Research Article ISSN 2639-9326

Diabetes & its Complications

# The Multiplex Cds Systems on The Basis of Technology Analysis of Genes: Researches of Consequences of Pre-Diabetes Accompanied With a Hypertonic Patients

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**Received:** 21 May 2017; **Accepted:** 13 June 2017

**Citation:** Nagay AV, Khamidullaeva GA, Srojidiniva NZ, et al. The Multiplex Cds Systems on The Basis of Technology Analysis of Genes: Researches of Consequences of Pre-Diabetes Accompanied With a Hypertonic Patients. Diabetes Complications. 2017; 1-5.

## ABSTRACT

***Objective:*** *CDS system testing on the example of the existing software of GS CDS: Some common mistaken in early design stage.*

***Design and Method:*** *Architecture - Opened, multiplex platform. Encryption- Advanced Encryption Standard AES. Data transmission- Fiber optic link,WLAN. Type of interaction- Triangulation: CDS, EMR, DNA database.*

***Results:*** *We recommend to consider several moments on the first steps of projection. In - the first to pay attention to an analytical stage. It is necessary to consider in advance all working platforms which will be served by CDS. Use Bayesian approach to frame a matrix of recognition of the damaging alleles and haplotype. It is necessary to adhere to standard forms of biological data. To strengthen enough genetic information, CDS has to be able to structure a superfine phenotype. For stratification of risk of rising of the ABP (the high, increased, average risk) use multi-sample option. It will lead to specificity increasing while sensitivity will remain invariable. Use heuristic and statistical algorithms; they will be able to identify the damaging genotype, without conflicting to clinical information of the patient.*

*We have also found dominance of European contribution (83%) to the development of hypertension/pre-diabetes. Heritage of hypertension in Uzbek population has been evaluated as 17% Eastern, 33% Southern, 25% Central Europe, 8% for Anatolia and 17% for South East Asia. The functional significance of all 12 genes in hypertensive patients with combination of atherosclerosis and pre-diabetes is similar for the most part with European type of heritage. However, a distinctive sensitivity to the exchange of sodium in these individuals is due to 17% of the Asian contribution.*

***Conclusions:*** *When an analysis is carried out, any acceptance or rejection must follow clearly defined rules. According to our study we suggest that applying the CDS technology as a first step within a diagnostic algorithm it is possible to increase the diagnostic accuracy reducing the rate of biological ageing of vessels.*

*We have also found dominance of European contribution (83%) to the development of hypertension/pre-diabetes. Perhaps this similarity in hypertension/pre-diabetes lineage between Uzbek and European populations, due to the fact that the ancient settlements of the Paleolithic Age could migrate to Central Asia from the east and west, not from north and south.*

## Keywords

Multiplex platform; Advanced Encryption Standard (AES); Single nucleotide polymorphism (SNP); Essential hypertension (EH); Pre-Diabetes, Clinical Decision Support (CDS).

## Introduction

The first CDS systems were received from researches of expert systems where developers sought to program the IT-system with rules which would allow it "to think" as the clinician. Proceeding

from this aspect similar systems, can undertake some routine tasks, warning the doctor about potential problems [1]. CDS covers a number of options, from the general references on the basis of the concrete principles of a cardiovascular state today, to offers which consider only unique biological data of an individual, for example genetic risk of a hypersensitivity to the drug Warfarin [2]. CDS can include regulations and standards at the national level on one extremity and local settings in other [3]. The most modern versions of "CDS" are used in many advanced clinics today. For example: the clinical system of support "Archimedes Indigo" applies a series of the mathematical equations to analyze clinical, administrative, or physiological data by method of computer modeling by considering 30 various variables. "Diagnosis One" represents the Smart Path platform which includes components for clinical support of decisions and the analysis on the basis of Microsoft, Oracle architecture. "Smart Consult" CDS the module checks all available data to identify dangers of the drawn-up treatment planning. The Smart Consult panel models data of EHR when the doctor makes the diagnosis. The system is intended, to state the exact diagnosis. The DXplain platform offers the list of the possible diagnoses based on signs, observations and experimental results of the most widespread diseases.

The question of working process is one of key questions of systemic IT designers [4]. Assessment of working process - the first stage of the project is that how CDS will fit in work of cardiologic sections. If assessment of requirements finds processes which need be redesigned they have to be installed before introduction. For example, it concerns to coherence between document flow and synchronization of CDS structure (for example: between DNA database, EMR, LIS). That's why the participation of doctors at all development stages of the project is necessary [5]. Specifics of cardiogenetics laboratories demand existence of 4 main CDS abilities which are originally put at a design stage. 1. CDS has to be able to update contemporary records on drugs, to have access to NSBI bases, to have a possibility of an upgrade each 5 years. 2. Each unit for example as: usually differ from each other on models of working process. This problem is solved by the adaptive interface. 3. As the protected genetic information is intended only for family members, the level of data security has to be higher, than at clinical tests. 4. Because of difficulty of technological process bound to booking, tracking of a case history and delivery of results all modules LIS, EMR, DNA database have to be tied to CDS [6].

Researchers showed that CDS which fits into working process likely will be used [7]. However, integration of CDS into working process of cardiology sectioning often demands local control. These settings are bound to specifics of the equipment. For example, standard offices of cardiologic units as ECG, ABPM Holter, the device Echocardiography have no option of communication with LIS. CDS also has to be minimum destructive for "cognitive process" of the clinician cardiologist and it can be a problem. Sometimes lack of data, can lead to inadequate preventions of CDS [8]. It, certainly, is a problem for hypertensive patients with pre-diabetes who are under the all time observation [9]. Other problem is maintenance of CDS knowledge base. For example, drugs for treatment of the high BP β-blockers are often updated and older drugs are replaced with new.

Today the multiplex or multinodal CDS systems of the next generation can apply technology of the effective analysis of genes. The technology of the effective genes analysis is the combined method of the sequential analysis, ROC-curve and relative risk of RR (Altman's theorem) with use of basic mathematical algorithms (Bayes' theorem) in diagnostics of in vitro [10]. In this article, we present the short review of CDS technologies of the next generation for the first time. We put in the forefront some of the problems bound to the biomedical analysis of data and we consider strategy in bioinformatics and computer facilities for various detection of SNP. We present our recommendations at the choice of various tools of the analysis, for superfine molecular diagnoses to cardiology. Also we represent step-by-step the projection of CDS for cardiologists, on the example of the existing software of GS CDS. We represent the multiplex CDS system with technology of the effective analysis of genes.

## Materials and Methods

### Encryption

Advanced Encryption Standard AES. Architecture - Opened, multiplex platform. Type of interaction- Triangulation: CDS, EMR, DNA database.

### Connection with the Internet

WiMax-router, EVO provider. Definition of the IP-address, Subnet mask and gateway.

### Online Instruments

Personal Computers (PC) - Multi-Touch. LED 19 / Intel (R), Core i3-2100. 3.1GHz, DDR3 4Gb, DVD-RW, x64-bit Lenovo. The diagnostic equipment - Clearview-350 Echocardiography PHILIPS, Ergometer X1 KETTLER, Cardiovit MS-2007 ECG SCHILLER, 24 Hour Holter monitoring ABPM SCHILLER, Vilber Lourmat Gel Emager 2.0 DNA, 9700 AB GeneAmp PCR system, Millipore AFS-15 Water Purification System, DT Prime, Real-Time PCR system DNA Technology.

### The Panels and their phenotype coverage

Hypertension/pre-diabetes panel - 6th genes. Arterial stiffness panel - 3th genes. Pharmacogenetics panel - 8th genes. Nutrigenetics panel - 6th genes. CVD risk panel-12th genes. Clinical panel – twenty five parameters: Blood Pressure (BP), Body Mass Index (BMI), Glycosylated Hemoglobin (HbA1c), Electrocardiography (ECG), 24-hour Ambulatory Blood Pressure Monitoring (ABPM), echocardiography, other tests.

### Sample Collection

The study included 240 patients with I-II grade of essential hypertension EH and pre-diabetes, all of them were Uzbek males in the mean age of 47.1 ± 7.1 years.

### Protection of subjects

The medical information gathered during the study was treated

confidentially except as may be required by the law. The study was approved by the medical ethical committee of the center of cardiology, Tashkent Uzbekistan. Informed consent was obtained from each individual recruited. Subjects were designated ID number from 1- 240 in the sequence of charts reviewed.

## Results

We connected CDS to the 4th units (arterial hypertension, arrhythmia, ischemic stroke, surgery) and to two laboratories (clinical genetics department and biochemical lab) (Figure 1).

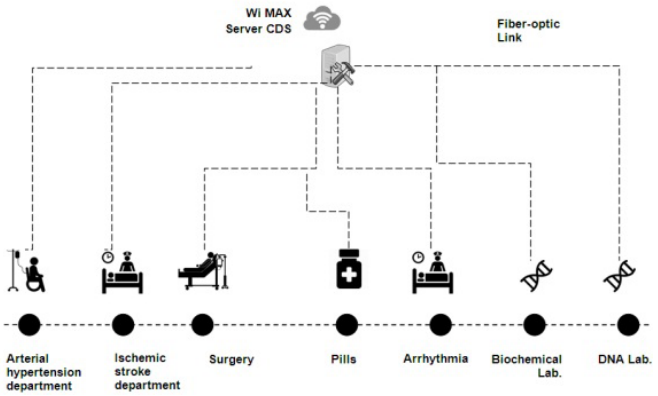


**Figure 1:** Roadmap CDS (RSCC UZ).

The network is equipped with fiber-optic communication for ensuring trouble-free operation of all knots. This network is bound to the Internet via the router. We connected a high-speed cable of 6 departments of the medical center. The server room has the area of 40 sq.m, and is cooled with one conditioner. The room has the sensor of temperature and fire-prevention system. The heterogeneous network supports operation of 35 computers, 30 printers, 5 scanners and 8 diagnostic units. The main computer is equipped with the uninterrupted power supply for 30 minutes of operating time. We chose the protected cluster archive with a multinodal control system of data (Figure 2).

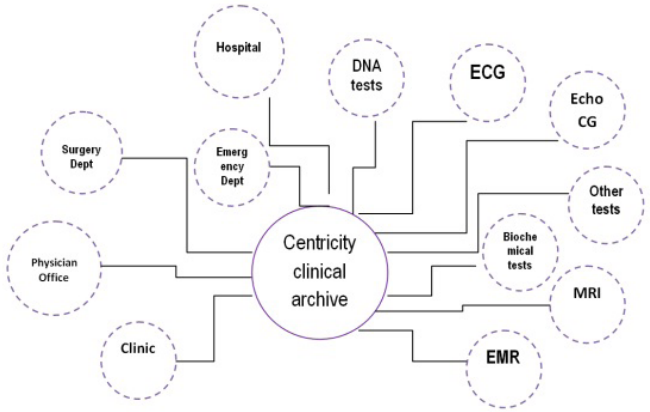


**Figure 2:** Centricity clinical archive: map.

We have highlighted the adaptive accompaniment of CDS, being based on standardized protocols and benchmarks for the diagnosis and treatment of essential hypertension end pre-diabetes. To prevent failures in the CDS system, we divided all stream of the EMR records into two matrixes of the analytical module (phenotype/genotype). Thus, we received separate technology of pharmacogenetics and nutrigenetics testing under control of the task manager. We automatically tied all electron records of the DNA test to CDS to avoid duplication of the profile (Table 1).

| Type of support | CDS Technology |
|---|---|
| Data transmission | Fiber optic link /WLAN |
| supports TCP/IP | Definition of the IP-address, Subnet mask and gateway |
| Encryption | AES (Advanced Encryption Standard) |
| Storage | Server (Dell G12 Tower), including more than 3 terabytes of storage |
| Quantity of computers in system | 24 |
| Connection with the Internet | Router WiMAX. EVO provider |
| The uninterrupted power supply | UPS ION G-3000 LCD. Online |
| Identification | Biometric recognition (BioTrack) |
| Online Instruments | 8 |
| Architecture | Opened, multiplex platform |
| PC operating systems | Windows 10 |
| Automatic tasks | Reserve copying |
| Options | Cloud, Sensor management |
| Panels | Pharmacogenetics panel (8-genes) Nutrigenetics panel (6- genes). DM/EH panel – (6-genes). Arterial stiffness panel – (3-genes). |
| Quantity of variables | The analytical filter -25 |
| Quantity of workplaces | 6 |
| Color of the interface | Ultraviolet |

**Table 1:** CDS description.

We applied technology of the effective genes analysis. For the first time we applied this technology for identification of genes mutations which enlarge a susceptibility to rising of weight, and also sensitivities to some drugs. Thus, using DNA identification, the developed algorithm can recommend an individual diet and a safe dose of drug. The algorithm is capable to transform pathogenic genetic data to the diagnostic tool which in a combination with clinical observation and biometric data can create the clinical decision. To avoid, an unnecessary flow of information, we limited access to information, according to the working state (Table 2).

| | |
|---|---|
| **Laboratory director** | Full access to patient information (family health history) |
| **Clinical geneticist (genetic expert)** | Full access to patient information (family health history) |
| **Consultant physician Ultrasound examinations** | Record of result |
| **Consultant physician Surgery** | Record of result |
| **Consultant Cardiologist** | Record of result |
| **Consultant Endocrinologist** | Record of result |
| **Nurse** | Registration |
| **Information manager** | Full access |

**Table 2:** Categories of CDS Users.

## Example of utility of CDS application

We have found that 17% of inheritance of hypertension in Uzbek population the most closely to Asian type. We have also found dominance of European contribution (83%) to the development of hypertension. Heritage of hypertension in Uzbek population has been evaluated as 17% Eastern, 33% Southern, 25% Central Europe, 8% for Anatolia and 17% for South East Asia. The functional significance of all 12 genes in hypertensive patients with combination of atherosclerosis and pre-diabetes is similar for the most part with European type of heritage. However, a distinctive sensitivity to the exchange of sodium in these individuals is due to 17% of the Asian contribution.

The testing of using CDS in prophylaxis of a essential hypertension, showed appreciable decline in mortality. However researches of consequences of pre-diabetes accompanied with a hypertonic not always showed positive effect of using CDS. In one case from ten we fixed CDS failures that didn't allow the clinician to analyze and interpret the difficult genomic information which is usually going beyond his training. The main characteristics of the offered multiplex panels are consolidated in table 3.

| Parameters | CDS efficiency | Genes | The reasons |
|---|---|---|---|
| **Cardiovascular Risk Factors** | | | |
| Pre-Diabetes/ Hypertension** | *no | FTO PPARG/PPARA APOE, APOA, DRD2 | The CDS are not always able to clearly determine the synergistic and intergenomic effect of analyzed genes. |
| hypertension /High BP | yes | ACE. mtDNA HV1/CYP11B2 | The operational clinical forecasting. |
| Vasoconstrictions | yes | B2BKR eNOS | |
| Vasodilatations** | no* | AGTR1/AGTR2 ADD1 | The discussion showed that there was insufficient data for arriving at meaningful assessments and conclusions. |
| Deep vein thrombosis** | no* | PAI-1 | |
| Arterial stiffness** | no* | MMP1/MMP3 | |
| **Nutrigenetics Panel** | | | |
| Risk of water-salt exchange disturbance | Yes | ACE CYP11B2 | The operational clinical forecasting. |
| Risk of the increased body weight development | Yes | ADRB3 B2-AR | |
| **Pharmacogenetics Panel** | | | |
| Warfarin | yes | CYP2C9*2 CYP2C9*3 VKORC1 | The operational clinical forecasting. |
| Klopidogrel | yes | CYP2C19*2 CYP2C19*3 | |
| Perindopril | yes | AGTR1 BDKRB1 | |
| Simvastatin** | no* | SLCO1B1 | There is no associations |

**Table 3:** CDS efficiency. no* - OR<1.7; 95% CI. p<0.05. **- ROC curve – no associations.

## Conclusion

Despite numerous disadvantages of the CDS program, the analysis of a big flow of genetic and clinical information it became real. We recommend considering several moments on the first steps of projection. In - the first to pay attention to an analytical stage. To provide sensory management of all knots of system. It is necessary to consider in advance all working platforms which will be served by CDS. Use Bayesian approach to frame a matrix of recognition of the damaging alleles and haplotype. It is necessary to adhere to standard forms of biological data. It is recommended to establish basic threshold values of the high normal ABP - 139/89 mm of mercury and optimum ABP of-120/80 mm of mercury. (ESH/ESC 2007). We also recommend that a normal HbA1C should be < 5.7 and impaired glycemic control, pre-diabetes ranges between 5.7-6.4% (ADA 2003). To strengthen enough genetic information, CDS has to be able to structure a superfine phenotype. For stratification of risk of rising of the ABP (the high, increased, average risk) use multi-sample option. It will lead to specificity increasing while sensitivity will remain invariable. Use heuristic and statistical algorithms; they will be able to identify the damaging genotype, without conflicting to clinical information of the patient. Use several locations to frame the adaptive interface.

We also recommend limiting access to genetic information. It is bound to the fact that information on existence of the inherited pathologies can affect a work arrangement and receiving insurance. In some countries laws of genetic non-discrimination (US Genetic Information Nondiscrimination Act GINA 2008) are adopted. GINA forbids genetic discrimination when obtaining the health insurance. However this law doesn't influence life insurance. Besides these laws are adopted only in a small amount of the countries.

We have also found dominance of European contribution (83%) to the development of hypertension/pre-diabetes. Perhaps this similarity in hypertension/pre-diabetes lineage between Uzbek and European populations, due to the fact that the ancient settlements of the Paleolithic Age could migrate to Central Asia from the east and west, not from north and south.

Unfortunately, adaptation of doctors to high - technological CDS interface wasn't complete. We believe this problem is caused by lack of basic knowledge on genomic pathology and bioinformatics.

Effective multinodal data management has been developed supporting clinicians and different users of EMR data. Such approach guarantees combination of results of different diagnostic tests in a patient story of illness. Despite a technological capability to process and make more exact clinical assessment of big data array, the problem of inaccessibility of resources and mechanisms of exchange of the annotated genetic information remains unresolved. Ability to authentically predict phenotypical results on the basis of a genotype, still remains a CDS task of the next generation.

## Acknowledgments

We wish to thank the director, physicians, and nurses from the Republican specialized center of cardiology hospitals for their assistance in blood collection. We also thank prof. Marietta R. Eliseyeva for the scientific contributions (IJBM International medical research & Development Corporation USA). We are grateful to working group of the Texno-soft company programmers for assistance in the development of the CDS program.

## Financial and Competing Interest Disclosure

This work was supported by a Grants ID 5259, kode: MUZ-2015-0905205928, ADCC-15.13.1 from the Department of Health, Science and Technological Development of the Republic of Uzbekistan. The authors have no other relevant affiliations or financial involvement in any organization or no financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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