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Karel Zvára
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Table 1: Age, period, cohort modelling of coronary heart mortality, men, 30-74 yrs., Czech Republic, 1980-2004.

No.	Model	D	*df*	*p*-value
0	Interception	355388.0	44	<0.001
1	Age	15148.0	36	<0.001
2	Age-Drift	3255.5	35	<0.001
3a	Age-Age*Drift	2922.5	27	<0.001
3b	Age-Period	388.2	32	<0.001
3c	Age-Cohort	1872.6	24	<0.001
4	Age-Period-Cohort	28.7	21	0.121

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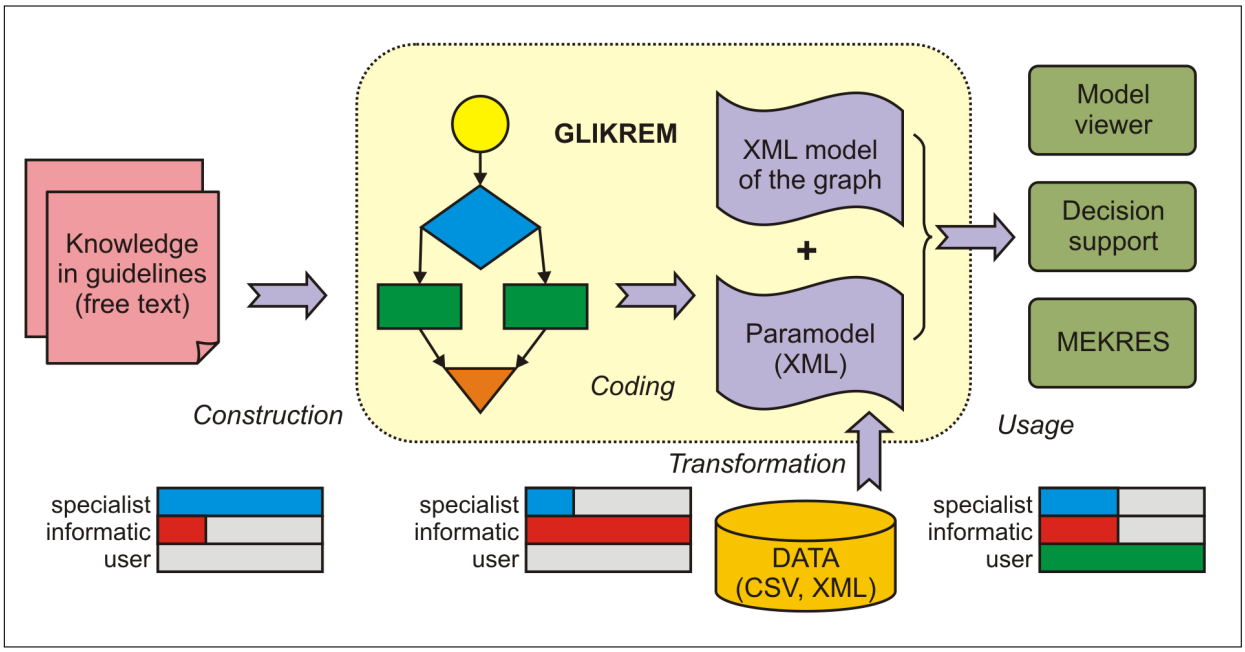

Figure 1: Construction, coding and use of GLIKREM.

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Contents

Biomedical Informatics Revolutionizing Changes in Health Care Delivery

Jana Zvárová[1]

[1]Editor-in-Chief, European Journal for Biomedical Informatics, Prague, The Czech Republic

The Symposium on *Biomedical Informatics: Confluence of Multiple Disciplines* held in Heidelberg, Germany at the University of Heidelberg´s Internationales Wissenschaftsforum in 2011 reflected opportunities, challenges and priorities of organizing, representing and analyzing data, information and knowledge in biomedicine and health care. As an outcome of the symposium, five manuscripts were published in the journal *Methods of Information in Medicine*, Volume 50, No. 6, 2011. Biomedical Informatics is a discipline that has a great impact on many other fields and is also influenced by them. For this reasons biomedical informatics based on collaborative research brings new opportunities for revolutionizing changes in health care delivery.

The aim of the editorial board of the *European Journal for Biomedical Informatics (EJBI)* is to reach the highest scientific level of the journal and to show the best practices of biomedical informatics applications to wide readership. It has been often important for health professionals to have the possibility to read important articles not only in English but also in their native language. For this reason EJBI publishes accepted peer-reviewed papers in English and other languages simultaneously. This opens new possibilities for faster transfer of scientific-research pieces of knowledge to a large international community of biomedical researches, physicians, other health personnel and citizens.

Since 2012 (Volume 8) the *European Journal for Biomedical Informatics* begins to implement several changes, which will bring new opportunities for authors and readers. The journal publishes peer-reviewed original articles, review articles, reports, opinions papers and editorials in the field of biomedical informatics and applications in health care. EJBI provides immediate open access to peer-reviewed papers, which will be published in the running first issue of EJBI during each calendar year. The other issues of EJBI in each calendar year are EJBI approved special issues related to different biomedical informatics topics.

Authors do not pay an article processing fee for the immediate release of peer-reviewed articles, but a small financial support is required in case that the support of projects or sponsors is acknowledged (see instructions to authors and template). However, for further development of EJBI and its multilingual objectives we offer the possibility of sponsorship of single issues of EJBI (see more information here) to support dissemination of new information and knowledge in other languages than in English.

Topics for special issues can be proposed to the editor-in-chief of EJBI using the Proposal of EJBI special issue form for further processing. The topic for special issue is specified by an open call or by a special event. In the year 2012 we will publish two special issues based on open calls with special topics *Support of eHealth Applications by Legal Systems in Europe* and *Standards and Solutions for eHealth Interoperability*. The other special issues in 2012 will be directly connected with different events, e.g. conferences, symposia, workshops etc. We plan to prepare special issues connected with the MIE 2012 conference (Pisa, Italy, August 28-31, 2012) and with the Ph.D. students´ conference *Semantic Interoperability in Biomedicine and Health Care* (First Faculty of Medicine of Charles University in Prague, November 22, 2012). In the year 2013 we plan to have a special issue connected with the forthcoming EFMI special topic conference *Data and Knowledge for Medical Decision Support* (Prague, April 17-19, 2013).

We invite you to propose special topics that would help to accelerate needed changes in health care by easy transfer of a new information and knowledge for health care delivery.

eHealth in Europe – Status and Challenges

Anne Moen[1], **Werner O. Hackl**[2], **Jacob Hofdijk**[3], **Lisette Van Gemert-Pijnen**[4], **Elske Ammenwerth**[2], **Pirkko Nykänen**[5], **Alexander Hoerbst**[2]

[1] Institute for Health and Society, University of Oslo, Norway

[2] UMIT, University for Health Sciences, Medical Informatics and Technology, Austria

[3] CaseMix, the Netherlands

[4] University of Twente, the Netherlands

[5] School of Information Sciences, University of Tampere, Finland

Abstract

Objectives: To present European reflections on the concept of eHealth and report challenges related to further development of eHealth in Europe.
Methods: A survey with 10 questions was distributed to representatives of the national member associations of the European Federation of Medical Informatics (EFMI). The material was summarized using content analysis techniques, generalized and discussed.
Results: The results document a shift from a focus on ICT-orientation to initiatives that will development of the entire health system where eHealth strategies, organizational change, and appropriate technological infrastructure are singled out as important aspects.
Conclusion: There are urgent needs to discuss eHealth strategies and policies to contribute to capacity building necessary to deploy eHealth applications that support sociable services and innovations in health care. As a contribution, the EFMI community will utilize arenas for capacity building on the European level, and stimulate collaboration across national boarders and health systems.

Keywords

eHealth, status and challenges, Europe, survey

Correspondence to:

Anne Moen
Institute for Health and Society, University of Oslo,
Address: P.O.Box 1130, Blindern, N-0318 Oslo, NORWAY
E–mail: anne.moen@medisin.uio.no

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1 Introduction

Over the last years, health informatics respectively medical informatics has matured. The field is committed to improve quality in health care, provide best evidence at the point of need, and also demonstrate benefits across settings, taking advantage of technological opportunities and applications [1].

On the European scene we observe that the terms health informatics, medical informatics, nursing informatics etc. are gradually substituted or used interchangeably with the term eHealth.

Time is overdue to actively promote health technology based on science-based evidence to ensure that the tools are deployed according to robust evidence [2, 3]. Such evidence would draw from technological, health professional and social perspectives. There are several reports and surveys, [4, 5] providing snapshots and interesting examples for eHealth evolution across Europe.

Publications prepared under the leadership of EFMI also points out key eHealth issues. These issues range from user-involvement and experiences of health professionals and patients working and living in ICT enabled environments [6], health informatics opportunities to deploy, evaluate, and adjust healthcare services [7] to internationally oriented policies and programs to support patient safety [8], interoperability for seamless care [9], cross border care, no boundaries perspectives [10], and adequate business models for health technologies [11].

Achievements in eHealth can support future demands within the health care system and improve the quality of life of citizens, patients and health providers'. The objective of this paper is to discuss the concept of eHealth through a European lens, and present challenges with regard to eHealth in Europe based on a survey administered to the national member societies of European Federation of Medical Informatics (EFMI). We will contribute experience and evidence to discuss current perspectives for eHealth opportunities and challenges identified in Europe.

2 Methods and Material

The current study is based on a survey research methodology. Participants were asked to answer a survey with 10 questions focusing on definitions, trends, challenges and priorities, cultural aspects and ICT infrastructure for the health care system, on an operational as well as strategic level. The questions were:

1. What definition for eHealth is used in your country?
2. What are the key trends and developments in the eHealth domain in your country?
3. What are the main difficulties for the development of eHealth in your country?
4. What are the priorities for the development of eHealth in your country?
5. What are the cultural factors influencing the development of eHealth in your country?
6. What is the link between ICT infrastructure and eHealth development in your country?
7. What is the link between eHealth systems and national health system in your country?
8. Provide evidence on eHealth by citations/copies of surveys, scientific/technical studies, progress/special reports, eHealth education for the workforce.
9. Highlight of one or two shining examples from your country, such as adoption of a national eHealth policy, establishment of a health informatics education program, public-private partnership.
10. What are the lessons to be learned from the country's eHealth experience.

The survey method was selected as it allows for overview and to understand a problem and its reasons by quantifying certain aspects of it. Although trying to quantify certain phenomena the study is primarily exploratory and can give direction for further, detailed research.

2.1 Data Collection

Representatives of the 32 national member associations of European Federation of Medical Informatics (EFMI) were identified via www.efmi.org, and invited to answer the questions listed above. They received the questionnaire electronically in July 2011. The national representatives answered the 10 questions on eHealth developments and experiences answered the their country and by their answers contribute with an appraisal of current eHealth developments and experiences in Europe. By October 2011 thirteen responses were received from EFMI members Austria, Croatia, Cyprus, Finland, France, Germany, Iceland, the Netherlands, Norway, Romania, Sweden and Turkey.

2.2 Data Analysis

The received answers were subject to qualitative and quantitative content analysis [12]. We sought to identify, abstract and quantify inductively findings from the narrative descriptions of eHealth provided in the national EFMI representatives' answers to the questions. We started off to summarize the descriptions and definitions of eHealth, and continued to extract and generalize eHealth challenges. The categories are labelled requirements, prerequisites, difficulties and obstacles encountered in the development and implementation of eHealth in Europe. As a first step, statements were extracted from all answers received, and then annotated and generalized by two researchers (WOH, AH). Based on the generalized statements disjunctive categories were grouped inductively by a team of four (WOH, AH, JH, AM). Arriving at a consistent set of categories required three revision cycles.

In addition, we quantified the material by counting the number of statements assigned to each generalized category. A relative weighting factor, for each category was then calculated by dividing the counts of statements for a category by the overall sum of statements (see table 1 for details). This factor was used in the final step when we created the tag cloud (see figure 1) to illustrate the relative importance of each category, expressed as font size for each tag.

3 Results

The responses to the survey were narrative descriptions related to each of the 10 questions. In this report of results we will therefore elaborate findings about the concept of eHealth (section 3.1), services and challenges related to eHealth initiatives (section 3.2), and challenges for eHealth deployment (section 3.3).

3.1 Descriptions of the Concept of eHealth

To better understand and appreciate the developments and initiatives across European countries in terms of eHealth it is necessary to establish a shared understanding of what is understood by the concept of eHealth.

In the narrative descriptions, the understanding of eHealth converges as a common name for design, development, implementation and evaluation of ICT in the health system, broadly understood. Drawing from the responses we see a consensus and convergence that eHealth primarily relates to the use and introduction of information and communication technology (ICT) in a practice, but also to calls for cross-institutional and interdisciplinary understanding of eHealth. Collaborative efforts and new way(s) of working in healthcare require arenas for interactions to attend to the needs by stakeholders including health professionals, patients or their relatives. Three descriptions stated explicitly that eHealth is not

just the use of ICT in health care, but should be considered broadly in relation to the plethora of needs within the healthcare system. ICT is an important, but not sufficient enabler to meet challenges in and to the national health care systems across Europe.

In line with previously published descriptions of eHealth [13, 14], the broader aim of eHealth is to support health professionals in their work and continuous, lifelong learning, as well as to assist all citizens in their own health care management and their search for reliable health information, disregarding organizational boundaries and functioning of the health systems. The provided descriptions allude to previously reported potentials of eHealth as contributor to meet challenges for health care provision and improve the health system across Europe [4, 13]. Privacy, security and the use of standards were seen as given; important, general requirements for achievements in eHealth. We found agreement in the narrative descriptions suggesting that for future developments in eHealth active integration to allow opportunities for participation by all citizens is required. eHealth should therefore not be restricted to health professionals.

3.2 eHealth Applications and Services

The majority of the responses contained examples of important initiatives to provide high quality health information for use at the point of need. Grouping the content in the narrative descriptions provided examples ranging from technical and social infrastructure for secure access to health data and strategies for collaboration of providers and patients; repositories and suits of applications for digital clinical records; and tools to actively encourage participation by patients.

A striking finding in the responses is that similar types of services are named differently. Likewise, the reports showed that infrastructure and connectivity to share information across different levels of care, between care facilities or providers or patients and relatives are considerable challenges across Europe. Along the same lines, several connected deployment and use of services that enable citizen to access their health data securely and participate in their treatment, care and health prevention to the current state of (poor) Internet access for citizens.

Overall, in their answers, representatives of the EFMI national member societies report on the importance of national leadership and a national eHealth strategy including administrative, professional and citizens' perspectives. In some countries regional strategies accompany the national strategy. The progress in deployment of services and applications varies. To elaborate on the deployment we clustered the reported initiatives as "technical and social eHealth infrastructure", "eHealth repositories" and "eHealth applications" based on the collected material.

Technical and social eHealth infrastructure would provide opportunities for secure, seamless transmission of health information between home care/primary care, hospitals and GPs, and between public and private health sector. Examples include efforts for data exchange and interoperability in terms of terminology, ontology and standard development, protocols for information sharing and semantic interoperability, as well as legal and ethical issues for correct authentication, confidentiality and maintained trust. eCards, eSignature, unique identifiers for patients and providers, and protocols for electronic exchange of health Information are examples pointing to the technical and social eHealth infrastructure.

eHealth repositories would be Electronic Health Records and Patient portals, and there is a plethora of labels reported including DMP, EPR, EHR, longitudinal medical record, eArchive or eView. Patients and healthcare professionals should be able to securely access resources in an eHealth repository for purposes of coordination, continuity, and self-management. A study from Germany and Austria indicates high interest of patients respectively citizens on these technologies [15]. The DMP (dossier médical personnel) initiative in France illustrates interdependent efforts for inter-operability, security of systems, organization of services and involvement of all stakeholders to develop a coherent e-health "ecosystem" [16]. The variety of different requirements to eHealth repositories respectively Electronic Health Records across Europe is covered in a systematic review by Hoerbst and Ammenwerth [17].

eHealth applications are specific services for workflow support and interaction between providers and patients across time and space given available eHealth infrastructures and repositories. Services like eReferral, Patient Summary and eDischarge, ePrescription and eMedication, eRadiology, eLaboratory, eCare Coordination and eSurveillance as well as Telemedicine and eServices for citizens are identified as building blocks.

Patient summaries and eDischarge applications offer a structured, focused summary of clinical findings from a health encounter. A study from Austria for example reports high satisfaction and positive impact of electronic communication of discharge letter between hospitals and GPs [18]. A survey from Scotland reports that eDischarge letter is faster and may lead to noteworthy cost savings [19]. ePrescription and eMedication refers to electronic support to the chain of actions in medication prescription. A study from Sweden reports that physicians were generally satisfied with their specific EHR-system and with the available ePrescribing functionality [20]. eReferral and eBooking automates the scheduling process to health care service. A survey from Scotland showed modest rates of adoption for e-referrals [21]. In a study of eRadiology, sharing MRI images between smaller and larger hospitals are reported as promising [22]. In the field of eMonitoring and telemedicine several studies from European colleagues report benefits for chronically ill patients. For example, telemonitoring of the lung function of patients affected by Cystic Fibrosis led to less hospitalization and reported economical saving [23], and home spirometry for outpatient lung transplants showed that eMonitoring was feasible, safe, and decreased anxiety [24]. Telemedicine

Figure 1: eHealth challenges, relative frequency correlates with font size.

enabled eConsultation facilitates supervised care, reduction of outpatient visits and more timely appointments [25, 26]. A study of telemedicine supported thrombolytic treatment of acute ischemic stroke in Denmark suggests that the macroeconomic costs may balance with savings in care and rehabilitation services within 2 years, and although long-term calculations are uncertain, potentially large long-term savings are associated with telemedicine support to this treatment [27]. In the area of eCoordination, evaluation of support for home care document improved communication, coordination and collaboration among nurses, psychologists and doctors [28]. And lastly, in a study of eService for patients, the authors report that a personal health record (PHR) did not increase patient empowerment, but, at the same time, a PHR did not have any significant adverse effects either [29].

3.3 Challenges for eHealth Deployment

Further categorizing the challenges found in the narrative descriptions about eHealth deployment in Europe gives the following picture (figure 1).

Figure 1 illustrates that quite heterogeneous challenges to eHealth deployment are reported in the received descriptions. We acknowledge that there are several ways to interpret the information in this tag cloud. For this presentation we choose to zoom in on the following dimensions: 'strategy policy', - 'technological' and 'organizational' - 'professional' to elaborate the perspectives for an integral or holistic perspective on eHealth.

Counts of frequencies, understood as how often we interpreted content of the narrative descriptions, are grouped in these dimensions and presented in Table 1.

The reader of the table and the tag cloud would be struck by the prominence of the strategy & policy – technical dimension. In the tag cloud strategy & policy is presented as blue colour, and technical is presented as orange colour. The importance of an appropriate legal framework and national strategy with sufficient funding is noticeably expressed by this dimension, and point towards a call for governmental priority to authorize eHealth bodies.

Another aspect is the strong national focus, and in the material from our respondents we only found the importance of international cooperation mentioned once. The technical dimension relates to efforts to establish a sound eHealth platform. The answers tap into well known challenges in the health informatics community, including efforts to harmonize standards, support semantic interoperability, optimize usability for integration of new and existing IT-solutions demonstrating a service orientation, and support the mobility of patients and health professionals.

In terms of the organizational dimensions, presented as green in the tag cloud, and the professional dimensions, presented as red-orange in the tag cloud, other issues stood out. As for organizational dimensions, the importance to balance interest between private and public sector, involving and educating all stakeholders, handle persistence and initiate change management and importance of driving forces for coordinated efforts stood out.

Clustered as the professional dimension are issues that relate to inherent complexity of clinical practice and the variety of professional issues that surface following development and introduction of eHealth across Europe. The importance of traceable benefits visible to all parties and appropriate incentives can help overcome challenges of "silo thinking" and lack of cooperation.

Table 1: Basic categories for eHealth challenges, grouped with frequency in the narrative descriptions.

Strategy & policy – Technological			
legal framework	8	integrate IT solutions	4
national strategy	8	harmonized standards	3
funding	6	usability	3
business models	5	semantic interoperability	2
governmental priority	5	service orientation	2
authorized eHealth bodies	3	common terminology	1
national eHealth platform	2	core IT systems	1
international cooperation	1	open standards	1
minimum quality level	1	structured data input	1
quality certification	1		
Organizational – Professional			
balance interests	5	kill silos	3
coordinate efforts	4	traceable benefits	3
educate stakeholders	4	incentives	2
involve all stakeholders	4	manage complexity	2
persistence	4	acceptance	1
driving forces	3	clinical use cases	1
link research and implementation	3	feedback mechanisms	1
different adoption speeds	2		
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project-management	1		

4 Discussion & Conclusion

The findings from analysis of the narrative descriptions point to important challenges related to eHealth in Europe. This is indeed an evolving field where there is a lot of activity, and our respondents added interesting national perspectives that add to previous reports [5]. The four dimensions identified in the responses to our 10-question survey are important starting points for further research and development to constitute progress in the eHealth area. The most important insight from this study is an urgent need to ensure that eHealth strategies and policies for further design and deployment of eHealth applications support sociable services and innovations in health care. Reported diversity in the current eHealth development and exploitation in Europe support a shift from a strict focus on ICT implementation to a comprehensive, holistic approach acknowledging that eHealth involves interplay of appropriate technical and social infrastructure, secure repositories and usable applications [3, 8]. The next steps would be to ensure that existing and new applications support sociable services and innovations in health care. More information about the interplay of product, project and impact evaluation to link research and implementation should be collected as evidence to enable learning from accumulating experiences.

Although this survey focused largely on national issues, the report highlights important challenges to overcome for future development of eHealth. We consider the emphasis on the policy & strategic, technological, organizational, and professional dimensions related to eHealth as overlapping and highly interdependent. The implications would be that the upcoming challenges should be approached and addressed by taking these dimensions into account [6]. Although the accumulated evidence demonstrates the complexity and importance of multiple interacting perspectives, more research on the interactions and implications of scientific findings for the everyday practice are needed for further achievements in eHealth.

Among important initiatives would be to create arenas for capacity building, exchange of experiences and new initiatives to bridge across the national concern. Concretely the EFMI community will contribute to capacity building and exchange in focused efforts in international meetings, and stimulate their national member associations to exchange their experiences for collaboration across national boarders and health systems.

There are obvious limitations to this survey, specifically reflected in the composition of the sample, and what those who responded chose to highlight from their country to answer the questions. The smaller cohort of the national member associations that chose to answer to the questions, thus limiting the representativeness of the results presented here. However, the findings are related to reported, on-going efforts across Europe, and this should add some to alleviate these limitations.

In conclusion, let us point out similarities in the identified challenges, specifically related to strategy & policy for eHealth across the received narrative descriptions. We believe lack of reference to ongoing efforts in other countries as well as meager attention to European leadership can point in the direction of national eHealth silos. Priorities in eHealth may be perceived as a national issue, since health care is a national responsibility across Eu-

rope. However, priorities stated on the European level [30] coupled with concerted efforts more broadly in the EFMI community can be a leading force for progress across the region, and influence the emphasis in eHealth policy and strategy nationally.

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Integration of Informatics and Health Informatics into Health Educational Programs of Higher Education in Greece

Maria-Aggeliki Stamouli[1], **Charalampos Balis**[2], **Ioannis Apostolakis**[3]

[1] Technological Educational Institute of Athens, Faculty of Management and Economics, Department of Health Care and Social Units Administration, Greece

[2] Laboratory of Health Informatics, Faculty of Nursing, National and Kapodistrian University of Athens, Greece

[3] Department of Health Services Organisation and Management, National School of Public Health, Athens, Greece

Abstract

Objective: The aim of this paper is to study the inclusion of Informatics and Health Informatics subjects in the health sciences departments' curricula of higher education in Greece. Its main purpose is to determine the level of health informatics knowledge, dexterities and skills that these departments provide for their graduates.
Method: Informatics and Health Informatics subjects were recorded from the departments' curricula available on their official Web sites. Afterwards, these subjects were categorised based on the description of the objectives, the content and the syllabus of each department and on the Goals of Informatics Education identified by the American Medical Informatics Association.
Results: Our research indicated that most of the subjects mainly focus on introductory concepts and applications rather than on advanced issues of informatics, resulting, mostly, in producing Information Technology users rather than Health/Medical Informatics specialists.
Conclusion: The study presented in this paper points out the imperative need of health educational programs of higher education in Greece to adjust their curricula to the current educational requirements in order to provide their graduates with the necessary knowledge in health information technologies.

Keywords

Health Informatics, Medical Informatics, Education, Health Sciences Curricula.

Correspondence to:

Maria-Aggeliki Stamouli
Technological Educational Institute of Athens,
Faculty of Management and Economics
Address: 67 Argostoliou str., 18345 Moschato, Greece
E–mail: mstamouli@yahoo.com

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1 Introduction

International technological developments in Information and Telecommunication Sciences, in relation to the evolution of medicine and the other basic sciences, have already radically transformed the entire health services spectrum in the developed countries. Health Informatics applications aim at implementing information systems and methods in healthcare organizations in order to provide solutions for problems related to information and knowledge processing and lead to the improvement of the administration of healthcare organizations and the quality of healthcare [1]. Furthermore, Health Informatics applications can help to overcome the conventional procedures of disease prevention, diagnosis and treatment, since the use of telemedicine can provide reliable health services even in the most remote places. Advanced tools, such as the electronic patient record, data accessibility from different places and the e-health card can radically change the scene by providing effective health services [2]. For these reasons, the need for continuous education and training of healthcare professionals in Information and Communications Technology (ICT) is indisputable so that they can acquire the appropriate knowledge and practical skills for the effective integration of Information Technology (IT) in the healthcare sector [3, 4, 5].

Many academic programs in health informatics are currently being offered worldwide, either at an undergraduate or postgraduate level. In addition, many health departments have included IT subjects in their curricula in order to provide their graduates with IT knowledge [3]. However, the term "health informatics professional" [6] has not yet been defined clearly. It may refer either to health information technology users or medical

informatics specialists [5, 6]. For this reason and, as there is a great variety of educational programs all over the world, the establishment of a common educational framework in the field of health/medical informatics is widely acknowledged. Therefore, the International Medical Informatics Association (IMIA) has submitted international educational proposals, which should be adopted by universities and educational organizations [7, 8, 9], determining whether their graduates are IT users or specialists.

Furthermore, in the US, certification in nursing informatics has been available for more than ten years, since the American Nurses Association adopted the Scope and Standards for Nursing Informatics Practice, which defines the IT competencies and knowledge that nurses should have in order to efficiently integrate information technology in their practice. These competencies comprise three different levels of knowledge/skills as follows:

i) basic computer literacy skills such as word processing, spreadsheets, databases etc;

ii) information literacy skills such as search and retrieval of information from the internet etc; and

iii) overall informatics knowledge such as privacy, confidentiality and security of information in nursing practice, interpretation of patients' information, informatics applications in nursing etc [10].

There are many surveys worldwide for recording informatics and health informatics subjects in health departments of higher education [11, 12, 13]. In Germany, for example, there have been obligatory medical informatics subjects for medical students since 1970 [13]. In the US, a survey in 266 nursing programs revealed that more than forty percent (40%) of the undergraduate programs and approximately one third (1/3) of the postgraduate programs include subjects covering IT topics, such as computer-based patient record, the ethical use of information systems, informatics nurse competencies, information systems in nursing practice, education, management, research and etc [14].

Such a survey in Greece has not been conducted so far. Therefore, the main purpose of this work is to record Informatics and Health Informatics subjects in health sciences departments of higher education in Greece. In addition, there is an attempt to investigate the educational trends of these departments according to their objectives, their content and curricula, through a categorisation based on certain rules identified by the American Medical Informatics Association (AMIA), regarding the basic level of IT knowledge of health professionals [15].

At this point, it is useful to point out that in Greece higher education comprises two different types of institutes: Universities and TEI (Technological Educational Institutes). Both of them provide bachelor degrees and include separate academic departments. Some of these departments, for administrative reasons, are grouped in academic units, though others, for practical or historical reasons, are not part of any unit. Therefore, we may have "school of medicine" and "department/faculty of medicine", which, however, lead to the same bachelor degree of medicine.

2 International – European Status

The European Union considers that Medical Informatics (the term is often used synonymously with the term Health Informatics) [16] may promote and evolve health care delivery and also may enable the provision of quality health services even in the most remote places of the world [16, 17]. Telemedicine services, electronic patient records and medical interconnected networks could help towards this direction.

Indicatively, we report that in England undergraduate and postgraduate programs in Health Informatics focus on providing e-health services. For example, at the City University of London, the postgraduate program of Health Informatics offers knowledge and skills that aim at:

i) how ICT can be used to enhance the organization and the delivery of efficient health services; and

ii) the acquisition of skills for the integration and usage of ICT in order to encounter complex problems and enhance the delivery of effective healthcare services [18].

In Austria, Medical Informatics studies focus on the quality of information, on the structure of medical information and on the planning and support of medical systems [19].

In Germany, innovative Medical Informatics courses, at an undergraduate and postgraduate level, aim at generating skilled personnel with:

i) knowledge that combines IT with the individuality of the medical sector; and

ii) knowledge that covers various topics, such as medical records, medical image processing, medical simulation, bioinformatics and standards of medical data transmission [8].

In Ireland, the M.Sc. program in Medical Informatics aims at providing special knowledge so that the students can acquire an integrated picture of the role of ICT in health and understand the principles of Health Informatics. Additional objectives are:

i) the study and application of Health Informatics with emphasis on theory and practice; and

ii) the assessment of medical legal and ethical issues and the necessary support on the methodology of research [20].

AMIA, in order to contribute to the achievement of the "Goals of Informatics Education for Health Professionals" specified in AMIA's spring conference in 1999 [15], established in 2005 the 10×10 Informatics Education Program with the ultimate goal of providing education and training for 10,000 healthcare professionals in applied

Table 1: The main findings concerning Information Technology subjects by level of study.

Level of Study	Number of departments and percentages	Number of IT subjects and percentages	Mean	Minimum number of IT subjects	Maximum number of IT subjects
Undergraduate	51 (58.6%)	113 (48.3%)	2.22	1	12
Postgraduate	36 (41.4%)	121 (51.7%)	3.36	1	20
Total	87 (100%)	234 (100%)	2.69	1	20

health and medical informatics across the United States within 10 years. Many academic institutions participate in the program and provide basic health informatics skills but, also, specialized knowledge in areas such as electronic health records, health information exchange, standards and terminology and error prevention [21]. Claremont Graduate University and Oregon Health Science University conducted, in 2007, a research aiming the assessment of the AMIA's 10×10 program. The participants where graduates of the program and the results indentified that the 10×10 program meets the AMIA's goals and participant's needs and expectations to a satisfactory degree and that there can be improvement modifications in the area of course content and course delivery [22].

Undergraduate and postgraduate programs in Medical Informatics are also held by other universities in Europe and the world. Their ultimate goal is to have specialized scientists, whose IT knowledge will help to provide efficient, effective and high quality healthcare services [23].

3 Methodology - The Categorization of Informatics and Health Informatics subjects of Health Sciences Departments

We accomplished the recording of informatics and health informatics subjects of the departments of health sciences from their curricula available on their official Web sites [24]. We, afterwards, classified these subjects in certain IT categories through their outlines, the detailed description of their contents and the teaching goals of each department, as specified in their curricula. The categories were set forth and the subjects included were classified based on the 'Goals of Informatics Education for Health Professionals' identified by the AMIA spring conference in 1999 [15], regarding the required core informatics knowledge, dexterities and skills for health care professionals. In detail, the IT categories set forth are the following:

- **Introductory Concepts:** This category includes the basic concepts and definitions of Informatics and Health Informatics, history, operating systems, hardware structure of computers, office automation, networking concepts, terminology of Health Informatics and the presentation of the most widespread applications of Information technology in health care organizations etc.

- **Applications on Health:** It includes the subjects that focus on the development, function and evaluation of computer applications at all levels of healthcare, such as hospital information systems, electronic patient record, databases, telemedicine and bioinformatics applications, processing of biomedical signals-images etc.

- **Software:** The subjects of this category cover concepts that include the principles of programming, application design and development using programming languages, problem solving using computers etc. The most common programming languages taught are C, C + +, Perl, Basic, Prolog, Visual Basic.net, Java etc.

- **Technology:** It includes subjects that focus on the management and operation of medical equipment, evaluation of medical devices, definitions of technology, nanotechnology, biomedical electronics, measuring instruments etc.

- **Hardware:** This category includes subjects whose basic aim is the understanding of the maintenance principles of medical devices and instrumentation, the limits and safety regulations of the laboratory equipment etc.

Following the determination of the above IT categories, all the undergraduate and postgraduate programs of Health Sciences were classified. This classification revealed that a department's curriculum might simultaneously pertain to more than one of the above categories since it might contain subjects that cover several topics of informatics, i.e. the basic concepts and definitions of informatics, the development, function and evaluation of computer applications and the evaluation of medical devices.

When the integration of the curricula in the above categories was completed, we carefully codified the resulting classification following all the rules of conceptual consistency [25] and afterwards we proceeded to data processing and analysis with the statistical processing program Predictive Analytics Software (PASW), former Statistical Package for the Social Sciences (SPSS).

Table 2: IT subjects by IT category in health science departments of higher education in Greece.

IT Categories	Number of IT subjects	Percentage %
Introductory concepts	24	10.3%
Applications on Health	20	8.5%
Technology	4	1.7%
Introductory concepts and Applications on Health	66	28.2%
Introductory concepts and Technology	8	3.4%
Introductory concepts and Applications on Health and Technology	16	6.8%
Introductory concepts and Applications on Health and Technology and Software	22	9.4%
Applications on Health and Technology	3	1.3%
Introductory concepts and Applications on Health and Software	14	6.0%
Applications on Health and Technology and Hardware	10	4.3%
Applications on Health and Technology and Software	5	2.1%
Introductory concepts and Applications on Health and Software and Hardware	12	5.1%
Introductory concepts and Applications on Health and technology and Software and Hardware	10	4.3%
Applications on Health and Technology and Software and Hardware	20	8.5%
Total	234	100.0%

4 Results - Key Findings

4.1 Information Technology Subjects by Level of Study

A list of all the health sciences departments of Universities and TEIs of the country was obtained from the site of the Ministry of Education, Lifelong Learning and Religious Affairs [24]. According to their curricula, almost sixty percent (58.6%) of the departments contain IT subjects at undergraduate level and about forty percent (41.4%) have IT subjects at postgraduate level.

The total number of IT subjects at undergraduate and postgraduate level is 234. On average, we recorded 2.69 subjects by department. The maximum number of IT subjects in a department's curriculum is twenty (20), while the minimum number is one (1), which is also the mode. In undergraduate studies, the average number of subjects on informatics is 2.22 and the total number is 113 subjects. Postgraduate studies present a better picture since these numbers are 3.36 and 121 respectively. All the findings described above are presented in detail in Table 1.

4.2 Total Picture of IT subjects by Category

The curricula of health sciences departments of Greek Universities and Technological Educational Institutes mainly focus on the teaching of introductory concepts of informatics and applications on health since we recorded 66 subjects (28.2%) that cover the above IT categories. We additionally recorded 24 subjects (10.3%) that cover just the category of introductory concepts of informatics and 9.4% of the total subjects (22 out of 234 subjects) that combine introductory concepts of informatics, applications on health, technology and software. We furthermore identified that the curricula of health departments of higher education in Greece focus on applications on health (20 subjects, 8.5%), the combination of applications on health, technology, software and hardware (20 subjects, 8.5%), and the combination of introductory concepts, applications on health and technology (16 subjects, 6.8%). The curricula of health sciences departments cover other categories too but with lower percentages. All these findings are presented in Table 2.

4.3 Information Technology Subjects by Level of Study and IT Categories

The recording of the subjects by level of study revealed that at undergraduate level, teaching is mainly focused on introductory concepts of informatics (19 out of 113 IT subjects of that educational level, 16.8%) and the combination of introductory concepts of informatics and applications on health (38 IT subjects, 33.6%). It is worth mentioning that at the same level teaching also covers the combination of introductory concepts, applications on health and technology (16 IT subjects, 14.2%) and other categories too but with much lower percentages (see Table 3). Indicatively we report: introductory concepts, applications on health and software and hardware (10.6%), introductory concepts, applications on health, technology, software and hardware (8.8%) etc.

At postgraduate level, the picture is slightly different since approximately twenty three percent (23.1%, 28 out of 121 IT subjects of that educational level) focus on introductory concepts and applications on health and more than sixteen percent of the subjects (16.5%, 20 IT subjects) focus on the combination of applications on health, technology, software and hardware. We also recorded 17 IT subjects (14.0%) focusing only on applications on health and approximately twelve percent (11.6%) of the total IT subjects covering the combination of introductory concepts, applications on health and software. Of course, at postgraduate level teaching covers other IT categories too, but with lower percentages. These percentages and all the above results are presented in detail in Table 3.

Table 3: IT subjects by level of study and categories.

IT Categories	Undergraduate Level		Postgraduate Level	
	Number of IT subjects	Percent %	Number of IT subjects	Percent %
Applications on Health and Technology and Software and Hardware	0	(0.0%)	20	(16.5%)
Introductory concepts and Applications on Health and Technology and Software and Hardware	10	(8.8%)	0	(0.0%)
Introductory concepts and Applications on Health and Software and Hardware	12	(10.6%)	0	(0.0%)
Applications on Health and Technology and Software	0	(0.0%)	5	(4.1%)
Applications on Health and Technology and Hardware	0	(0.0%)	10	(8.3%)
Introductory concepts and Applications on Health and Software	0	(0.0%)	14	(11.6%)
Applications on Health and Technology	0	(0.0%)	3	(2.5%)
Introductory concepts and Applications on Health and Technology and Software	9	(8.0%)	13	(10.7%)
Introductory concepts and Applications on Health and Technology	16	(14.2%)	0	(0.0%)
Introductory concepts and Technology	6	(5.3%)	2	(1.7%)
Introductory concepts and Applications on Health	38	(33.6%)	28	(23.1%)
Technology	0	(0.0%)	4	(3.3%)
Applications on Health	3	(2.7%)	17	(14.0%)
Introductory concepts	19	(16.8%)	5	(4.1%)
Total	113	(100%)	121	(100%)

4.4 IT Subjects by IT Category and Department(s)

The study of the curricula by department showed no major differentiations from the findings that we have already presented. Indicatively, we report that the curricula of the Greek Nursing departments mainly cover material related to introductory concepts and applications on health (33 out of 61 IT subjects, 54.1%) or material related to introductory concepts, applications on health and software (14 out of 61 IT subjects, 23.0%). We also point out that the curricula of the departments of Medicine mainly cover material that combine introductory concepts of informatics, applications on health, technology and software (13 out of 63 IT subjects, 20.6%), material that combine introductory concepts, applications on health and technology (11 out of 63 IT subjects, 17.5%) and material related to applications on health, technology and hardware (10 out of 63 IT subjects, 15.9%). The above results together with the findings for the rest of the departments are presented in Figure 1.

5 Discussion – Conclusions

The need for health professionals with the necessary dexterities, essential skills and appropriate knowledge, which render them specialized in the field of Information Technology, is widely accepted not only in Greece but also worldwide [19, 23].

This need has led higher education to continuously incorporate more Health Informatics subjects into the curricula of health sciences departments.

This study focused on the recording of Informatics and Health Informatics subjects in health sciences departments of higher education in Greece. It is the first time that such a survey has been conducted in Greece and it also attempted to investigate the educational trends of these departments according to their curricula, through a categorisation based on certain rules that have been identified by the American Medical Informatics Association (AMIA), regarding the basic level of IT knowledge of health professionals [15].

The recording of Informatics and Health Informatics subjects is accomplished through the departments' curricula that are available on their official Web sites. These subjects were classified in certain IT categories according their outlines, contents and the teaching goals of each department. Five IT categories were determined:

i) Introductory concepts,

ii) Applications on health,

iii) Software,

iv) Technology and

v) Hardware.

The formation of those categories was based on the Goals of Informatics Education for Health Professionals' that have been identified by the AMIA spring conference in 1999 [15], regarding the required core informatics knowledge for health care professionals. Afterwards, all the undergraduate and postgraduate programs of Health Sciences were classified in those categories. A department's curriculum could simultaneously pertain to more than one of those categories since it might contain subjects that cover several topics of informatics. When the integration of the curricula in the categories was completed, the resulting classification was carefully codified following all the rules of conceptual consistency [25] and after that we proceeded to data processing and analysis.

This analysis revealed that in Greece, at undergraduate level, the curricula of health sciences departments of

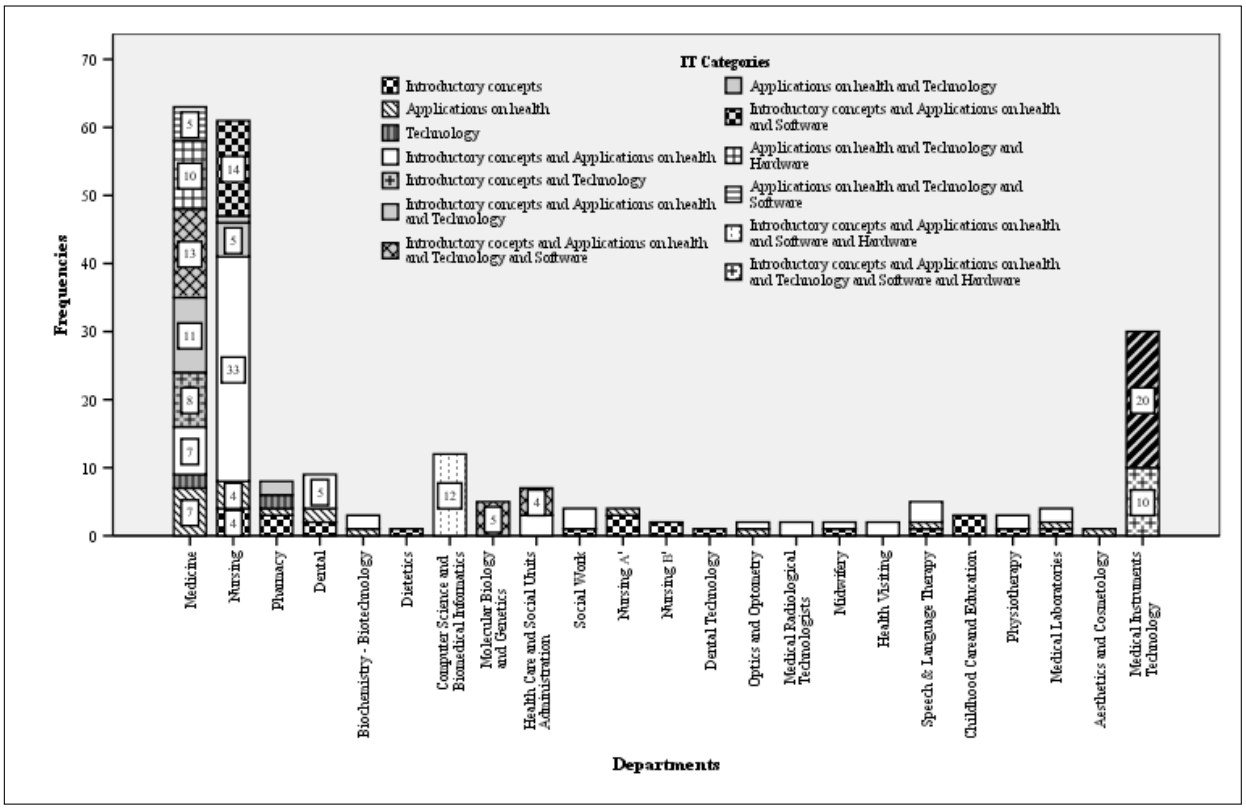

Figure 1: Number of IT subjects (frequencies) by IT category and departments. All the frequencies not shown in the chart are less or equal to three (<=3).

higher education mainly focus on introductory concepts of informatics and health informatics, as well as on the presentation and familiarization with computer applications in the health sector. This finding is consistent with the findings of other similar surveys, which, despite the well-documented importance of including informatics knowledge and skills within the curricula of health educational programs [14], have revealed equivalent results. In the U.S., for example, a survey showed that undergraduate educational programs for nursing emphasize mostly computer literacy skills rather than information literacy skills [14] and in Croatia, educational programs for health professionals mostly focus on the teaching of the basic IT knowledge in order to enable health professionals to manage health information properly [11].

At postgraduate level our study showed that the picture is slightly different since apart from introductory concepts of informatics and computer applications on health, the curricula of health sciences departments also includes subjects that focus on technology, software and hardware. In the U.S., a similar survey in nursing postgraduate educational programs revealed that the greatest percentage of nursing programs rated faculty at the "advanced beginner level" in teaching nursing informatics applications [14], which approximates our results. In a previous chapter we mentioned more postgraduate educational programs in universities in Europe and throughout the world that according to their curricula seem to focus on advanced topics of health and medical informatics (postgraduate programs in England, postgraduate programs in Germany etc.). However, no national surveys in these countries defining the level of informatics knowledge and competences provided by these programs have been conducted recently.

The fact that in Greece, more than one academic institute may cooperate in offering a postgraduate program, may have played an important role in creating this situation, since, as the scientific background of the students varies, the provision of specialized knowledge becomes extremely difficult. Information literacy skills that students have acquired in secondary education may have also played a significant role. First-year students should already have acquired basic informatics knowledge in secondary education, so that TEI and University educational programs could expand this knowledge in more advanced IT subjects. Specific validating tools and strategies for this informatics knowledge should be formed not only for entering the undergraduate programs but also for the postgraduate ones.

Based on the above observations we could point out that despite the growing need for highly specialized professionals in health information technologies, the departments of health sciences of higher education institutes in Greece, mainly, prepare their students to be IT users rather than Health and Medical Informatics specialists. These two categories are defined into the IMIA's Recom-

mendations on Education in Health and Medical Informatics, regarding the level of informatics knowledge and practical skills acquired by health educational programs of higher education [7]. Few are the departments of health sciences of higher education in Greece that constitute an exception to this observation and provide advanced knowledge and skills in the field of health informatics. This outcome may have an impact on the smooth function of health care organizations, due to the lack of professionals specialized in information technologies and in modern information systems management. It also reveals the imperative need for undergraduate and postgraduate programs of health departments in Greece to adjust their curricula to the current educational requirements in order to provide their graduates with the necessary knowledge in health information technologies and train them on the development, implementation and evaluation of health IT systems according to the recommendations of IMIA [7]. We highlight that in order to obtain a well-documented and complete picture of the level of informatics knowledge provided by health educational programs of higher education in Greece we intend to perform a study, through which, we will thoroughly determine the compliance of these programs with the international educational recommendations proposed by IMIA [7]. This way, we will have acquired a detailed picture of the situation in Greece, as we will have made all the appropriate comparisons not only according to AMIA categorization but also according to IMIA recommendations.

In addition, as a future work, we also intend to conduct a survey in order to record the integration of information technology subjects in secondary education in Greece. Our purpose is to determine the level of information literacy that students have acquired before entering the TEI and Universities and thus to find out the reasons why health sciences departments of higher education in Greece keep providing the basic IT knowledge that should have been provided in secondary education.

To conclude, we report that the rapid development of ICT, as well as their implementations and influence in the health care sector, have imposed continuous specialized education and training of health professionals in information technology subjects, in both theoretical and practical issues [26]. These issues may cover subjects such as smart cards, telematics, telemedicine, medical image processing, health management information systems, security of health information systems etc. The basic aim of the institution authorities should be the constant adjustment and enrichment of the curriculum of health sciences departments, in order to create capable and skilful professionals that could fully utilize the advantages of new technologies, having as an ultimate goal the promotion of health care [27].

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Determination of Guidelines Complience: Comparison of Clinical Guidelines with the Patient's Record

Arnošt Veselý[1,2], **Jana Zvárová**[2]

[1] Department of Information Engineering, Czech University of Life Sciences, Prague, Czech Republic

[2] Department of Medical Informatics, Institute of Computer Science AS CR, Prague, Czech Republic

Summary

Many clinical guidelines were elaborated to improve quality of medical care and to achieve standardization of patient's treatment. Originally clinical guidelines are written in everyday language and then they are converted into formal model that can be implemented and processed by computer. If all relevant patient's treatment data are stored in patient's Electronic Health Record, the guidelines formal model may be, in principle, compared with patient's data to determine, if the patient was treated according to the recommended clinical practice. In this article we present an algorithm that enables to compare patient's data record with EGLIF (Enhanced GLIF) model. EGLIF is a simple enhancement of the standard GLIF model and it was devised to render the comparison more transparent and more convenient. Comparing algorithm is proposed for GLIF models with unambiguous decision steps and for patient's data records containing all relevant patient's treatment information. Its modification for arbitrary decision steps can be easily done. However, comparing GLIF or EGLIF model with incomplete patient's data record is more difficult issue. Some suggestions how to tackle this problem are discussed in the conclusion.

Keywords

Clinical guidelines, GLIF model, Electronic Health Record, Reminder facility, Execution engine algorithm

Correspondence to:

Arnošt Veselý
Department of Information Engineering
Czech University of Life Sciences
Address: Kamýcká 129, Prague 6, Czech Republic
E–mail: vesely@pef.czu.cz

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1 Introduction

Clinical guidelines (CG) contain a set of care decisions to assist the physician with patient care decisions about appropriate diagnostic, therapeutic, or other clinical procedures. They are intended to ensure high quality clinical practice [1]. CG are developed as textual recommendations by groups of medical experts on topics selected by a local scientific authority, e.g. expert medical society or by a national health institution. Usually their text focuses on the specific group of physicians or health professionals. Several international organizations create and maintain web repositories with guidelines in different domains [2, 3]. In the Czech Republic the Catalog of Clinical Guidelines as the web repository was created [4, 5].

The development of clinical guidelines is a quite expensive process. First, paper-based guidelines have to be developed. Second, the paper-based guidelines have to be translated into computer based guidelines representation language. This process is described in general in [6, 7, 8, 9] and [10, 11].

More groups have translated paper-based guidelines into computer readable format. Good literature overview of used methods and achieved results can be found in [12]. Here we mention only some of them. The paper [13] describes successfully implemented two cardiovascular guidelines and hypercholesterolemia guidelines into computer system. Guidelines were represented in GLIF format and connected with the Electronic Health Record. GLIF is a tool that was developed specially for formalization of medical guidelines. Alternatively, notions and tools developed in the field of business process modeling also proved to be useful. The paper [14] compared guidelines development with business process modeling and described some of their strengths and weaknesses. Medical guidelines need to be developed by experts from different fields. The papers [15] and [16] designed parallel guidelines development strategy, in which a multidisciplinary

group cooperated in creating both textual and computer-interpretable guidelines. This strategy of parallel guidelines development and formalization appeared to be successful. Parallel development gave the opportunity to eliminate vague concepts or errors already in the early stage of their development.

Overviews of computer-interpretable formalisms and modeling approaches were presented in [1, 17] and [18].

Arezzo for representing guidelines uses PROforma language [19, 20]. Arezzo tool consists of three parts: Composer, Tester and Performer. The Performer inference engine runs the guidelines taking into account the patient data stored in the health care database.

DeGel (Digital Electronic Guidelines Library) is a web based modular and distributed architecture, which facilitate conversion of a text form of guidelines into Asbru representation language [21].

GLARE (Guidelines Acquisition, Representation and Execution) has graph-based representation [22, 23]. The graph nodes represent atomic actions of four kinds: queries that allow to input information into the system, work actions that represent actions to be carry out, decision actions that represent selection among alternative actions according to the set of conditions and conclusions that allow to describe outputs of decisions.

NewGuide framework for modeling clinical guidelines [24, 25] uses a representing language GUIDE, which is based on Petri nets [26]. It allows to model concurrent processes and temporal data.

SAGE (Standards-based Sharable Active Guidelines Enviroment) was created in collaboration among several research groups in the United States [27]. The main goal was to encode guidelines using some standard representation to facilitate its deployment in different clinical information systems. Guidelines representation is based on a set of Protégé classes and plug-ins. Medical care plans are specified by activity graphs that consist of context nodes that specify clinical setting and relevant patient's attributes, decision nodes, action nodes and routing nodes that are used for branching and synchronization.

HeCaSe2 (Health Care Services release 2) is an agent-based platform [28]. There is not any central control. Agents act independently using their own knowledge and data and perform different tasks. Guidelines Agent performs all actions related to the clinical guidelines. Clinical guidelines are represented using the PROforma representation language [20]. Medical terms use UMLS terminology and they are stored in ontology.

In this article we are using Guidelines Interchange Format (GLIF). GLIF is a result of collaboration among different institutions and universities in the United States. The description of its version 2.0 (GLIF2) may be found in [29] and description of the newer version 3.0 (GLIF3) in [30]. Guidelines Execution Engine (GLEE) that is a tool for execution of guidelines encoded in GLIF3 format is described in [31].

GLIF specifies a process-oriented model for guidelines representation. It can be represented in a form of oriented graph. The nodes of the graph are guidelines steps and edges represent continuation from one step to the other one. Guidelines steps are of a different kind. Guidelines step might be: action step, decision step, branch step, synchronization step and patient state step.

Action steps specify clinical actions that are to be carried out. It can be an application of some therapy, carrying out some examination or measurement etc. Action step may also name sub-guidelines that provide greater detail for the action.

Decision steps are used for conditional branching. A decision step specifies criteria for each possible alternative decision.

Branch and Synchronization steps enable parallelism in the model. The guidelines steps that follow the branch step and that are on different branches can be carried out concurrently or in an arbitrary sequence. The branches with root in the branch step eventually converge in the synchronization step, where they are synchronized. It means that the actions that follow the synchronization step could not be carried out unless the synchronization condition is fulfilled. A simple synchronization condition, for example, might require that all actions specified on the branches between the branch step and the synchronization step must have been carried out.

Patient state step names the current state of the patient.

There is a lot of benefits that clinical guidelines may provide. The most evident and the most important are the following.

1. CG can improve the quality of clinical decisions, since CG help physicians to use the clinical knowledge in the appropriate patient clinical state.
2. CG can be effectively used in teaching, since they support rapid dissemination of updates and changes.
3. Health care professionals can use CG for comparing health care standards in different institutions.
4. If all relevant information is stored in patient's Electronic Health Record (EHR), then it is possible to check if the applied treatment procedure complies with recommended treatment standards.

In our paper we focus on acquiring the benefit mentioned in the item 4 above. The first ideas how to compare patient's data and formalized guidelines we examined in [32, 33, 34] and [35]. Here we continue further and we propose algorithm, which is capable of doing it. We assume that all relevant information about the patient's treatment is stored in the patient's Electronic Health Record (EHR). Our task is to contrive a method how to compare patient's data in EHR with medical treatment standards described in clinical guidelines and check if the data in EHR are in compliance with them.

The comparison may be ex post or on-line. In the case of ex post comparison we have at our disposal patient's record from a long time period and we would like to know ex post if the patient was treated according to the

appropriate standard described in CG. On line comparison means that patient's data record is compared with the standard each time when it is updated with a new data item. An on-line remainder system, which warns the physician if his/her action does not comply with the treatment standard, might be based on such on-line comparison.

The algorithm we are proposing in this paper assumes that the following two conditions are fulfilled.

1. The EHR record comprises all relevant information, i.e. all physician actions during patient's treatment are recorded.

2. Each guidelines contain decision points, in which the decision how to continue must be taken. According to the patient's state, which is determined by the values of already examined parameters, some alternatives are recommended and some are not. We assume that recommendation is unequivocal. It means that according to CG in each decision point one and only one alternative must be chosen. Such guidelines we call strict. The designed comparison algorithm generates error message if a physician does not follow the uniquely determined way. Non- strict guidelines usually in a decision point recommend more than one alternative. Comparing algorithm may be adapted to fit this case as well. How to do it we discuss in the conclusion.

In patient's treatment important recommendations concerning the time intervals between two actions or between some action and its repetition are often given. For example some examination must be repeated at least or at most after 1 week, 2 months etc. In GLIF model a condition that interval between two consecutive actions must fulfill can be represented using decision node. However, it is more illustrative and for formulation of our comparing algorithm more convenient, to represent these time conditions with a new type node called Time node.

The paper has the following structure. In the paragraph 2 the principles underlying the comparison of patient's data record and guidelines model are briefly sketched and a rough description of comparing algorithm is given. Then there follows the definition of enhanced GLIF model (EGLIF). The enhancement was necessary so that the comparing algorithm could have been established. In paragraph 3 the comparing algorithm is defined and its behavior is demonstrated on several simple examples. In the conclusion paragraph the possible generalization of the algorithm for non-strict guidelines models and for incomplete patient's data records is discussed.

2 Methods

The objective of this paper is to present an algorithm, which could be used for comparing patient's clinical data with formalized guidelines that prescribe the way the patient should be treated. We suppose that during patient's visits physician examines state of patient's health and prescribes therapies. During examination physician is looking for symptoms or carries out examinations of physiological quantities. We assume that each examination results in determination of a value of some patient's physiological parameter or symptom P in a certain time. The result we will write in the form

$$P(time) = value.$$

For example parameter SBP (systolic blood pressure) has been measured at time t and its value has been 145. Then the result is written as $SBP(t) = 145$. We suppose that also application of some therapy may be written in this way. Then P denotes the used therapy and with $value = 1$ we denote the fact that the therapy was applied. For example $Diet(t) = 1$ means that the therapy $Diet$ at time t has been prescribed. Moreover, by means of the parameter $value$ the further specification of the therapy might be given. For example $Penicilin(t) = Daily - 2mg$ might mean that at time t the $Penicilin$ has been prescribed and that the prescribed dose has been 2mg daily.

We assume that patient's clinical data are stored into patient's EHR. We do not stipulate how the data format of the health record ought to look like, but we assume that this record can be converted into the following sequence of performed examinations and therapy prescriptions (further called data sequence)

$$\mathbf{S} = \{P_1(t_1) = c_1, \ldots, P_n(t_n) = c_n\}, t_1 < \ldots < t_n,$$

where $P_i(t_i)$ denotes the value of the parameter P_i at time point t_i. To simplify notation we suppose that time scale consists of days and that time is written in the date format $day.month.year$, e.g $t = 1.1.02$ or $SBP(1.1.01) = 150$ etc. Of course, in real applications the time scale will be more detailed. For example, time t might be system time.

Table 1: The guidelines data model of the small guidelines from Example 1.

action	**parameter** P	**value type**
Measurement of systolic blood pressure	SBP	numeric
Measurement of diastolic blood pressure	DBP	numeric
High density cholesterol test	HDL	numeric
Low density cholesterol test	LDL	numeric
Prescription of diet regime	$Diet$	Boolean
Medication prescription	$Medication$	Boolean

All physiological parameters and therapies occurring in the clinical guidelines must be specified. It could be done using guidelines data model. The guidelines data model should contain the list of all possible examinations and therapies together with the description of their possible values. Typical parameter value types will be Boolean,

nominal and numerical. Example of a very simple guidelines data model that will be used in further examples is given in the Table 1.

As the formalized guidelines will be compared with data from the patient's health record an existing data model of health record data is assumed. That model must comprise the set of all parameters $\mathbf{P}_G$ occurring in the formalized guidelines model.

To be able to compare the patient's health record with the guidelines, the guidelines must be formalized and coded into computer readable format. For this purpose we use enhanced GLIF model (EGLIF model). As we have already said, we assume that patient's health record can be converted into data sequence **S** described above. The comparison is carried out with comparative algorithm CA specially designed for this purpose (see Fig. 1). The CA algorithm consequently deletes data items from the sequence **S** generated by the EHR system and compares them with the coded EGLIF model. If some data item is not in compliance with the EGLIF model, the CA algorithm warns the user. The EGLIF and CA algorithm are described in detail further. Here we give only their rough description.

EGLIF model is an oriented graph with nodes of different type. To the nodes there are assigned parameters and conditions. The node parameters have nothing in common with patient's parameters mentioned above. The most important node parameters are the parameter *next* that defines EGLIF graph structure and the parameter *token* that enables to follow passing through the model. Some types of nodes have parameters for storing tokens. We say that these nodes are able to store or to catch tokens. When the comparison starts only one token placed in the node $START$ exists in the EGLIF model. During comparison tokens are moving along graph branches among nodes that can store them. The CA algorithm subsequently deletes items $P(t) = c$ from data sequence **S** and compares them with those action steps in EGLIF model that have tokens. Each action node has three main parameters $action, result$ and $time$. The parameter $action$ determines the prescribed action. Its value is compared with P of the current data item. If they are identical, the result c of the current action $P(t)$ is written into the node parameter $result$ and its time t is written into the node parameter $time$. Then the node's token is handed over to the node, which is the nearest node on the same graph branch and can store it. The token passing through a branch node BRN is multiplied. If the branch node has n outgoing branches, then n tokens stem from the passing through token. Newly created tokens continue along different branches. In the synchronization node $SYNC$ with n inputs the incoming tokens are stored in the n token parameters $token_1, \ldots, token_n$. As soon as the synchronization condition of a $SYNC$ node is satisfied, one token comes out of the synchronization node and at the same time all tokens residing in the same $BRN - SYN$ subgraph are removed. The comparative algorithm (CA) is described more rigorously in the §3. To be able to formulate this algorithm we must at first give detailed description of the enhanced GLIF model.

2.1 Description of the Enhanced GLIF Model (EGLIF Model)

The EGLIF model is an oriented graph with nodes of types $A, D, BRN, SYN, TIM, START, STOP, GLF, ERROR$. Nodes of the same type are distinguished using indexes, e.g. A_1, A_2, etc. To each node one or more parameters or conditions are assigned. The parameter *par* or the condition *cond* of the node N will be denoted $N(par)$ or $N(cond)$ respectively, e.g. $A_1(result)$ or $TIM_2(\beta)$. The parameter *next* contains the pointer to the following node and the parameter *token* stores tokens ($token = 1$ indicates that the node contains token and $token = 0$ indicates that it does not).

The EGLIF node types are the following.

Action node $A(token, action, result, time, ref, next)$

Action node represents an action. The kind of the action is specified with parameter *action*. The result of the action is written into parameter *result* and the time when the action has been carried out is written into parameter *time*. Parameter ref contains a pointer to some time node or it contains the null pointer NULL. If ref value is not NULL, then parameter ref points to the time node, whose condition β must be checked.

Decision node $D((\alpha_1, next_1), \ldots, (\alpha_n, next_n))$

Decision node represents the decision that should be done on the base of evaluation of conditions $\alpha_1, \ldots, \alpha_n$, defined for the alternative branches. We assume that conditions are so called strict-in conditions. It means that if α_i condition is fulfilled, then the i-th branch must be chosen. Moreover, we assume that one and only one condition is fulfilled, i.e. we assume that for each decision node the following expressions hold

$$\alpha_1 \vee \ldots \vee \alpha_n = \mathbf{t}(\text{true}),$$

$$\alpha_i \wedge \alpha_j = \mathbf{f}(\text{false}), \text{ for all } i, j = 1, \ldots n \text{ and } i \neq j.$$

Conditions $\alpha_1, \ldots, \alpha_n$ are made up of parameters of action steps by means of basic relational and logical operators. For example an condition might be

$$(A_1(result) > 10) \wedge (A_2(result) < 100).$$

Branch node $BRN(next_1, \ldots, next_n)$

Branch node introduces parallelism into the model. From branch node one may continue taking any branch. Branches can be followed simultaneously, however, sequence of steps on each branch must be retained.

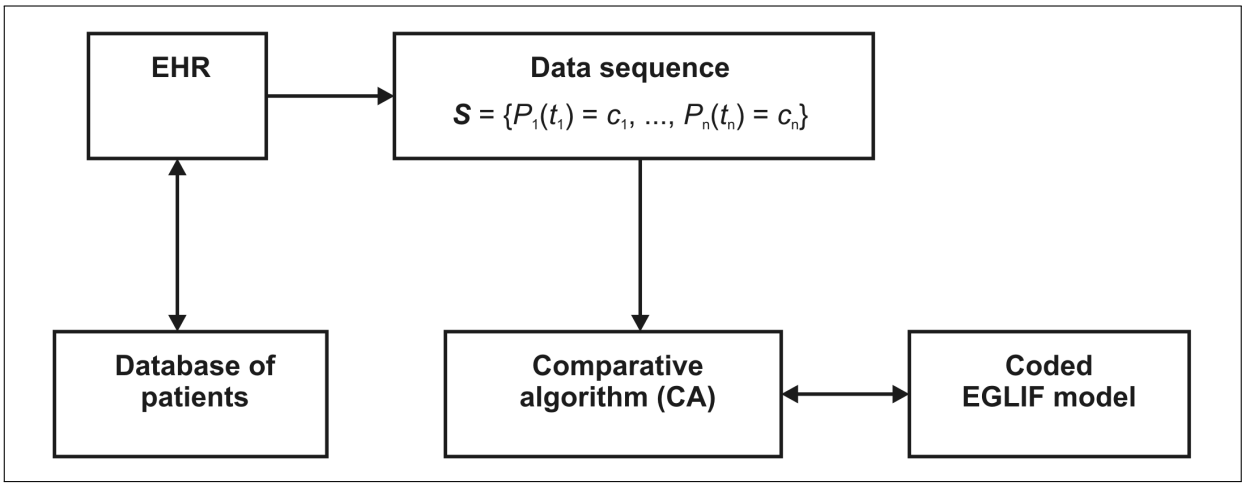

Figure 1: Comparing patient's health record with coded guidelines.

Synchronization node $SYN(token_1, \ldots, token_n, \alpha, \beta, time, next)$

Synchronization node connects and synchronizes branches. If the synchronization node SYN connects n branches, it has n inputs represented with n pointers $SYN(1), \ldots, SYN(n)$.

If a token comes from the i-th branch, then it is stored into the i-th token parameter $token_i$. One can pass through the synchronization node only if the condition α is satisfied. Condition α is a propositional formula made up of the parameters $token_1, \ldots, token_n$. For example,

$$\alpha = (token_1 \wedge token_2) \vee token_3.$$

Whenever a token is stored into the node, the time t taken from the last deleted data item $P(t) = c$ is written into the node parameter $time$. Condition β is the time condition that must be fulfilled for the time parameter value of all actions that take place in the subgraph $BRN - SYN$. In the definition of the β there occurs key word $atime$, whose meaning is obvious from the following example.

Assume the following condition

$$\beta = ((atime - A(time) \leq year).$$

This condition posits that if some node B is contained in the subgraph $BRN - SYN$ and $A(time)$ is the time parameter of a node A, then the condition $(B(time) - A(time)) \leq year$ must hold.

State node $STATE(name, next)$ denotes the patient's current state with string $name$.

Time node $TIM(time, \beta, next)$

Time node sets time limits of the next action. When a token passes a time node TIM, the current time is written down into the parameter $TIM(time)$. Condition β is a time condition that must be valid for the time parameter of the following action. In the definition of the condition β the time parameter of the following action is denoted $ftime$.

For example

$$\beta = ((ftime - TIM(time)) \leq year).$$

Start node represents the starting point

$$START(token, next).$$

Stop node represents the end

$$STOP(token).$$

Error node represents stop after error

$$ERROR(token, text).$$

Call node represents jump into another EGLIF model

$$GLF(name, next).$$

Definition of EGLIF model

EGLIF model is a set of above described nodes that by means of pointers (stored in their parameters $next$) constitute connected oriented graph, if the following conditions $C_1 - C_4$ are satisfied.

- C_1 The set contains just one $START$ node.
- C_2 For each BRN node there exists one SYN node, in which all branches starting in BRN node end. A subgraph of EGLIF model that starts with node BRN and ends with node SYN is called $BRN - SYN$ subgraph of EGLIF model.
- C_3 If G_1 and G_2 are two $BRN - SYN$ subgraphs, than only one of the following assertions can hold:

a) $G_1 \subset G_2$ (i.e. every G_1 node is also G_2 node)

b) $G_2 \subset G_1$

c) $G_1 \cap G_2 = \emptyset$ (i.e. G_1 a G_2 have no common node).

C_4 Topology of the graph is such that during token hand over, the token passes through at most one node TIM and it passes this node at most once.

Example 1

Small guidelines for heart failure prevention

When a patient comes for a visit, his/her physician examines patient's blood pressure parameters SBP, DBP and let to determine his cholesterol parameters LDL, HDL in laboratory.

1. If blood pressure is not normal, i.e. if the condition

$$\alpha = (SBP < 145) \wedge (DBP < 90)$$

is not satisfied, the physician prescribes diet and invites the patient for repeated examination after 1-2 months:

   (a) If patient's blood pressure is not normal again, the physician prescribes medicament treatment.

   (b) If patient's blood pressure is normal, the physician evaluate patient's risk index

$$i_R = (LDL - HDL)/HDL.$$

   If the risk index is small ($i_R < 4.2$), the patient is invited for the next examination not later than after a year. If the risk index is greater than 4.2, the patient is invited not later than after half a year.

2. If blood pressure is normal, i.e. condition α is satisfied, physician evaluates patient's risk index i_R. If the risk index is small ($i_R < 4.2$), the patient is invited for the next examination not later than after a year. If the risk index is greater than 4.2, the patient is invited not later than after half a year.

The EGLIF graph model of Small guideline for heart failure prevention is given in Fig. 2. Its coded form is given in Fig. 3.

3 Results

In this paragraph we present an algorithm for comparing of a strict guidelines EGLIF model with a complete patient's data record. We start with an example.

Example 2

We assume that the physician stores values of all examined patient's parameters (HDL, LDL, SBP, DBP) and all prescribed therapies $(Diet, Medication)$ into patient's health record. We assume further that patient's data stored in EHR can be output in the form of the data sequence described above. Let us suppose that from EHR we have got the following data sequences $\mathbf{S_A}, \mathbf{S_B}, \mathbf{S_C}, \mathbf{S_D}$ for 4 patients A, B, C and D.

$\mathbf{S_A} = \{SBP(1.1.01) = 150, DBP(1.1.01) = 85, HDL(2.1.01) = 1,$
$LDL(2.1.01) = 6, Diet(2.1.01) = 1, DBP(10.2.01) = 85,$
$SBP(10.2.01) = 140, SBP(1.5.01) = 130, DBP(1.5.01) = 85,$
$HDL(2.5.01) = 1, LDL(2.5.01) = 5, SBP(1.4.02) = 130,$
$DBP(1.4.02) = 90, LDL(2.4.01) = 7, HDL(2.4.01) = 2\}$

$\mathbf{S_B} = \{SBP(1.1.01) = 150, DBP(1.1.01) = 85, HDL(2.1.01) = 1,$
$LDL(2.1.01) = 6, DBP(10.2.01) = 85, SBP(10.2.01) = 140,$
$SBP(1.5.01) = 130, DBP(1.5.01) = 85, HDL(2.5.01) = 1,$
$LDL(2.5.01) = 5, SBP(1.4.02) = 130, DBP(1.4.02) = 90,$
$LDL(2.4.01) = 7, HDL(2.4.01) = 2\}$

$\mathbf{S_C} = \{SBP(1.1.01) = 150, DBP(1.1.01) = 85, HDL(2.1.01) = 1,$
$LDL(2.1.01) = 6, Diet(2.1.01) = 1, DBP(1.4.01) = 85,$
$SBP(1.4.01) = 140, SBP(1.5.01) = 130, DBP(1.5.01) = 85,$
$HDL(2.5.01) = 1, LDL(2.5.01) = 5, SBP(1.4.02) = 130,$
$DBP(1.4.02) = 90, LDL(2.4.01) = 7, HDL(2.4.01) = 2\}$

$\mathbf{S_D} = \{SBP(1.1.01) = 150, DBP(1.1.01) = 85, HDL(2.1.01) = 1,$
$LDL(2.1.01) = 6, Diet(2.1.01) = 1, DBP(10.2.01) = 85,$
$SBP(10.2.01) = 140, SBP(1.5.01) = 130, DBP(1.5.01) = 85,$
$HDL(2.5.01) = 1, LDL(2.5.01) = 5.5, SBP(1.4.02) = 130,$
$DBP(1.4.02) = 90, LDL(2.4.01) = 7, HDL(2.4.01) = 2\}$

If the patient's health record is complete we can compare generated data sequence with the guidelines and determine if the patient has been treated according to it. Let us compare data sequences $\mathbf{S_A}, \mathbf{S_B}, \mathbf{S_C}$ and $\mathbf{S_D}$ with the Small guidelines for heart failure prevention described in Example 1.

Comparing $\mathbf{S_A}$ with the guidelines we see that treatment of the patient A complies with the guidelines.

Comparing $\mathbf{S_B}$ with the guidelines we see that treatment of the patient B does not comply with guidelines. The reason is that at the first visit patient's blood pressure was not normal. Therefore, the physician should have prescribed diet, but the diet item is missing in the data sequence $\mathbf{S_B}$.

The treatment of the patient C does not comply with guidelines as well, because at the visit 1.1.01 patient's blood pressure was not normal and therefore the patient should have come for repeated visit not later than after 2 months. Nevertheless, he came later as we can see from the data sequence item $DBP(1.4.01) = 85$.

We can easily see that treatment of the patient D does not comply with guidelines as well. As $HDL(2.5.01) = 1$ and $LDL(2.5.01) = 5.5$, the risk index during patient's visit 2.5.01 had value $i_R = 4.5$. Hence patient's following visit should have been sooner than after half a year. But

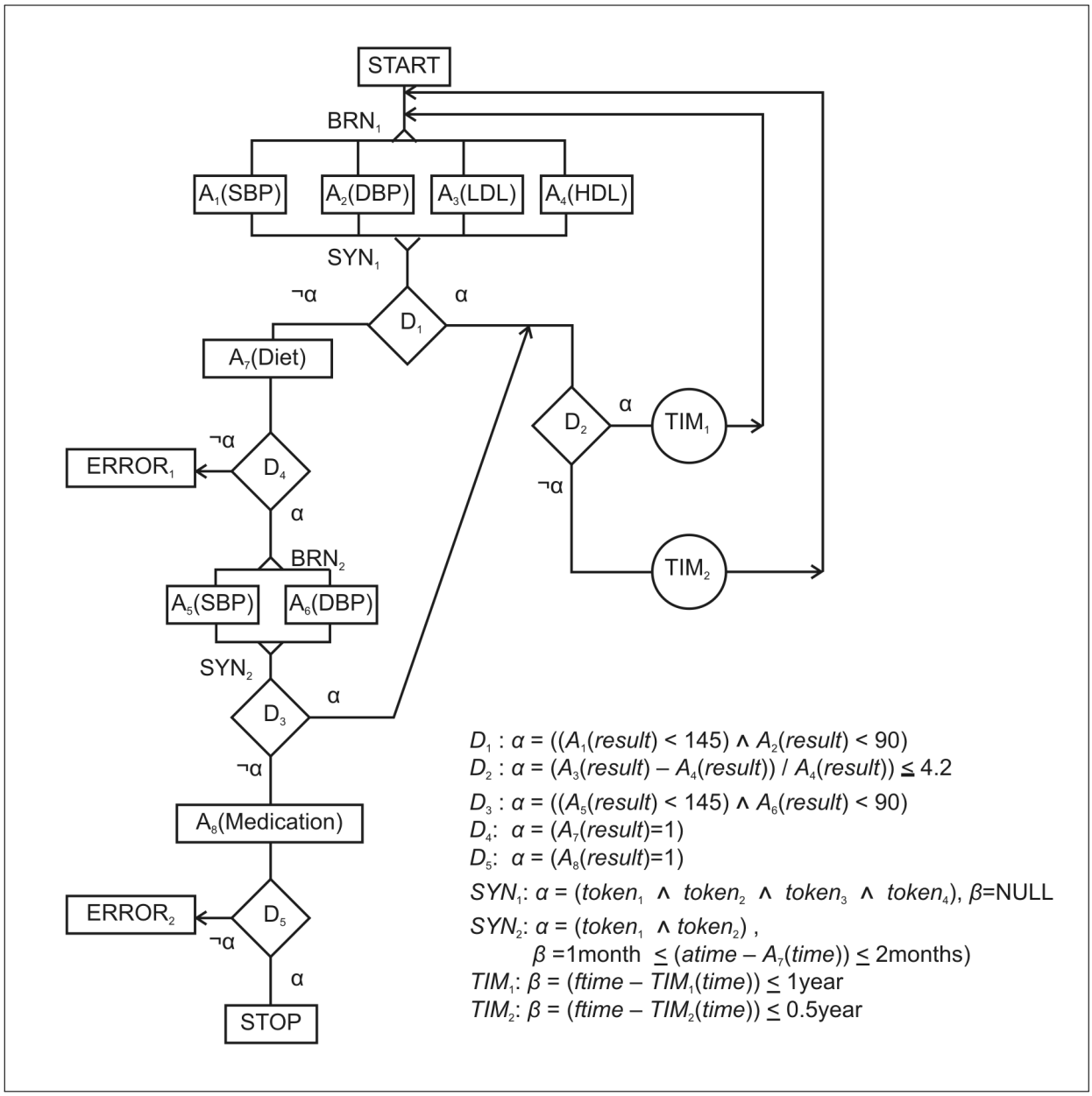

Figure 2: EGLIF graph model of the Small guidelines for heart failure prevention from Example 1. For better readability the value of parameter *action* of each action node is put into brackets and written after node name.

his next visit was 1.4.02 as we can see from the data item $SBP(1.4.02) = 130$.

Algorithm for comparing EGLIF with data sequence (algorithm CA)

Comparing a data sequence with clinical guidelines is a time consuming and tiring process prone to errors. Therefore, having at hand a possibility to do it using computer would be very appealing. For comparing we need an algorithm that would be able to compare a given data sequence with a coded EGLIF model and answer the question if the physician followed the recommended treatment specified in the guidelines or did not. In the following we describe an algorithm that is able to give the answer.

In the §2 we have already given a very rough description of the algorithm to sketch out the principles on which it is based on. Here we will at first shortly remind the main features of the algorithm and then we will describe it in full detail.

The algorithm compares an EGLIF model and a data sequence $\mathbf{S} = \{P_1(t_1) = c_1, \ldots, P_n(t_n) = c_n\}$. The algorithm subsequently deletes the elements from the data sequence. Let us assume that in the i-th step of the algorithm the item $P_i(t_i) = c_i$ of the data sequence is processed. Algorithm will find out all action nodes that have token and whose parameter *action* has value P_i. In each found node the algorithm will write t_i into its parameter *time* and c_i into its parameter *result*. After it the algorithm will propagate tokens from the found *action* nodes

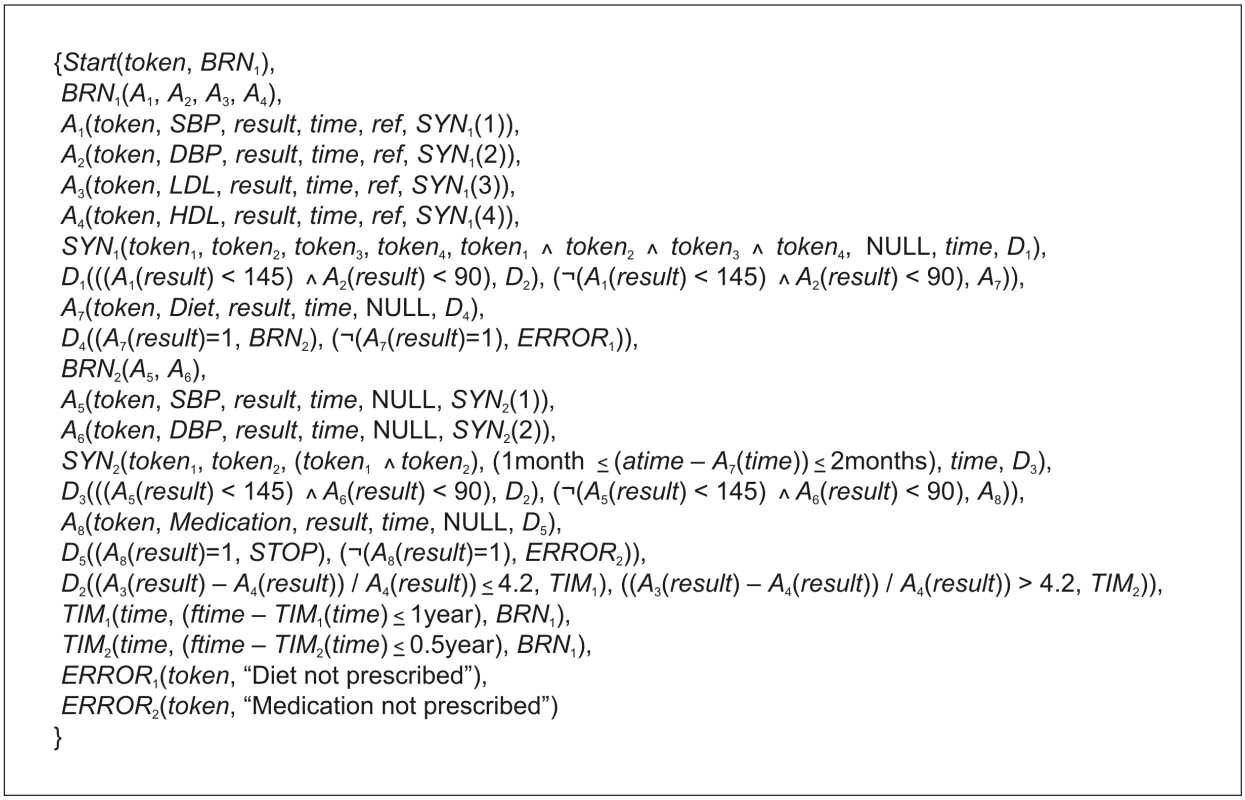

Figure 3: Coded EGLIF model of Small guideline for heart failure prevention.

to the following nodes capable of storing tokens. If no node with properties described above has been found, the error is generated and the comparison ends unsuccessfully.

Definition of the CA algorithm

Definition of the CA algorithm is given in two parts. The run of the algorithm is described in the first part. However, in the description the notion of token propagation is used that also must be precisely specified. The specification of the token propagation is given in the second part.

Part 1

1. In the 0-th algorithm step initialize node parameters:
   (a) In all nodes set parameters $time = 0$, $result = 0$ and $ref = NULL$.
   (b) In all nodes except $START$ set parameter $token = 0$.
   (c) Set $START(token) = 1$ and carry out its propagation from the $START$ node.
2. In the n-th algorithm step delete subsequently from the beginning of the data sequence $\mathbf{S}$ its members $P(t) = c$ until $P \in \mathbf{P_G}$ holds. (It means: actions that are not mentioned in the guidelines are not taken into consideration). Then denote $\mathbf{N_0}$ the set of all action nodes with parameters $token = 1$ and $action = P$.
   (a) If the set $\mathbf{N_0}$ is void, print "Error in sequence of actions" and finish.
   (b) If the set $\mathbf{N_0}$ is non void, then in each action node $A \in \mathbf{N_0}$ set $A(time) = t$ and $A(result) = c$. Here t and c are taken from the last deleted element $P(t) = c$ of the sequence $\mathbf{S}$. Denote as $\mathbf{N_1}$ the set of all nodes A from $\mathbf{N_0}$ that satisfy the following conditions *cond1* and *cond2*.

   cond1 If A is inside a subgraph $BRN - SYN$, then the time condition *cond2* of the node SYN is fulfilled.

   cond2 If the parameter ref of A contains the reference to a TIM node (i.e. $TIM(ref) \neq NULL$), the time condition β of node TIM is fulfilled.

   If the set $\mathbf{N_1}$ is void print "Time error" and finish. Otherwise for each node $A \in \mathbf{N_0}$ set $A(token) = 0$ and for each $A \in \mathbf{N_1}$ propagate its token to the nearest node capable of storing tokens. If the propagated token is caught by a node SYN, then set $SYN(time) = t$. Here t is taken from the last deleted element $P(t) = c$.

   At the end of the n-th step propagate tokens from those SYN nodes, the condition α of which is fulfilled. If α condition is fulfilled for some node SYN, then only one token

Table 2: Comparison of the data sequence $\mathbf{S_A}$ with EGLIF. After the step 15 the data sequence is void and $STOP$ node does not contain token. It means that patient A has been treated according to guidelines and that the treatment has not yet finished.

Step	Data item S_i	A_1	A_2	A_3	A_4	$SYN_1(1)$	$SYN_1(2)$	$SYN_1(3)$	$SYN_1(4)$	A_5	A_6	A_7	$SYN_2(1)$	$SYN_2(2)$
0	Start	•	•	•	•									
1	$SBP(1.1.01) = 150$		•	•	•	•								
2	$DBP(1.1.01) = 85$			•	•	•	•							
3	$HDL(2.1.01) = 1$			•		•	•		•					
4	$LDL(2.1.01) = 6$					•	•	•	•			•		
5	$Diet(2.1.01) = 1$									•				•
6	$DBP(10.2.01) = 85$									•				•
7	$SBP(10.2.01) = 140$	•	•	•	•								•	•
8	$SBP(1.5.01) = 130$		•	•	•	•								
9	$DBP(1.5.01) = 85$			•	•	•	•							
10	$HDL(2.5.01) = 1$			•		•	•		•					
11	$LDL(2.5.01) = 5$	•	•	•	•	•	•	•	•					
12	$SBP(1.4.02) = 130$		•	•	•	•								
13	$DBP(1.4.02) = 90$			•	•	•	•							
14	$LDL(2.4.01) = 7$				•	•	•	•						
15	$HDL(2.4.01) = 2$	•	•	•	•	•	•	•	•					

is propagated from this node. If the propagated token is caught by a node N, then set $N(time) = SYN(time)$.

3. If the stopping condition is not fulfilled, increase the number of algorithm steps $n = n + 1$ and go to 2.

   Stopping condition: The algorithm stops if the following conditions (a) or (b) hold.

   (a) Some $ERROR$ or $STOP$ node contains a token.

   (b) The current data sequence is void.

Part 2 (Rules of token propagation)

1. Tokens are propagated along graph branches. In a decision node a token continues along that branch i, for which the condition α_i is fulfilled. In a branch node with n branches new $n - 1$ tokens are created. Each of n tokens coming of the branch node then continues along a different branch.

2. An action node hands over its token to the nearest node that receives tokens. If a token passes a branch node and new tokens are created, then also each newly created token is caught by the nearest node that is capable to catch it.

3. Synchronization node SYN hands over only 1 token and it does it in the same way as an action node. Moreover, the following actions are done:

   (a) All tokens present in the SYN node are discarded.

   (b) All tokens, stored in the nodes on branches between SYN node and its corresponding BRN node, are discarded.

4. If a node N hands over its token to another node and if the token during its handover passes through a node TIM, then the parameter $time$ of the node TIM is set to be $TIM(time) = N(time)$.

5. If a token was handed over to an action node A and if it passed during its handover a node TIM, then into parameter ref of the node A the pointer to the node TIM is written. If the token has not passed through any time node TIM, then into parameter ref of the node A the pointer $NULL$ is written.

If CA algorithm has not finished with error, it might stop due to one of two following reasons.

1. All data items S_i have been already removed from the data sequence $\mathbf{S}$. In this case the patient has been treated in accordance with guidelines. However, according to guidelines, his/her treatment should continue.

2. In the last step of the algorithm a token has been stored in a node $STOP$. In this case the patient has been treated in compliance with guidelines and the treatment in accordance with guidelines was finished. If all data items have been removed from data sequence $\mathbf{S}$, the physician finished the treatment. On the other hand, if some data items remained in $\mathbf{S}$, the patient has been cured further, perhaps due to some other health problems.

To check behavior of the CA algorithm we can apply it to comparison of the Small guidelines for heart failure prevention from Example 1 with data records of the patients A, B, C and D given above. We suppose that guidelines were formalized using EGLIF model and that data records of patients were transformed into data sequences

Table 3: Comparison of the data sequence $\mathbf{S_B}$ with EGLIF. In the step 5 the error signal "Error in sequence of actions" is generated due to the void set $\mathbf{N_0}$.

Step	Data item S_i	A_1	A_2	A_3	A_4	$SYN_1(1)$	$SYN_1(2)$	$SYN_1(3)$	$SYN_1(4)$	A_5	A_6	A_7	$SYN_2(1)$	$SYN_2(2)$
0	Start	•	•	•	•									
1	$SBP(1.1.01) = 150$		•	•	•	•								
2	$DBP(1.1.01) = 85$			•	•	•	•							
3	$HDL(2.1.01) = 1$			•		•	•		•					
4	$LDL(2.1.01) = 6$					•	•	•	•			•		
5	$DBP(10.2.01) = 85$											•		

Table 4: Comparison of the data sequence $\mathbf{S_C}$ with EGLIF. In the step 6 the error signal "Time error" is generated, because the set $\mathbf{N_1}$ is void.

Step	Data item S_i	A_1	A_2	A_3	A_4	$SYN_1(1)$	$SYN_1(2)$	$SYN_1(3)$	$SYN_1(4)$	A_5	A_6	A_7	$SYN_2(1)$	$SYN_2(2)$
0	Start	•	•	•	•									
1	$SBP(1.1.01) = 150$		•	•	•	•								
2	$DBP(1.1.01) = 85$			•	•	•	•							
3	$HDL(2.1.01) = 1$			•		•	•		•					
4	$LDL(2.1.01) = 6$					•	•	•	•			•		
5	$Diet(2.1.01) = 1$									•	•			
6	$DBP(1.4.01) = 85$									•	•			

$\mathbf{S_A}, \mathbf{S_B}, \mathbf{S_C}$ and $\mathbf{S_D}$. The runs of the algorithm for particular data sequences can be followed in the Tables 2–5. In the tables the movement of tokens is visualized. The presence of a token in some node (or tokens if the node is of type SYN) at the end of the n-th step is represented with a black point. For example a black point in the cell $(step = 0, A_1)$ of the Table 2 means that $A_1(token) = 1$ at the end of the 0-th step, a black point in the cell $(step = 3, SYN_1(2))$ means that $SYN_1(token_2) = 1$ at the end of the third step, void cell $(step = 2, SYN_1(3))$ means that $SYN_1(token_3) = 0$ at the end of the second step and so on. If the row of some step is divided into two sub-rows, then the first sub-row describes token layout after the first phase of the step, it means just before token propagation from SYN nodes takes place.

If the CA algorithm compares the EGLIF model of the guidelines with data sequence $\mathbf{S_A}$ (see Table 2), the comparative process stops at the step 15. The final data sequence is void and $STOP$ node does not contain token. It means that the patient A has been treated according guidelines and that the treatment has not yet finished.

If the CA algorithm compares EGLIF model of the guidelines with the data sequence $\mathbf{S_B}$ (see Table 3), the comparative process ends at the step 5 and the error signal "Error in sequence of actions" is generated. The error is generated because at the beginning of the step 5 only node A_7 has token, the last deleted data item used for comparing is $DBP(10.2.01) = 85$ and $A_7(action) = Diet$. As $Diet \neq DBP$, the set $\mathbf{N_0}$ is void and consequently the error signal "Error in sequence of actions" is generated.

If the CA algorithm compares EGLIF model of the guidelines with the data sequence $\mathbf{S_C}$ (see Table 4), the comparative process stops in the step 6 and the error signal "Time error" is generated. In the step 6 the current data item is $DBP(1.4.01) = 85$. The only action nodes having token at the beginning of the step 6 are the nodes A_5 and A_6. Their parameter $action$ has value $A_5(action) = SBP$ and $A_6(action) = DBP$ respectively. Hence the set $\mathbf{N_0} = \{A_6\}$ and $A_6(time)$ is set to be 1.4.01. The node A_6 is inside subgraph $BRN_2^{\smile}SYN_2$ and β condition of SYN_2 is

$$(1\,\text{month} \leq (atime - A_7(time)) \leq 2\,\text{months}).$$

Therefore the condition

$$(1\,\text{month} \leq (A_6(time) - A_7(time)) \leq 2\,\text{months}).$$

should hold. However, this condition does not hold, because $A_7(time) = 2.1.01$. Hence the error signal "Time error" is generated.

If the CA algorithm compares EGLIF model of guidelines with the data sequence $\mathbf{S_D}$ (see Table 5), the comparative process stops in the step 12 and the error signal "Time error" is generated. At the beginning of the step 12 the nodes with token are the nodes A_1, A_2, A_3 and A_4, but only the node A_1 has value of parameter $action$ equal to SBP. Hence $\mathbf{N_0} = A_1$ and $A_1(time) = 1.4.02$. As the token has been handed over to the node A_1 through the node TIM_2, we have $A_1(ref) = TIM_2$ and $TIM_2(time) = 2.5.01$. The β condition of TIM_2 is

$$ftime - TIM_2(time) \leq 0.5\,\text{year}.$$

As $ftime = 1.4.02$, the condition β is not fulfilled and the error signal "Time error" is generated.

Table 5: Comparison of the data sequence $\mathbf{S_D}$ with EGLIF. In the step 12 error signal "Time error" is generated, because the set N_1 is void.

Step	Data item S_i	A_1	A_2	A_3	A_4	$SYN_1(1)$	$SYN_1(2)$	$SYN_1(3)$	$SYN_1(4)$	A_5	A_6	A_7	$SYN_2(1)$	$SYN_2(2)$
0	Start	•	•	•	•									
1	$SBP(1.1.01) = 150$		•	•	•	•								
2	$DBP(1.1.01) = 85$			•	•	•	•							
3	$HDL(2.1.01) = 1$			•		•	•		•					
4	$LDL(2.1.01) = 6$					•	•	•	•			•		
5	$Diet(2.1.01) = 1$									•	•			
6	$DBP(10.2.01) = 85$									•				•
7	$SBP(10.2.01) = 140$	•	•	•	•								•	•
8	$SBP(1.5.01) = 130$		•	•	•	•								
9	$DBP(1.5.01) = 85$			•	•	•	•							
10	$HDL(2.5.01) = 1$			•		•	•		•					
11	$LDL(2.5.01) = 5$	•	•	•	•	•	•	•	•					
12	$SBP(1.4.02) = 130$		•	•	•	•								

4 Conclusion

In this paper we designed an algorithm that compares a patient's treatment described with a patient's health record with a formal model (EGLIF) of some clinical guideline. The algorithm works correctly under two conditions:

1. The EGLIF model must be strict, which means that the choice of the branch in all decision nodes must be unambiguous.

2. The data record must be complete, which means that all examined patient's parameters and prescribed or applied therapies must be recorded.

However, guidelines often recommend for a particular patient's state more possible ways how to continue with treatment. In a GLIF model it is modeled with in-conditions, strict in-conditions, out-conditions and strict out-conditions. If a strict in-condition or a strict out-condition of the branch is satisfied, this branch is strictly recommended or strictly prohibited and the physician is strictly urged to follow or not to follow it. In-conditions and out-conditions are soft conditions and should be taken only as hints how to continue.

So in practice GLIF models are rarely strict and some specification what the compliance of a non-strict guidelines with a patient's data record actually means is needed.

Here we introduce one possible specification. At first we define the notion of admissibility of a decision branch.

When a token passes a decision node, then each branch originating in this node and satisfying conditions C_1 and C_2 is called admissible.

C_1 All the strict out-conditions and out-conditions on the branch are evaluated as false.

C_2 At least one strict in-condition or in-condition on the branch is evaluated as true.

Subsequently we may define compliance of a patient's treatment with non-strict guidelines. The treatment is in compliance with the given non-strict guidelines if all decisions made resulted in following of admissible branches only.

We may easily modify the comparing algorithm CA introduced above so that it could compare a patient's record and non-strict guidelines and determine the compliance of patient's treatment with it. Modification consists in token multiplication in the decision nodes. If a token passes a decision node new tokens are created so that one token could continue along every admissible branch.

The second assumption is that about completeness of patient's data record. It is clear that in the situation when we know that only some data about patient's treatment are stored in his/her data record, the possibility to test compliance of his treatment with guidelines model is strongly limited. However, in some cases non-compliance can be discovered in spite of the missing data. This happens if the data record would be non-compliant with the guidelines model whatever the missing data were.

If we used the algorithm CA described above, it would generate error for every missing item. However, it might not be our intention. We might admit missing data and we might want to get warnings only if the non-compliance is obvious from the remaining data themselves. If so, some modification of the CA algorithm is needed. To find such modification is much more difficult, than to enhance the algorithm for non-strict guidelines models. At present it is a subject of the further research.

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Impact of the Use of an Electronic Template on Clinicians Adherence to Follow Guidelines for Diabetes Care

Vishal Mundra[1], **Shadi Yaghoubian**[2], **Viet Nguyen**[3], **Darby Sider**[4], **Jose Muniz**[4], **Carmen V Villabona**[5]

[1] Department of Internal Medicine, St. John Medical Centre, Tulsa, OK, USA

[2] Medical Student-IV, Ross University, USA

[3] Three Lower Counties Community Services, Salisbury, MD, USA

[4] Department of Internal Medicine, Cleveland Clinic Florida, USA

[5] Department of Endocrinology, Cleveland Clinic Florida, USA

Summary

Introduction: Diabetes mellitus (DM) was the seventh leading cause of death in 2006. The number of patients is expected to double by 2050. Simple non-adherence to follow guidelines by physicians is a significant source of morbidity and mortality. Our goal was to study the impact of an electronic template on adherence to follow ADA guidelines for diabetes care by general internist.

Methods: We designed an electronic template based on the 8 point ADA guidelines for management of diabetes type 2 including: glycosylated hemoglobin (HgbA1c) assessment, blood pressure (BP), lipid control, smoking cessation counseling, diabetic foot exams, pneumococcal vaccination (PCV), renal assessment and annual retina exam.A randomly selected pre-intervention control group was compared after 6 months of template use to a randomly selected post-intervention group independent of age and sex variables. Same patients were not followed in the control and intervention group.

Results: Our intervention group consisted of 212 subjects, they were compared with a control group of 154. Significant improvements were detected in HbA1c testing (57.5% vs. 94.1%; p<0.001), BP control/intervention done (53.3% vs. 89.1%; p<0.001), low-density lipoprotein (LDL) control/intervention done (65.6% vs. 90.0%; p<0.001), compliance with diabetic foot exams (88.3% vs. 99.1%; p 0.001), compliance with annual eye exams (38.3% vs. 94.8%; p<0.001). Non-significant improvements were detected in smoking cessation counseling (97.3% vs 100%; p 0.578), renal assessment (92.8% to 92.9%; p 0.72). No pre intervention data on PCV was available, so no comparisons were done.

Conclusion: Utilization of a template in the EMR showed a significant improvement in diabetes care including HbA1c assessment, BP control, LDL control, foot examination, and annual eye examination. Use of templates in the EMR system showed increased adherence to guidelines by physicians, this might extrapolate to other chronic diseases.

Keywords

diabetes mellitus type II, electronic reminder, electronic medical record, ADA guidelines, randomized clinical trial

Correspondence to:

Carmen V Villabona
Department of Endocrinology
Address: 2950, Cleveland Clinic Blvd, Weston, Fl, 33331, USA
Phone: 954 659 5271
Fax: 954 659 5272
E–mail: villabonac@ccf.org

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1 Introduction

Diabetes Mellitus (DM) is one of the major health problems in the USA. DM was the seventh leading cause of death in 2006 [1, 2]. The number of patients is expected to double by 2050 [1, 2]. Prevention of long term complications depends on the provision of evidence based services in the entire spectrum of the disease. The American Diabetes Association (ADA) has proposed guidelines for comprehensive care of diabetic patients [3]. Successful implementation of these guidelines could potentially decrease long term complications of DM. Despite the existence of these guidelines, the adherence from physicians to follow them remains unacceptably low. Only 4 out of 10 US adults reported receiving multiple preventative services for diabetes [4]. As per CDC statistics for diabetics in

ADA Diabetes Care

1. HgbA1C checked with in 6 months if at target or 3 months if not in target: {YES/NO:55541}
2. BP<130/80 or interventions done: {YES/NO:55541}
3. LDL<100 or LDL<70 for pts with CAD: {YES/NO:55541}
4. Smoking cessation counseling done and documented in the EMR: {YES NO BR NO DEFAULT:65594}
5. Foot exam including pulses {YES/NO:55541}, ankle reflexes {YES/NO:55541} and sensation to monofilament {YES/NO:55541}
6. Pneumovax vaccine: {YES/NO:55541}
7. Albumin/creatinine ratio checked and ACE/ARB therapy if abnormal alb/cr ratio: {YES/NO:55541}
8. Annual Eye exam: {YES/NO:55541}

Figure 1: ADA guidelines based Diabetes Mellitus template.

2009, 62.7% had a dilated eye exam, 67.3% had foot exam, 69.2% had HbA1c checked twice a year, 49.5% had influenza vaccine and 43.0% had pneumococcal vaccine [5].

Physicians' have a poor compliance to standard guidelines for many chronic diseases [6, 7, 8, 9, 10]. Implementation and use of Electronic medical records (EMR) have shown an improvement in outcome of many chronic diseases [11, 12, 13, 14]. Electronics reminders have also shown to increase the rate of adult immunizations and various screening procedures [15, 16]. They have shown that EMR use can improve the clinician adherence to guidelines and documentation [17, 18, 19]. However, few of the previous studies have failed to show improvement in out come of care for diabetes [20]. To further clarify we developed in our EMR a phrase reminder for various clinical parameters based on ADA guidelines and assessed its impact of clinician's compliance which was approved by institutional review board.

2 Methods

The study was conducted at a community teaching hospital in South Florida. The clinic uses EPIC as the electronic medical record system. We designed a template based on ADA guidelines for standard management of DM including:

1. HbA1C assessment (to be checked every 3 months if not at goal or every 6 month if at goal),
2. BP control/intervention (goal <130/80),
3. Lipid control/intervention (Goal LDL<100 or <70 if coexisting coronary artery disease),
4. Smoking cessation counseling,
5. Annual foot exam done with check of pulses, monofilament and ankle reflexes,

Table 1: Pre intervention and post intervention comparison of various parameters for DM care.

	Pre Implementation n=154	**Post Implementation n=212**	**p value**
HbA1c checked in 3 months / 6 months if at target	57.5%	93.8%	<.001
BP <130/80 mmHg or Intervention	53.3%	89.1%	<.001
LDL at goal or Intervention	65.5%	90.0%	<.001
Annual Eye Exam	38.3%	94.8%	<.001
Annual Foot Exam	88.3%	99.1%	<.001
Nephrology Assessment	92.8%	92.9%	0.578
Smoking Assessment	97.3%	100.0%	0.718
Pneumococcal Vaccine		92.9%	

Table 2: Odds ratio and NNT for various parameters.

	Odds Ratio	**95% C.I.**	**NNT**
HbA1c checked in 3 months / 6 months if at target	12.3	6.3-24.3	3
BP <130/80 mmHg or Intervention	7.2	4.2-12.3	3
LDL at goal or Intervention	4.1	2.3-7.2	4
Annual Eye Exam	28.6	14.5-58.8	2
Annual Foot Exam	13.9	3.2-58.8	9
Nephrology Assessment	1.0	0.4-2.2	1000

6. Pneumonia vaccination,
7. Renal assessment (patient on Angiotensin converting enzyme inhibitors (ACE)/Angiotensin II receptor blocker (ARB) or microalbumin/cr ratio checked) and
8. Annual eye exam.

200 patients with DM irrespective of age or sex were randomly selected from the database of internal medicine clinic in November 2009. Patients with a diagnosis of Type 2 DM for at least 1 year and under follow-up with the same clinician were included in the study. Pre-intervention (control) data was collected for 154 patients as 46 patients were excluded due to loss of follow up or death. Patients with type 1 DM were also excluded. Then the electronic template was launched. The entire template could be brought up by using a dot phrase. DMTEMP in the clinic note. (Figure 1) Repeated reminders were sent to the staff physicians and residents by use of emails and announcements in the noon conference. Various reminders were also placed in the resident's room to use the template. The template was used by physicians and residents for 6 months after which post intervention (test group) data was collected for 212 patients in May 2010. The post intervention group was also selected irrespective of age or sex. Same patients were not followed in the control and intervention group.

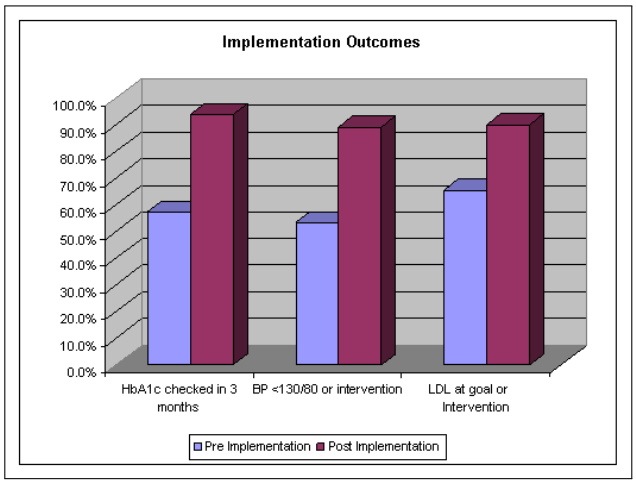

Figure 2: Bar graph for comparison of pre intervention and post intervention data.

The data was analyzed by a professional statistician using chi square method and statistical significance was set at p value less than 0.05.

3 Results

Baseline characteristics of 154 patients were collected in terms of all the parameters for DM treatment. These numbers for LDL screening, HbA1c control, eye exam, medical attention for nephropathy, smoking cessation and pneumococcal vaccine were well above the cut off set by National Committee for Quality Assurance (NCQA) for their certification in the diabetes care [18].

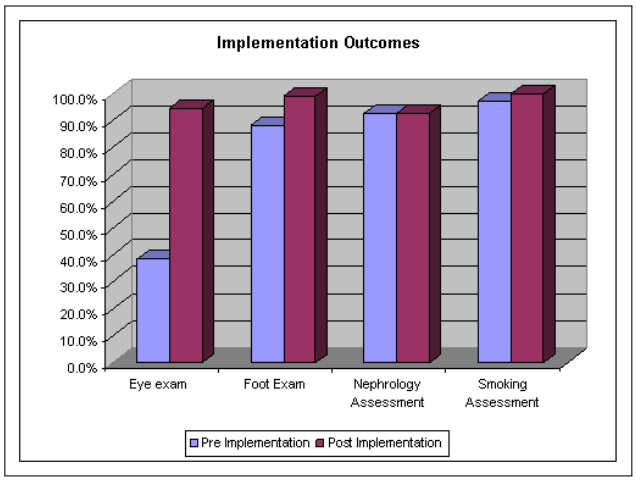

Figure 3: Bar graph for comparison of pre intervention and post intervention data.

For control of hyperlipidemia, in the control group, the LDL was at goal or checked and treated only in 65.6% which increased to 90.0 % showing an improvement of 25.4% [p<0.001, Odds ratio (OR) 4.1, Number needed to treat (NNT) = 3] in the post intervention group. For blood pressure control, in the control group, 53.3% had goal blood pressure or intervention done in the pre intervention group. It increased to 89.1% in the post intervention group with an improvement of 35.4% (p<0.001, OR 7.2, NNT = 3). For HbA1c check, in the control group, 57.5 % of patients had an HbA1c checked periodically in accordance with the guidelines. In the post intervention group, 94.1% of patients had their HbA1c checked and showed an improvement of 33.8% (p<0.001, OR 12.3, NNT = 3). For annual dilated eye exam, only 38.3% had documented eye exam in control group where as it improved to 94.8% in the post intervention group, improving by 56.5% (p<0.001, OR 28.6, NNT = 2). For annual foot examination, in the control group 88.3% had foot exam which improved to 99.1% in the post intervention group (p 0.001, OR 13.9, NNT = 9). For pneumonia vaccination, in the post intervention group about 92.9% received a pneumococcal vaccine. No pre intervention data was collected. 92.8% of patients had renal assessment in control group which improved to 92.9% showing an improvement of 0.1% (p=0.718, OR 1.0, NNT = 1000). Lastly, 97.3% of patient had smoking cessation counseling done in the control group where as 100% of patients received smoking cessation counseling in the post intervention group. Ex-smokers and nonsmokers were excluded from both groups. No additional data is available. Very low NNT obtained in our study for most of the interventions further stresses the effectiveness of this study (Figure 2 and 3).

4 Discussion

Our review of the literature reveals mixed results when studying the impact of the use of EMRs on quality of care [21, 22, 23]. Some studies have shown that the computerized system only improves the frequency of the tests without any improvement in clinical outcome [24]. We have data supporting that the use of clinical informatics to remind patients about scheduling tests and physician appointments lower LDL-cholesterol, blood pressure and HbA1c [13, 14, 25, 26, 27]. EMR use has also shown to improve the sensitivity of diagnosis for a few diseases and to identify the risk factor for post op lung injury [28, 29]. Our study showed remarkable results in improvement of adherence to the guidelines by the clinicians in diabetes care as recommended by the ADA. However, we believe that the duration of study was suboptimal to assess the impact on the clinical outcomes. Some of these numbers like, annual eye exam could be due to improved documentation rather than increased frequency of testing which we think is also important. The increased frequency of testing in compliance with the guidelines should improve the quality of care. The importance of such reminders is even more significant in today's era when many of these patients are seen by primary care physicians and they have many clinical co-morbidities which need to be addressed in a timely and efficient manner. A previous study showed that physicians prefer electronic reminder than paper chart [30].

5 Limitation

The study was a small single center trial. Secondly, there were different subjects studied during the pre and post intervention group. However, the aim of the study was to assess the adherence of clinicians follow standard guidelines regardless of patient's outcomes. Another limitation was that some of these patients were seen by an endocrinologist and they were not excluded from the study. The template was not entered into the patient's encounter automatically; it had to be entered by the clinicians which very likely affected their compliance on using it.

6 Conclusion

Utilization of a template in the EMR showed a statistically significant improvement in physicians' adherence to guidelines to treat Diabetes including checking HbA1c, LDL-cholesterol, BP, foot examination and annual eye examination. Implementing a reminder in the EMR improved quality of care for patients at no extra cost and minimal time. Further research is needed to elucidate the role of these interventions on clinical outcomes. These tools can add a valuable adjunct to the clinical decision making and patient management especially of chronic complicated diseases.

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Determinants of Excess Genetic Risk of Acute Myocardial Infarction – A Matched Case-control Study

Zdeněk Valenta[1], Ivan Mazura[1], Michal Kolář[1], Hana Grünfeldová[2], Petra Feglarová[1], Jan Peleška[1], Marie Tomečková[1], Jan Kalina[1], Dalibor Slovák[1], Jana Zvárová[1]

[1] Center of Biomedical Informatics, Institute of Computer Science AS CR, Prague, Czech Republic

[2] Centre of Biomedical Informatics, Municipal Hospital Čáslav, Czech Republic

Summary

Background: Myocardial infarction and stroke represent a major public health problem in most developing countries. This study explores genetic predisposition of acute myocardial infarction in the Czech population.

Methods and Results: Genome-wide expression study used matched case-control design. Peripheral blood samples of the controls were matched to those of cases based on gender, age, status of diabetes mellitus and smoking status. Six months cardiovascular survival status of the cases was used to identify two distinct subgroups among the cases. Linear models for microarray data were employed to identify differential gene expression. Shrunken centroids technique helped in identifying the subsets of differentially expressed genes with predictive properties in independent samples. Predictive properties were evaluated using bootstrap sampling. Sixty transcripts were found to be both clinically and statistically differentially expressed among the cases not surviving the six months follow-up period relative to controls, while no such transcripts were observed among other surviving cases. The two subgroups of cases exhibited fourteen differentially expressed transcripts. Predictive modeling indicated sixteen out of sixty transcripts to best discriminate between the controls and cases that died during the follow-up period from cardiovascular causes, while for the surviving cases the already non-significant set of transcripts could not be further reduced. Eleven out of fourteen transcripts were found to best discriminate between the two groups of cases using shrunken centroids.

Conclusions: The study identified genes associated with excess genetic risk of acute myocardial infarction, including those associated with the six months fatality of the cases.

Keywords

genome-wide association study, gene expression; myocardial infarction, genetic predisposition, predictive modeling

Correspondence to:

Zdeněk Valenta
Dept. of Medical Informatics and Biostatistics
Institute of Computer Science AS CR
Address: Pod Vodárenskou věží 2, 182 07 Prague, Czech Republic
E–mail: valenta@cs.cas.cz

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1 Introduction

Morbidity and mortality from atherosclerotic complications, such as acute myocardial infarction and stroke, continue to represent major public health issue in most developing countries. They are caused by multiple environmental and genetic factors and the interaction between them. While there are clinical risk factors known to be associated with the incidence of acute myocardial infarction, genetic profile of an individual may represent additional factors independently associated with the incidence of this outcome.

Genome-wide expression profiling provides comprehensive summary of mRNA levels in a tissue sample, allowing for identification of the sets of genes and transcripts associated with individual condition. Microarray studies of human diseases are often limited by challenges in obtaining human tissues. Peripheral blood has become an attractive prime tissue for biomarker detection because of its critical role in immune response, metabolism, communication with cells and the extracellular matrix in almost all tissues and organs in the human body, as well as for the simplicity and low invasiveness of sample collection [1].

2 Study Design and Methods

Experimental design of this study aimed at identifying the genes associated with excess genetic risk for the incidence of acute myocardial infarction which is not necessarily captured through known clinical risk factors.

Forty five cases with confirmed diagnosis of acute myocardial infarction were enrolled between September 2006 and January 2011. The diagnosis had to satisfy the clinical criteria, ECG outcome and laboratory findings according to medical guidelines. Coronary angiography was performed in most patients. The cases had to be less than 80 years old and no subjects could be actively treated for cancer.

Venous blood samples were drawn from each subject enrolled. Paired controls were selected out of patients hospitalized for motoric complications with no evidence of coronary artery or peripheral artery disease, normal ECG and no history of stroke. They were matched to cases based on their gender, age (the controls could be up to 5 years older than cases), status of Type II diabetes mellitus and smoking status. These variables represent clinical and underlying genetic factors associated with the incidence of acute myocardial infarction. This study focuses on identifying the profiles associated with excess genetic risk which are not necessarily expressed through these risk factors.

Six months following the cardiac event cardiovascular survival status was assessed for all the cases. We hypothesized that the cases who have not survived the six months follow-up period (AMID6) and those who did (AMI) would each differ in their genetic make-up from the controls. We also hypothesized differences in genetic profiles between the two groups of cases (AIMD6 vs. AMI). While the average paired gene expression differences between the cases and their corresponding matched controls capture the primary prevention perspective, the differences between AMID6 and AMI reflect the secondary prevention point of view.

The study complies with the Declaration of Helsinki and was approved by the local ethics committee. All participants gave written informed consent. Basic descriptive characteristics of the data are provided in Tables 1 and 2 below and supplementary Table S10 in [44].

3 Microarray Analysis

The study utilized Illumina microarray technology for analyzing gene expression intensities across the full human genome. Samples of peripheral whole blood were collected from all subjects using commercial 3 ml Vacutainer® sets with EDTA. The tubes were inverted several times and 2.4 ml of the content was immediately mixed with 7.6 ml RNAlater® (Applied Biosystems) in 15 ml tubes, stabilized blood samples were inverted several times until they were homogenous and the samples were stored in -70°C. The RNA was isolated from 1.8 ml aliquot of stabilized blood with RiboPure^{TM}-Blood Kit (Applied Biosystems, U.S.A.), precipitated and purified with GLOBINclear^{TM}–Human kit (Applied Biosystems, U.S.A.). The quantification was made on Nanodrop (Thermo Scientific, U.S.A.) and the integrity of the RNA was measured on Bioanalyzer 2100 (Agilent Technologies Inc., U.S.A.). The cRNA was amplified using Illumina® TotalPrep^{TM} RNA Amplification Kit, precipitated and controlled on Nanodrop (Thermo Scientific, U.S.A.) and Bioanalyzer 2100 (Agilent Technologies Inc., U.S.A.). The cRNA samples (1.5 μg) were hybridized on HumanWG-6 v2 Expression BeadChips (Illumina Inc., U.S.A.) according to manufacturer's protocol.

4 Statistical Analysis

Statistical analysis used the R system for statistical computing, graphics and data analysis [2]. We used several packages which are part of the Bioconductor project [3]. The 'beadarray' package [4] was used for reading in the gene expression data from Illumina analyzer scans, the 'BASH' method [5] was used to identify defective beads on Illumina chips. We adopted 'normal-exponential convolution' method [6] for separating background noise from the signal. The $\log_2$-transformed quantile-normalized gene expression intensities were modeled using two explanatory variables, the matched pair indicator and the sampling group indicator ('AMI', 'AMID6', 'Controls') using the 'limma' package accounting for correlated data due to several biologically replicated samples [7]. Applying the empirical Bayes approach to model fit rendered moderated t-tests for each transcript/gene and contrast of interest. Multiple testing issues were handled using the q-value approach [8]. The two principal contrasts of interest estimated the mean paired differences in gene expression intensities between the cases (AIMD6, AIM) and their matched controls, respectively. Of interest were also the gene expression differences between the two groups of cases. Statistical significance was reached for transcripts with q-value below 0.05, clinical significance was reached when the $\log_2$-fold change was greater or equal to 1 in absolute value.

To identify subsets of genes possessing predictive properties in independent samples we employed shrunken centroids approach [9] implemented in the 'Predictive Analysis for Microarrays' (PAM). Subsets of genes identified as differentially expressed using the limma package were further analyzed using PAM. The final sets of genes so identified are believed to possess predictive properties in independent samples, which were evaluated using bootstrapping. PAM modeling technique was also applied to the full genome.

5 RT-qPCR Validation

Modeling results were validated by RT-qPCR analysis which used available RNA samples from the four

cases, their matched controls and 6 other randomly selected controls. The genes ADORA3, VNN3, IL18R1, IL18RAP, ERLIN1, FOS and ARG1 were quantified while 18S and HPRT were used as housekeeping references for each tested sample. Gene SPATC1 was selected as negative control.

6 Results

6.1 Limma Modeling Results

Comparing the matched controls with the cases who died from cardiovascular causes within six months following the cardiac event (contrast 'AMID6 vs. Controls') implicated 60 differentially expressed genes/transcripts which met the criteria of both statistical ($q < 0.05$) and clinical ($|log_2 FC| \geq 1$) significance. Of those genes, 40 were up- and 20 down-regulated. Without regard to clinical significance, statistical significance was attained for 323 transcripts; see the Venn diagrams in Figure 1.

Comparing the cases who survived the 6 months follow up period with their matched pair controls (contrast 'AMI vs. Controls') revealed no genes that would meet the above mentioned criteria for either statistically or clinically significant differential expression.

The population gene expression differences between the two groups of cases (contrast 'AMID6 vs. AMI') were associated with 14 transcripts which met the criteria of both statistical and clinical significance, out of which 4 were up- and 10 down-regulated. Statistical significance was observed for 60 genes/transcripts, out of which 13 were up- and 47 down-regulated.

Supplementary tables S1, S4 and S7 in [44] present a detailed view of limma modeling results assessing the three linear contrasts in gene expression intensities.

6.2 Predictive PAM Modeling

For all three types of contrasts considered in this study we were particularly looking for the candidate sets of genes which would possess predictive properties in independent samples. Therefore, the available samples were studied further using shrunken centroids approach. The corresponding results are summarized in Table 3. With each

Table 1: Group counts and percentages for categorical variables.

Variable	Level	Group Counts and Percentages		
		AMI	AMID6	CONTROL
Gender	Male	28 (68%)	2 (50%)	30 (67%)
Smoking	Smokers	10 (24%)	0 (0%)	10 (22%)
Type 2 DM	YES	12 (29%)	2 (50%)	14 (31%)
Dyslipidemia	YES	17 (41%)	2 (50%)	15 (33%)
Hypertension	YES	32 (78%)	2 (50%)	29 (64%)
First AMI	YES	32 (78%)	4 (100%)	–
STEMI	YES	26 (63%)	3 (75%)	–
Heart failure	YES	5 (12%)	3 (75%)	–
PCI	YES	6 (15%)	0 (0%)	–
ACEI*	YES	21 (51%)	1 (25%)	16 (36%)
Betablockers*	YES	19 (46%)	0 (0%)	15 (33%)
Diuretics*	YES	11 (27%)	1 (25%)	14 (31%)
Ca blockers*	YES	12 (29%)	3 (75%)	11 (24%)
Statins*	YES	14 (34%)	2 (50%)	15 (33%)
Fibrates*	YES	2 (5%)	0 (0%)	2 (4%)
Other*	YES	20 (49%)	3 (75%)	36 (80%)

*) Chronic medication

Table 2: Descriptive characteristics of continuous variables.

Variable	Group Means and Standard Deviations*		
	AMI	AMID6	CONTROL
Age	63.6 (9.18)	72.3 (4.73)	65.5 (9.42)
Height (cm)	167.3 (10.0)	163.3 (10.4)	165.4 (10.2)
Weight (kg)	85.2 (17.9)	81.0 (17.0)	80.3 (12.1)
SBP (mmHg)	140.0 (27.8)	137.5 (12.6)	142.3 (18.0)
DBP (mmHg)	82.7 (15.8)	84.3 (16.5)	82.8 (9.2)

*) At ICU entry

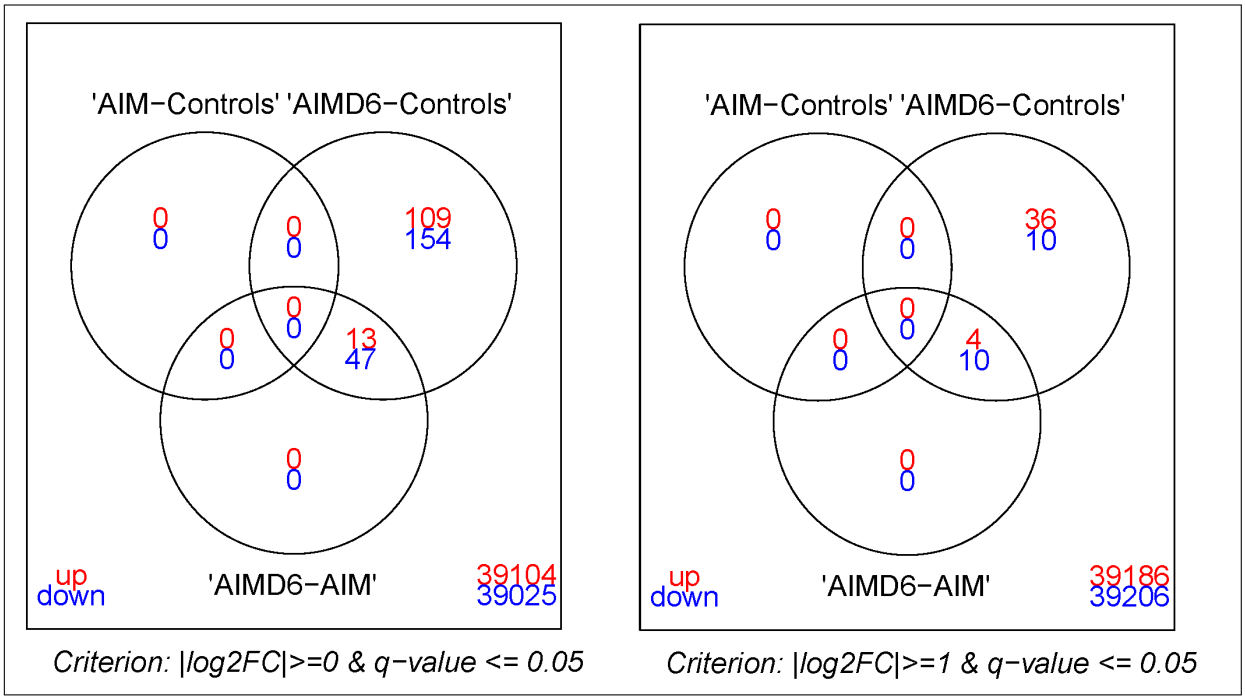

Figure 1: Counts of statistically significant differentially expressed transcripts (left panel) and those reflecting both statistical and clinical significance (right panel).

contrast Table 3 presents two candidate sets of genes. The Set ♯1 resulted from further reducing the gene set obtained from the limma modeling using PAM while the Set ♯2 was obtained by applying the PAM technique to all 39 226 available transcripts. Grey shading accentuates simultaneous presence of both statistical and clinical significance, as defined for this study. Comprehensive results covering the full genome reduction using PAM may be found in supplementary tables S3, S6 and S9 in [44], tables S2, S5 and S8 in [44] show PAM reduction of the gene sets obtained using limma.

6.3 AMID6 vs. Controls

Applying the shrunken centroids technique to the set of both statistically and clinically significant transcripts identified via limma modeling (top 60 genes of Table S1 in [44]) rendered 16 genes (Set ♯1) with predictive properties in independent samples shown in Table 3. Initiating the PAM modeling with the full genome resulted in a set of 14 genes (Set ♯2) of which only IL18R1 and DUSP1 would not pass the criterion of statistical significance within limma modeling framework while adhering to the clinical one in all instances. Remarkably, the two corresponding sets have a large proportion of genes in common.

6.4 AMI vs. Controls

The set of genes obtained using limma modeling for this contrast (Table S4 in [44]) did not exhibit statistical or clinical significance as defined for our study and could not be further reduced using PAM modeling. The set obtained by applying the PAM technique to the full genome was quite extensive, counting 228 transcripts. Table 3 presents truncated list of top thirteen genes (Set ♯2) which includes five genes from the corresponding Set ♯1.

6.5 AMID6 vs. AMI

PAM reduction of 14 statistically and clinically significant transcripts identified via limma modeling (see Table S7 in [44]) rendered 11 predictive transcripts, two of which pertain to gene 'CLYBL'. Initiating the PAM analysis with the full genome resulted in a set of 22 transcripts, four of which also appeared in the corresponding Set ♯1.

Table 4 presents estimates of sensitivity and specificity of the PAM classifier obtained from three bootstrap studies evaluating predictive properties of the two sets of genes identified for each contrast of interest. The studies used 1000 samples from the target population with replacement. We report the mean values along with the 5^{th} and 95^{th} percentile for both quantities of interest.

Predictive properties assessed using the PAM classifier appeared generally more favorable when the gene sets ♯2 were employed while notable improvements were observed in relation to sensitivity rather than specificity. Some improvements, however, came at a price of large number of genes required. This was the case of contrast 'AMI vs. Controls' where the Set ♯1 was of size 13 while the Set ♯2 counted 228 transcripts. This is a likely consequence of having observed no statistically or clinically significant

Table 3: Predictive sets of genes identified using PAM for each contrast of interest, with the ranks in the Set ♯1 and Set ♯2, respectively, q-values and $\log_2$FC based on limma results.

Symbol	Ref Seq ID	Definition	Set ♯1 Rank*	Set ♯2 Rank†	q-value	$\log_2$FC
Contrast AMID6 vs Controls						
ECHDC3	NM$_0$24693.2	enoyl Coenzyme A hydratase domain containing 3	1	1	0.0498	2.03
IL18RAP	NM_003853.2	interleukin 18 receptor accessory protein	2	3	0.0195	1.28
PFKFB2	NM_006212.2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	3	5	0.0085	1.93
IRS2	NM_003749.2	insulin receptor substrate 2	4	6	0.0308	1.43
PHACTR1	NM_030948.1	phosphatase and actin regulator 1	5	4	0.0352	1.86
ERLIN1	NM_006459.2	ER lipid raft associated 1	6	2	0.0416	1.77
VNN3	NM_001024460.1	vanin 3	7	7	0.0290	1.44
ADORA3	NM_020683.5	adenosine A3 receptor	8	9	0.0525	2.10
CLEC4E	NM_014358.1	C-type lectin domain family 4, member E	9	11	0.0288	1.75
ASPRV1	NM_152792.1	aspartic peptidase, retroviral-like 1	10	12	0.0352	1.01
PFKFB2	NM_001018053.1	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	11	5	0.0416	1.69
CPD	NM_001304.3	carboxypeptidase D	12	10	0.0397	1.31
FKBP5	NM_004117.2	FK506 binding protein 5	13	—	0.0596	1.03
PRKDC	NM_006904.6	protein kinase, DNA-activated, catalytic polypeptide	14	—	0.0075	1.10
NPM1	NM_199185.1	nucleophosmin (nucleolar phosphoprotein B23, numatrin)	15	—	0.0223	–1.15
SAMSN1	NM_022136.3	SAM domain, SH3 domain and nuclear localization signals 1	16	—	0.0478	1.37
IL18R1	NM_003855.2	interleukin 18 receptor 1	—	8	0.0525	2.10
DUSP1	NM_004417.2	dual specificity phosphatase 1	—	13	0.0596	1.03
LOC645649	XM_928663.1	hypothetical protein LOC645649	—	14	0.0075	1.10
Contrast AMI vs Controls						
OLIG2	NM_005806.2	oligodendrocyte lineage transcription factor 2	1	1	0.0756	–0.89
VNN3	NM_001024460.1	vanin 3, transcript variant 3	2	2	0.0756	0.50
MS4A3	NM_006138.4	membrane-spanning 4-domains, subfamily A, member 3, transcript variant 1	3	6,7	0.0756	–0.64
CEBPE	NM_001805.2	CCAAT/enhancer binding protein (C/EBP), epsilon	4	5	0.0756	–0.45
FOS	NM_005252.2	v-fos FBJ murine osteosarcoma viral oncogene homolog	5	4	0.0756	0.39
LIPA	NM_000235.2	lipase A, lysosomal acid, cholesterol esterase, transcript variant 2	6	—	0.0756	–0.37
LOC645649	XM_928663.1	hypothetical protein LOC645649	7	—	0.0906	0.29
TCRB	M97723	T cell receptor beta locus	8	—	0.0756	0.38
EPAS1	NM_001430.3	endothelial PAS domain protein 1	9	—	0.0756	–0.31
CLINT1	NM_014666.2	clathrin interactor 1	10	—	0.0756	–0.25
MYCT1	NM_025107.1	myc target 1	11	—	0.0756	–0.15
VPS29	NM_016226.2	vacuolar protein sorting 29 (yeast), transcript variant 1	12	—	0.0756	–0.15
LOC130951	NM_138804.2	hypothetical protein BC014602	13	—	0.0756	–0.13
CCL23	NM_005064.3	chemokine (C-C motif) ligand 23, transcript variant CKbeta8-1	—	3	0.2633	–0.84
MYB	NM_005375.2	v-myb myeloblastosis viral oncogene homolog (avian)	—	8	0.1397	–0.47
C13orf18	NM_025113.1	chromosome 13 open reading frame 18	—	9	0.1347	0.40
PER1	NM_002616.1	period homolog 1 (Drosophila)	—	10	0.2012	0.31
CCL23	NM_005064.3	chemokine (C-C motif) ligand 23, transcript variant CKbeta8-1	—	11	0.3385	–0.50
OLIG1	NM_138983.1	oligodendrocyte transcription factor 1	—	12	0.1347	–0.49
PRSS33(**)	NM_152891.1	protease, serine, 33	—	13	0.3606	–0.58
Contrast AMID6 vs AMI						
ADORA3	NM_020683.5	adenosine A3 receptor	1	15	0.0490	1.78
TCRB	M97723	T cell receptor beta locus	2	8	0.0130	–1.52
ERLIN1	NM_006459.2	ER lipid raft associated 1	3	11	0.0490	1.19
CLYBL	NM_206808.1	citrate lyase beta like	4	19	0.0234	–1.08
TCEA3	NM_003196.1	transcription elongation factor A (SII), 3	5	—	0.0381	-1.66
TCRA	BC070337	T cell receptor alpha locus	6	—	0.049	–1.42
CLYBL	NM_206808.1	citrate lyase beta like	7	19	0.0130	–1.18
HSD17B8	NM_014234.3	hydroxysteroid (17-beta) dehydrogenase 8	8	—	0.0490	–1.06
FLT3	NM_004119.1	fms-related tyrosine kinase 3	9	—	0.0490	1.14
AXIN2	NM_004655.2	axin 2 (conductin, axil)	10	—	0.0388	–1.49
—	CR596519	full-length cDNA clone CS0DI056YK21 of Placenta Cot 25-normalized	11	—	0.0490	–1.45
BCAT1	NM_005504.4	branched chain	—	1	0.1146	1.05
—	AW337887	he12d07.x1 NCI_CGAP_CML1 cDNA clone IMAGE:2918797 3'	—	2	0.0130	0.84
AMPH	NM_001635.2	amphiphysin (AMPH), transcript variant 1	—	3	0.0814	1.20
—	BM682470	UI-E-EJ0-aig-b-14-0-UI.s1 UI-E-EJ0, cDNA clone UI-E-EJ0-aig-b-14-0-UI 3'	—	4	0.0490	–0.76
C7orf53	NM_182597.1	chromosome 7 open reading frame 53	—	5	0.1371	0.86
—	CR592039	full-length cDNA clone CS0CAP005YH21 of Thymus	—	6	0.0994	–1.48
C2orf58	NM_173652.1	chromosome 2 open reading frame 58	—	7	0.1053	0.78
ASPRV1	NM_152792.1	aspartic peptidase, retroviral-like 1	—	9	0.0847	1.19
—	CN484989	hx21e11.y1 primary human ocular pericytes. Equalized (hx) cDNA clone hx21e11 5'	—	10	0.0721	1.44
ETS2	NM_005239.4	v-ets erythroblastosis virus E26 oncogene homolog 2	—	12	0.1218	0.73
NDUFB3	NM_002491.1	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa	—	13	0.4508	0.43
—	X00437	mRNA for T-cell specific protein	—	14	0.0721	–1.44
ZNF516	XM_496278.2	zinc finger protein 516	—	16	0.2826	0.48
SLC26A8	NM_052961.2	solute carrier family 26, member 8, transcript variant 1	—	17	0.0721	0.63
KIF20B	NM_016195.2	kinesin family member 20B	—	18	0.0130	–0.86
ARG1	NM_000045.2	arginase, liver	—	20	0.0814	3.05
IL18RAP	NM_003853.2	interleukin 18 receptor accessory protein	—	21	0.0542	1.61
CD59	NM_203329.1	CD59 molecule, complement regulatory protein, transcript variant 3	—	22	0.2374	0.65

*) PAM reduction of the set of statistically and clinically significant genes obtained from limma modeling
†) PAM reduction of the whole genome (represented by 39,226 transcripts)
**) Truncated list of genes

transcripts using the limma modeling (see Table S4 in [44]).

6.6 RT-qPCR Validation Study

Results of the RT-qPCR validation are summarized in supplementary Table S12 in [44]. One observation in the AIMD6 group of cases (ID=C078) appeared fairly similar to controls, its removal lead to the overall improvement. Details concerning the subjects from AMID6 group are shown in supplementary Table S11 and S12 in [44] presents the summary of validation study results.

7 Discussion

7.1 AMI vs. Controls

This contrast identifies genes which were differentially expressed between general population and the cases who survived the six months follow-up period following the MI episode. Although no statistically significant results were obtained for this contrast, several genes shown in Table 3 were previously linked to MI and cardiovascular or coronary artery disease. The FOS gene plays a role in functional organization of central cardiovascular pathways; its expression in certain central neurons may lead to sustained changes in cardiovascular function [10]. VNN3 is part of pantetheinase gene family which regulates hydrolysis of pantetheine into pantothenic acid (vitamin B5) and cysteamine, a potent antioxidant. Human neutrophils express transcripts encoding multiple splice variants of VNN3 [11]. In relation to oxidative stress VNN3 may play a role in tissue repair [12]. Phosphorylation of clock protein PER1 was shown to regulate its circadian degradation in normal human fibroblasts [13]. Mutations in the LIPA gene were shown to be related to cholesterol metabolism [14] and the gene was described as susceptibility gene for the incidence of coronary artery disease [15, 16]. Genes OLIG1 and OLIG2 encode transcription factors expressed in both the developing and mature vertebrate central nervous system and may have additional functions in a variety of neurological diseases [17]. Wojakowski et al [18] report up-regulation of OLIG2 in stroke patients. Inouye et al [19] report gene MS4A3 as one of only three strong predictors of lipid leukocyte module from their genome-wide study. Other genes showing significant evidence of association with lipid traits identified also in our study using PAM reduction of the whole genome include GATA2, CPA3, C1ORF186, C1ORF150, SLC45A3, SPRYD5 and CEBPD (Supplementary Table S6 in [44]), all with potential contribution to the pathogenesis of coronary artery disease. Gene EPAS1 was identified as a significant promoter of angiogenesis [20]. Castillo et al [21] demonstrated that inflammatory chemokine CCL23 is independently associated with coronary atherosclerosis. The MYB gene plays essential role in adult vascular smooth muscle cells survival [22].

7.2 AMID6 vs. Controls

This contrast targets differentially expressed genes among the cases not surviving the 6 months follow-up relative to general population. All predictive genes of the Set ♯2 in Table 3 have shown both clinically and statistically significant differential expression based on limma modeling. Gene ADORA3 is known as a receptor mediating cardioprotective functions during ischemia [23]. In our study the gene was overexpressed in cases that died within 6 months from cardiovascular complications relative to controls. The same was true relative to surviving cases ('AIMD6 vs. AMI') while the gene was under expressed among surviving cases relative to controls (supplementary Table S6 in [44]). Increased activity may be observed with genes involved in the overall immune response (IL18R1, IL18RAP). Liangos et al [24] uncovered highly intertwined signaling underlying ischemia reperfusion and inflammatory response. The corresponding genes identified in our study include IL18R1, IL18RAP, IL1RAP, LCN2 and TLR4 (tables S1 and S6 in [44]). Mallat et al [25] report significant expression of proinflammatory cytokine IL-18 and its signaling receptor IL-18R in human atherosclerotic plaques. Rosenberg et al [26] validated diagnostic test based on the expression of 23 genes previously found to be associated with the presence of CAD. From the genes they used in predictive modeling those identified in our study involve IL18RAP, TLR4 and CLEC4E, a mediator of immune and inflammatory re-

Table 4: Bootstrap estimates of sensitivity and specificity of the PAM classifier.

		Predictive Set ♯1 (based on limma results)			**Predictive Set ♯2** (based on 39 226 transcripts)		
Contrast	**Item**	**Mean**	**5%**	**95%**	**Mean**	**5%**	**95%**
AMID6 vs. Controls	Sensitivity	0.90	0.75	1.00	1.00	1.00	1.00
	Specificity	0.93	0.84	1.00	0.96	0.87	1.00
AMI vs. Controls	Sensitivity	0.73	0.63	0.83	0.89	0.78	0.98
	Specificity	0.87	0.80	0.93	0.85	0.76	0.96
AMID6 vs. AMI	Sensitivity	0.89	0.50	1.00	1.00	1.00	1.00
	Specificity	0.95	0.90	1.00	0.96	0.90	1.00

sponse. Tiret et al [27] related genetic variability in IL18, IL18R1 and IL18RAP to cardiovascular mortality. The gene SAMSN1 was found to be preferentially expressed in mast cells [28] containing large amounts of heparin and histamine. Protein encoded by the PFKFB2 gene mediates control of glycolysis in eukaryotes. IRS2 gene was shown to be associated with severe obesity and insulin sensitivity in Type II diabetic patients [29, 30]. The gene VNN3 reappears also with this contrast. Gene PHACTR1 was cited for the association with CAD, CVD and MI based on several recent genome-wide studies [31, 32]. The ERLIN1 gene was recently identified as a member of the prohibitin family of proteins that define lipid-raft-like domains of the ER [33]. Polymorphisms in FKBP5 may be associated with increased vulnerability to posttraumatic stress disorder [34]. Gene PRKDC is a central regulator of DNA double-strand break repair. Down-regulation of NPM1 was previously linked to cardiac cell differentiation [35], the DUSP1 gene was found to be associated with oxidative stress response [36]. No references in relation to CVD, CAD or MI could be found for the genes ECHDC3 and ASPRV1.

7.3 AMID6 vs. AMI

This contrast signifies population gene expression differences between the surviving cases and those who died within 6 months following the acute MI episode. Both statistical and clinical significance based on limma modeling was attained for Set ♯1. Several predictive genes are repeated here from the 'AIMD6 vs. Controls' contrast. They include ADORA3, IL18RAP, ERLIN1, ASPRV1, gene TCRB is repeated from 'AIM vs. Controls'. Strongly down-regulated genes TCRA, TCRB and AXIN2 participate in V(D)J recombination, T-cell and leukocyte differentiation, antibody-dependent cellular cytotoxicity and signal transduction. Dumont et al [37] report association of ARG1 polymorphisms with the risk of AMI and common carotid intima media thickness. Harpster et al [38] report ARG1 as the single most highly induced transcript in post-myocardial infarction subjects. Complement regulator CD59 is a potent inhibitor of the membrane attack complex (MAC). Acosta et al suggest that in diabetes glycation–inactivation of endothelial CD59 would contribute to the development of vascular complications [39]. CD59 was shown to protect against atherosclerosis by restricting the MAC formation [40]. Transcription factor ETS2 was recently identified to determine inflammatory state of endothelial cells in advanced atherosclerotic lesions [41]. Meta-analysis of 15 GWAS studies [42] revealed a few genes associated with resting heart rate, a predictor of cardiovascular mortality, including BCAT1 gene.

Number of genes and transcripts identified in our study as being associated with the outcome represent novel candidates which were not previously linked to the incidence of acute myocardial infarction. We illustrate four up-regulated (AMPH, FLT3, ZNF516) and five down-regulated genes (AXIN2, CLYBL, KIF20B, TCEA3, TCRA) identified in our study. Amphiphysin-synaptic vesicle-associated protein (AMPH) observed in Stiff-Man syndrome includes SH3 domains in C-terminal region. Up-regulated activity of the gene FLT3 is linked to hematopoiesis activation, angiogenesis, hematopoietic progenitor cell differentiation, macrophage differentiation and interleukin, natural killer activation. ZNF516 (zinc finger protein 516) is a gene family member, coordinating Zn-ions in stabilizing different cellular processes. AXIN2 plays important role in beta-catenin stabilization. CLYBL encodes beta-like citrate lyase. KIF20B, kinesin family member 20B, is a structure required for completion of cytokinesis. The group of down-regulated genes includes the gene TCEA3 providing interaction with the enzyme RNA polymerase II during the transcription process. TCRA is a T-cell antigen receptor, alpha-subunit.

Furthermore, we identified novel up-regulated (LOC645649, c13orf18, AW337887, c7orf53, c2orf58, CN484989) and down-regulated structures (LOC130951, CR596519, BM682470, CR592039, X00437) that are listed in Table 3. Recently, Puigdecanet et al [43] identified C13orf18 being part of a molecular signature characterized with an upregulation of inflammatory genes related to neutrophil activation and thrombosis.

Text mining search of medical literature performed at PubGene.com using MeSH term 'Myocardial Infarction' and the set of genes found to be predictive for MI (see Table 3) rendered 10 genes most cited for their association with MI plus four genes (ADORA3, FOS, ARG1, CD 59) indicated in our study which appear to be related to these genes. Figure 2 shows that the four genes are linked to positive regulation of Interleukin 12 production (ADORA3), co-regulation of insulin secretion (FOS), regulation of reverse cholesterol transport, co-regulation of insulin secretion, cholesterol absorption, cardiac muscle contraction and glycoprotein biosynthetic process (ARG1) and activation of membrane attack complex (CD59). Supplementary Figure S1 in [44] uncovers relationships of these four genes with other genes. Biological processes associated with the genes shown in Table 3 are summarized in supplementary Table S13 in [44].

Only a partial agreement with the gene sets reported to be associated with the incidence of MI from other studies may in part be explained by the differences in statistical design, studied population and respective sample sizes, use of non-homogenous subgroups (diabetics, nondiabetic patients), population distributions of related risk factors, therapy (especially use of statins), exclusion criteria, existence of concomitant diseases and other inflammatory conditions, heart failure, smoking, extent of non-coronary atherosclerosis, and examination of circulating cells and other cells in tissues.

Due to significant costs involved in microarray analysis our study is limited by a relatively small sample size. Synthesis of the genetic and clinical information gathered from genomic studies is expected to refine personalized approaches to managing the risk of CAD. Genetic risk scores

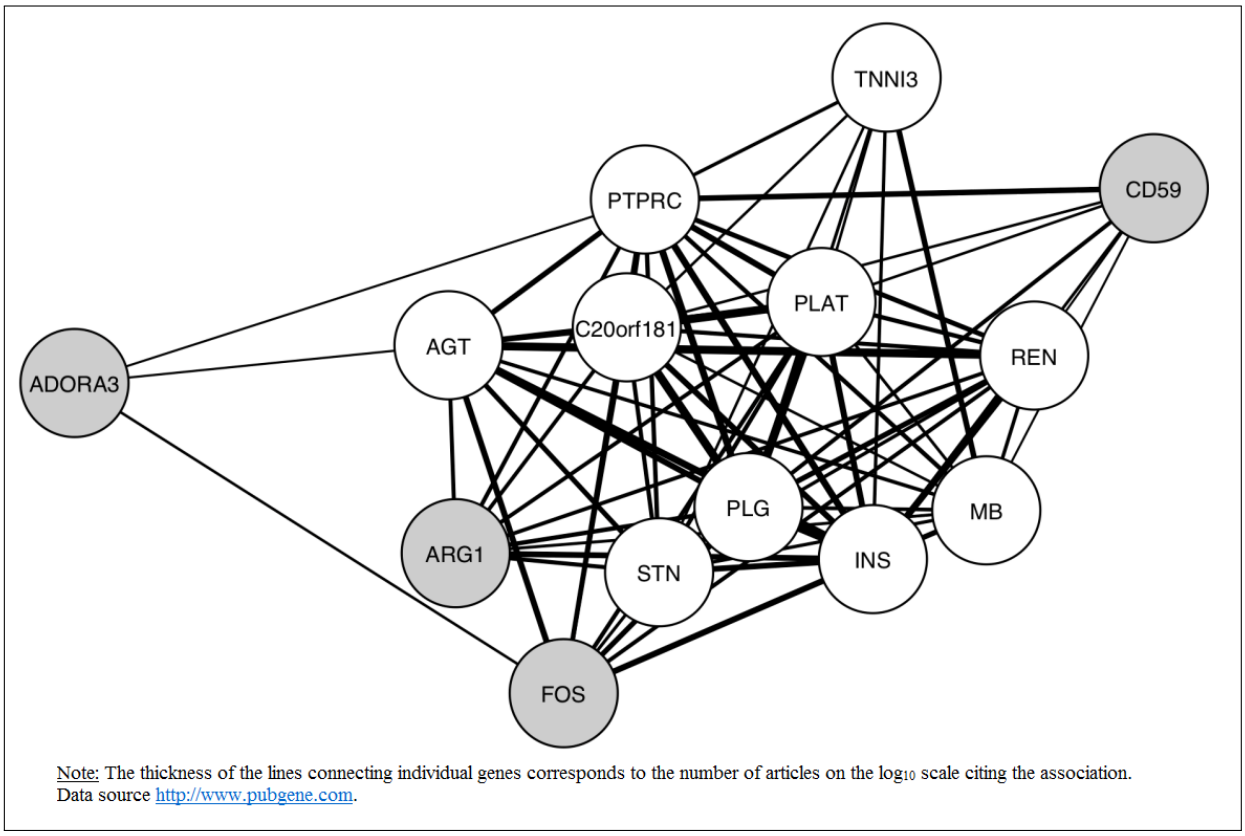

Figure 2: Literature search of 10 genes most frequently cited for their association with MI and their relation to predictive genes identified in Table 3.

derived from several functional single nucleotide polymorphisms (SNPs) or haplotypes in multiple genes may improve the prediction of CAD.

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Disclosures

The authors declare no conflict of interest.

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