Towards Clinical Bioinformatics: Advancing Genomic Medicine with Informatics Methods and Tools

Findings from the IMIA Yearbook of Medical Informatics 2004

P. Knaup[1], E. Ammenwerth[2], R. Brandner[1], B. Brigl[3], G. Fischer[2], S. Garde[1], E. Lang[4], R. Pilgram[2], F. Ruderich[5], R. Singer[5], A. C. Wolff[1], R. Haux[2], C. Kulikowski[6]

[1]University of Heidelberg, Department of Medical Informatics, Heidelberg, Germany
[2]UMIT — University for Health Sciences, Medical Informatics and Technology, Innsbruck, Austria
[3]University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany
[4]University of Applied Sciences Darmstadt, Information and Knowledge Management, Darmstadt, Germany
[5]University of Applied Sciences Heilbronn, Department of Medical Informatics, Heilbronn, Germany
[6]Rutgers University, Department of Computer Science, Piscataway, New Jersey, USA

Summary

Objectives: To summarize the challenges facing clinical applications in the light of growing research results in genomic medicine and bioinformatics.
Methods: Analysis of the contents of the Yearbook of Medical Informatics 2004 of the International Medical Informatics Association (IMIA).
Results: The Yearbook of Medical Informatics 2004 includes 32 articles selected from 22 peer-reviewed scientific journals. A special section on clinical bioinformatics highlights recent developments in this field. Several guest editors review the promises and limitations of available methods and resources from biomedical informatics that are relevant to clinical medicine. Integrated data and knowledge resources are generally regarded to be central and key issues for clinical bioinformatics. Further review papers deal with public health implications of bioinformatics, knowledge management and trends in health care education. The Yearbook includes for the first time a section on the history of medical informatics, where the significant impact of the Reisensburg protocol 1973 on international health and medical informatics education is examined.
Conclusions: Close collaboration between bioinformatics and medical informatics researchers can contribute to new insights in genomic medicine and contribute towards the more efficient and effective use of genomic data to advance clinical care.

Keywords

Medical informatics, International Medical Informatics Association, clinical bioinformatics, yearbook

Introduction to Clinical Bioinformatics

The rapid, substantial completion of the human genome project [1, 2] is often given as a reason for stating that we have now moved into a post-genomic era [3, 4]. Large scale genomic data are available and biomedical informatics research provides the resources that can represent, analyse and visualize these data flexibly and efficiently (e.g. [5-9]). The availability of genomic and proteomic information contributes to research in genomic medicine [10, 11]. The results will have a considerable impact on clinical research and clinical practice [12, 13]. To use these research results for patient care, clinical application systems have to face new challenges [14, 15] like integrating genomic data into the electronic patient record [4].

According to [16] "Bioinformatics is defined as the application of computational techniques to biology, in particular, molecular biology. The goal is to provide computer-based methods for coping with and interpreting large volumes of diverse data obtained by high-throughput approaches". The broad dissemination of genomic information (cf. e.g. [17-19]) will not only change the patient-physician relationship but also bring about closer cooperation between bioinformatics and medical informatics researchers [20-24].

The International Medical Informatics Association (IMIA) has already recognized the growing importance of clinical bioinformatics research and established a section on bioinformatics in 2001. The rapid expansion of this field has now led the recent Yearbook 2004 to use clinical bioinformatics as its main theme. In this paper we summarize its contents and discuss how the selected research contributes to the development of clinical bioinformatics.

The IMIA Yearbook of Medical Informatics 2004

The IMIA Yearbook of Medical Informatics has been an annual publication of IMIA since 1992 [25]. The aim of the yearbook is to give an overview of the latest outstanding research contributions in the field of health and medical informatics [26-28]. Recently published excellent scientific papers in the area of medical informatics are considered as candidates for inclusion, and are ranked according to criteria of: topic significance, coverage of literature, quality of research, results and presentation [29]. The papers in the IMIA yearbook for 2004 were originally published between April

2002 and March 2003. This years' special section on 'clinical bioinformatics' is accompanied by the 'traditional' sections on health and clinical management, patient records, health information systems, medical signal processing, biomedical imaging, decision support, knowledge representation and management and education and consumer informatics. Besides these sections, the yearbook for 2004 contains 4 invited review papers, 5 papers on research and education, 8 synopses of papers included in the different disciplinary fields covered, and comprehensive information on IMIA's organisational structure and activities.

In the following sections we summarize the content of the IMIA Yearbook 2004 and discuss it in the context of clinical bioinformatics. Table 1 gives an overview of the papers and authors.

Preface

In the preface *'Towards Clinical Bioinformatics'* Russ B. Altman from the Department of Genetics at Stanford University outlines the necessity of supporting genomic medicine with informatics to advance clinical care and emphasizes the ubiquity of the WWW as a source of health information. He foresees that progress in the disciplines of clinical bioinformatics and consumer informatics will result in a change of the physician-patient relationship. Additionally, he states the relevance of the yearbook for providing specialists a broad overview of the field of medical informatics.

Information on IMIA

IMIA regards itself as a bridge organisation which strives to "play a major global role in the application of information science and technology in the field of healthcare and research in medical, health and bioinformatics" [30]. The IMIA Yearbook 2004 summarizes the goals and organisational structure of IMIA in detail. K. C. Lun, the IMIA president in 2003, provides a progress report. Descriptions of forty IMIA societies from all continents as well as the 19 IMIA Working Groups are given, and Evelyn Hovenga as a guest editor introduces the Special Interest Group on

Nursing Informatics. Structure, objectives and activities of IMIA regional members are presented for EFMI (European) by Arie Hasman, APAMI (Asian Pacific) by Chun Por Wong, HELINA (African) by Sedick Isaacs, IMIA-Lac (Latin-American and Caribbean) by Lincoln A. de Assis Moura Jr. and NAMI (North American) by Jochen Moehr and Charles Safran. Finally, the Healthcare Information and Management Systems Society (HIMSS) is represented as institutional member and the International Federation of Health Records Organizations (IFHRO) as an affiliated member organization.

Review Section

The Review Section of the IMIA Yearbook presents invited articles contributing directly and indirectly to the Yearbook topic. Englbrecht and colleagues from Neuherberg (Germany) give a comprehensive overview of genome and genome-related information resources relevant to clinical research. They discuss the challenges and limitations of how to analyze and structure the enormous amount of heterogeneous genomic data. Maojo and Martin-Sanchez from Madrid (Spain) point out that the fields of public health and epidemiology are eager to use bioinformatics methods and tools for managing genomic information. Researchers, practitioners and policy makers should carefully address all ethical and social implications that arise from applications of bioinformatics research results. The article by Stefanelli from Pavia (Italy) carefully investigates the role of cognitive-organisational factors in adapting systems to user working practices. He contends that this should lead to the design and deployment of more flexible and interoperable health information systems, which are able to support collaborative work and knowledge management. This could also include bioinformatics knowledge. Progress in information and communication technology is not only advancing biomedical research but also health care education. Dev from Stanford (USA) analyzes these trends, available resources and discusses research opportunities that arise from the shift towards more active learning environments.

Education and Research in Medical Informatics

Every year the IMIA Yearbook provides a sample from the variety of educational and research approaches that characterize medical informatics throughout the world. This year a description of the biomedical informatics training programme at Vanderbilt University (Nashville, USA), which has evolved substantially over the past decade, is given by Aronsky and colleagues.

Lun from Taiwan summarizes the results of an IMIA workshop on 'Challenges of Medical Informatics' focusing on the following major aspects: application of genomic and proteomic data in the clinical management and treatment of patients, development of a wide-area network of health information systems which can support the prediction and prevention of bioterrorism, and the deployment of telemedicine approaches for remote medical rehabilitation.

Marquez et al. report on their four-year experience with a Brazil/USA training programme, which has had the aim of reducing the severe shortage of health informatics specialists in Brazil. Masic from Sarajevo summarizes the approaches to medical informatics education at biomedical faculties in Bosnia and Herzegovina.

In Spain a National University for Distance Education was founded in 1972, and Diez from Madrid describes this institution with a strong emphasis on the course on Probability and Statistics in Medicine, which is supported by a software tool.

History of Medical Informatics

To document the beginnings and evolution of the field of medical informatics the editors of the Yearbook 2004 for the first time included a section on the *history of medical informatics*. The Reisensburg protocol of 1973 on medical informatics education is a summary of the results of an invited workshop in Germany. The aim was to define contents and approaches to education in health informatics. Moehr from Victoria (Canada) translated the protocol as a participant of the workshop, so that it can be presented in the Yearbook. In the accom-

Table 1 Table of contents of IMIA Yearbook of Medical Informatics 2004

Preface	Altmann RB. Towards Clinical Bioinformatics.
Editorial	Kulikowski CA, Haux R. Towards Clinical Bioinformatics.
Review Section	Englbrecht CC, Han M, Mader MT, Osanger A, Mayer KFX. Curated databases and their role in clinical bioinformatics. Maojo V, Martin-Sanchez F. Public health implications of bioinformatics. Stefanelli M. Knowledge Management in Health Care Organizations. Dev P. Trends in Health Care Education: Research Opportunities in Teaching and Learning.
Research and Education Section	Aronsky D, Aliferis CF, Johnson KB, Lorenzi N, Miller RA. Biomedical Informatics Training Program at Vanderbilt University. Díez FJ. Teaching probabilistic medical reasoning with the Elvira software. Lun KC. New Challenges for Health Informatics. Marques EP, Marin HF, Massad E, Ohno-Machado L. Training in Health Informatics in Brazil. Masic I. Medical Informatics Education in Bosnia and Herzegovina.
History of Medical Informatics	Haux R, Kulikowski C. Introduction: A New Section in the IMIA Yearbook. Moehr J. The Quest for Identity of Health Informatics and for Guidance to Education in it – The German Reisensburg Conference of 1973 Revisited. Moehr J. English Translation of the Minutes of the Invitational Workshop - Goals, Contents and Methods for Education in Medical Informatics.
Special Section: Towards Clinical Bioinformatics	de Groen P. Towards Clinical Bioinformatics. Synopsis. Antoniadis A, Lambert-Lacroix A, Leblanc F. Effective dimension reduction methods for tumor classification using gene expression data. *Bioinformatics* 2003 Mar 22;19(5):563-70. Beerenwinkel N, Schmidt B, Walter H, Kaiser R, Lengauer T, Hoffmann D, Korn K, Selbig J. Diversity and complexity of HIV-1 drug resistance: a bioinformatics approach to predicting phenotype from genotype. *Proc Natl Acad Sci* USA 2002 Jun 11;99(12):8271-6. Cariou A, Chiche JD, Charpentier J, Dhainaut JF, Mira JP. The era of genomics: impact on sepsis clinical trial design. *Crit Care Med* 2002 May;30(5 Suppl):S341-8. Martin-Sanchez F, Maojo V, Lopez-Campos G. Integrating genomics into health information systems. *Methods Inf Med* 2002;41(1):25-30. Nagl SB. Computational function assignment for potential drug targets: from single genes to cellular systems. *Curr Drug Targets* 2002 Oct;3(5):387-99.
Section 1: Health and Clinical Management	Monga B. Health and Clinical Management. Synopsis. Eccles M, McColl E, Steen N, Rousseau N, Grimshaw J, Parkin D, Purves I. Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial. *BMJ* 2002 Oct 26;325(7370):941. Hahn U, Romacker M, Schulz S. MEDSYNDIKATE—a natural language system for the extraction of medical information from findings reports. *Int J Med Inf* 2002 Dec 4;67(1-3):63-74. Oniki TA, Clemmer TP, Pryor TA. The effect of computer-generated reminders on charting deficiencies in the ICU. *J Am Med Inform Assoc* 2003 Mar-Apr;10(2):177-87. Zeng Q, Cimino JJ, Zou KH. Providing concept-oriented views for clinical data using a knowledgebased system: an evaluation. *J Am Med Inform Assoc* 2002 May-Jun;9(3):294-305.
Section 2: Patient Records	Shabo A. Structuring the Medical Narrative in Patient Records – A Further Step towards a Multi-Accessible EHR. Synopsis. Brandner R, van der Haak M, Hartmann M, Haux R, Schmücker P. Electronic signature for medical documents—integration and evaluation of a public key infrastructure in hospitals. *Methods Inf Med* 2002;41(4):321-30. Branston LK, Greening S, Newcombe RG, Daoud R, Abraham JM, Wood F, Dallimore NS, Steward J, Rogers C, Williams GT. The implementation of guidelines and computerised forms improves the completeness of cancer pathology reporting. The CROPS project: a randomised controlled trial in pathology. *Eur J Cancer* 2002 Apr;38(6):764-72. Ross SE, Lin CT. The effects of promoting patient access to medical records: a review. *J Am Med Inform Assoc* 2003 Mar-Apr;10(2):129-38.

Table 1 (continued)

	Weir CR, Hurdle JF, Felga MA, Hoffman JM, Roth B, Nebeker JR. Direct text entry in electronic progress notes. An evaluation of input errors. *Methods Inf Med* 2003;42(1):61-7.
Section 3: Health Information Systems	Winter A. Health Information Systems. Synopsis.
	Doupi P, van der Lei J. Towards personalized Internet health information: the STEPPS architecture. *Med Inform Internet Med* 2002 Sep;27(3):139-51.
	Fraenkel DJ, Cowie M, Daley P. Quality benefits of an intensive care clinical information system. *Crit Care Med* 2003 Jan;31(1):120-5.
	Lazarus R, Kleinman K, Dashevsky I, Adams C, Kludt P, DeMaria A Jr, Platt R. Use of automated ambulatory-care encounter records for detection of acute illness clusters, including potential bioterrorism events. *Emerg Infect Dis* 2002 Aug;8(8):753-60.
	Mekhjian HS, Kumar RR, Kuehn L, Bentley TD, Teater P, Thomas A, Payne B, Ahmad A. Immediate benefits realized following implementation of physician order entry at an academic medical center. *J Am Med Inform Assoc* 2002 Sep-Oct;9(5):529-39.
Section 4: Medical Signal Processing	Dua S, Iyengar SS. Advances in Medical Signal Processing. Synopsis.
	Kim JH, Kohane IS, Ohno-Machado L. Visualization and evaluation of clusters for exploratory analysis of gene expression data. *J Biomed Inform* 2002 Feb;35(1):25-36.
	Duverney D, Gaspoz JM, Pichot V, Roche F, Brion R, Antoniadis A, Barthelemy JC.
	High accuracy of automatic detection of atrial fibrillation using wavelet transform of heart rate intervals. *Pacing Clin Electrophysiol* 2002 Apr;25(4 Pt 1):457-62.
	Signorini MG, Magenes G, Cerutti S, Arduini D. Linear and nonlinear parameters for the analysis of fetal heart rate signal from cardiotocographic recordings. *IEEE Trans Biomed Eng.* 2003 Mar;50(3):365-74.
	Zhang X-Y, Chen F, Zhang Y-T, Agner SC, Akay M, Lu Z-H, Waye MMY, Tsui SK-W. Signal Processing Techniques in Genomic Engineering. *Proceedings of the IEEE* 2002 Dec; 90(12):1822-33.
Section 5: Biomedical Imaging	Pullan A. Biomedical Imaging. Synopsis.
	Frangi AF, Rueckert D, Schnabel JA, Niessen J. Automatic construction of multiple-object three-dimensional statistical shape models: application to cardiac modeling. *IEEE Trans Med Imaging* 2002 Sep;21(9):1151-66.
	McInerney T, Hamarneh G, Shenton M, Terzopoulos D. Deformable organisms for automatic medical image analysis. *Med Image Anal* 2002 Sep;6(3):251-66.
	Shenton ME, Gerig G, McCarley RW, Szekely G, Kikinis R. Amygdala-hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data. *Psychiatry Res* 2002 Aug 20;115(1-2):15-35.
Section 6: Decision Support, Knowledge Representation and Management	Kozmann G. Decision Support, Knowledge Representation and Management. Synopsis.
	Morrison ML, McCluggage WG, Price GJ, Diamond J, Sheeran MR, Mulholland KM, Walsh MY, Montironi R, Bartels PH, Thompson D, Hamilton PW.
	Expert system support using a Bayesian belief network for the classification of endometrial hyperplasia. *J Pathol* 2002 Jul;197(3):403-14.
	Peleg M, Yeh I, Altman RB. Modeling biological processes using workflow and Petri Net models. *Bioinformatics* 2002 Jun;18(6):825-37.
	Peters A, Lausen B, Michelson G, Gefeller O. Diagnosis of glaucoma by indirect classifiers. *Methods Inf Med 2003;42(1):99-103.*
	Prado M, Roa L, Reina-Tosina J, Palma A, Milan JA. Virtual center for renal support: technological approach to patient physiological image. *IEEE Trans Biomed Eng* 2002 Dec;49(12):1420-30.
Section 7: Education and consumer informatics	Safran C. Education and Consumer Informatics – the need for collaborative tools. Synopsis.
	Harden RM, Hart IR. An international virtual medical school (IVIMEDS): the future for medical education? *Med Teach* 2002 May;24(3):261-7.
	Kamin C, O'Sullivan P, Deterding R, Younger M. A comparison of critical thinking in groups of third-year medical students in text, video, and virtual PBL case modalities. *Acad Med* 2003 Feb;78(2):204-11.
	Neafsey PJ, Strickler Z, Shellman J, Chartier V. An interactive technology approach to educate older adults about drug interactions arising from over-the-counter self-medication practices. *Public Health Nurs* 2002 Jul-Aug;19(4):255-62.
	Zeng Q, Kogan S, Ash N, Greenes RA, Boxwal AA. Characteristics of consumer terminology for health information retrieval. *J Am Med Inform Assoc* 2002 May-Jun;9(3):294-305.

panying article he gives the background and results of a literature review on the effects of the Reisensburg meeting. He comes to the conclusion that it had a significant international impact on medical informatics education and its establishment as a separate discipline.

Selected Papers and Synopses

For the IMIA Yearbook 2004, 32 original papers from 22 different international journals were selected. After the review process was completed, experts in each field were invited to be guest editors and write synopses based on the papers selected for each section.

The guest editor for the special section *'Towards Clinical Bioinformatics'* is de Groen from Rochester (USA). He sees the use of genetic and proteomic data for clinical decision making as a great challenge for bioinformatics research. He indicates how the five articles in this section can contribute to the necessary infrastructure. The selected papers present a data reduction method for microarray experiments in a way that the results can still be classified, decision algorithms to predict drug resistance of HIV type-1 virus based on genetic information, understanding the bacterial genome and its interaction with the human genome, computational techniques for function prediction based on the sequence-structure-function paradigm and a framework for integrating genomic data into health information systems. Integrated data resources are generally regarded to be a key issue for clinical bioinformatics.

The section on *Health and Clinical Management* is guest edited by Monga from Abidjan (Ivory Coast). It comprises two evaluation studies, one on the effect of a decision support system, which implements evidence-based guidelines for the management of asthma/angina patients and the other on the effect of computer-generated reminders on nurse charting deficiencies in intensive care units. The other articles in the section describe and evaluate a knowledge-based system that generates a concept-oriented view for clinical data and a natural language processor which automatically extracts medical information from finding reports. Monga concludes that the

articles have shown that computerized health information systems can improve the quality of health and clinical management if they are adequately integrated in the workflow of health care professionals.

According to the guest editor for the section on *Patient Records* Shabo from Haifa (Israel), clinical documents serve – in the current view of patient records – as its fundamental constituents. This is underlined by the papers of this section on electronic signatures for clinical documents, reporting guidelines and form-based reports, and on direct text entry in electronic progress notes. The section is completed with a review paper on the benefits and risks of patient access to medical records.

Winter from Leipzig (Germany) – guest editor for the section on *health information systems* – has observed the worldwide trend towards a better coordination of care, e.g. by a patient-oriented care process spreading over institutional boarders. In this context he analyzes the papers on integrating patient data with Internet health information with the aim of patient education and empowerment, a monitoring system for detection of acute illness clusters, which is used as a regional information system, and two evaluation studies, one of an application of a clinical information system in an intensive care unit and the other on physician order entry.

The guest editors Dua and Iyengar from Louisiana (USA) of the section on *Medical Signal Processing* regard their papers as a "unique assortment of research articles addressing some exigent and important problems in the area of medical signal processing". These are a computational framework for visualisation and evaluation of clusters for exploratory analyses of gene expression data, a wavelet transform based approach for automatic detection of arterial fibrillation, a methodological approach for fetal monitoring including spectral parameters from autoregressive models and nonlinear algorithms, and an overview of the application of signal processing techniques in genomic engineering.

Pullan from Auckland (New Zealand) introduces in his synopsis the history and current techniques of the field *Biomedical Imaging*. The papers in the section of the same name all deal with MRI data set, but

according to Pullan they are much more widely applicable. They deal with the construction of three-dimensional shape models from a series of MR images, automatic image segmentation by combining deformable model methods with concepts from the field of artificial life, and clinical application of three-dimensional shape models to volumetric MR data of the brain.

The guest editor for the section on *Decision Support, Knowledge Representation and Management,* Kozman from Veszprém (Hungary) points out that the selected articles address different novel technologies for knowledge management and decision support. These are a Bayesian belief network to classify endometrial hyperplasia, the representation of knowledge about complex biological processes using workflow and Petri Net models, the combination of medical and statistical knowledge to improve diagnostic performance in glaucoma, and a tele-healthcare architecture for renal support involving quantitative models for patients and therapy equipment. Kozman argues that the application of these technologies in addition to human abilities can support routine decisions as well as complex diagnostic and therapeutic decisions.

Safran from Harvard (USA) emphasizes the need for collaborative tools in *Education and Consumer Informatics.* In this section the following approaches are introduced: An international virtual medical school that embodies a blended curriculum with e-learning approaches and face-to-face teaching, an exploratory study on how the mode of case presentation affects the way of students' critical thinking using problem-based learning, an approach using interactive technology to educate older adults about potential drug interactions, and a study on the terminology consumers use for health information retrieval. Safran concludes that students and citizens will both benefit from research and advances in these fields.

Conclusions and Outlook

The papers selected for the IMIA Yearbook 2004 clearly indicate that contributing to high quality patient care [31-33] and efficient patient management is a major task of

medical informatics. This is underlined by the new challenges arising from the emerging discipline of bioinformatics and the development of genomic medicine. Not only in the field of clinical bioinformatics, new information and communication technologies increase the potential of medical informatics methods and tools, and offer new opportunities. As an example, it can be observed that the ubiquitous availability of clinical information is a major trend in medical informatics research [34, 35]. The next IMIA Yearbook – which is to appear in March, 2005 – will have 'Ubiquitous Health Care Systems' as its theme. It will focus on the medical informatics contributions that enable the development and widespread dissemination of these systems.

Up-to-date information about current and future issues of the IMIA Yearbook is available at http://www.yearbook.uni-hd.de.

References

1. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature 2001; 409: 860-921.
2. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. Science 2001; 291: 1304-51.
3. Voit EO. Models-of-data and models-of-processes in the post-genomic era. Math Biosci 2002; 180: 263-74.
4. Maojo V, Martin-Sanchez F, Billhardt H, Iakovidis I, Kulikowski C. Establishing an agenda for biomedical informatics. Methods Inf Med 2003; 42: 121-5.
5. Friend SH. How DNA microarrays and expression profiling will affect clinical practice. BMJ 1999; 319: 1306-7.
6. Bodenreider O, Mitchell JA. Graphical visualization and navigation of genetic disease information. Proc AMIA Symp 2003; 792.
7. Kellam P, Holzerlandt R, Gramoustianou E, Jenner R, Kwan A. Viral bioinformatics: computational views of host and pathogen. Novartis Found Symp 2003; 254: 234-47; discussion 247-52.

8. Kikuno R, Nagase T, Nakayama M, Koga H, Okazaki N, Nakajima D, Ohara O. HUGE: a database for human KIAA proteins, a 2004 update integrating HUGEppi and ROUGE. Nucleic Acids Res 2004; 32 Database issue: D502-4.
9. Peri S, et al. Human protein reference database as a discovery resource for proteomics. Nucleic Acids Res 2004; 32 Database issue: D497-501.
10. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. JAMA 2001; 285: 540-4.
11. Subramanian G, Adams MD, Venter JC, Broder S. Implications of the human genome for understanding human biology and medicine. JAMA 2001; 286: 2296-307.
12. Collins FS, Guttmacher AE. Genetics moves into the medical mainstream. JAMA 2001; 286: 2322-4.
13. McKusick VA. The anatomy of the human genome: a neo-Vesalian basis for medicine in the 21st century. JAMA 2001; 286: 2289-95.
14. Kulikowski CA. The Micro-Macro Spectrum of Medical Informatics Challenges: From Molecular Medicine to Transforming Health Care in a Globalizing Society. Methods Inf Med 2002; 41: 20-4.
15. Martin-Sanchez F, et al. Synergy between medical informatics and bioinformatics: facilitating genomic medicine for future health care. J Biomed Inform 2004; 37: 30-42.
16. Warner GC, Reis PP, Makitie AA, Sukhai MA, Arora S, Jurisica I, Wells RA, Gullane P, Irish J, Kamel-Reid S. Current applications of microarrays in head and neck cancer research. Laryngoscope 2004; 114: 241-8.
17. Riva A, Kohane IS. A web-based tool to retrieve human genome polymorphisms from public databases. Proc AMIA Symp 2001; 558-62.
18. Mitchell JA, McCray AT, Bodenreider O. From phenotype to genotype: issues in navigating the available information resources. Methods Inf Med 2003; 42: 557-63.
19. Crass T, et al. The Helmholtz Network for Bioinformatics: an integrative web portal for bioinformatics resources. Bioinformatics 2004; 20: 268-70.
20. Altman RB. The interactions between clinical informatics and bioinformatics: a case study. JAMIA 2000; 7: 439-43.
21. Kohane IS. Bioinformatics and clinical informatics: the imperative to collaborate. JAMIA 2000; 7: 512-6.
22. Miller PL. Opportunities at the intersection of bioinformatics and health informatics: a case study. JAMIA 2000; 7: 431-8.
23. McDonald CJ. Hickam 2000: the maturation of, and linkages between, medical informatics and bioinformatics. J Lab Clin Med 2001; 138: 359-66.
24. Maojo V, Kulikowski CA. Bioinformatics and medical informatics: collaborations on the road to genomic medicine? JAMIA 2003; 10: 515-22.
25. van Bemmel JH, Mc Cray AT. IMIA Yearbook of Medical Informatics. Stuttgart: Schattauer. Annual appearance since 1992. Editors since 2001: Haux R, Kulikowski CA.

26. Ammenwerth E, Knaup P, Maier C, Mludek V, Singer R, Skonetzki S, Wolff AC, Haux R, Kulikowski C. Digital Libraries and Recent Medical Informatics Research – Findings from the IMIA Yearbook of Medical Informatics 2001. Methods Inf Med 2001; 40: 163-167.
27. Kulikowski C, Ammenwerth E, Bohne A, Ganser K, Haux R, Knaup P, Maier C, Michel A, Singer R, Wolff AC. Medical Imaging Informatics and Medical Informatics: opportunities and constraints. Findings from the IMIA yearbook of Medical Informatics 2002. Methods Inf Med 2002; 41: 183-9.
28. Ammenwerth E, Haux R, Kulikowski C, Bohne A, Brandner R, Brigl B, Fischer G, Garde S, Knaup P, Ruderich F, Schubert R, Singer R, Wolff AC. Medical informatics and the quality of health: new approaches to support patient care – findings from the IMIA Yearbook of Medical Informatics 2003. Methods Inf Med 2003; 42: 185-9.
29. Ammenwerth E, Wolff AC, Knaup P, Ulmer H, Skonetzki S, van Bemmel JH, Mc Cray AT, Haux R, Kulikowski C. Developing and Evaluating Criteria to Help Reviewers of Biomedical Informatics Manuscripts. JAMIA 2003; 10: 512-4.
30. Haux R, Kulikowski C. IMIA Yearbook of Medical Informatics. Stuttgart: Schattauer. Annual appearance since 1992. Editors since 2001: Haux R, Kulikowski CA.
31. Bates DW, Cohen M, Leape LL, Overhage JM, Shabot MM, Sheridan T. Reducing the Frequency of Errors in Medicine Using Information Technology. JAMIA 2001; 8: 299-308.
32. Ball MJ, Garets DE, Handler TJ. Leveraging IT to Improve Patient Safety. In: Haux R, Kulikowski CA. IMIA Yearbook of Medical Informatics. Stuttgart: Schattauer 2003; 153-158.
33. Hasman A, Safran C, Takeda H. Quality of health care: informatics foundations. Methods Inf Med 2003; 42: 509-18.
34. Pierre S. Mobile computing and ubiquitous networking: concepts, technologies and challenges. Telematics and Informatics 2001; 18: 109-31.
35. Kunze C, Grossmann U, Stork W, Muller-Glaser KD. Application of ubiquitous computing in personal health monitoring systems. Biomed Tech (Berl) 2002; 47 Suppl 1 Pt 1: 360-2.

Correspondence to:
Dr. Petra Knaup
University of Heidelberg
Department of Medical Informatics
Im Neuenheimer Feld 400
69120 Heidelberg
Germany
E-mail: petra_knaup@med.uni-heidelberg.de