GLOBAL PHARM

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Personalized medicine - a new organizational model for structuring patient care

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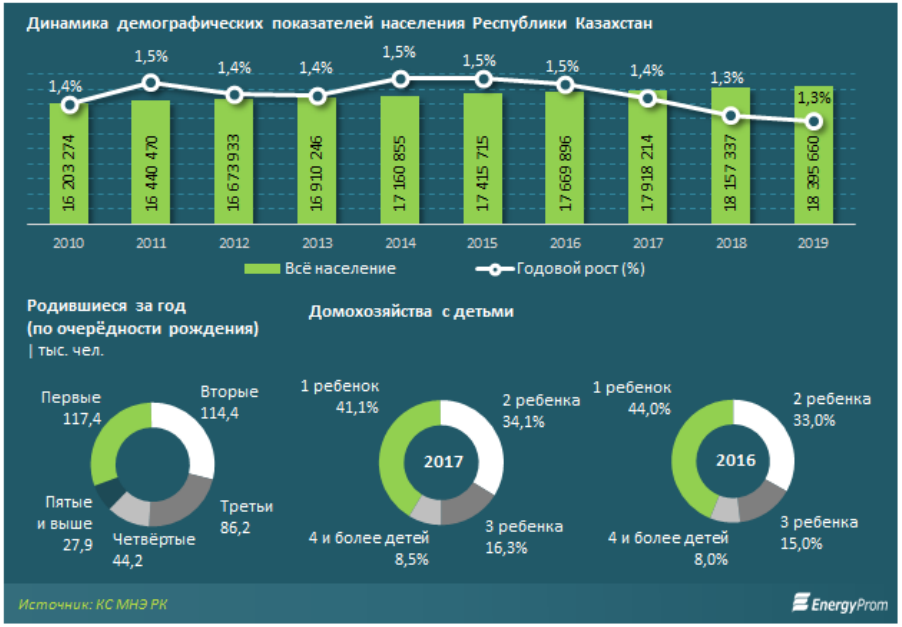
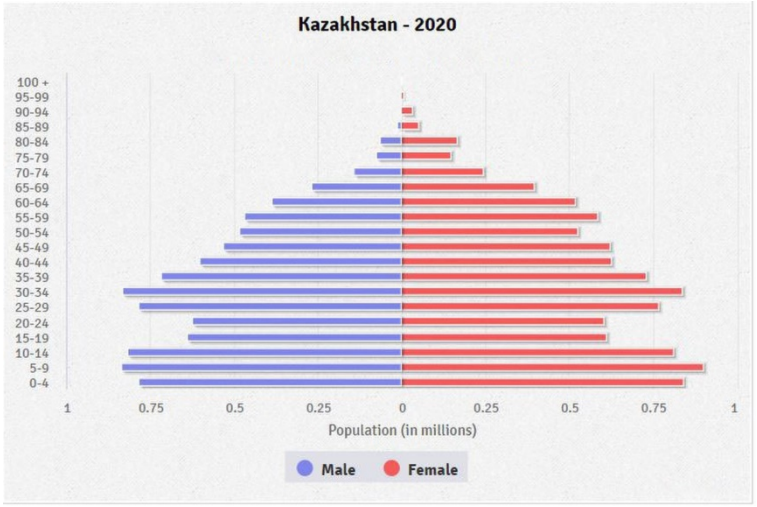
Astana,

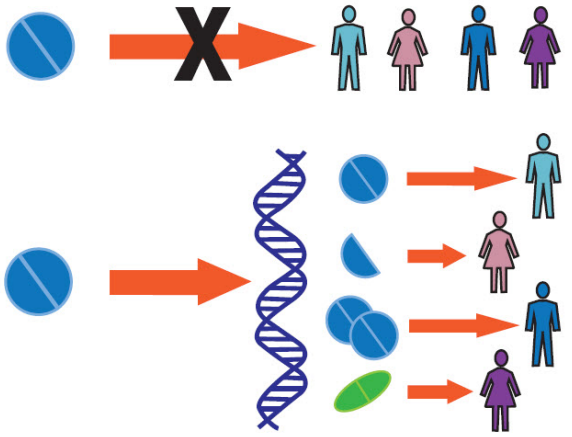
October 26, 2022

Kazakhstan demographics



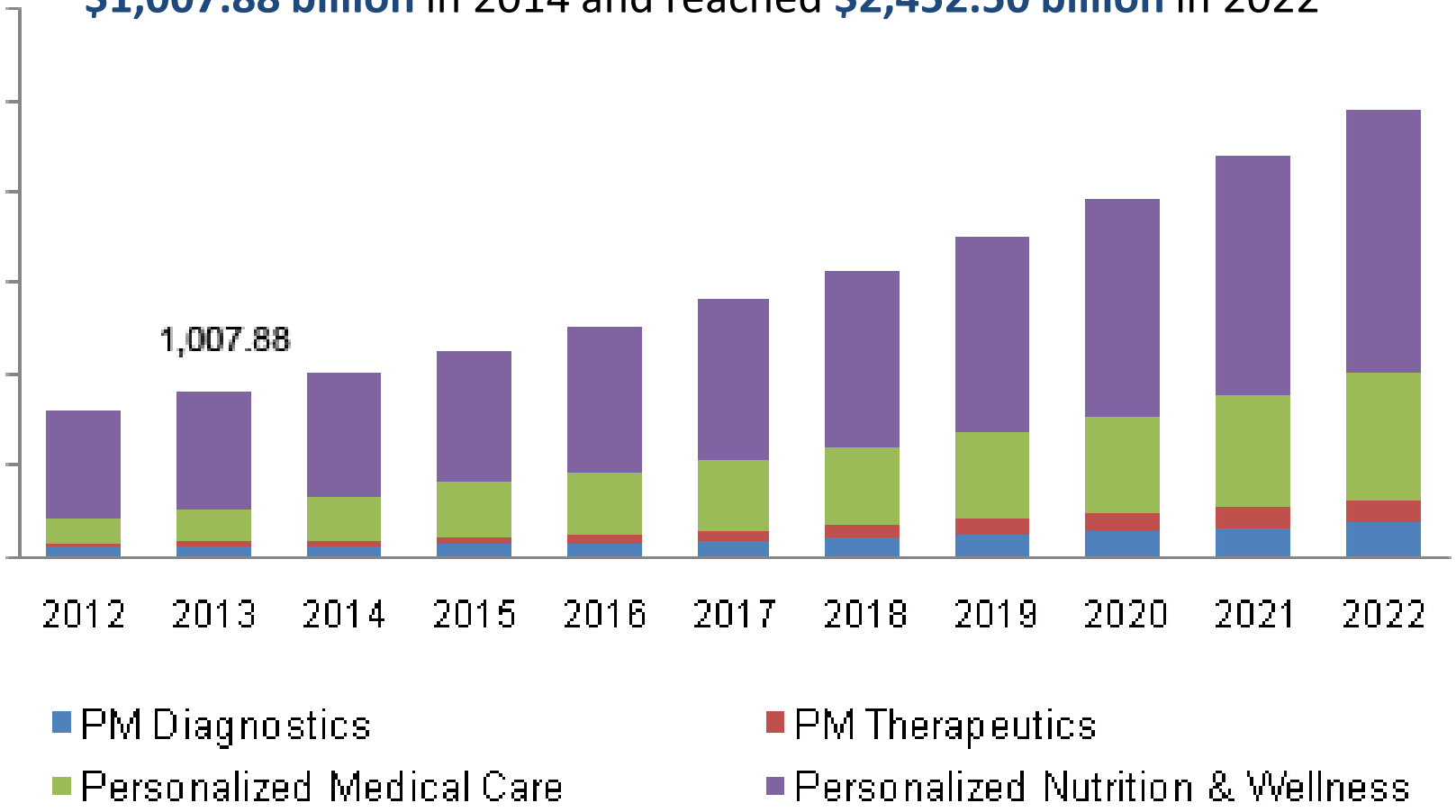


Recent advances in biomedical research and biotechnology offer new possibilities - strategies broadly known as personalized medicine (PM)



Personalized medicine market

The global market for personalized medicine has been valued at **$1,007.88 billion** in 2014 and reached **$2,452.50 billion** in 2022



http://www.grandviewresearch.com/industry-analysis/personalized-medicine-market

Precision Medicine Initiative

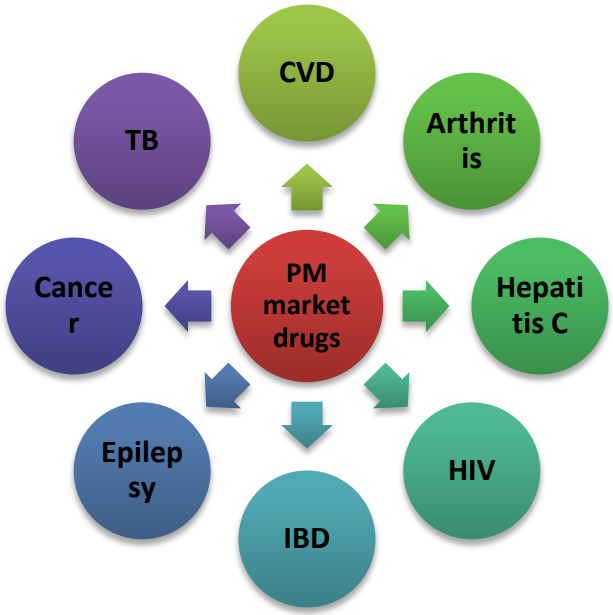
- January 20, 2015 - Obama announces the launch of an **Precision Medicine Initiative** focusing on cancer. For 2016**, $215 million has been allocated,** of which **$170 million** is allocated to the NIH to create a national, large-scale study group (cohort), and **$70 million** is given to the National Cancer Institute to focus efforts in the field of cancer genomics.

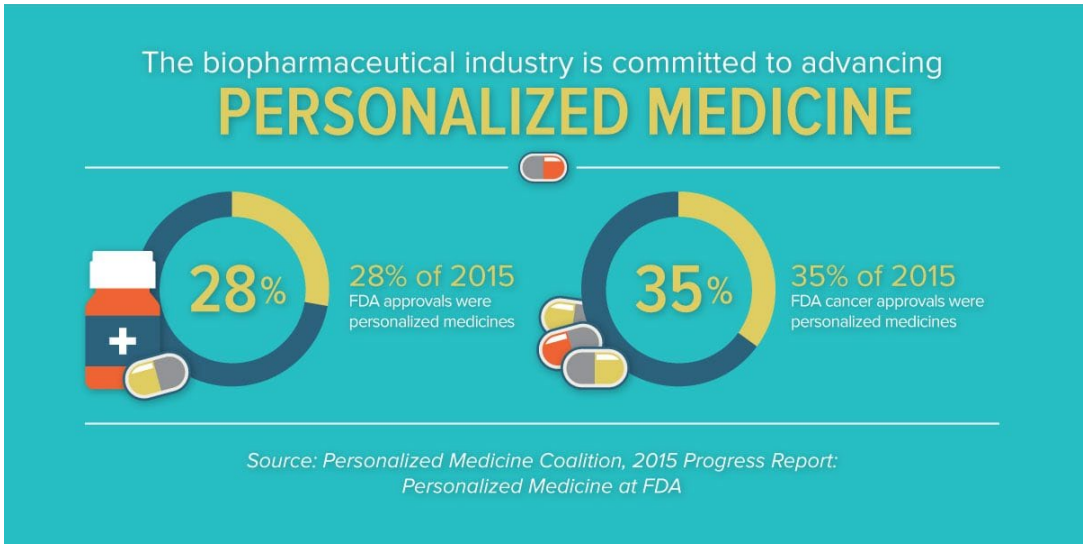
> "Tonight, I'm launching a new precision medicine initiative to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

- In Europe, the European Commission has since 2007 committed over €1 billion of health research funding to the development of '-omics' technologies and targeted therapies, and more funds are expected to be released in the coming years

  - An even larger personalized medicine program has been initiated in China. The option of allocating about **$ 9 trillion for 15 years for sequencing 1 million genomes** is being considered. The program is likely to consist of hundreds of small projects sequencing the genome and collecting information on cardiovascular disease, cancer and diabetes.

Available drugs and diagnostic tests in the field of personalized medicine





- Approximately 1 (28%) of 4 innovative new drugs approved by the FDA in 2015 were personalized medicine drugs (13 out of 45).
- 35% of innovative new cancer drugs approved by the FDA in 2015 were also personalized medicine drugs.

List of drugs

http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/2015_Progress_Report_PM_at_FDA.pdf

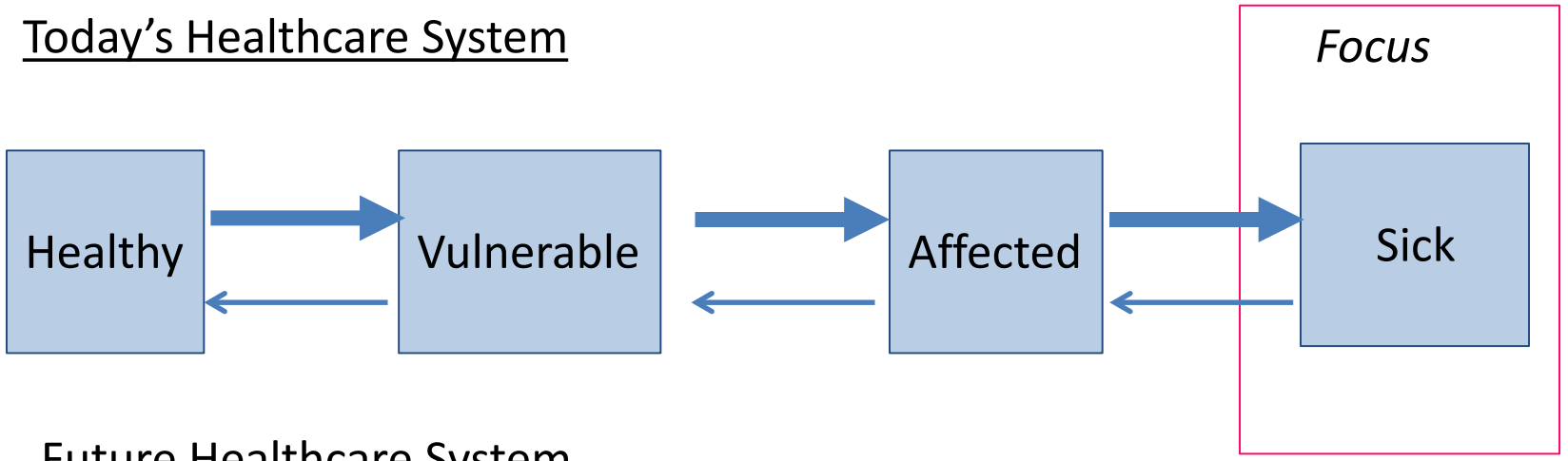
http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/the_case_for_pm1.pdf

European Council Conclusion on personalised medicine for patients (2015/C 421/03

- Personalised medicine was defined as "*a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.*"

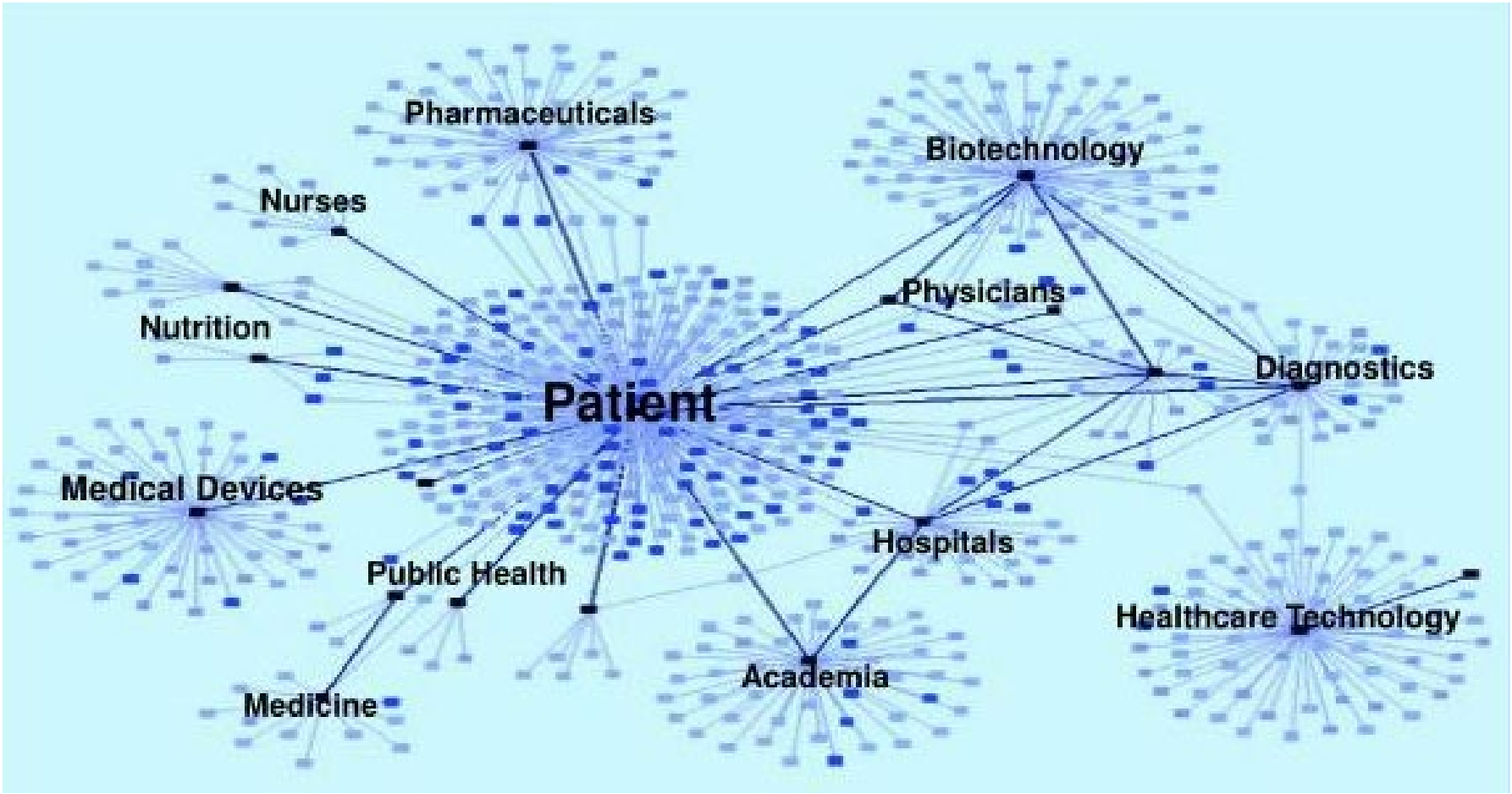
- The term PM is synonymous with other terms such as precision medicine, individualised medicine, tailored therapy, personalised health care, etc.

The Healthcare System is Expanding in Scope and Shifting Toward Personalized Medicine



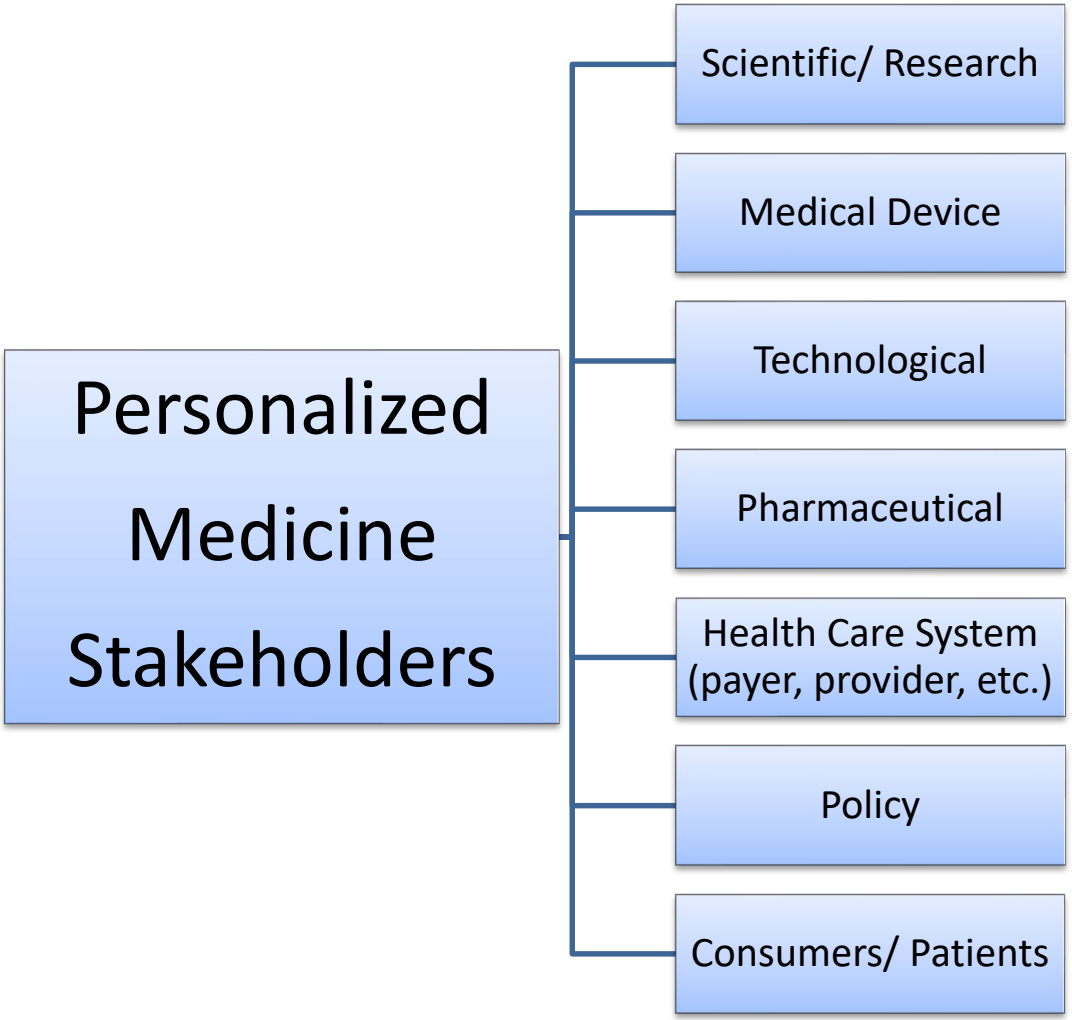
The health system as a networked environment

Today, doctors and hospitals are the primary axes in the healthcare system, but in the future they will be nodes in a large and complex network.



Fundamentally new ideas need new organizational structures

The future of medicine has a wide range of stakeholders



All of these players need to come together to create changes in the healthcare model

Change will require substantial investment: both in time and money

Personalized Medicine will generate new health and business models

P4 Medicine

Predictive:

- Probabilistic health history--DNA sequence
- Biannual multi-parameter blood protein measurement

Personalized:

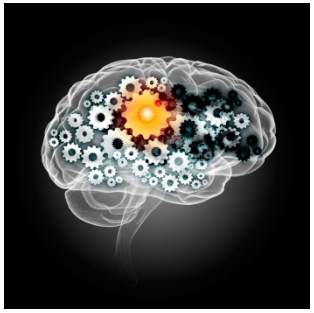
- Unique individual human genetic variation mandates individual treatment
- Patient is his or her own control
- Perturb blood cells for dynamic measurements
- Go directly to patient and skip doctor--patient will have all medical information •

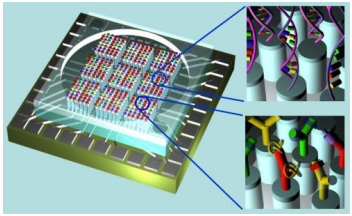
Preventive:

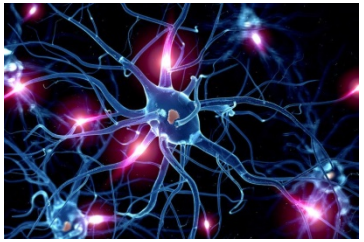
- Strategies for re-engineering the behavior of disease-perturbed networks with drugs
- Vaccines
- Focus on wellness

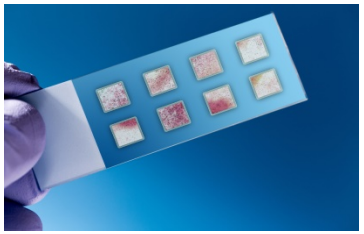
Participatory:

- Patient understands and participates in medical choices









From Genes to Public Health: The Applications of Genetic Technology in Disease Prevention

Muin J. Khoury, MD, PhD, and the Genetics Working Group

American Journal of Public Health December 1996, Vol. 86, No. 12

TABLE 1—Public Health Core Functions in Applying Genetic Technology to Disease Prevention

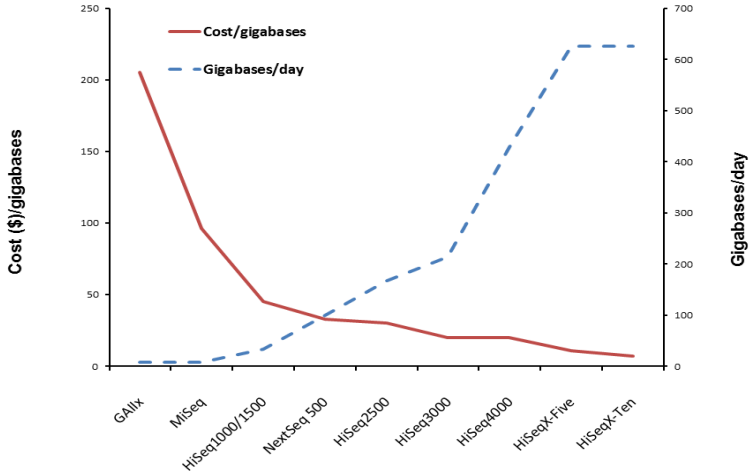
Step	Description of Activities	Disease/Gene Examples
Assessment	Epidemiological studies (assess risks and attributable fractions; gene–environment interactions)	Rheumatoid arthritis, Alzheimer's disease, breast cancer
Policy development	When and how genetic tests are to be applied in disease prevention programs	Testing for various genes
Assurance	Development of public health genetic programs, evaluation of prevention effectiveness, quality assurance	Newborn screening for sickle cell disease, proficiency testing for newborn screening

Issues in Personalized Medicine

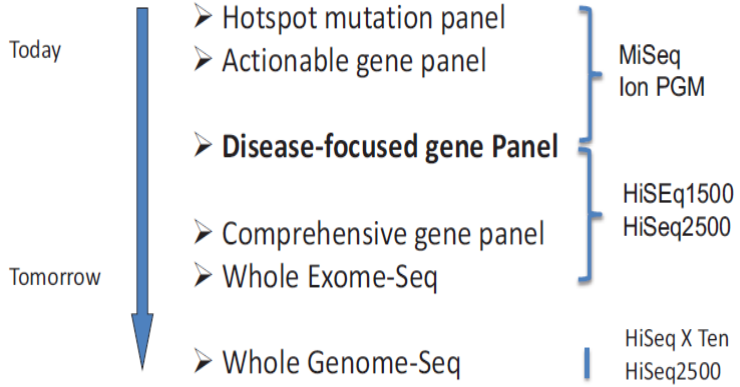
- Reimbursement for new diagnostics
- Regulation
- Payer reactions (Ministry of healthcare, MIF)
- Social challenges/racial/ethnical/cultural
- Implications of nanotechnology
- Implications of regenerative medicine/stem cells
- Clinical workforce adoption

Evolution of NGS

- The Evolution of Sequencing Cost and Throughput with Different Sequencers



- The Evolution of the NGS-Based Clinical Testing



Cost per 1 Gb
S4 – 3000 Gb – 18$
S2 – 1250 Gb – 24$
S1 – 500 Gb – 32$

PromethION P48
Run 48 flow cells individually or in parallel
Flow cell capable of generating 48 x ~ 180 Gb in full 72 h run : 12-16 Tb

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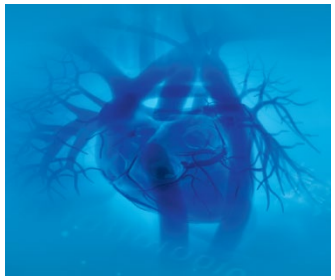
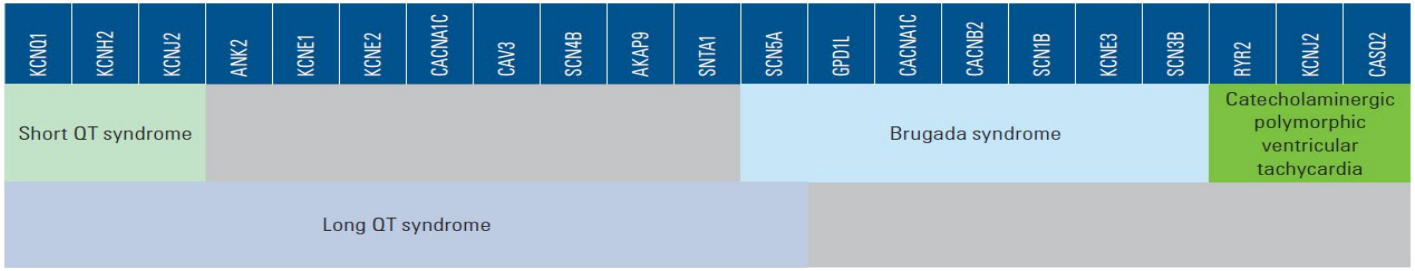
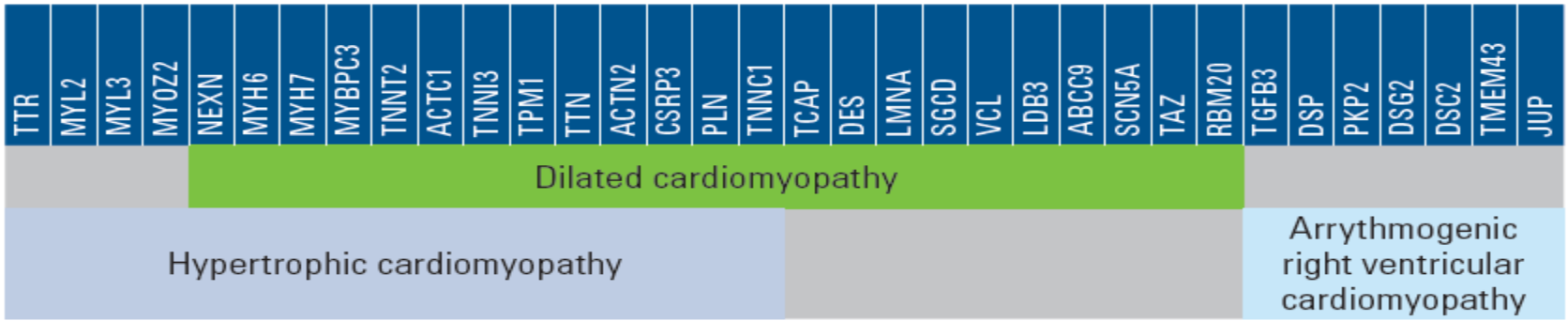
Cardiopanel development

HALOPLEX Cardiomyopathy (34 gene) and Arrythmia Research Panels (21 gene)



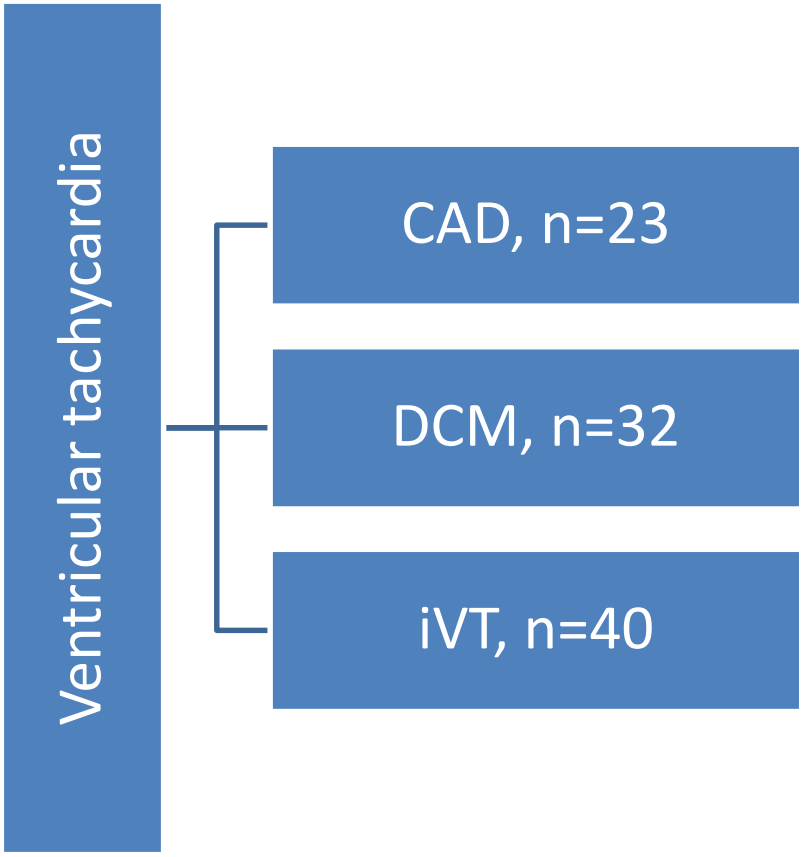




Designed cardiopanel 96 genes for targeted exome sequencing Haloplex technology , Agilent Technologies

Medizinische Universität Graz

Design of study



Material and Methods

- DNA isolation
- Library prep
- HaloPlex Target Enrichment System Protocol (version D.5, May 2013, Agilent Technologies, CA, US) using the standard HaloPlex 96 indexing primer cassette.
- Quality check - 2100 BioAnalyzer (Agilent Technologies, CA, US)
- Sequencing - HiSeq2000 platform using 2x150bp paired-end standard sequencing conditions.

JSC «NATIONAL RESEARCH CENTER FOR CARDIAC SURGERY»
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The development and clinical testing HALOPLEX cardiogenic panel to identify genetic predisposition and diagnostics of cardiac arrhythmias

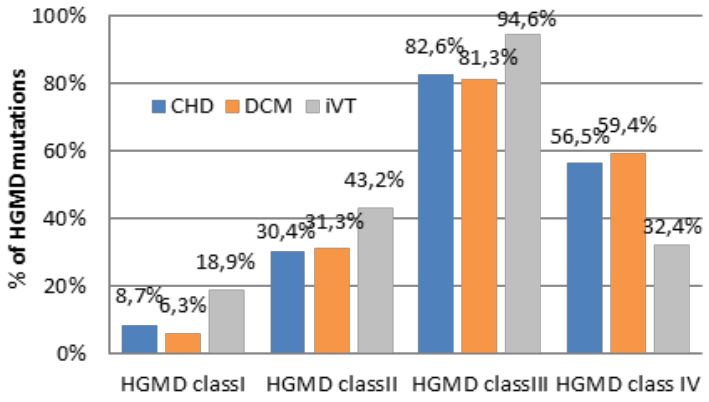


Figure 1. Incidence of HGMD variants per clinical subgroup.

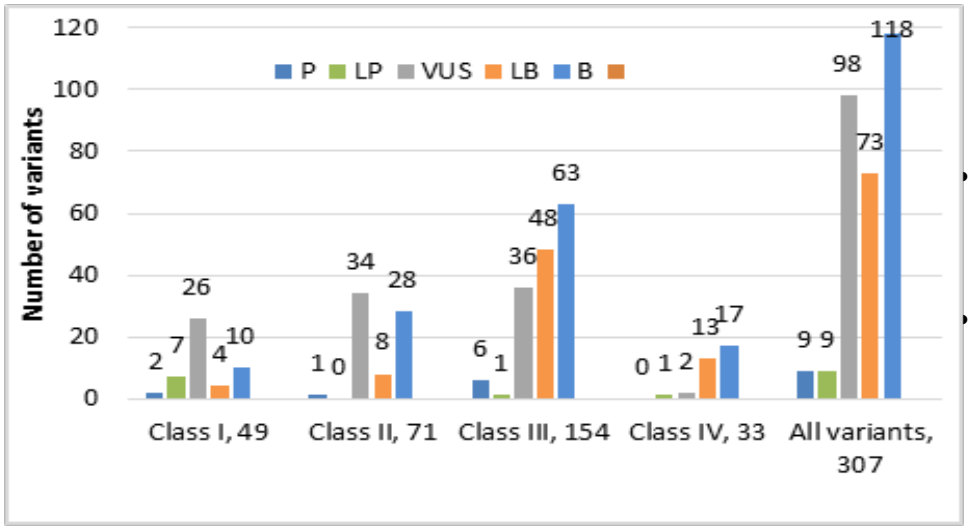


Figure 2. Distribution of variants according to ACMG guidelines among all classes of 307 genetic variants of rare variants according to ACMG classification

- **Cardiac Gene panel including 96 genes was designed to identify genetic predisposition and differential diagnosis of cardiac rhythm disorders.**
- In 92 patients with coronary heart disease (CHD), dilated cardiomyopathy or idiopathic ventricular tachycardia genetic profile and variation in known cardiac risk genes were studied using this panel.
- Targeted sequencing and stepwise filtering of the annotated variants identified a total of **307** unique variants in **74 genes** totaling up in 456 variants for the overall study group. 168 HGMD mutations (65 unique) were observed in 37 genes.
- Variants included one in/del variant, four splice-site variants and 470 single-nucleotide variants (SNV) within the coding exonic regions.
- Seven (0.15%) of the class II SNVs were unique stop-gain variants, three of those residing in the *TTN* gene.

Guelly C, Abilova Z, Nuralinov O….Zhumadilov Z, Bekbossynova M, Akilzhanova A.. Patients with coronary heart disease, dilated cardiomyopathy and idiopathic ventricular tachycardia share overlapping patterns of pathogenic variation in cardiac risk genes // PeerJ. 2021 Jan 19;9:e10711. doi: 10.7717/peerj.10711

The development and clinical testing HALOPLEX cardiogenic panel to identify genetic predisposition and diagnostics of cardiac arrhythmias

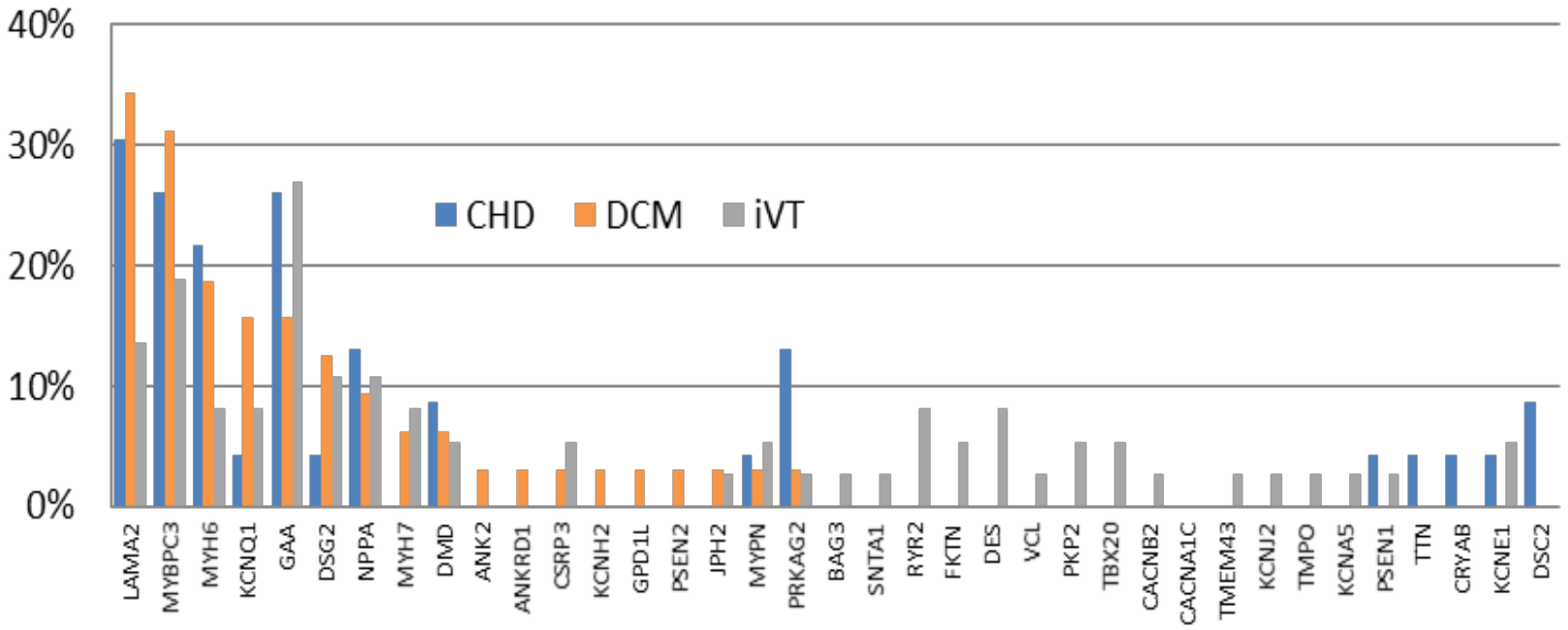


Figure 3. Combined frequency of mutations and rare variants. *Statistical testing using Fishers exact t-test suggests a trend for a difference in the frequency of MYH6 and PRKAG2 variants (p-value of 0.053 and 0.054. respectively) between CHD and the other subgroups.

VT patients carry multiple rare mutations and potentially pathogenetic sequence variants in classical cardiac risk genes.

Guelly C, Abilova Z, Nuralinov O….Zhumadilov Z, Bekbossynova M, Akilzhanova A.. Patients with coronary heart disease, dilated cardiomyopathy and idiopathic ventricular tachycardia share overlapping patterns of pathogenic variation in cardiac risk genes // PeerJ. 2021 Jan 19;9:e10711. doi: 10.7717/peerj.10711

Patient ID № 239

Woman 23 years old, Kazakh.
The onset of CPVT is 13 years old.

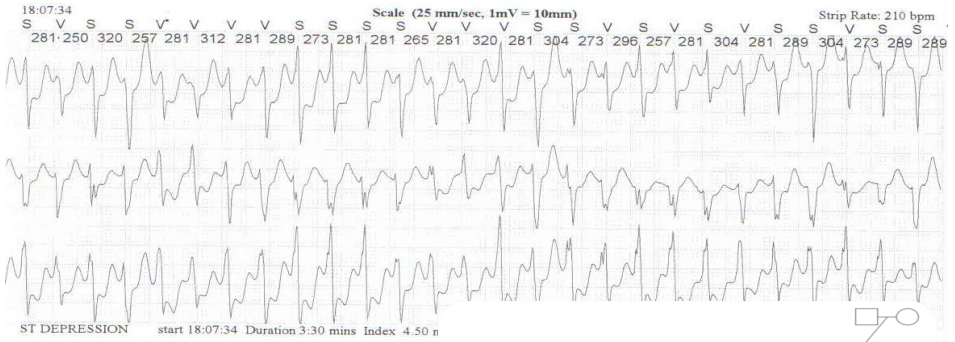
Ds: Idiopathic ventricular arrhythmia: CPVT

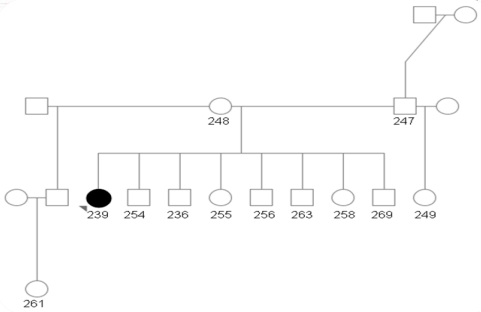
Family history is negative for syncope and SCD episodes.

CPVT was identified by a history of syncope and the appearance of characteristic ECG patterns with mono / polymorphic ventricular premature strokes, followed by bidirectional ventricular tachycardia and areas of polymorphic ventricular tachycardia.

Complaints of heart attack, shortness of breath on exertion, weakness and fatigue.
She had palpitations, dizziness, convulsions, episodes of fainting, frequent respiratory infections, chronic pyelonephritis, scoliosis since childhood.

At the age of 16, idiopathic heart rhythm disturbance was diagnosed, and in 2009, KZHT was verified. During the subsequent period, she did not have syncopal attacks.

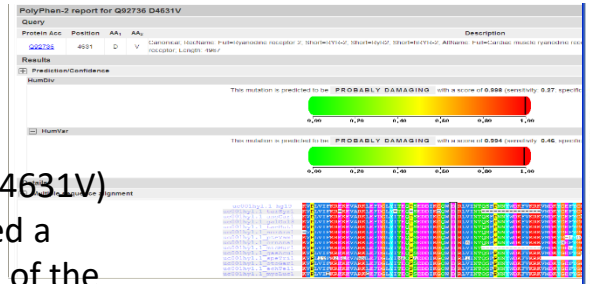


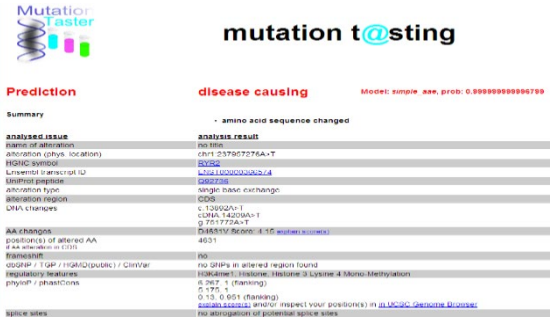


The variant found in patient No. 239 is very likely **de-novo**, since both parents (# 247 and # 248) were investigated, this genetic variant was not found in them.
Both parents show no pathological heart symptoms.
In addition, all brothers and sisters No. 239 were tested, showing a negative result.

Polyphen-2: #239: *RYR2*
c.A13892T; p.D4631V

http://genetics.bwh.harvard.edu/pph2





Mutation detected in exon 95 (c.A13892T; p.D4631V)
In-silico analysis using Mutationtaster predicted a probability score of 0.99999 for pathogenicity of the variant.

www.**mutationtaster**.org/

Akilzhanova A et al // PLoS One. 2014 Jun 30;9(6):e101059

Genome-associated personalized antithrombotic therapy in patients with high risk of thrombosis and bleeding

- Genome guided treatment approach in anti-thrombothic therapy for patients with high risk of thrombosis and bleeding were implemented into practice of the National Scientific Cardiac Surgery Center, Astana, Kazakhstan.
- 100 patients with implanted left ventricular assist device (LVAD) operated at National Scientific Cardiac Surgery Center, Astana, Kazakhstan were included into study .
- Polymorphisms in genes involved in the metabolism of antithrombotic drugs (VKORC1, CYP2C9, GGCX, ITGB3, CYP4F2, UGT1A9, PTGS1 etc) were genotyped. According to the genotyping results optimal dose of Warfarin were calculated and recommended.

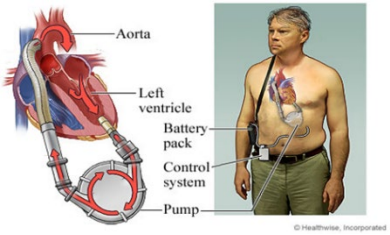


Table. Genotype frequency of SNPs between Control group and HF patients

Gene, SNP rs number	Genotype	Control group, No. (%)	Allele frequency control group	HF patients, No. (%)	Allele frequency HF patients	*P* value
VKORC1*1 **rs8050894**	CC	17 (17.9)	C : G = 0.39 : 0.61	55 (56.1)	C : G = 0.68 : 0.32	**0.0001**
	CG	41 (43.2)		24 (24.5)		
	GG	37 (38.9)		19 (19.4)		
ITGB3 **rs5918**	TT	71 (74.7)	T : C = 0.87 : 0.13	48 (49.0)	T : C = 0.66 : 0.34	**0.0001**
	TC	23 (24.2)		34 (34.7)		
	CC	1 (1.1)		16 (16.3)		

Table Genotype frequency of SNPs between HF patients with/without complications

Gene, SNP rs number	Genotype	Without complication, No. (%)	Allele frequency in Group 1	With complication, No. (%)	Allele frequency in Group 2	*P* value
VKORC1*2 **rs9934438**	GG	14 (18.9)	G : A = 0.39 : 0.61	0	G : A = 0.35 : 0.65	**0.008**
	GA	29 (39.2)		17 (70.8)		
	AA	31 (41.9)		7 (29.2)		
VKORC1*3 **rs9923231**	CC	14 (18.9)	C : T = 0.40 : 0.60	0	C : T = 0.35 : 0.65	**0.012**
	CT	31 (41.9)		17 (70.8)		
	TT	29 (39.2)		7 (29.2)		
ITGB3 **rs5918**	TT	42 (56.8)	T : C = 0.70 : 0.30	6 (25.0)	T : C = 0.56 : 0.44	**0.005**
	TC	19 (25.7)		15 (62.5)		
	CC	13 (17.6)		3 (12.5)		
UGT1A6 **rs2070959**	AA	28 (37.8)	A : G = 0.66 : 0.34	12 (50.0)	A : G = 0.65: 0.35	**0.03**
	AG	41 (55.4)		7 (29.2)		
	GG	5 (6.8)		5 (20.8)		

Zhalbinova MR, Rakhimova SE, Kozhamkulov UA, Akilzhanova GA, Kaussova GK, Akilzhanov KR, Pya YV, Lee JH, Bekbossynova MS, **Akilzhanova AR**.J Pers Med. 2022 May 4;12(5):744. doi: 10.3390/jpm12050744.PMID: 35629166

Mutation spectrum in Kazakhstani sudden cardiac death victims revealed by targeted next-generation sequencing of 96 genes associated with cardiac diseases

- The cohort of SCD victims included 37 deceased autopsied individuals (11 females/26 males; aged 18 to 50 years) (Figure1, Table).
- Based on macroscopic and/or histopathological evaluations, structural changes of the heart were found in 10 (27%) of the individuals, of which 8 (78%) had macroscopic and/or histopathological structural changes of the heart suggesting cardiomyopathy, i.e. the cardiomyopathy group. In 27 (83%) individuals, no structural change of the heart was identified at autopsy, and no cause of death could be established, i.e. the SCD group (Table).

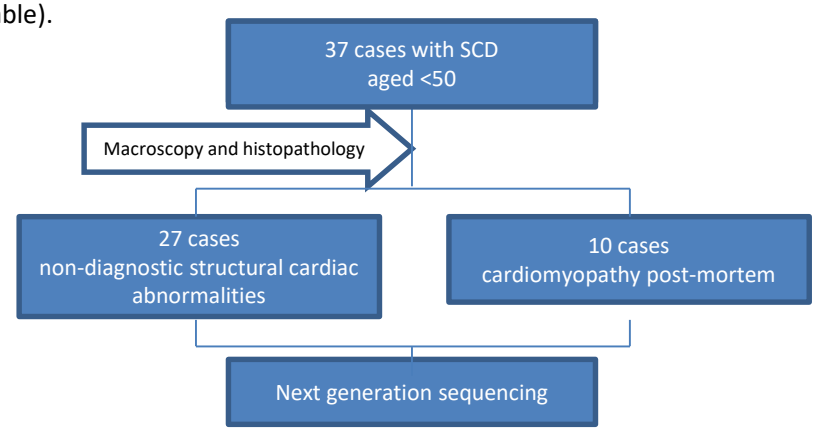


Figure 1. Categorization of SCD individuals

Table . Characteristics and observed genetic (rare) variants in SCD individuals

Characteristics	All (n = 37)	SCD (n = 27) non-diagnostic structural cardiac abnormalities	SCD (n = 10) Cardiomyopathy postmortem
Gender (male/female)	26/11 (70%/30%)	15/12 (57%/43%)	9/1 (89%/11%)
Median age in years (range)	30 (18-49)	32 (18-49)	28 (18-49)
BMI > 30	5[a] (13%)	3 (11%)	2[a] (17%)
Increased heart/body weight ratio	18 (49%)	12 (44%)	6 (57%)
Left ventricle > 15 mm	5 (13,5%)	2 (7,4%)	3 (30%)
Toxicology screening	35 (96%)	25 (94%)	10 (96%)
Negative	27 (73%)	19 (70%)	8 (85%)
Antiepileptic drugs	1 (3%)	0 (0%)	1 (6%)
Anxiolytics/hypnotics	1 (2%)	0 (0%)	1 (6%)
Antidepressants	2 (3%)	1 (5%)	1 (10%)
Antipsychotics	0	0	0
Illegal drugs	1 (3%)	1 (3%)	0
Strong analgesics	1 (3%)	1 (3%)	0 (0%)
Other[b]	6(16%)	5 (18%)	1 (9%)
Observed genetic rare variants	21(57%)	17(63%)	4(35%)

BMI - body mass index, SUD - sudden unexplained death
[a] The BMI of one individual was not calculated as the height was not recorded
[b] Alcohol, antiparkinsonian medicine, salicylic acid and antiemetic

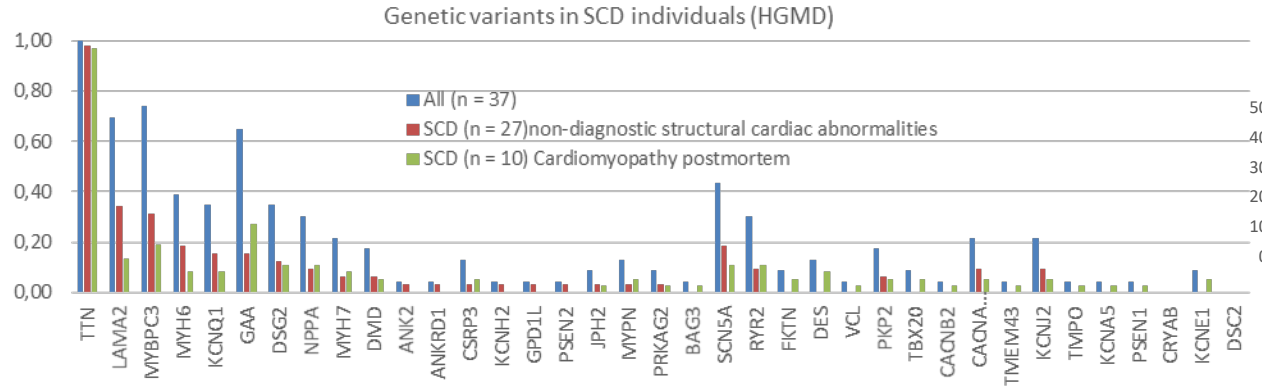


Figure 2. Frequency of genetic variants in SCD individuals (HGMD), %.

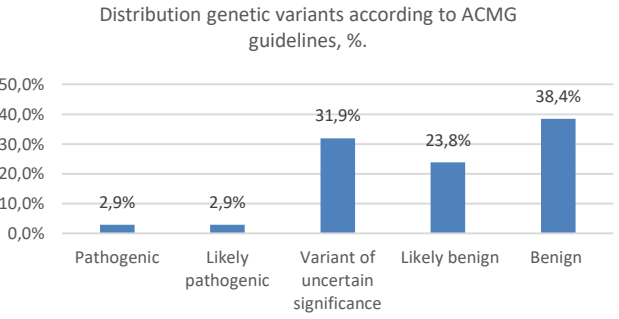


Figure 3. Distribution genetic variants according to ACMG guidelines, %.

Whole genome sequencing program in Kazakhstan

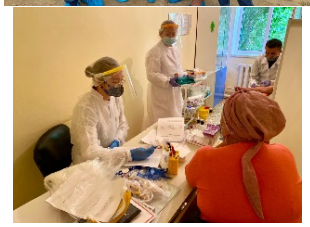
Our team is sequencing large heterogeneous Kazakhstani population to understand how

- rare genetic variants contribute to cardiovascular and other diseases.

- Whole genome sequencing program in Kazakhstan will be instrumental in building a reference genome of Kazakhs and other ethnic groups that will serve as a primary source of data for clinical genomic studies (cardiovascular diseases, cancer, metabolic syndrome and others).

- To understand the genetic architecture of the Kazakh population, it is important to conduct large-scale whole genome research using various technologies on a large number of participants in the study. Building a reference genome of Kazakhstani population and creation of Reference genetic database enable to use information in clinical and biomedical research more precisely.

Kazakh Reference Genome



Recruitment (field work trips)
Adults, 18+
information (age, gender, lifestyle) and Medical history Questionnaire, anthropometry
Blood samples collection

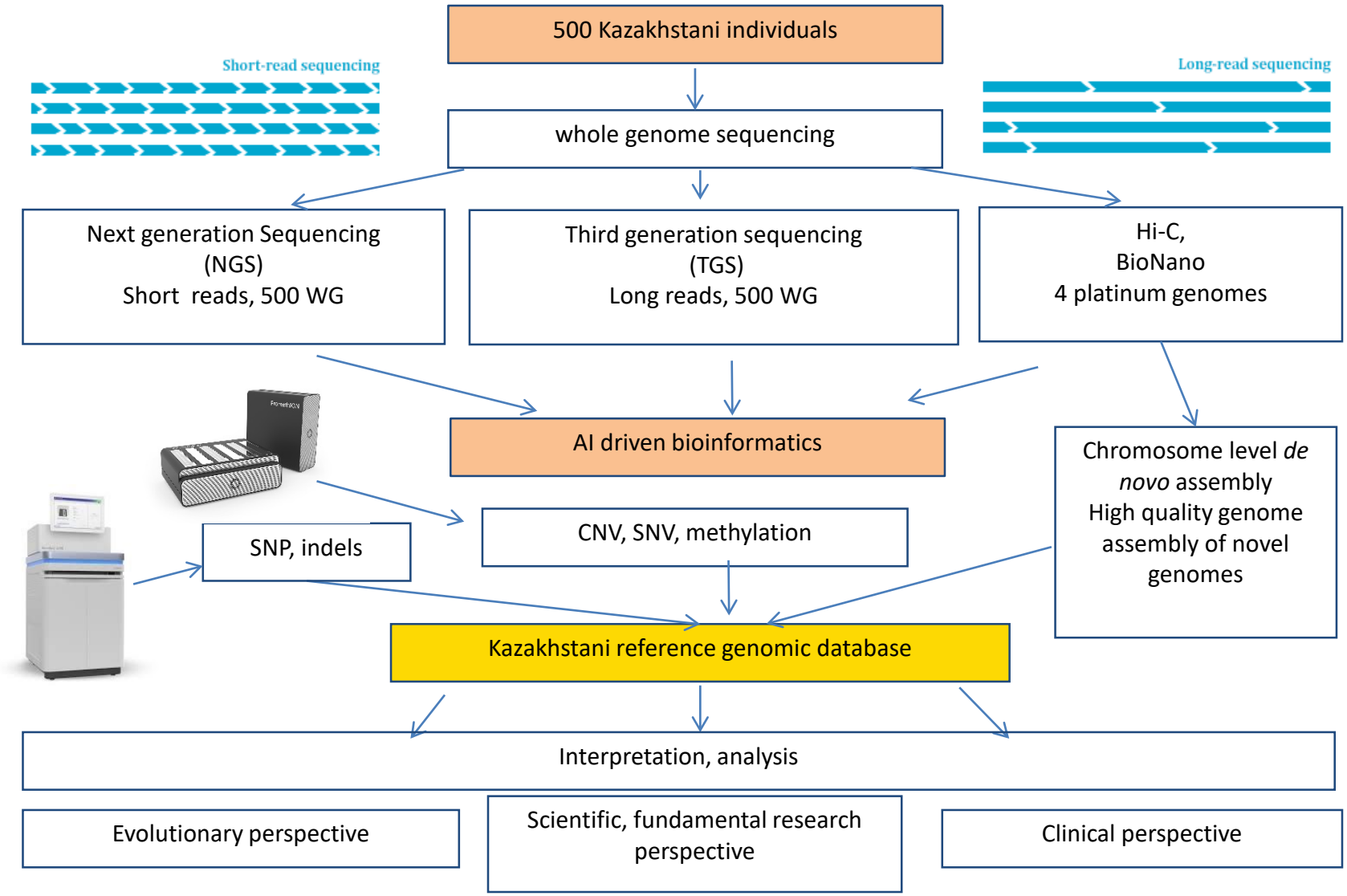
Population
NLA, NU - 87
Kostanay region – Torgay -151
Karagandy region -
Temirtau -119
Zhansary -112
Akmola region, Rodina village - 50
Uzbeks – South KZ - 78

Cases / Hospitals/Clinics
Cardio, Metabolic syndrome

	Asian				Caucasian		Total
	KZ	UZ	UYG	other	RU	others	
Male	**187**				**47**		**234**
	129	54	3	1	30	16	
Female	**216**				**50**		**266**
	196	16	1	3	33	17	
Total	**403**				**97**		**500**

	Male	Female	Total
Cardio	53	16	69
Met Syn	20	45	65
			134

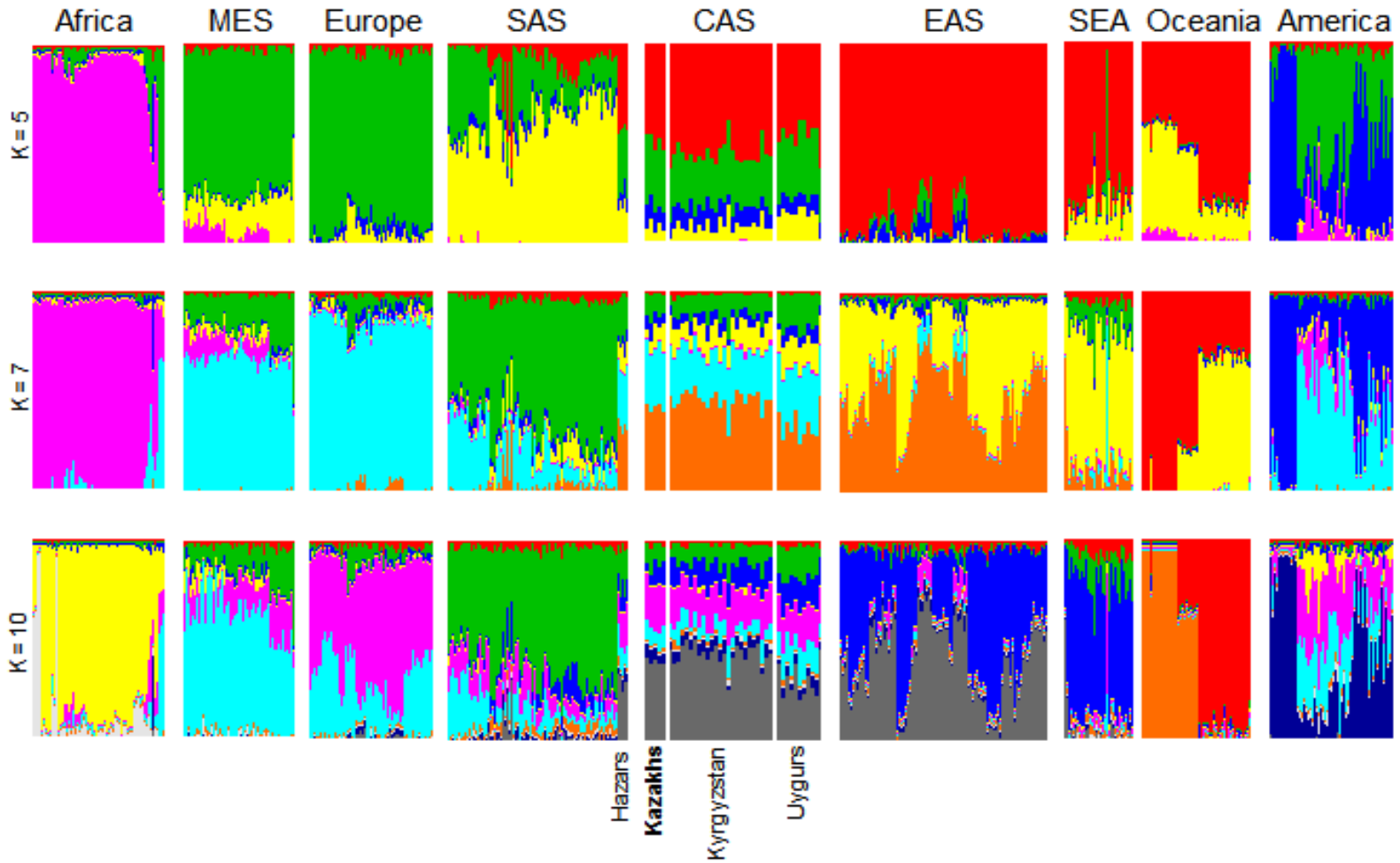
Kazakh Reference Genome



Genome sequencing and analysis results

Since 2012 for the first time in Kazakhstan, our group has been conducting studies to determine the whole genomes/whole-exomes of Kazakhs using NGS technology.

We sequenced and analyzed more than 20 whole-genomes and 125 whole-exomes of Kazakh individuals. We revealed high admixture and heterogeneity of Kazakh individuals on whole-genome and whole-exome level.



A vision for the future of genomic research (F. Collins prognosis)

2010

- Preimplantation diagnosis

2020

- Cancer treatment
- Diagnosis and treatment of psychiatry diseases
- Genotherapy on embrio level

2030

- Genetic sequencing before birth

2040

- Genomic medicine
- Know ledge of genetic susceptibility to most of diseases before birth
- Preventive medicine
- Drug development on gene products

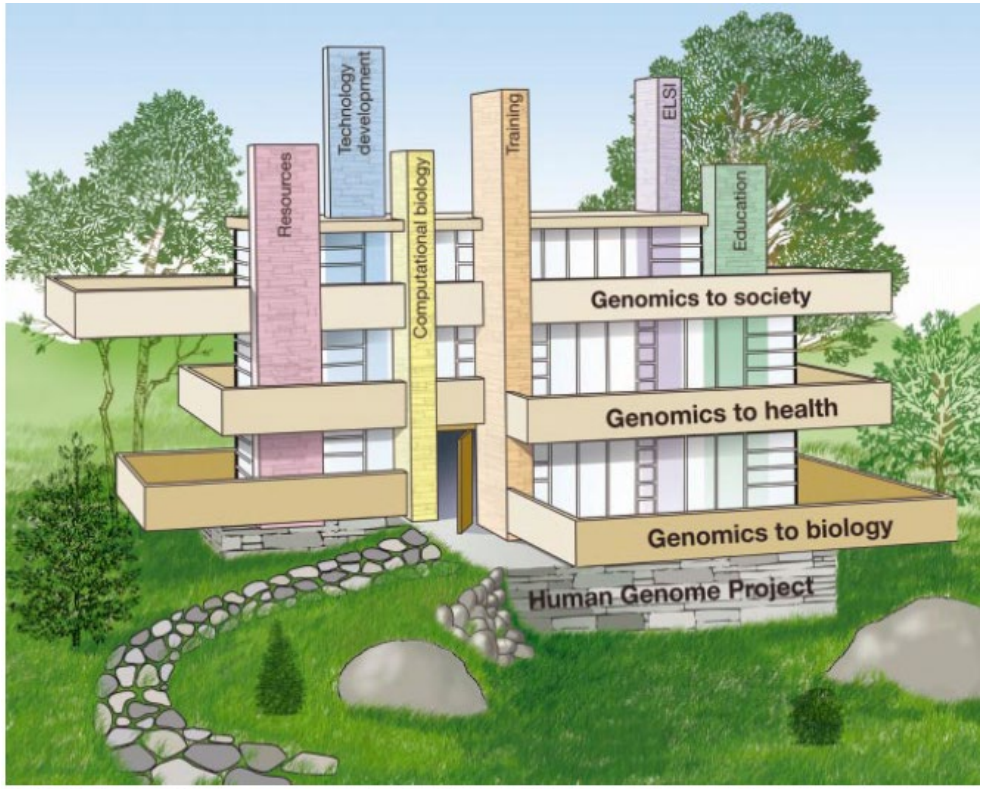


Fig 2 The future of genomics rests on the foundation of the Human Genome Project.

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Thank you for attention!