



MINISTRY OF  
EDUCATION AND  
SCIENCE OF THE  
REPUBLIC OF  
KAZAKHSTAN

Қазақстандық  
Технологияларды  
Коммерцияландыру  
Жобасы



Kazakhstan  
**Technology**  
Commercialization  
Project



The World Bank

# Pharmacogenetic kit for individual correction of Warfarin and Clopidogrel dosage in the Central Asian population

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# Pharmacogenetics and adverse drug reactions

- ▶ 106,000 deaths and 2.2 Million serious events caused by adverse drug reactions occur in the US each year
- ▶ Information on the patient's pharmacogenetic status minimizes occurrence of side effects and complications after the appointment of drugs
- ▶ FDA has approved usefulness of genetic information for prescription of Warfarin and Plavix in 2007 and 2010, respectively.

## **FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug**

[Safety Announcement](#)

[Additional Information for Patients](#)

[Additional Information for Healthcare Professionals](#)

[Data Summary](#)

### **Safety Announcement**

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a *Boxed Warning* to the label for Plavix, the anti-blood clotting medication. The *Boxed Warning* is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

**Consumer Inquiries:**

888-INFO-FDA

### **FDA NEWS RELEASE**

**FOR IMMEDIATE RELEASE**

August 16, 2007

### **FDA Approves Updated Warfarin (Coumadin) Prescribing Information**

***New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients***

<http://www.fda.gov>



**Central Asia**

**Population – 66 M**



**Kazakhstan**

**Population – 17 M**

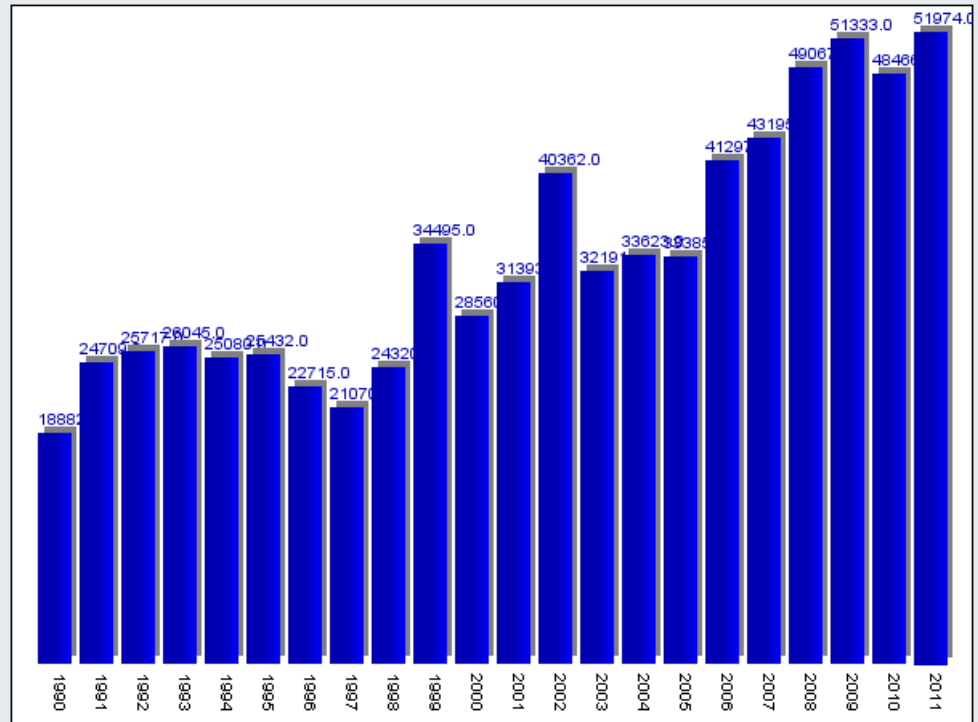
**PHARMACOGENETIC TESTING IS NOT CONDUCTED IN  
THE CENTRAL ASIA REGION**

# General Genetics LTD

- ▶ **General Genetics** is a young start-up company (est. in 2012) with a focus on pharmacogenetics.
- ▶ **Problem to solve** – unawareness about pharmacogenetic testing in the region, absence of genetic testing
- ▶ Our goal is introduction of pharmacogenetic testing to healthcare system of Kazakhstan (health centers, hospitals)
- ▶ We received funding from the World Bank and Ministry of Education and Science of the Republic of Kazakhstan to develop pharmacogenetic kit for individual dosage correction of Warfarin and Plavix
- ▶ Starting in 2013 our pharmacogenetic services were provided to the National Cardiosurgery Center (Astana, Kazakhstan) and National Medical Research Center (Astana, Kazakhstan)

# Focus on pharmacogenetics of cardiovascular drugs

- Cardiovascular disease is the leading cause of morbidity and mortality in Kazakhstan and Central Asia.
- Introduction of genetic testing will minimize side effects and complications after the appointment of the CVD drugs (Warfarin and Plavix).



Morbidity of CVD increases by ~50,000 new cases every year

# Pharmacogenetics of cardiovascular drugs

**Social impact:** Increase of lifespan and decrease in mortality when the dosing of CVD drugs is corrected individually. Warfarin is cheap and efficient; however, there is a high risk of hemorrhages.

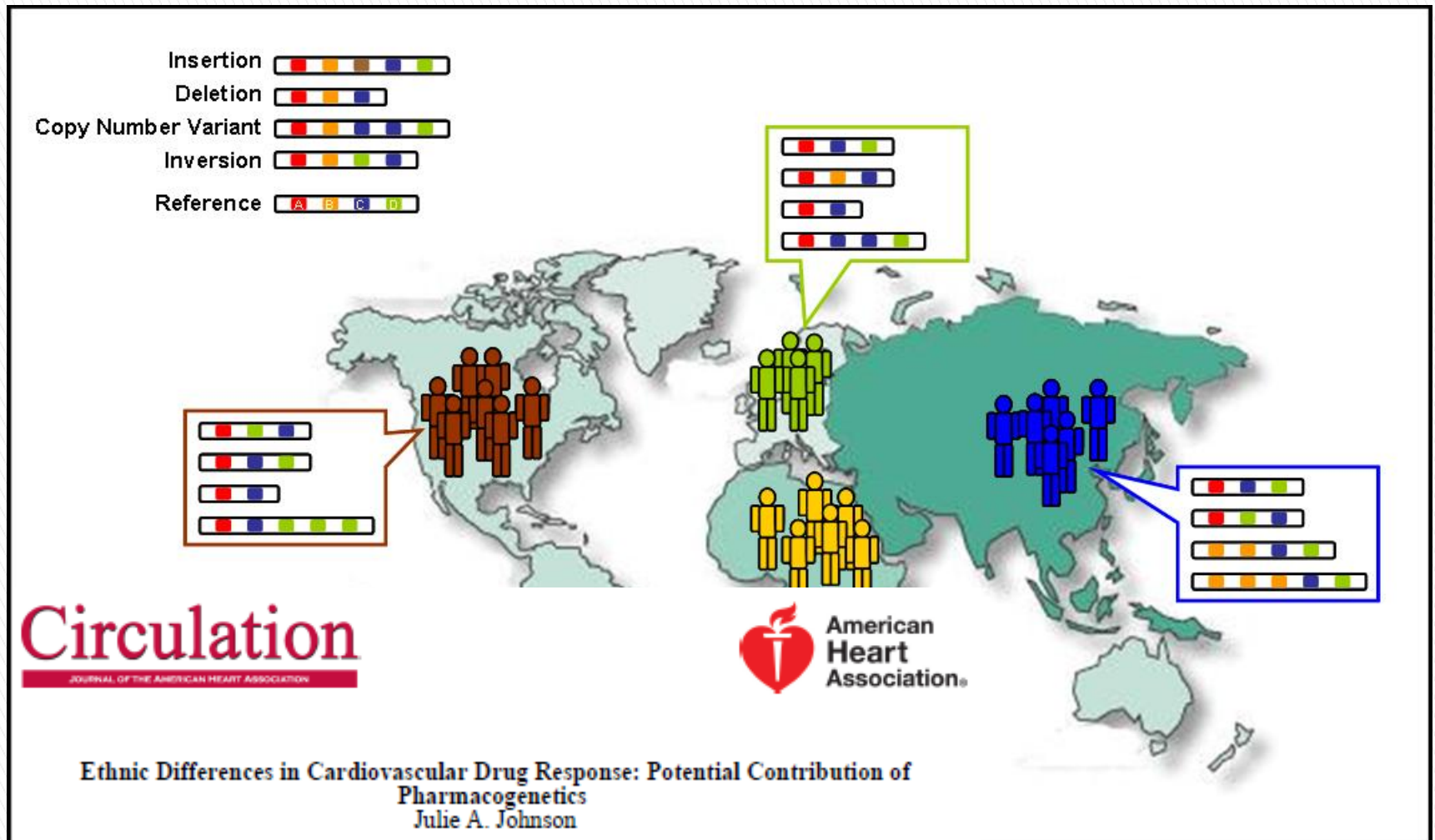
**Economic impact:** correction of individual dosage will decrease treatment price twofold. Warfarin is prescribed for lifetime what makes decrease in treatment price very significant.

**Application:** First of all, our product will be applied in healthcare institutions of Kazakhstan and clinical diagnostic labs.

We are planning gradual expansion of the product market to the Central Asia region.



# Ethnic Differences and Pharmacogenetics



Sensitivity of various ethnic groups to the drugs is different

# Ethnic Differences in Central Asia

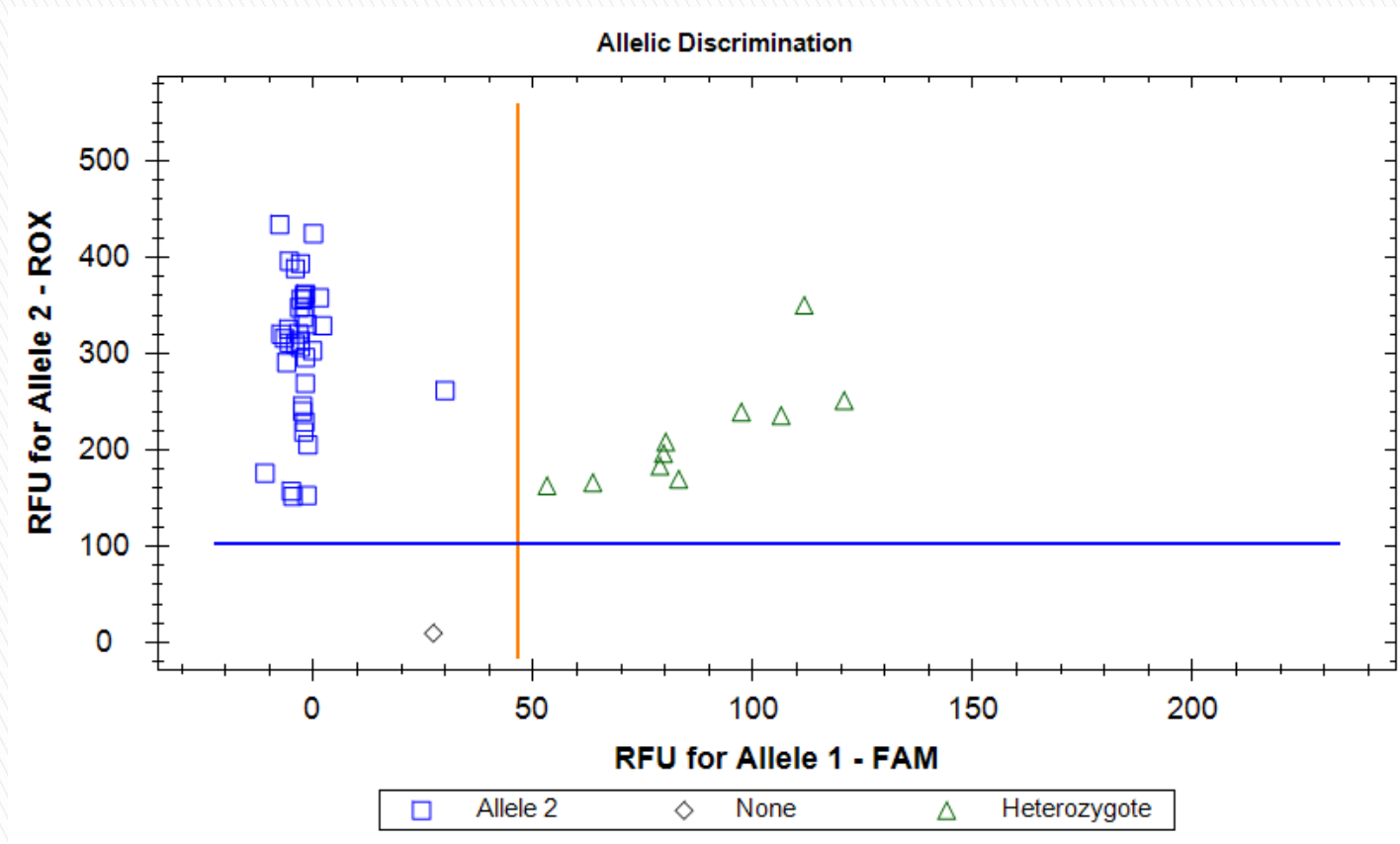
- Central Asia and its population is one of the least-studied regions of the world
- Historically, Central Asia has always been a crossroad between West and East leading to the current high population genetic admixture and diversity
- The studies of the region indicate that population of Central Asia has a mixed genetic composition intermediate between those of Asian and European populations



# Population study of the Central Asian population



# Genotyping of drug biotransformation enzymes



Example of cluster analysis for CYP2C19\*2 variant with real-time PCR

- Kazakh population sample was genotyped to study genetic variability of the drug biotransformation enzymes and compare to other populations

# Allele frequency and genotype distribution in Kazakh population

Polymorphisms	Number of samples	Hardy – Weinberg equilibrium	Allele	n <sup>a</sup>	Frequency	Genotype	n <sup>b</sup>	Frequency
CYP2C9*2	437	p=0.66	C	856	0.98	CC	419	0.96
			T	18	0.02	CT	18	0.04
						TT	0	0.00
CYP2C9*3	444	p=0.54	A	863	0.97	AA	419	0.94
			C	25	0.03	AC	25	0.06
						CC	0	0.00
VKORC1 1173	286	p=0.76	C	162	0.28	CC	24	0.08
			T	410	0.72	CT	114	0.4
						TT	148	0.52
VKORC1 1542	259	p=0.65	G	142	0.28	GG	18	0.07
			C	376	0.72	GC	106	0.41
						CC	135	0.52
CYP4F2	284	p=0.26	G	396	0.70	GG	134	0.47
			A	172	0.31	GA	128	0.45
						AA	22	0.08
CYP2D6*3	287	p=0.86	A	568	0.99	AA	281	0.98
			del	6	0.01	A/del	6	0.02
						del/del	0	0
CYP2D6*4	343	p=0.15	G	637	0.93	GG	294	0.86
			A	49	0.07	GA	49	0.14
						AA	0	0.00
CYP1A2*1F	257	p=0.63	A	332	0.65	AA	109	0.42
			C	182	0.35	AC	114	0.44
						CC	34	0.13

# Frequencies of biotransformation genes in different populations

	<b>2c9*2</b>	<b>2c9*3</b>	<b>VKORC rs9934438</b>	<b>VKORC rs8050894</b>	<b>CYP4F2</b>	<b>2d6*3</b>	<b>2d6*4</b>	<b>1a2*1F</b>
<b>Kazakh</b>	<b>0.02</b>	<b>0.03</b>	<b>0.72</b>	<b>0.72</b>	<b>0.31</b>	<b>0.01</b>	<b>0.07</b>	<b>0.35</b>
African-American (1000 Genomes)	0.02	0.01	0.07	0.21	0.09	0.0	0.06	0.46
African-American*	0.01-0.027	0.005-0.02	0.02-0.13	0.19-0.28	0.05-0.1	0.0-0.01	0.01-0.12	0.35- 0.54
Caucasians (1000 Genomes)	0.12	0.06	0.4	0.41	0.27	0.02	0.19	0.31
Caucasians*	0.11-0.2	0.06-0.16	0.39-0.48	0.37-0.41	0.23-0.32	0.0-0.04	0.07-0.21	0.22- 0.52
Asians (1000 Genomes)	0.0	0.02	0.92	0.92	0.21	0.0	0.0	0.37
Asians*	0.0-0.05	0.02-0.1	0.9-0.95	0.89-0.94	0.19-0.34	0.0	0.0-0.15	0.33- 0.61

\* - different sources with a population sample of more than 100 people (including HapMap data)

# Conclusion from population data

Contribution of the genetic component to drug sensitivity in Kazakh population has Asian-specific pattern with several European traits.

Pharmacogenetic diagnostics of the following polymorphic markers, namely, CYP2C9\*2, CYP2C9\*3, VKORC1 (1639) C>T, CYP4F2 (G23454A) and GGCX (G1958) should be carried out to determine sensitivity to Warfarin in the Kazakh population.

Genotyping of the following polymorphic markers: CYP2C19\*2, CYP2C19\*3, CYP2C19\*17 and CYP2C19\*4 is required to determine sensitivity to Plavix in the Kazakh population.



## ДНК тест-система «Фармако-Экспресс»

Фармакогенетический экспресс-тест на основе полимеразной цепной реакции в режиме реального времени для индивидуальной дозировки лекарственных препаратов (Варфарин, Плавикс)



Серия № 00001  
Годеи до: 13.12.2013  
Количество анализов 100

**Состав комплекта:**  
1. Смесь праймеров для ПЦР  
2. Буфер для ПЦР  
3. ДНК-полимераза  
4. Комплексный контрольный образец

Хранить при температуре от 4 до 8° С,  
в защищенном от света месте

ТОО «General Genetics»

Казахстан, 010000, Астана, ул. Валиханова 13/1, тел. +7 (7172) 21-40-20, www.biolab.kz



# Pharmacogenetic kit for diagnostics

## Composition:

1. PCR master mix
2. Primer/probe mix
3. Taq polymerase
4. Control samples



Real-time PCR

## WARFARINDOSING

www.WarfarinDosing.org

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> [Outcomes](#)

> [Hemorrhage Risk](#)

> [Patient Education](#)

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User:  
Patient:  
Version 14.0  
Build : Apr 29, 2008

### Required Patient Information

Age: 68 Sex: Male Ethnicity: Non-Hispanic  
Race: White, Caucasian, or Middle Eastern  
Weight: 167 lbs or 76 kgs BSA 1.92  
Height: (5 feet and 9 inches) or (176 cms)  
Smokes: No Liver Disease: No  
Indication: Atrial fibrillation  
Baseline INR: 1.2 Target INR: 2.5  
CYP2C9 Genotype: CYP2C9\*1/\*3  Randomize & Blind  
VKORC1-1639/3673 Genotype: AG  
Amiodarone/Cordarone® Dose: 200 mg/day  
Statin/HMG CoA Reductase Inhibitor: Atorvastatin/Lipitor®/Caduet®  
Any azole (eg. Fluconazole): No  
Sulfamethoxazole/Septtra/Bactrim/Cotrim/Sulfatrim: No

Accept Terms of Use

> ESTIMATE WARFARIN DOSE

Genetic testing of 136 clinical samples was carried out with the selected SNPs



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**Thank you for your attention!**

