analysis** **of tissue and liquid biopsies, molecular tumor boards, and well-designed prospective trials** **are needed to move the field forward.**

Davis AA, et al. Am Soc Clin Oncol Educ Book. 2018; 38: 998

Aims of Personalized Medicine

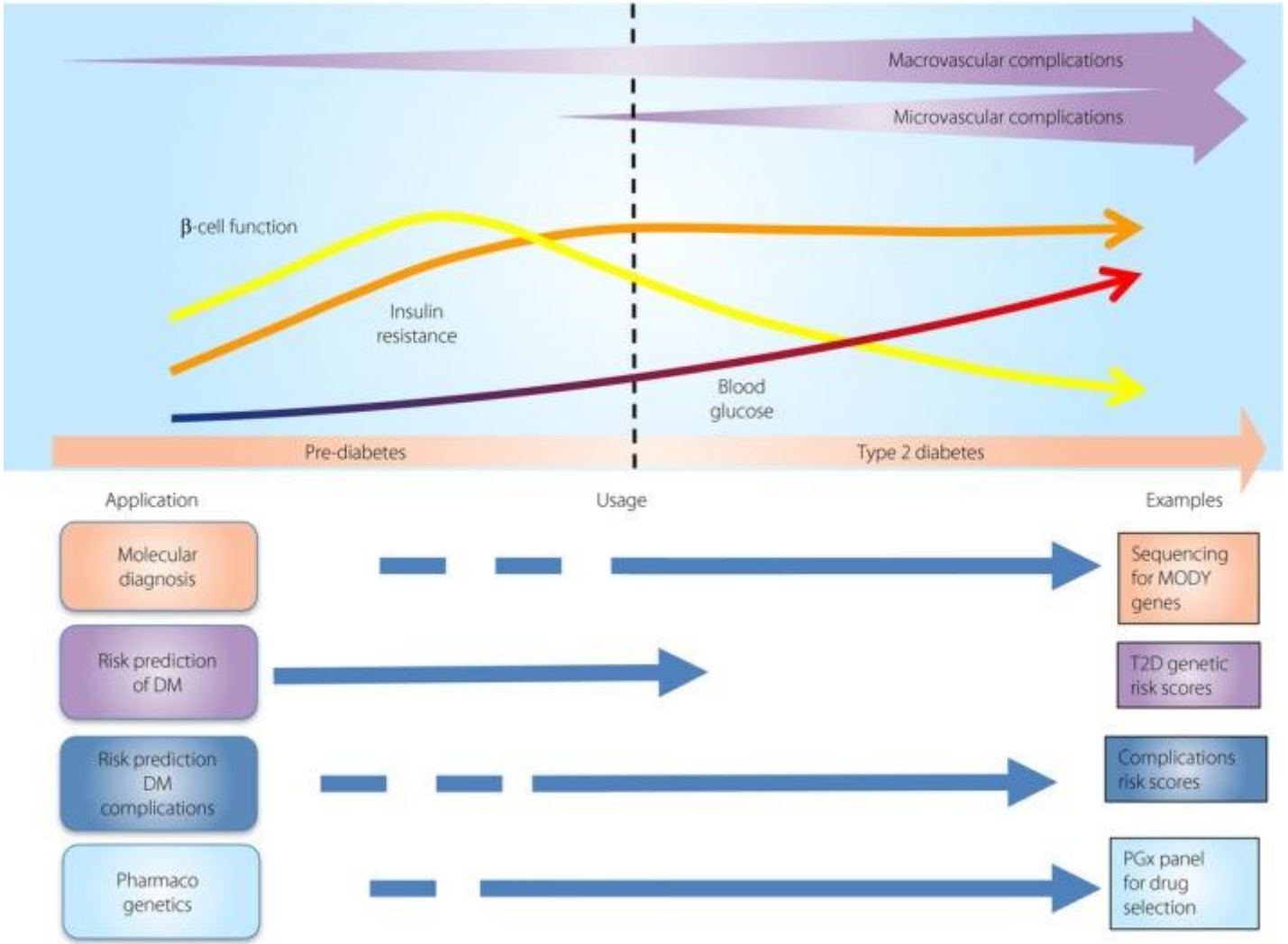
To couple large amounts of data available from the human genome with established clinical-pathological indexes to devise diagnostic, preventive, prognostic, and therapeutic policies specifically adapted to each patients needs and the ensuing research wave of the molecular basis of disease.

The basic concept of personalized intervention and substantial interaction of genetic and modifiable risk



Xie F, et al. J Diabetes Investing 2018; 9: 998

Potential application of precision medicine in diabetes at different stages of diabetes. DM, diabetes mellitus; MODY, maturity-onset diabetes of the young; T2D, type 2 diabetes



Xie F, et al. J Diabetes Investig. **2018; 9**: **998**

Precision prevention

- **Includes taking data about a person's biology, environment, clinical characteristics, social factors, or other features of their context to optimise health interventions focused on maintaining a healthy state (precision health), slowing progression to disease once underway, or reducing complications and consequences of disease.**

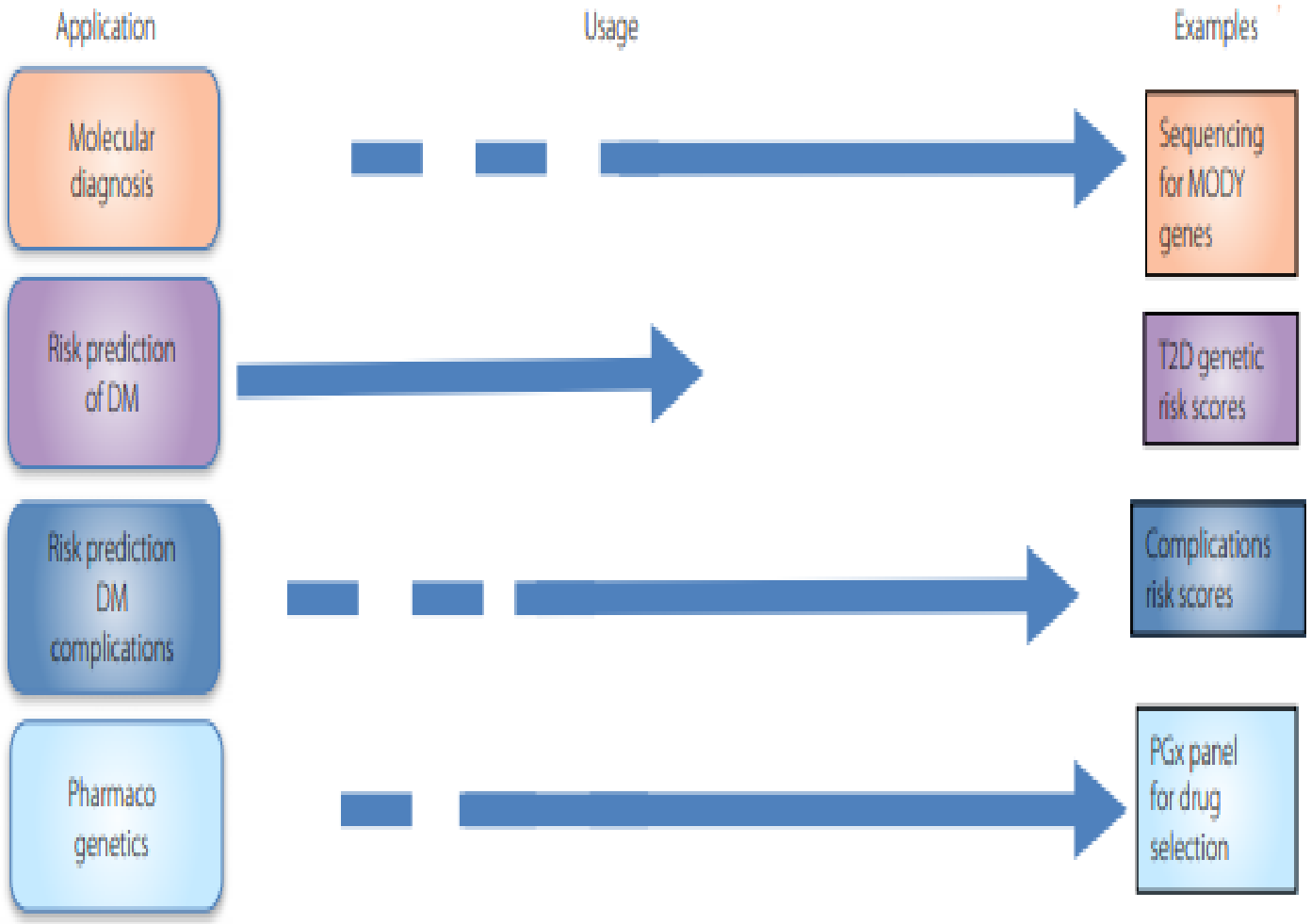
Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Prevention, monitoring

❖**Precision prevention of diabetes should determine the likely responses to health interventions and risk factors, optimise interventions, and minimise risk factor exposure for an individual.**

❖**Precision monitoring includes an array of concepts including measuring blood sugar, biological markers, diet, sleep, and psychological and physiological states.**

Potential application of precision medicine in diabetes at different stages of diabetes



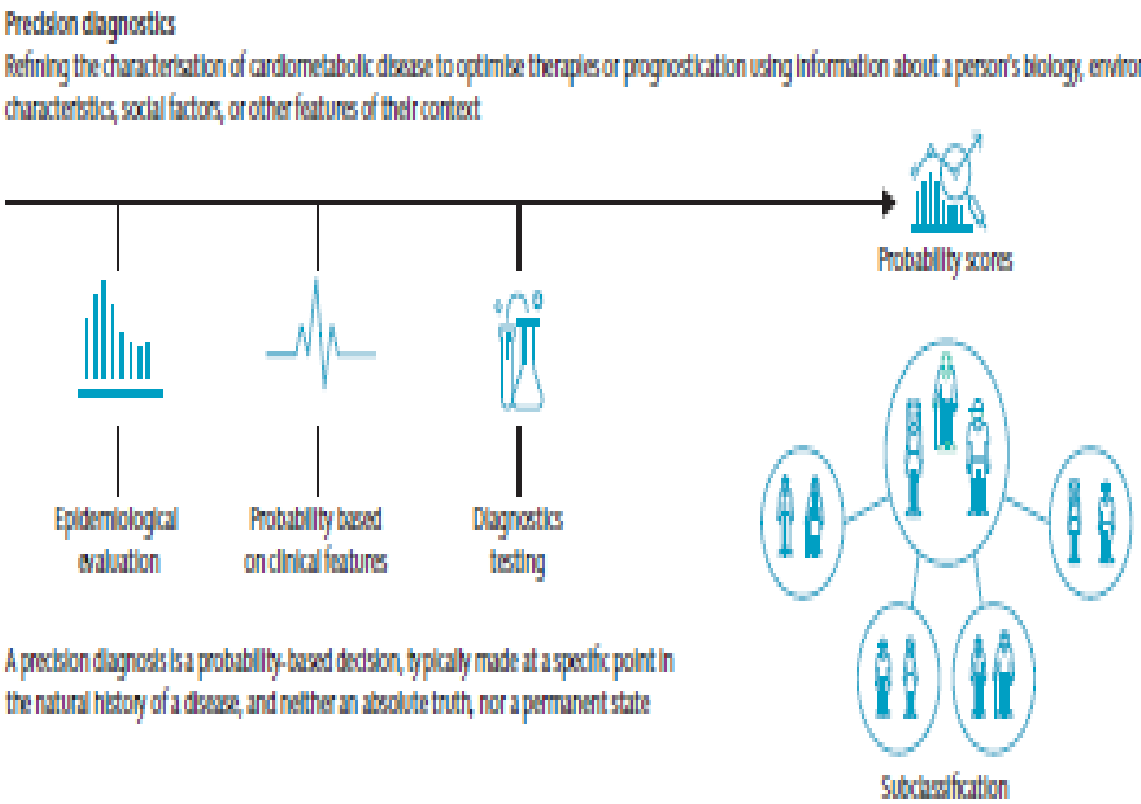
Xie F, et al. J Diabetes Investing 2018; 9: 998

Precision diagnosis

- **Is a refined characterisation of disease diagnosis for therapeutic optimisation or prognostic clarity by use of information about a person's biology, environment, clinical characteristics, social factors, or other features of their context.**
- **Can use a combination of biological markers and data, for example on socioeconomy, gender, lifestyle behaviours, diet, sleep, and psychophysiological stress, to minimise error in the prediction of disease caracteristics.**

Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Precision diagnosis



Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Precision prognosis

- **Focuses on predicting progression through the disease state, including the development and severity of complications and adverse consequences of treatment or non-treatment.**
- **Precision monitoring can include the detailed assessment of biological markers, such as continuous glucose or blood pressure monitoring, behaviours (eg, physical activity, smoking, or alcohol consumption), diet, sleep, and psychophysiological stress, in addition to assessment of changes in amount of organ damage.**

Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Precision treatment

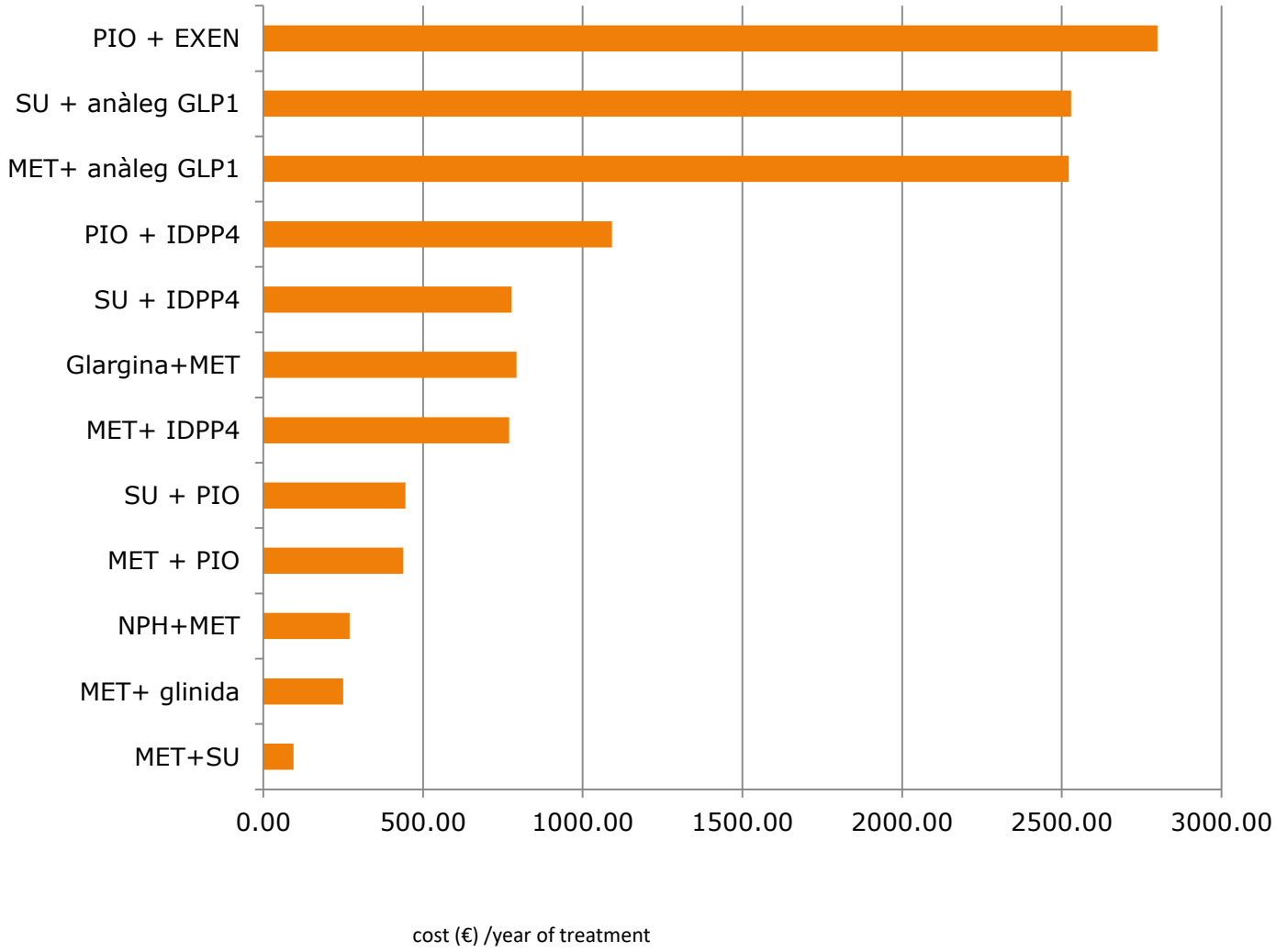
- **Includes taking information about a person's biology, environment, clinical characteristics, social factors, or other features of their context to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome, while reducing side-effects and costs.**

Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Pharmacogenomics

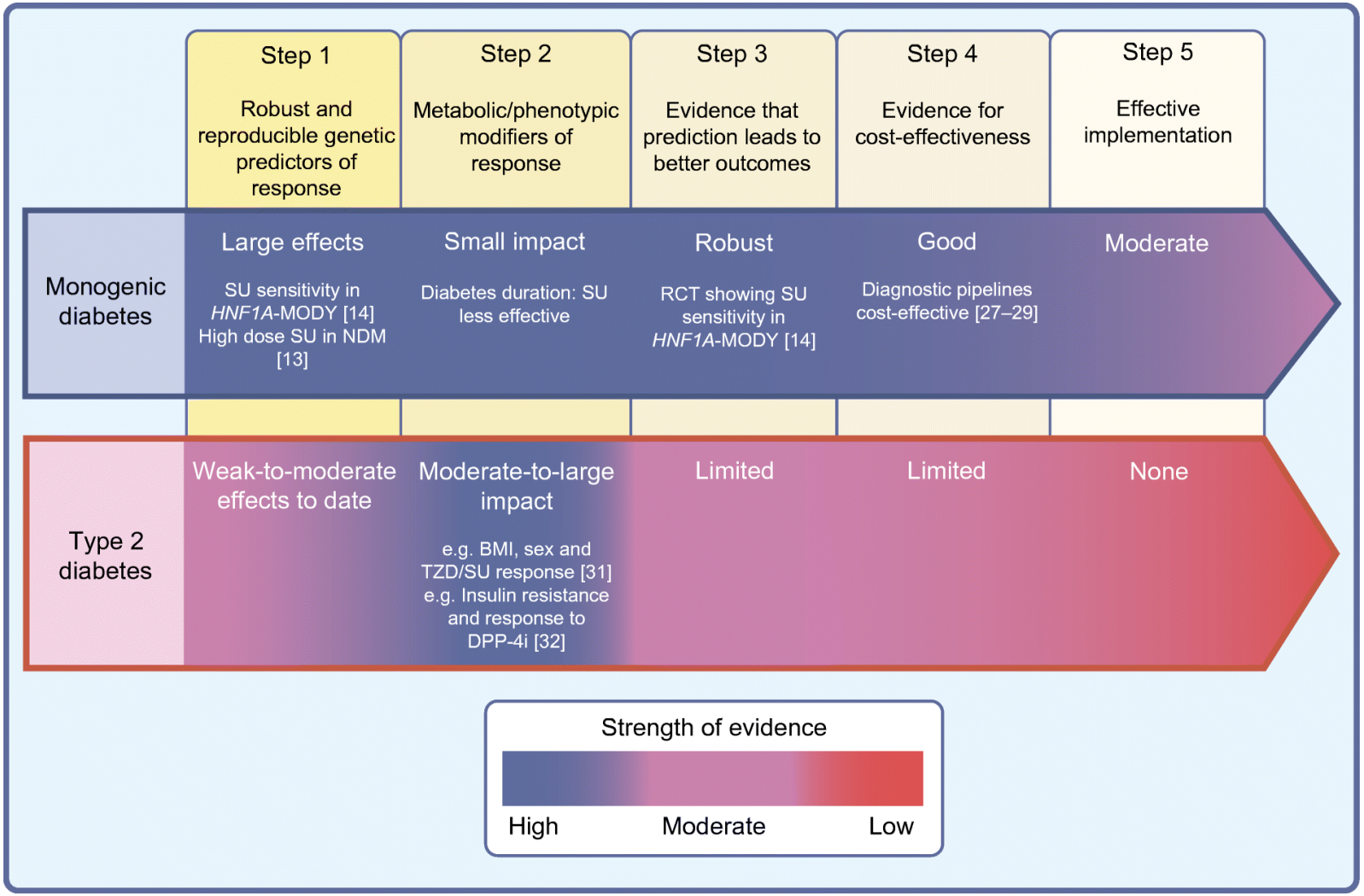
Pharmacogenomics is the study of how a person's reactions to medications is affected by their genetic constitution. It integrates pharmacology and genomics to develop efficient, safe medications and doses individualized to a person's genetic makeup.

Type 2 diabetes mellitus cost



Source: CatSalut – Generalitat de Catalunya (Local government), 2013

A roadmap to achieve pharmacological precision medicine in diabetes



Florez JC, et al 2022; Diabetologia Published online

Precision Medicine in Iran

- **Where are we today on the generation and interpretation of big data with respect to diabetes?**

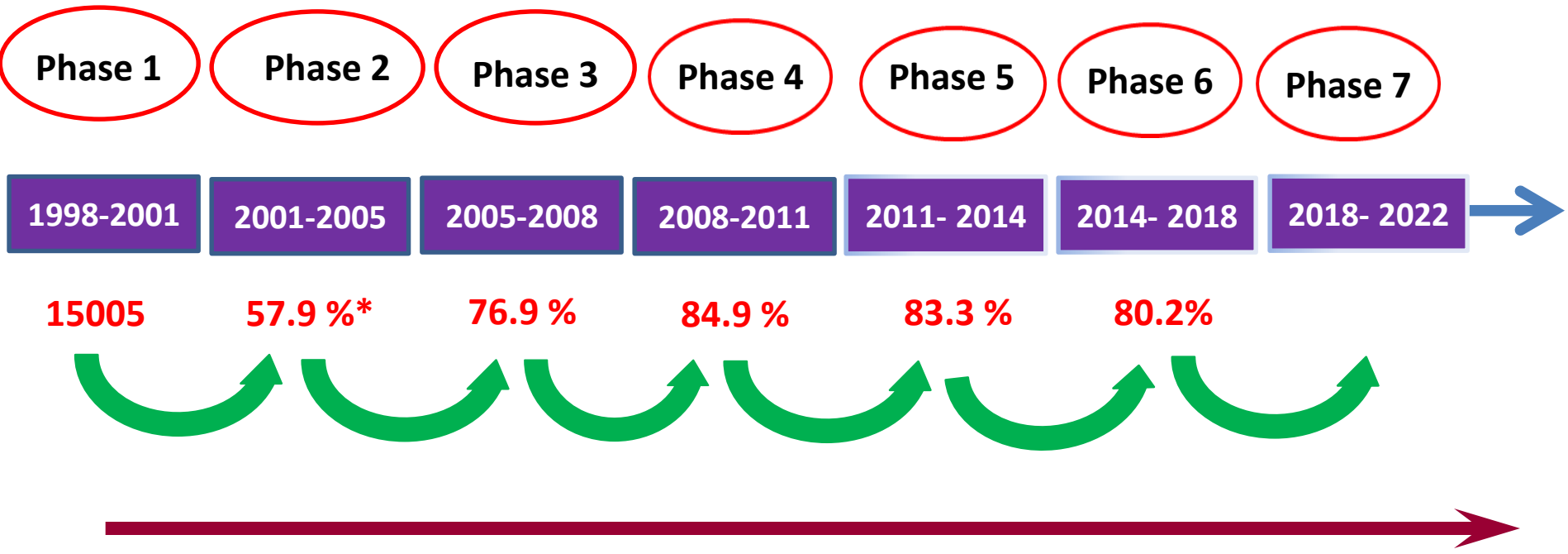
- **Are we producing the body of knowledge that can be applied to the individual patient in an effort to enhance precision in diagnostics and therapeutics?**

Prospective Studies of Cardiometabolic Disease and Risk Factors

- Framingham Heart Study in US (1948)
- Puerto Rico Heart Health program (1965)
- Bogalusa Heart Study in US (1972)
- Honolulu Heart Program among Japanese Americas (1980)
- MONICA (multinational Monitoring of trends and determinants in Cardiovascular isease) in 21 countries (1980)
- ARIC (Atherosclerosis Risk in Communities Study) in four US communities (1987)
- CHS (Cardiovascular Health Study) in US (1989)
- SHS (Strong Heart Study) in America Indians (1989)
- Rotterdam Study in the Netherlands (1990)
- AusDiab (Austrailian Diabetes, Obesity and Lifestyle Study) (1999)
- TLGS (Tehran Lipid and Glucose Study) in Iran (1998)

Tehran Lipid and Glucose Study

TLGS Cohort: follow-up phases and Response Rates



* Denotes percent of participation from previous phase

Tehran Cardiometabolic Genetic Study

23676 person in 4497 family

More than 100 phenotypes in 20 years and 6 phases

1400 0

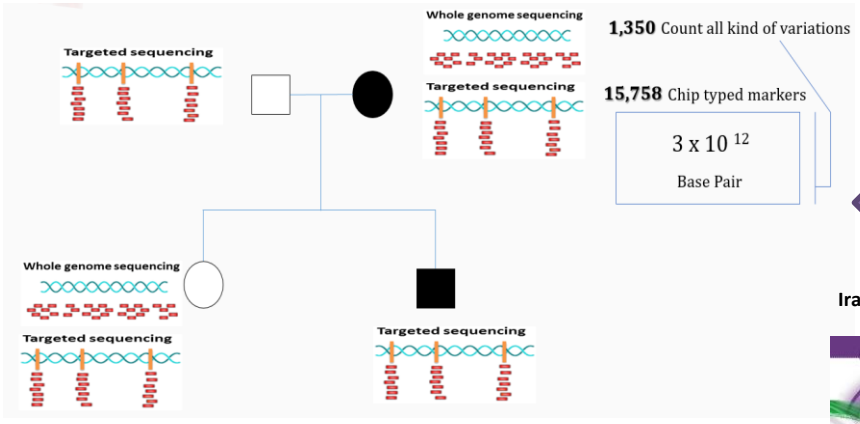
More than 600000 marker in genome

Quality control and familial relationship assessment

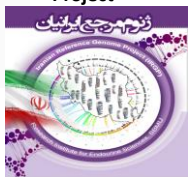
22801 person in 3098 family and 875 unrelated person

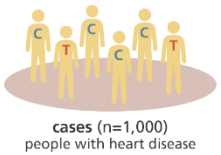
Imputation

Reference				Observation	Prediction	
A	A	A	G	A/G	A	G
A	T	A	A	A/A	A	A
T	T	G	T	./.	T	T
G	G	G	G	./.	G	G
A	G	A	A	A/A	A	A
T	T	T	T	T/T	T	T
C	G	G	C	C/G	C	G

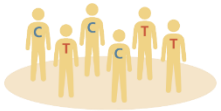


Iranian Genome Project

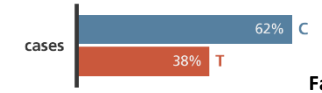




cases (n=1,000)
people with heart disease



controls (n=1,000)
people without heart disease



Familial

Association analysis

Case-Control

کاربردهای ژنوم مرجع ایرانیان

- بستر سازی برای مطالعات عمیق تر ژنتیک پزشکی
- انتقال تکنولوژی به ویژه آنالیز داده های حجیم ژنوم انسانی
- توانمندسازی متخصصان داخلی
- سرعت بخشیدن به تحقیقات این حوزه از سلامت
- کاربرد در تشخیص زودهنگام بیماری ها
- به کارگیری در اقدامات پیشگیری اولیه و ثانویه
- استفاده از طراحی داروها
- پیش آگهی پاسخ به درمان های پزشکی
- به طور اخص ایجاد و گسترش پزشکی شخصی (Personalized Medicine) در ایران

- تفاوت های ساختاری و بنیادی لزوم هرچه بیشتر استفاده از نقشه ژنومی مطابق با جمعیت ایرانی را در بررسی های گسترده ژنومی، فارماکو ژنتیک و پزشکی فرادقیق نشان می دهد.
- وجود داده های ژمیران همراه با داده های متابولومیکس و گنجینه داده های فنوتیپی "مطالعه قند و لیپید تهران" نویدبخش حرکت به سوی "پزشکی فرادقیق" ایران در دیابت است.

Framework for clinical translation

- **PM is, a process that seeks to reduce error and improve accuracy in medical decisions and health recommendations. By reducing the time from disease onset an event that is often asymptomatic to diagnosis**
- **Most evidence-based medicine focuses on population-averaged estimates of exposure risk, and treatment efficacy or safety.**
- **Involves the statistical interrogation of a reference population's high-dimensionality data to obtain precise and accurate estimates of risk and response.**
- **Stratifying the reference population into homogeneous subgroups sharing similar risk and response characteristics.**

Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Five steps towards the future implementation of pharmacological precision medicine

1. **Robust genetic predictors of response**
2. **Metabolic or phenotypic biomarkers that modify response**
3. **Evidence of better outcomes with a precision medicine approach**
4. **Evidence for cost-effectiveness**
5. **Effective and equitable clinical implementation**

Florez JC, et al 2022; Diabetologia Published online

Advantages of PM

- **Deploying therapeutics in a one-size-fits-all manner fails many of those in need.**
- **Standard healthy lifestyle recommendations, even when followed for decades, might have little or no impact on mortality.**
- **Precision medicine optimises health interventions to individual-level characteristics**
- **PM offers safer and more efficacious, more equitable, and less expensive solutions for cardiometabolic disease prevention and treatment.**

Franks PW et al. Lancet Diabetes Endocrinol 2023; 11(11): 822-835

Challenges and conclusions

- **The information captured on a given biological axis in an individual is often incomplete, static & imprecise.**
- **The enormous quantity of information available lends itself to data dredging and spurious findings.**
- **Effect sizes are too modest to be detected.**
- **The multiple dimensions of biological data typically reside in silos.**
- **Tissues of relevance to diabetes are difficult to access.**
- **Results from big data are seldom reproducible, interpretable and seldom clinically useful.**
- **To leverage big data in precision medicine requires a multidisciplinary approach.**

Ways Ahead

All medical personels are called upon to take part in the development of precision medicine for management of their patients, by accepting the complexities and heterogeneities of disorders and their burden in the population health. This will be a worthwhile investment with significant positive medical and socioeconomic outcomes for achieving "Health for All".