THE CROATIAN ACADEMY OF SCIENCES AND ARTS

The Department of Biomedical Sciences in Rijeka

JEAN MONNET INTER - UNIVERSITY CENTRE OF EXCELLENCE OPATIJA

UNIVERSITY OF RIJEKA

Faculty of Law

Faculty of Medicine

Department of Biotechnology

THE CROATIAN MEDICAL ASSOCIATION – Branch office Rijeka

21st Symposium

PERSONALIZED MEDICINE: BASIC AND SOCIAL ASPECTS

Challenges for social security systems

Rijeka, November 20-21, 2017

1st day: November 20th, 2017
10:00 am
University Campus Rijeka, University Departments, Lecture Hall 0-030,
Radmile Matejčić 2, Rijeka

Scientific Committee

Daniel Rukavina, president

Nada Bodiroga - Vukobrat, Krešimir Pavelić

Organizing Committee

Nada Bodiroga - Vukobrat, president

Marija Kaštelan Mrak, Ana Pošćić, Adrijana Martinović, Gordan Gulan

Registration: 9,00 – 10:00 am

Participants who want a certificate from the Croatian Medical Chamber need to register on the day of the symposium.
Lunch and refreshments during break will be provided free of charge.
Parking is free and provided in the building of the Student Center Rijeka (Radmile Matejčić 5)

Information

Željana Mikovčić, Department of Biomedical Sciences in Rijeka,
Radmile Matejčić 2, Rijeka
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P R O G R A M
OPENING
(10,00 – 10,30 h)

Introduction

Daniel Rukavina, Head, Department of Biomedical Sciences in Rijeka, Croatian Academy of Sciences and Arts, Rijeka, Croatia

Nada Bodiroga - Vukobrat, PhD., Professor, Faculty of Law, University of Rijeka, Rijeka, Croatia, President of the Organizing Committee

Welcome speeches

Tomislav Rukavina, M.D., PhD., Professor, Dean of the Medical Faculty, Rijeka, Croatia

Vesna Crnić - Grotić , PhD., Professor, Dean of the Faculty of Law, Rijeka, Croatia

Snježana Prijić - Samaržija, PhD., Professor, Rector of the University of Rijeka, Rijeka, Croatia

10,30 – 12,15 h

I. PERSONALIZED MEDICINE – MEDICAL ASPECTS

Chairmen: Daniel Rukavina and Nada Bodiroga Vukobrat

Hans - Peter Zenner, M.D., PhD., Chairman Ethics Commission, Medical Faculty, University of Tübingen, Tübingen, Germany

Personalized Medicine - Impact on Ethics and Processes

Ivan Đikić, M.D., PhD. Professor, Institut for Biochemistry, Goethe University, Frankfurt, Germany

Understanding causes of human diseases and individual patient differences

Lunch with a panel of speakers: 12:15 – 13:15

13,15 – 15,30 h

Chairmen: Krešimir Pavelić and Sonja Pavlović

Jasna Peter Katalinić, PhD., Croatian Proteomics Society and Department of Biotechnology, University of Rijeka, Rijeka, Croatia

Potentials of mass spectrometry for personalized medicine

Sonja Pavlović, PhD., Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia

A new era of personalized medicine: CRISPR gene editing

Davor Štimac, M.D., PhD., Professor, Medical Faculty and Clinical Hospital Center Rijeka, Rijeka, Croatia
Fecal microbial transfer – Personalized medicine in gastroenterelogy

Damir Miletić, M.D., PhD., Professor, Medical Faculty and Clinical Hospital Center Rijeka, Rijeka, Croatia
MR imaging in personalized treatment planning for patients with rectal cancer

II. CLOSING REMARKS: Daniel Rukavina

2nd day - November 21st, 2017
10:00 am
Location: Faculty of Law, Hahlić 6, Rijeka

III. HEALTH ECONOMICS AND LAW IN PERSONALIZED MEDICINE

10,00 – 10,45 h

Chairmen: Nada Bodiroga Vukobrat and Hana Horak

Lucia Ruggeri, PhD., Professor, School of Law, University of Camerino, Camerino, Italy
Rethinking data protection in personalized medicine

Elvio Baccarini, PhD., Professor, Faculty of Philosophy, University of Rijeka, Rijeka, Croatia
The right to Live and Competing Needs

Coffee break: 10,45 – 11,15 h

11,15 – 13,40 h

Maks Tajnikar, PhD., Professor, Faculty of Economics, University of Ljubljana, Slovenia; **Petra Došenović Bonča,** PhD., Assistant Professor, Faculty of Economics, University of Ljubljana, Slovenia
Personalised medicine from the socio-economic perspective: evolutionary or revolutionary?

Davor Mance, PhD., Faculty of Economics, University of Rijeka, Croatia; **Diana Mance,** PhD, Department of Physics, University of Rijeka, Rijeka, Croatia;
STEM as a stem of a more cost-effective personalized medicine

Marija Kaštelan Mrak, PhD., Professor, Faculty of Economics, University of Rijeka, Croatia; **Danijela Sokolić,** PhD., Assistant Professor, Faculty of Economics, University of Rijeka, Croatia

Implementation of Personalized Medicine in Croatia: Where do we Stand and how to Proceed

Nenad Vretenar, PhD., Assistant Professor, Faculty of Economics, University of Rijeka, Croatia; **Jelena Jardas Antonić,** PhD., Assistant Professor, Faculty of Economics, University of Rijeka, Croatia

Security of data and exposure to moral hazard under GDPR

Ana Pošćić, PhD, Assistant Professor, Faculty of Law, University of Rijeka, Rijeka, Croatia

Recent EU Developments on the Reverse Payment Settlements in the European Pharmaceutical Market

Mijo Božić, PhD., LLM, University of applied sciences Ludwigsburg, Ludwigsburg, Germany

Regulatory Requirements relating to Certification of Medical Devices

Nada Bodiroga - Vukobrat, PhD., Professor, Faculty of Law, University of Rijeka, Rijeka Croatia; **Hana Horak,** PhD., Professor, Faculty of Economics and Business, University of Zagreb, Croatia

Connected Health and Data Protection in Personalised Medicine

IV. CLOSING REMARKS : Nada Bodiroga - Vukobrat

Lunch with a panel of speakers: 13:40

The scientific symposium is supported by the **Croatian Science Foundation project No. 5709** "Perspectives of maintaining the social state: towards the transformation of social security systems for individuals in personalized medicine", and the **University of Rijeka project No. 13.08.1.2.03 "Social security and market competition"** and with friendly support of **Hanns-Seidel-Stiftung.**

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Hrvatska zaklada za znanost

Personalized Medicine - Impact on Ethics and Processes

Hans - Peter Zenner
Medical Faculty, University of Tübingen, Tübingen, Germany

Individualized medicine implicates a series of ethical questions. The use of predictive information requires a balance between therapy and anonymization for the protection of third party personal rights. Predictive information may help but also may produce severe burden to patients. Thus, in addition to the right of informed consent patients should have the right of non-knowledge that may result in conflicts. Thoughts may be instrumental how to perform preventive measures without violating patients rights of autonomy and non-knowledge. A general discussion of the society may be suggested.

Understanding causes of human diseases and individual patient differences

Ivan Đikić [1,2]
[1]Institute of Biochemistry II, Frankfurt/Main, Germany
[2]Buchmann Institute for Molecular Life Sciences, Goethe University, Frankfurt/Main, Germany

The basic principle of personalized or "precision" medicine is the notion that the specific causes of diseases are rooted in individual patients' genomic, epigenetic and proteomic characteristics. Based on these premises clinical approaches to diagnosis, treatment, and prevention commonly incorporate these individual differences. For example, the unique biology and genetics of a patient's tumors often determines the progress of the disease as well as the optimal treatment strategies. Modern technologies enable us today to collect with deep resolution individual genetic and molecular markers of a patient tumor and healthy tissues before and during therapy. The high density of collected data is processed via informatics resulting in a therapeutic power to predict who is going to respond to a therapy but also after responding who is likely to relapse or what the causes of relapse might be, thus being at the frontier of personalized cancer medicine. More recently, we have started to comprehend that individualized human microbiota also has an effect on human diseases development (diabetes, allergy, cancer, neurodegeneration) and success of personalized medicine. This topic will be discussed focusing on the influence on microbiota on cell metabolism in gastrointestinal tumors. Lastly, diseases in general have a complex multicomponent process during their onset and progression. However, recent evidence indicates to common molecular principles are shared between different diseases such as cancer, neurodegeneration and infectious diseases. Few recent examples from our lab will be presented to indicate how this new knowledge has an impact in clinics on therapy efficacy and individualized approaches to treat different human diseases.

Potentials of Mass Spectrometry in Personalized Medicine

Jasna Peter Katalinić
Croatian Proteomics Society, Rijeka, Croatia

Mass spectrometry (MS) is an analytical technique which identifies molecular composition of compounds as charged entities in the gas phase without changes to their structure. The applications of mass spectrometry are broad and powerful, encompassing analysis of gas, liquid and solid materials in chemistry, physics, biology and medicine. In this way MS became a most general source of structural information in environmental analysis, isotope dating and tracking, trace gas analysis, proteomics, lipidomics, metabolomics, and finally in clinical applications and forensics.

The concept of personalized medicine was implied by observations on heterogeneous character of human diseases, where the underlying molecular mechanisms can vary dramatically between patients. By stratifying patients according to their genetic patterns, mRNAs, proteins and other biological molecules in subgroups, important level of information leading to clustering of data and new concepts for individual diagnosis and therapy can be obtained and the data sets leading to subtype models integrated.

MS in proteomics plays a central role for personalized medicine, where it contributes to identification of protein molecular structure on the level of primary gene products and their co- and post-translational modifications, as well as to the patterns of their processing. Mass spectrometry differentiation technologies across multiple platforms encompass different configurations for sample handling, different levels of separation, MS data acquisition and bioinformatics. Chief techniques used for differentiating proteins in discovery proteomics experiments and monitoring their changes are relying on either in-vivo isotopic labeling and on chemical labeling of headgroups for fragmentation analysis, or on label-free strategies based on integration of extracted ion chromatograms.

To evaluate potential impacts for personalized medicine quantitative proteomics strategies and the tissue analysis by imaging will be presented in this lecture and critically assessed.

A new era of personalized medicine: CRISPR gene editing

Sonja Pavlović
Institute of Molecular Genetics and Genetic Engineering
University of Belgrade, Belgrade, Serbia

Medicine was always aspired to be personalized, directed to each patient as a unique case. In our time, genomics has provided a solid foundation of knowledge for personalized medicine. Genetic differences between individuals impact their morphological and physiological characteristics, as well as their health and individual's disease risk. Personalized medicine, also called genome-based medicine and precision medicine, uses the knowledge of genetic basis of the disease to individualize treatment for each patient. The most important achievement of ge-

nome-based medicine and the ultimate goal of medical science is to develop gene therapy which will fight or prevent a disease by targeting disease causing genetic defect. Additionally, cellular and tissue therapies have opened new possibilities for personalized treatment of many patients.
The goal of gene therapy is substitution of a defective or missing protein by introducing an intact copy of a faulty gene or by induction of a genetic material which modifies the effect defected gene has on a cell. Various types of vectors have been considered for gene transfer, with viral vectors emerging as a potent transporter of a gene of interest. Although gene therapy demonstrated remarkable results in some cases, it also pointed out some of the limitation of viral gene transfer, which include the need for improved efficiency of gene delivery and insertion of the gene into non-oncogenic sites. With the recent development of genome editing technologies, the direct DNA-level repair of primary mutations in the absence of off-target activity has been achieved. This gene therapy approach avoids the risk of insertional mutagenesis inherent to integrating vectors, giving rise to a much "safer" gene therapy strategies.
Genome editing is a set of related techniques that make it possible to introduce precise genetic changes to a specific section of DNA. The last few years have seen a rapid change in ease, affordability and accessibility of the genome editing technique. Genome editing with engineered nucleases is a type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of a living organism using "molecular scissors". Among them, the CRISPR system is commonly used. CRISPR systems are adaptable immune mechanisms used by many bacteria to protect themselves from foreign nucleic acids, such as viruses or plasmid. Recently, a simple version of the CRISPR/Cas system, CRISPR/Cas9, has been modified to edit human genomes. Cell-based therapies have already employed genome editing in effort to cure patients with severe forms of inherited diseases and hematological malignancies.
Predictions in the field of genomics and other "omics" promise that in next decade personalized medicine will be applied on an everyday basis in health care systems. Precisely, the development of new technologies that enable rapid genome sequencing of each patient, genome editing and bioinformatics programs that correlate genetic profile and clinical data indicate that we are getting closer to personalized medicine.
Key words: personalized medicine, gene therapy, cell therapy, genome editing, CRISPR/Cas system

Fecal microbiota transfer – personalised medicine in gastroenterology

Davor Štimac [1,2]
[1]Clincal Hospital Center Rijeka, Rijeka, Croatia
[2]Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Personalised medicine could shortly be defined as giving right dose of the right drug to the right patient at the right time. Nowadays personalised medicine is widely accepted because with such an approach, we can treat our patients more efficiently.

The human microbiome project says that the human body has 100 trillion microscopic life forms living in it. While human genome project has 23 000 genes, human microbioma project has more than 1 million genes and therefore is the new challenge in the field of personalised medicine. Distribution of most important groups of bacteria like Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria and others differs widely in our body and has specific characteristics in mouth, oesophagus, stomach, small and large intestine and other organs of every human. Human microbiota therefore is a new challenging field in personalised medicine. Curable potential of human microbiota transfer is the treament of many diseases, especially those involving small and large intestine. Mostly accepted indication for faecal microbiota transfer is Clostridium Difficile infection in antibiotic resistant patients. There are also other potential diagnosis like IBD, IBS, metabolic syndrome and many others.

Faecal material for transfer can be prepared as fresh or frozen. Fresh stool should be used within 6 hours after defecation. To protect anaerobic bacteria the storage and preparation should be as brief as possible. Faecal material should be suspensed in saline using a blender and sieved in order to avoid the dogging of infusion syringes and tubes. Frozen faecal material should be stored at – 80^{o} C, and on the day of faecal infusion faecal suspension should be thawed in a 37^{o} C warm water bath and infused within 6 hours. Transfer can be made via upper or lower GI tract endoscopically through a tube.

Faecal microbiota transfer is a new approach to personalised medicine without drugs, but with natural transfer of healthy donor microbiota to patient with potentially curable disease. In the lecture we will present our first experiences in patient with Clostridium difficile infection treated in our institution.

MR imaging in personalized treatment planning for patients with rectal cancer

Damir Miletić [1,2]

[1] Faculty of Medicine, University of Rijeka, Rijeka, Croatia

[2]Clinical Hospital Centre Rijeka, Rijeka, Croatia

Colorectal cancer is the second leading cause of death from cancer for men and the third for women in Western countries with significant male predominance for rectal cancer. Optimal management of rectal cancer requires multidisciplinary decision making procedure and accurate staging which is critical for treatment planning. Magnetic resonance imaging (MRI) has become the imaging gold standard for local staging as it allows stratification of patients into distinct prognostic groups. MRI features other than T and N include tumour invasion of the potential circumferential resection margin (CRM) and extramural rectal veins (EMVI), discontinuous tumour deposits, relationship to the intersphincteric plane in low rectal tumours and to pelvic compartments in advanced disease. MRI enables the identification of high risk tumours where the use of neoadjuvant therapy is justified and is a robust method of identifying patients with a strong likelihood of complete response after preoperative treatment. Reliable assessment of the local extent of tumour is mandatory for surgical planning. The mesorectal fascia forms the boundary of the surgical excision plane

during total mesorectal excision (TME). Tumour extending to within 1 mm of the surgical TME plane (mesorectal fascia and intersphincteric plane) is associated with a high risk of local recurrence. Patients who have CRM threatened by tumour involvement are recommended to undergo preoperative neoadjuvant chemoradiotherapy. Reassessment of MRI scans after preoperative treatment has implications for surgical planning, the timing of surgery, sphincter preservation, deferral of surgery for good responders, and planning of alternative treatment for radiologically identified poor responders. High resolution T2 weighted sequence is fundamental for the assessment of locoregional tumour propagation. Diffusion-weighted MR imaging measures Brownian motion of extracellular water molecules. Diffusion restriction reflects high cellular density and can be used to indirectly predict tumour aggressiveness and reveal early-stage radiation-induced fibrosis and prevent overstaging. A key challenge in MRI remains the interpretation of post-radiation fibrosis. Magnetic transfer (MT) imaging utilizes differences in the magnetization interaction of free water protons and macromolecular-bound protons. Fibrosis is rich in macromolecules due to the presence of collagen and transfer of magnetization will be high. The perfusion index is used to quantify tumour microcirculation. Regression of tumour microcirculation is considered an important early prognostic factor for treatment response, before reductions in tumour volume. Whole-body molecular imaging is used to assess all lesions in the body which has significant advantage over in vitro diagnostic testing, as not every lesion can be biopsied. Furthermore, analysis of small biopsy samples is insufficient to assess intratumoral heterogeneity or phenotypic dedifferentiation over time. PET is well-established phenotypic imaging that can assess glucose metabolism which is elevated in most cancers. Hyperpolarized MRI allows direct insights into metabolic pathways. In preclinical studies it was shown that tissue pH, as an important biomarker for diagnosis and therapeutic monitoring of tumours, can be assessed noninvasively via hyperpolarized MRI. Non-invasive and repetitive measurements of biological tumour characteristics have the potential to predict which patients will benefit from a particular treatment and enable more specific patient selection. MRI with use of existing capabilities plays pivotal role in local staging of rectal cancer and has become an important tool for personalized treatment planning in these patients. There is a tremendous potential for further development in this challenging area.

Rethinking data protection in personalized medicine

Lucia Ruggeri
University of Camerino, Camerino, Italy

Personalized medicine is not so much preoccupied with the current state of health, as it is with the future health condition of a person. Its addressees are new categories of patients, or better said ‘non-patients’: healthy persons, for which medical science predicts future pathologies. The advancement of personalized care amplifies the necessity to develop collections of big health data concerning an increasing number of persons, which allows studying groups with similar genetic structure in a homogenous manner. This is the reason why new sources of data collection are being developed in addition to the traditional biobanks, such

as smartphone apps or portable devices for monitoring health related physical activities and habits of millions of people.
The use of biological samples and data is mostly self-regulated, based on the principles and rules devised in non-EU member states, because biobanks and companies operating the big health data are situated predominantly outside of the EU. Biological sample transforms into an electronic record, which can be shared and accessed by third parties in contractual relations with the biobank or technological platform managing the data. The new EU data protection regulation and the EU clinical trial regulation safeguard the development of research, but also require balancing this interest with the protection of fundamental rights. Genetic data may be used to prevent the development of a disease, but they can also be used to block access to employment or health insurance. It is therefore necessary to establish the appropriate mode of using the data, their dissemination to third parties associated with the biobank or the platform, as well as safety measures adopted to protect not only the biological sample, but also the electronic record associated therewith.
In order to preserve the right to control the use and the potential disclosure of data (i.e. informational privacy), it is necessary to reform the existing models of informed consent, so that they include:

1. information about the use of biological sample for research or other purposes,
2. adequate description of the data management system (opt-in or opt-out),
3. clear rules on periodic renewal of consent,
4. specification on traceability or non-traceability of data,
5. indication about the data use policy applied by the biobank or the platform,
6. stipulation on third-party dispute resolution body, especially since subject-matter of disputes often involves different legal systems and non-uniform rules on data protection,
7. rules providing the right to be informed in case the use of biological sample has been revoked for various reasons not related to research (problems of biological waste), and
8. rules on the relationship between the holder of data and biological group, especially the right to know or the right not to know genetic data.

Healthcare Justice and the Personal Perspective

Elvio Baccarini
Faculty of Philosophy, University of Rijeka, Rijeka, Croatia

It is still uncertain whether personalized medicine will increase or reduce healthcare costs. In the case of increase of costs, issues of health care justice will be exacerbated. We must be ready for the bad scenario. Elsewhere I endorse a justification of decisions in healthcare justice that is respectful of slightly idealized personal perspectives. Justification of allocation of healthcare support must be provided by reasons for which we can reasonably expect that they will be accepted by all relevant agents as reasonable (free and equal). At the end, I justify a strong, but not absolute, priority of life-prolonging therapies.
I the present paper I analyse reasons that are relevant in the debate. Precisely, my main question is which kind or reasons an agent must accept as reasonable (free and equal) in order to renounce to life prolonging-therapies, in the context of competing demands in conditions of scarcity. My main focus is on fair distribution of primary goods and the fair opportunity to realize human goods.

Personalised medicine from the socio-economic perspective: evolutionary or revolutionary?

Maks Tajnikar and Petra Došenović Bonča
University of Ljubljana, Faculty of Economics, Ljubljana, Slovenia

Cutting and reassembling DNA, choosing your baby's gender, 3D printed body parts, big data in healthcare, robotic surgeries etc. are no longer science fiction. All these new developments are already changing medicine and many times innovations are breath-taking. But the question arises whether the development of personalised medicine will indeed be revolutionary from the socio-economic perspective. Will it revolutionize our economic system in a similar way as the steam engine during the industrial revolution? Competition in the Middle Ages led to the development of new factors of production resulting in important societal changes and development of capitalism – economic system based on private ownership of the means of production and their operation for profit. How profound will be the impacts of personalised medicine on our society and market economies?
Supply based on available production technologies will continue to be based on both labour and capital and personalised medicine will not change this fact although types and forms of both labour and capital will likely change due to personalised medicine. This implies that personalised medicine will not shake the foundations of capitalism. It could, however, have an impact on the functioning of the markets. Both simple prehistoric forms of markets and markets today play two roles.
The first role of the market is to adjust the supply to the demand and use the price mechanism to rationalize demand to the level of available supply. In some economic activities such as education, health care and public transport these two functions have already lost their role. Satisfaction of needs is no longer a reflection of preferences at a given budget constraint. Accessibility is not based

on willingness and ability to pay but on more objectively identified needs of the population. Big data, genetic medicine, virtual image of the body as elements of future personalised medicine are becoming tools for identifying actual needs of the target population making the market inefficient and thus redundant for allocating rare resources to maximise social benefit. A more objective identification of needed goods and services will also enable a more precise planning of their supply instead of prices signalling surplus or shortage of demand. All described changes will impact how the needed services are funded and also how their supply is organised implying that personalised medicine could have an impact on the role of markets and competition between different sectors.

In addition to intersectoral competition personalised medicine will also impact competition within sectors which is the second role of the market. Successful innovations that are more cost-efficient and cost-effective will replace many of the existing approaches for patient care. Development of such new approaches, techniques, medicines and equipment is motivated by extra profits – reward that is harvested by capitalists and created through within sector competition. This implies that any intervention that will target this reward and private ownership of extra profits will impede further development of personalised medicine. Preventing reward for innovation to a select few thus cannot result in the spread of the benefits over the population. Spread of benefits requires wide accessibility that requires an increased role of collective funding not only through the state but – in case of personalised medicine – also life-long insurance. This will play a vital role in achieving that the overall population and not only the wealthiest benefit from breakthrough advances in medicine.

All described impacts of personalised medicines are large but they are less a revolution and rather an evolution given that they are not likely to change the existing capitalist economic system.

STEM as a stem of a more cost-effective personalized medicine

Davor Mance[1], Diana Mance[2] and Sergej Nadalin[3]

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STEM is an acronym for academic disciplines of Science, Technology, Engineering and Mathematics and is used to describe scientific education. A comprehensive list of STEM disciplines does not exist but the list among others includes: physics, chemistry, biology, biochemistry, genetic research, neurobiology, neuropsychology, psychology, biomechanics, bioinformatics, nanotechnology, robotics, mechanical engineering, industrial engineering, chemical engineering, pharmacology, mathematics, mathematical biology, operations research, statistics, electronics, information technology, acoustical engineering, radiology, and environmental sciences, just to mention the ones of interest to personalized medicine.

Economics considers a Pareto improvement if at least one of the two, or preferably both of the following results are achieved: firstly, one may achieve the same effects

at lower costs, and secondly, one may achieve better results at same costs. Finally, one tends to achieve both: better results at lower costs. The three combinations are all Pareto improvements and are part of the economic evolutionary development process called innovation.
Innovation is a process of ideas hybridisation. Just as biological sexual evolution, the human technological evolution is also based on recombination of information, and that is not a metaphor. Innovation with recombination of ideas for humane purposes requires virtue, and virtue equals cooperative behaviour that requires institutions. Institutions are rules shaping human behaviour, strengthening mutual trust for the purposes of cooperative behaviour. Without cooperation there is no recombination of ideas, no multidisciplinary research, and no progress. One scientific discipline is not enough. Cooperation among and between sciences in a multidisciplinary environment is a necessary precondition for innovation and improvements in medicine in general and in the subfield of personalized medicine in particular.
Personalized medicine is an attempt to make medicine more efficient and less costly, by making it more patient centred and thus less redundant. We shall give some examples of how interdisciplinary work may create some innovation in personalized medicine. Medical problems are getting more complex, more specific, and more personal indeed. Personalized medicine gives us thus the ability to analyse problems more quickly, and more specifically. Only the availability of sophisticated and specialised technologies in an open, networked, dynamic and collaborative social environment enables us to combine and recombine the available scientific resources so that they better address the requirements at hand.

Implementation of Personalized Medicine in Croatia: Where do we Stand and how to Proceed

Marija Kaštelan Mrak[1], Danijela Sokolić[1] and Renata Dobrila Dintinjana[2]
[1]Faculty of Economics, University of Rijeka,Rijeka, Rijeka, Croatia
[2]Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Personalized medicine is a powerful health care technology that enables higher precision of predictions, informed decisions and probably more effective individually based treatments. On the other hand, it requires modeling of a new system that takes into consideration the need to (re)design the whole infrastructure evolving R&D advancement, treatment dissemination and creation of awareness, both by the medical profession, regulators and the broader public. An interdisciplinary teams and personnel with various competencies (from genomic testing to big data interpreting) is needed for supporting the emergence of an adaptive medical infrastructure capable of developing technology and processes. In order to accommodate all those changes, new architecture of health care system is needed. The role of economists is to forecast differences in cost-efficiency on a set of processes and agents.It is of utmost importance to assess current state in the sector. In order to do so, we have conducted a survey on Croatian medical doctors in the medical categories most exposed to personalized medicine tools and

methods` developments (i.e. oncology, gastroenterology, etc.). Research focuses on standpoints of Croatian medical doctors regarding **current state of personalized medicine implementation** in the Croatian health care system, **institutions relevant for enabling** its development into existing system, as well as **perceived obstacles**, most important challenges and necessary steps that have to be taken in order to implement new technology, processes and regulation into Croatian health care system. Lastly, we summarize open issues that require substantial research efforts in the future.

Keywords: Personalized medicine, health care infrastructure, organizational design

Recent EU Developments on the Reverse Payment Settlements in the European Pharmaceutical Market

Ana Pošćić
Faculty of Law, University of Rijeka, Rijeka, Croatia

The presentation will discuss the major EU competition law developments in the pharmaceutical sector. Decisions in Lundbeck, Servier and J&J/Novartis provide guidance on how the European Commission approaches intellectual property and regulatory issues that delay generic entry. Special attention is on the concept of the reverse patent settlements or pay for delay agreements. Reverse patent settlements are situations where patent holder agree to make a payment to potential competitors who have threatened to enter the market and challenge the patent's holder right to the patent. Particular emphasis will be on the General Court decision that upheld the Commission's Lundbeck decision and ruled for the first time that pharma pay-for-delay agreements breach EU antitrust rules.

Regulatory Requirements relating to Certification of Medical Devices

Mijo Božić
University of applied sciences Ludwigsburg, Ludwigsburg, Germany

In April 2017, two new regulations on medical devices were adopted. They entered into force on 25 May 2017. The new rules will apply after a transitional period – three years after entry into force for the regulation on medical devices and five years after entry into force for the regulation on in vitro diagnostic medical devices. Provisions on notified bodies, competent authorities, cooperation among member states and establishing medical device coordination group become effective on 26 November 2017. The presentation examines issues of practical relevance to certification of medical devices, whereby a special focus is on individualized medical products.

Connected Health and Data Protection in Personalised Medicine

Nada Bodiroga Vukobrat[1] and Hana Horak[2]
[1]Faculty of Law, University of Rijeka, Rijeka, Croatia
[2]Faculty of Economics, University of Zagreb, Zagreb, Croatia

One of the most challenging issues today in digital economy are the legal issues. Data protection in the digital world, and processing on a daily basis a number of information is one of the most important achievements that must be done when considering regulatory framework in micro and macro surrounding. Data and data protection are crucial and the most important issue in process of connecting and consolidating information. Data protection reform is one of the cornerstones of the Digital Single Market. Third Pillar of the Digital Market Strategy "Maximising the Growth and Potential of the Digital Economy" is dedicated among other issues to deal with emerging legal issues and obstacles in establishing European Data Economy. Despite the new existing regulation on EU level we are facing numerous obstacles and "grey zones" which enable disclosure of data. The idea on supranational and national level is to remove all existing obstacles and establish interoperable system within EU member states until 2020. Special focus among others must be in bringing down the legal barriers. Into deep analysis and studies have shown that the main discrepancies are between different regulatory frameworks of the Member States and within the different stages of implementation of EU legal actions on national level. Within the eHealt one of the most important issues, beside the data protection, is standardisation of Electronic Health Record systems and laws.

The advancement of new technologies in medical, biomedical and technical sciences, especially nanotechnology; coupled with an ever-growing development of science is also faced with various legal obstacles. Legislation is by its very nature rigid, and development of specific relations and occurrences precedes any legislative activity. Legislation reacts to these developments, often restrictively. The personal data protection in the patient-doctor relationship is a perfect example, which has stirred a lot of doctrinal debates. The scientific discoveries of modern, highly technicised medicine bring many advantages. However, they also elevate the risk of experimentation and manipulation in relation to personality rights. Patients represent a particularly vulnerable group when this data is used and processed as "Big Data". Patient-doctor relationship is faced with new challenges. Informatisation of health care systems is not accompanied by sufficient education of doctors and other medical staff, especially in post-socialist European countries. The systems are interconnected, and the sensitive information that should, by its nature, be available only to doctors involved in the treatment is accessible to broader categories of persons. The main question is whether legal actions are fast enough to ensure the flow of personal data in real time and whether protection of personal data in a digital economy will become a reality that ensures safety.