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A Multifunctional System of the National Genetic Register

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Abstract

The National (Federal) Russian Genetic Register operates as a multifunctional system. It is designed for finding solution to the following key problems: 1. Information provision to watch families having children with hereditary and congenital diseases. 2. Follow up of the diagnostic process (including that associated with molecular-cytogenetic studies) and making predictive decisions concerning a risk of hereditary disease in the family. 3. Monitoring of new cases of congenital/hereditary disease under the effect of genotoxic and general toxic environmental factors. 4. Rendering consulting services to those concerned and reference information on the organizational/methodological problems.

The relational database is composed of textual and graphical data. This enables the doctors to enter and review the pedigree in the form they have got accustomed to. Numerous built-in classification schemes help simplify and speed up the completion of the medical records. An additional information can be entered in the textual form. When requested by the user, the information about the patient and his (her) family, stored in the database, can be displayed as a summary document (a statement). To do so, a special algorithm based on the results of the logical information analysis, as well as medical history of the patients themselves and their families' members has been put forward. The document thus compiled is open for being edited by the doctor. The local computer network is operated in the "user-server" mode. For information protection purposes, an authorized access system has been devised to protect various data categories. The software tools operate in the Windows environment for IBM-compatible personal computers. Also, use is made of Microsoft SQL-Server, Visual Fox-Pro 3.0, Visual C++2.1, and FORTRAN 5.1. The doctor decision modules are activated with mathematical models, an expert system, and a self-learning recognizing system. The Windows NT system is a choice for the existing Federal and Regional Genetic Centers. For territorial consulting purposes other alternatives might be Windows for Workgroup 3.11 or Windows 95. The local computer networks in individual organizations will be integrated to form a Corporate Medical Genetics Service of Russia. The system is to be completed before the year 2000 in a number of phases. Up to now, program packages for family database management and recurrent risk calculations have been worked out and tested.

Keywords

Relational Database, Decision Support System, Expert System, Recurrent Risk Calculation, Corporate Network.

Introduction

Today, most populations are not clearly understood in terms of how frequently the genetically determined diseases occur, what is their structure, and what should be done to effectively rehabilitate the patients affected . Moreover, a need for the reasonable solution of these problems is associated with the idea of applying information technologies to the routine operations of Medical Genetics Clinics (MGC) and Centers (MGC). The new Russian Federal Genetic Center is to replace all kinds of the existing computer-based territorial systems differing in the information bases and technologies employed. It will comprise a multifunctional system. The result will be a substantially improved assistance to the families which suffer from hereditary pathologies. The computer-based register will be capable of doing the following: (a) computer-aided management of medical documentation; (b) genetic consulting with the use of the family tree data; (c) supporting the decision-making process in the clinic environment; (d) laboratory diagnostics; (e) obtaining reference information on organizational-methodological problems arising from family examinations and consulting sessions with the use of medical telecommunication facilities. This is coupled with the possibility of studying the geography of hereditary diseases and monitoring the birth defects.

Thus, the Computer-Aided Federal Medical Genetics Register will assist in the implementation of all the key tasks of this service, namely:

1. Medical genetics consulting, including the following:
   (a) analysis of the family-related data (a family tree);
   (b) estimating the genetic and teratogenic risks;
   (c) calculating the genetic risk.
2. Prenatal diagnostics of congenital diseases.
3. Large-scale (neonatal) screening for hereditary diseases.
4. Exposing and detailing the nosological pattern of birth

defects (BD), beginning from the new-born time.

5. Preventive examination of families with hereditary diseases, including:

   (a) gathering genealogical information (a graphic family tree);

   (b) maintaining medical records;

   (c) conducting laboratory and instrumental studies.

6. Organizational aspects.
7. Statistical analysis of a Medical/Genealogical Consulting Clinic (a Center).
8. Monitoring BD and hereditary diseases.
9. Epidemiological studies of hereditary diseases.
10. Maintenance of reference information services on organizational/methodological and treatment/diagnostic problems.

The Federal Genetic Register is intended to be a typical system for all levels, namely, territorial, regional, Genetic Consulting Clinics, and Federal Centers. In fact, this will lead to the establishment of a distributed database (DB) for the medical genetics services in Russia, supported by a unified information base and using telecommunication facilities.

Materials and Methods

In Interregional and Federal Genetic Centers it will be very important to operate in a multitask mode (data reception/transmission, database compiling/analysis, reporting, etc.), which generates a need for creating an environment capable of doing this with an active network support. This consideration, together with the possibility of using RISK-type computers, have been critical for choosing the Windows NT 3.51 operating system for the Genetic Centers with extended loads (a wide range of data to be handled with and a need for their integration). For the territorial Medical Genetics it is intended to use Windows for Workgroup 3.11 or Windows'95 systems.

For large Centers where the patient population may be one hundred thousand people or so, the on-line information management is problem number one, so that the use of the "client-server" architecture is a preferred alternative. Our choice has been made in favor of the Microsoft SQL Server which combines the efficiency of the Windows NT and the capabilities of a powerful relational database management server to meet the requirements imposed by the "client-server" applications. This approach is promising in that relatively small computers capable of accessing the database-contained information can be used. To do so, the FoxPro 3.0 tools are employed, and the application programs are implemented through the Visual C++ language (the genetic risk evaluation tasks are evaluated with FORTRAN 5.1).

The register programs employed in our system allow the user to work in both textual and graphical (local) network modes. All subroutines covering the medical genetics record sections for children follow up/prenatal diagnostic purposes as applied to hereditary diseases are integrated into a single package which is made accessible through the main menu. In so doing, the data can be loaded, corrected, stored, viewed, and analyzed.

The graphic pedigree "word processor" makes it possible for the family tree to appear on the display in a form commonly accepted in genetic applications. The graphics is accompanied by text comments associated with specific tree elements. The information of interest can be viewed, and following the selection of the appropriate element, the user obtains information on one or another family member. To make it easier for the user-doctor to perceive the graphic information, the following can be done: (a) vertical and horizontal screen scrolling to look at big trees which are not accommodated on a single screen; (b) a prompt scaling up of the tree to view it as a whole on the same screen, no matter how big it is, followed by coming back to the big scale to see the selected fragment; (c) screen/background resizing, as well as changing colors of the elements and connecting lines using the Windows color scheme (in a specific system configuration).

The graphic information is mainly edited through the use of a tool bar panel and the "Hereditary Tree Data" dialogue box. As the data for a given family member is entered, the graphic information element is automatically adjusted in respect with the record type. Along with the menu options; the same operations can be carried out using active "hot keys". The graphic editor software helps directly record the elementary data in the register database, while the graphic image is retained as a file.

The program support for the patient's medical card including case history and clinical examination, laboratory, functional, and expert's advises units comprises individual R-tables from within the relational database. The timing of the various proband code indicators in various program card modules produces an instantaneous response to the user looking for a specific record. The in-built classificators enable the doctor to supplement the card with any useful comments. The information can be also enriched, if necessary, with some additional information (in vanishing and permanently open windows). This assists in reflecting the specific clinical disease manifestations as applied to a given patient.

The branched (dendrite-type) menu including its pop up system, helps the user to find an easy path to the screen required.

A special software package has been created to prepare a database-stored document for each patient, and the appropriate algorithm together with support programs developed. This algorithm is based on the logical analysis of the information from the database, including genealogical evidence. At a later stage, such a system-originating document (a statement or an extract) can be amended by the doctor.

Special programs operated in the Excel environment enables the user to display tables which give numerical data for the laboratory indexes selected, "tied" to the examination dates (i. e., the dynamic factor) or present them in the graphic form. The medical users can make (at their discretion and at any time) further use of the forms they prefer, such as histograms, diagrams, and circular charts. The same method is applied to the visual arrangement of the output material forms. This software has been developed with the use of the Visual FoxPro 3.0 OLE technology.

An Expert System is being set up to automatically study the hereditary disease transfer mechanism based on the family tree data. To do so, tools have been created to process formalized knowledge and shape hypotheses as to the type of inheritance to some certainty. The DB request and output units function as DDE-exchange servers in the FoxPro environment. The units in this structure are interconnected in the ODBC format (as in the case of the register, in the integrated form). The units written in the FoxPro 3.0 language operate as DDE servers which, when initialized, register a back function to response to the transactions (requests) coming from the clients. Genetic information from the DB, derived by sending the appropriate requests to the enabled system, comes to the system input. The governing units formulated in the C++ language operate as DDE clients. They instruct the DDE to retrieve data from the DB, send them commands to do so, and recover the required information from the servers. Such a process permits the units to be isolated from one another and the inter unit exchange interface unified.

The Expert Knowledge is formally represented through a combined frame-production method. It gives a comprehensive description of the knowledge within one or another data domain and permits to build an associative-semantic network. The logical inference mechanism rests upon the Bayes algorithms and is constructed through the use of a direct scan technique. At the output of the Expert System the user gets the inference on whether the patient bears any hereditary monogenic disease together with its inheritance type accompanied by the certainty factor (the probabilistic nature).

The program package for recurrent risk calculations in families with autosomal-dominant, autosomal-recessive, and X-linked (dominant or recessive) inheritance types employs special formulas. Information contained in the input file is used as original data. In each specific case the name of such a file is specified by the user, and its length and structure are limited by the capabilities of the operating system alone. This package will be integrated into the Expert System to be applied to family tree studies. Today, this unit is directly connected to the medical card software.

The computerized chromosome analysis system includes the numbered images entered by the user, which are then classified and reviewed. In this situation use is made of a self-learning procedure with the possibility of providing additional instructions when performing practical operations.

Results and Outlook

Today, the first phase of the system has been completed and the second one is under way. Program packages for family DB together with a genetic risk calculations module have been created and tested. Tools for the Expert System have been developed and formal knowledge base procedures for family tree analysis described. The first phase of the Russian Computerized Federal Genetic Register is suitable for the following jobs to be performed:

1. Providing information support to geneticists with the patients under regular observation and rendering consulting assistance to families with hereditary diseases and birth defects.
2. Providing information support to managerial staff at all levels in the analysis of the Medical Genetics Register services in Russia as a whole and its individual Regions when planning these services.
3. Unification of diagnose coding regulations in the case of monogenic and chromosomal diseases, insurance of their consistence with the WHO's requirements and similar foreign systems in conformity with the International Disease Classification and MIM codes (as presented in the Mendelian Inheritance Catalogue by Victor McKusick).
4. Improvement of the procedures used to keep medical documentation (including laboratory and functional data), as applied to families with hereditary and congenital diseases.
5. Genetic risk calculations for various forms of monogenic inheritance.
6. Creating statistical report forms for the Federal and Regional levels and issuing the required information in the request mode.

   The typical unified medical card (which is also designed for carrying the additional text information to describe the specific disease manifestation characteristics) forms the information basis for the complex-structured DB in the system and comprises its medical core which is open for other highly specialized ("satellite-type") DB, e. g., in echography and dermatoglyphics.

The system can accommodate some modules to support the following medical statements:

- To provide diagnostic consulting, the Register can incorporate the Intellectual diagnostic system "DIAGEN" due to the same authors (B. Kobrinsky et al., 1991; B. A. Kobrinsky, 1993).
- The final end of the computerized Expert System for the pedigree analysis is expected to be writing a statement on the probable existence of a genetic disease for a given patient and its inheritance pattern. In the event a hereditary monogenic disease has been revealed in a family for the first time, the probability of a fresh mutation event should be considered.
- The computerized molecular-cytogenetic analysis system using the Fluorescent In Situ Hybridization method – FISH) enables one to process signals and analyzes the images obtained. The chromosomes recognition process consists, among other things, in their classification by the generally accepted groups and finding the labels typical of congenital defects.

The integral and initial data relating to the genotoxic and teratogenic environmental factors (in the spatial-temporal reference system), which build up progressively in the special DB of the Hygienic-Environmental Monitoring Centers, will be accessible to the geneticists who work for the Federal Genetic Register. Together with the statistics for the fresh dominant- and X-

linked hereditary cases (the so called "sentinel phenotypes"), this will enable the user to perform the territorial monitoring of congenital and hereditary diseases.

The administrative functions of the Register will be implemented through analysis the information accumulated in the distributed DB to prepare forms essential for taking decisions at the various managerial levels. The second phase of the Register project covers such steps as personal data exchange between the various levels of medical services in the real time mode and establishing information-reference services at the Regional and Territorial levels, designed to take care of families with hereditary pathologies. Such a reference service for territorial consulting purposes will be operated in the electronic mail "ask-and-get-answer mode". To solve these problems, the development of the appropriate corporate network is under way. Formerly, the Regional network developments relied on the Internet modems. The recent tests indicate that the server is mainly loaded and, consequently, spend most of its functional time not to cope with computing tasks but rather with processing information transfer inquiries.

Discussion

Genetic registers are subdivided into single- and polifuctional types, the latter dominating the scene in the last few years. Furthermore, they can be adapted to a single nosological form, a group of diseases, and inborn defects as a whole. Multiline registers which our system belongs to include modules intended for performing a variety of functions such as genetic consulting, supervision, special and epidemiological studies, monitoring, etc. The unified medical card (which makes it possible, in addition, to incorporate supplemental textual information to describe the specifics of the clinical disease manifestations), comprises the core of the system around which various highly specialized ("satellite-type") DB similar to those implemented in the South Alabama Register can be clustered (W. Wertelecki and D. W. Superneau, 1987).

As compared to such Registers as RAPID (Scotland), GENTIC (France), and HGDBMS) databases (USA) (Emery A. et al., 1978; Ayme S. et al., 1982; Seucher S. A and Skolnik M. H., 1988), we are planning (along with family consulting and patient observation tasks) to exercise the monitoring and epidemiological control of hereditary diseases in the Russia's Regions. As distinct from the Alabama Medical Genetic Consulting Center in the USA (Wertelecki W. and Superneau D. W., 1987), we are planning epidemiological studies, and, as compared to the American GENE.SERV System (. Johnson W. E et al., 1984), congenital and hereditary diseases will be monitored. As distinct from all other similar systems, the future Register will differ by that it incorporates tools designed for the medical diagnostic and genetic consulting statement support at the intellectual level. At the same time, unlike the MEGADATS Register (Yount E. A. et al., 1987) oriented mostly toward the solution of research problems, such subjects as genetic heterogeneity, coherence, and mapping are to be omitted.

Conclusion

The multifunctional system of the Federal Genetic Center allows for the solution of all major problems that face the Territorial, Regional, and Nation-Wide Medical Genetic Consulting Clinics and Centers. Therefore, it differs from all other systems existing in Russia and some other countries, including the first Russian Register established by us in early 1980's (B. A. Kobrinsky, 1991). The new Register is aimed at settling major problems of the medical genetic services, as prescribed by the WHO. At the same time, each genetic assistance level differs in a set of modules to be used for the solution of specific problems.

Analysis of new (fresh) cases of congenital and hereditary diseases in the presence of the environmental teratogenic and genotoxic factors will be organized as dictated by the European genetic consulting model. Moreover, the integration of the MAN networks which match the country's geography will be beneficial to the creation of the unified corporate medical genetic services network in Russia. The development and putting into practice of the individual Register units will run as parallel processes. Similarly, the network will be built up in a phased manner.

References

[1] Kobrinsky B, Kazantseva L, Feldman A, and Veltishcev Ju. Computer Diagnosis of Hereditary Childhood Diseases. Med Audit News 1991:1 (4) pp. 52-53.

[2] Kobrinsky B, Kazantseva LZ, Feldman AE, et al. Computerized Genetic Register and Computer Support of the Diagnostic Doctor's Statements. Genetika (in Russian) 1993:29 (10) p. 1733-1740.

[3] Wertelecki W and Superneau DW. A Genetic Services Microcomputer Database. Part I: Design and Implementation. Alabama J Med Sci 1987: 24 pp. 281-289.

[4] Wertelecki W and Superneau DW. A Genetic Services Microcomputer Database. Part II: Results and Trends. Alabama J Med Sci 1987: 24 pp. 397-399.

[5] Amery A, Brough C, Crawford M et al. A Report on Genetic Registers, Based on the Report of the Clinical Genetics Society Working Party. J Med Genet 1978: 15 (6) pp. 435-442.

[6] Ayme S, Julian C, Maurin N and Gambarelli D. Birth Defects Monitoring Systems: Accuracy of Many Diagnoses in Question. Clin Genet 1985: 28 (5) p. 411.

[7] Seuchter SA and Skolnick MH. HGDBMS: A Human Genetic Database Management System. Comput and Biomed Res 1988: 21 (5) pp. 478-487.

[8] Johnson WE, Vincent G, Boukaabar B and Glorioso LR. GENE.SERV: Implementation of the Clinical Genetics Data Management System throughout Ohio. Am J Hum Genet 1984: 36 (4) p. 57S.

[9] Yount ET, Connally PM and Gersting JM. Applications of the Medical Database System in Medical Genetics. Amer. J Med Genet 1987: Vol. 26, pp. 331-335.

[10] Kobrinsky B. Computer Support of Medical Decisions in Pediatrics: Register and Diagnostic system for hereditary Diseases (in Russian). Bull All-Union Informatics and Computers Soc 1991: 1. pp. 20-25.

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