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Medical, Legal and Economic Implications for Croatian Healthcare System

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Information

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Personalized medicine: German experience

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Individualized medicine allows the physician to select a therapy producing an extremely high probability of efficacy or low probability of unwanted side effects. This high success rate may be based on the analysis of a patient' s genom, proteom, metabolom or imageing. Mostly used is genomics. Analysis not only requires cutting edge technology but frequently also biomathematics due to the tremendeous amount of data produced. Due to the low number treated in vain individualized medicine may contribute to cost reduction in a health care system.

Mass spectrometry in personalized diagnostic

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Even in Hippocrates' time, a limited form of Personalised Medicine existed, with the practitioner observing symptoms, and applying some logic to create a bespoke treatment. However, prior to Garrod's Croonian lectures in 1908, medicines still treated many human diseases with little regard to age, gender, build or ethnicity. Garrod's genius was in his Mendelian genetics to diseases with apparent familial connection, with no experimental way of determining the causal mechanism.

John Dalton's assertion that atoms of an element must have a characteristic "relative weight" seems obvious in hindsight, but in the vacuum of supporting data was true genius. One of Garrod's contemporaries, J. J. Thomson was the first person to be able to provide proof of Dalton's theory when he built what we consider to be the first mass spectrometer.

A hundred years later, more than 12 million babies are screened annually using mass spectrometry for the inborn errors of metabolism such as those first discussed by Garrod. Mass spectrometry has been used to understand the nature of disease progression, to diagnose many conditions, and to monitor drugs in a clinical setting. Advances in *in-vivo* technology has brought mass spectrometry to the operating theatre, whilst unbiased large-scale studies of all biochemical entities (small molecules, lipids, proteins) offers insight into the epigenetic contribution to the individual molecular fingerprint, or as Garrod said "the progress of chemical physiology is teaching us that behind a superficial uniformity there exists a diversity which is no less real than that of (physiological) structure, although it is far less obvious." The promise of personalized medicine depends on understanding the molecular phenotype, and reconciling this with the individual's genomic starting point.

Implementation of proteomics in personalized medicine

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The medicinal research is taking full advantage of recent fulminant development of the high-throughput genomic, transcriptomic, proteomic and metabolomics ("omics") technologies. Integration of omics data and the use of bioinformatics for their evaluation and integration is the only way for decoding the basic rules that control the function of the whole organisms, by integral view to the the function of the cells, tissues and organs. This systematic approach will lead to theranostic strategy with the discovery of novel molecules as biomarkers that will pave the way to personalized medicine as the final goal. Here, se present different approaches to reach this target – use cultured cells and laboratory animals as well as the analysis of patient samples in order to study malignant modifications and discover possible disease markers. The critical molecular and cellular mechanisms involved in development, progression and metastasis of tumors remain elusive. In the rat models we demonstrated that normal prostate epithelial cells (PEC) undergo spontaneous transformation after more than 85 repeating passage steps ("high passage" p>85). This effect can be observed by the acquisition of anchorage independent growth and tumorigenicity of the cell when injected into immunodefficient mice. Minor subpopulation of these cells (SAI) had the ability to migrate through soft agar and they also showed marked differences in morphology, proliferation, motility and expression of signaling proteins as well as higher tumorigenic potential. In addition, the changes of extracellular vesicles (EV) of rat liver before and after injury were presented. Extracellular vesicles from stem-like liver epithelial cell line WB-F344, their chemically transformed lines GP7TB and GP7TB.SAI, a soft agar invasive population were investigated. Apart from changes in number, size and proteomic content, the GP7TB.SAI derived EVs significantly simulated NK-mediated cytotoxicity opposite to those purified from the less malignant GP7TB line. The information about possible communication between prostate tumor cells and possible mechanisms of bone metastasis were studied by studying changes in cell secretome and identification of proteins that can be involved in this kind of interaction. Furthermore, we investigated changes in IgG and IgM antibody glycosylation patterns in patients undergoing image guided tumor ablation. Although the glycosylation of antibodies in patients was found to vary with cancer type, discernable patterns of glycosylation change of both antibodies based on successful treatment of tumors by ablation were not identified. These findings suggest that glycosylation patterns are indicative of an immune system that is unable to prevent different types of cancer, rather than products an

immunostimulatory response to the ablation and destruction of tumor itself. Present strategy opens a way for parallel determination of proteomic and glycomic changes by use of high-resolution, high throughput methods, and their future use for detection of new biomarker for disease diagnosis and prognosis.

Pharmacogenomics of acute leukemia in children: a path to personalized medicine

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Childhood acute lymphoblastic leukemia (ALL) represents one of the best examples of progress in disease treatment based upon the incorporation of the principles of pharmacogenomics and personalized medicine. The combination of mercaptopurine (6-MP) and methotrexate therapy represents the standard "backbone" of childhood ALL maintenance treatment. Administering of drugs in patients with variants in the genes involved in drug transport and metabolism leads to severe hematologic toxicity.

We have investigated genetic variants of *TPMT*, *ITPA*, *MDR1* and *MRP4* genes, relevant for metabolism of mercaptopurine drugs, as well as variants in *DHFR*, *TYMS*, *MTHFR* and *SLC19A1* genes, involved in methotrexate metabolic pathway. We detected genetic variants in exons and promoter regulatory elements using PCR and sequencing methodology. Additionally, we have analyzed *TPMT* gene expression and 6-MP toxicity *in vitro* and *in vivo* using functional CAT, EMSA and Real Time PCR assays.

We showed that genetic variants in *TPMT* exons accounted for 7.5% of all analyzed alleles. The therapy for pediatric ALL patients with these genetic markers was modified, which contributed to the efficiency of treatment. Administering reduced 6-MP dosages in the initial phase of maintenance, allowed *TPMT*-deficient and heterozygous patients to later receive full protocol doses of 6-MP. In order to elucidate the 6-MP tolerance kinetics, we investigated the influence of 6-MP on *TPMT* gene expression. Functional assays *in vitro* showed that *TPMT* promoter activity depended on the architecture of VNTRs, a regulatory element in the promoter. Promoter of *TPMT* gene responded to 6-MP treatment in a VNTR-dependent manner. Study of *TPMT* gene expression in childhood ALL patients before and after administering 6-MP therapy, revealed that 6-MP has a positive effect on transcription of *TPMT* gene. Increase of median 280% in *TPMT* gene transcription was detected in the maintenance phase of therapy, Analysis of variants in *ITPA*, *MDR1*, *MRP4*, *DHFR*, *TYMS*, *MTHFR* and *SLC19A1* genes indicates their pharmacogenomics potential.

Our research points out that VNTR region of *TPMT* gene is a new candidate pharmacogenomic marker. The transcription of *TPMT* gene is influenced by 6-MP therapy. Patients are more susceptible to 6-MP induced toxicity in the early stages of the therapy. Increase of *TPMT* gene transcription after administering 6-MP is detected. Therefore, for *TPMT* -deficient and heterozygous pediatric ALL patients, administering of reduced 6-MP dosages in the initial phase of maintenance is recommended.

Successful integration of data from pharmacogenomic studies into clinical practice has greatly improved the outcome for children with ALL. Implementation of the individualized therapy,

based on patient's genotype and gene expression profile, in regular treatment of childhood ALL indicates that we are getting closer to personalized medicine.

Laboratory grown microbiome

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Terms microbiome and microbiota are often used as synonyms although strictly speaking first describes the collective genomes of the microorganisms that reside in an environmental niche and the latter the microorganisms themselves. Humans have clusters of bacteria in different parts of the body, mainly the surface or deep layers of skin or mucosa. However, microbial populations are not limited to our epidermis they also populate our gut. Our gut microbiome contains almost as many microorganisms as our bodies have cells, including at least 1000 different species of bacteria with approx. 3×10^6 genes (which is order of magnitude more than human genes). Each microbiota is unique, a parallel made to a fingerprint. While each of us has a unique microbiota composition, it still fulfills the same physiological functions, with direct impact on our health. It helps us to digest certain foods; it helps with the production of vitamins. It helps us fight of pathogens and it plays an important role in the immune system. All this is performed by a healthy and balanced gut microbiota. Similarly, a loss of balance in gut microbiota, state called dysbiosis may be linked to health problems such as bowel disorders, inflammatory bowel disease, allergies, obesity and diabetes. Taking into account the major role gut microbiota plays in the normal functioning of our body and the different functions it accomplishes, experts nowadays consider it to be an "organ". However, it is a very volatile organ, since we are born sterile, colonization starts right after birth and evolves as we grow. Gut microbiota balance is affected by numerous external factors even normal ageing. However, long-term dietary habits and antibiotics have the most profound impact. Better insight into this dynamic equilibrium could provide us with answers on how to affect it in targeted fashin and in a positive direction, e.g. reversing dysbiosis. Unfortunately, since the microbiota is incredibly complex and the interplay with human host even more so, this is a difficult task. Transferring microbiota in a laboratory bioreactor makes this easier since we remove host from the equation and can concentrate only on microbial community within. If we consider microbiota to be an unexplored organ, this transfer to bioreactor can be regarded as organ preservation and if done properly it gives us a window of approx. 36 hrs to study the dynamics of microbial community. Most important technique used to study entire microbial communities within samples taken at different time points of bioreactor growth is 16S rRNA sequencing, a cost-effective technique to identify strains that may not be found using other methods. Therefore we often use terms microbiota – microbiome interchangeably, since it is the micobiome which we actually observe. Not only does this laboratory grown microbiome solve the sampling issue, which is critical if we want to learn about the balance, it can also be utilized to investigate direct effect of prebiotics and probiotics on microbiota balance and provide us much needed answers.

Personalized medicine, cognitive enhancement and future eugenics

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Medical advances in personalized medicine, in understanding of molecular basis of disease and genomics have transformed previously speculative character of discussions on human enhancement, transhumanism and future eugenics into a real-life issue. Advances in personalized medicine will follow common-sense approach to medicine. Nevertheless, speculations about its potentials for allegedly dubious uses among philosophers, ethicists and lay people still abound. The point of this paper is to erase some fears among intellectuals and common people quoted against such uses.

The targeted treatment of breast cancer

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Breast cancer is the most commonly diagnosed tumor and the leading cause of death in females. It is considered that every eight woman will develop breast cancer over the course of her lifetime. Breast cancer is a heterogeneous phenotypically different disease which has several biological subtypes of specific clinical course and behavior. Multiplication or enhanced expression of oncogenes of human epidermal growth factor receptor 2 (HER2) is present in about 18-20 primary invasive breast carcinoma. Until discovery and application of clinical targeted anti-HER2 therapy these tumors were associated with higher aggression and poorer disease outcome. The application of targeted therapy has significantly altered the natural course and prognosis of HER2 positive breast cancer. Due to this prognostic and predicative significance, the expression of HER2 protein must be determined in all patients with newly diagnosed primary breast cancer or immune-histochemical (IHC) or in situ hybridization (ISH), which is accomplished by applying clear algorithms of pathological and oncological societies such as ASCOCAP algorithm (American Society of Clinical Oncology College of American Pathologists Guidelines). HER2 is a transmembrane receptor which belongs to the ErbB/HER receptor family with tyrosine-kinase activity. Besides HER2, this receptor family includes EGFR/ErbB1, HER3/ErbB3 and HER4/ErbB4 which differ according to the available ligands and receptor tyrosine-kinases.

Trastuzumab is a recombinant humanized monoclonal IgG_1antibody that interferes with the HER2 receptor part out of the cell and which is nowadays regularly applied in targeted treatment of early or metastatic HER2 positive breast cancer. This monoclonal antibody was approved by the American Food and Drug Administration (FDA) in 1998, firstly in treating HER2 positive metastatic breast cancer in combination with paclitaxel, or with docetaxel, and then later in adjuvant therapy. Trastuzumab achieves antitumor effect by different mechanisms which include not only blocking of signal pathways, but are also related to induction of antibody-dependent cell cytotoxicity (ADCC) and its effect on angiogenesis and remedy of DNA.

Clinical application of Trasuzumab in adjuvant treatment of early breast cancer is based on the results from large clinical studies of III phase such as HERA study, Fin-Her (Finland Herceptin), BCIRG006 (Breast Cancer International Research Group 006), NCCTG (North Central Cancer Treatment Group) N9831and NSABP (National Surgical Adjuvant Breast and Bowel Project) B-31 study which were based on about 12000 females. Trastuzumab has

significantly prolonged the disease-free period and overall survival. Based on these results, a one-year application of adjuvant Trastuzumab is the standard therapy in women with HER2 positive early breast cancer.

The development of immune therapy has influenced the treatment of metastatic breast cancer, primarily HER2 positive one, in a significant way. Monoclonal antibody Trastuzumab has brought about significant headway in targeted therapy of patients suffering from HER2 positive breast cancer. It has also significantly prolonged the survival period and become an indispensable drug. Besides Trastuzumab, Pertuzumab has also been applied lately. T-DM1 – Trastuzumab-DM1, a conjugate of antibodies and cytostatics, must also be mentioned. Patients suffering from metastatic HER2 positive breast cancer, if treated with these targeted drugs, nowadays live a few years longer. This data can indirectly be read by examining the results of particular clinical studies, but also from monitoring our patients in everyday work. It can be concluded without any doubt that the targeted therapy of metastatic breast cancer has experienced a revolution and changed the fate of numerous patients.

Personalized medicine and system of social security

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Der Beitrag untersucht die Entwicklung der Arzneimittelausgaben in Deutschland vor dem Hintergrund unterschiedlicher Maßnahmen der Kostendämpfung. In der Vergangenheit wurden vielfältige Steuerungsinstrumente eingeführt, um den Ausgabenanstieg zu begrenzen. Die Entwicklung der letzten Jahre verdeutlicht jedoch, dass diese Maßnahmen nicht ausreichen. Es ist daher notwendig, Regelungen zu finden, die eine überproportionale Ausgabensteigerung im Arzneimittelbereich wirksam begrenzen und gleichzeitig die Versorgung mit innovativen Arzneimitteln nicht gefährden.

Die schnelle Einführung von Arzneimitteln mit Zusatznutzen für die Versorgung zumeist schwerkranker Patienten ist eine elementare Stärke des deutschen Gesundheitssystems. Gleichzeitig gefährden insbesondere die hohen Preise bei innovativen Arzneimitteln und die Entwicklungen bei der personalisierten Medizin die Stabilität der Gesetzlichen Krankenversicherung. Wie lassen sich somit beide Ziele in Einklang bringen, ohne dass durch die Auswirkungen einer unnötigen Rationierungsdiskussion die Versorgung großflächig verschlechtert wird?

Potentielle Lösungsansätze müssen die Preisfindung für innovativen Arzneimittel berücksichtigen. Im Beitrag werden daher verschiedene Strategien zur Preisfindung diskutiert, die einschränkend auf die Monopolposition des pharmazeutischen Herstellers wirken. Im Verhältnis zum aktuellen Preisfindungsmechanismus bedarf es im deutschen Gesundheitssystem einiger Anpassungen, die das Verhandlungsgleichgewicht zwischen GKV-Spitzenverband und den pharmazeutischen Hersteller so austarieren, dass niedrigere Preise für Arzneimittel mit Zusatznutzen erzielt werden können, ohne dass der Hersteller mit einer Marktrücknahme die Versorgungssituation in Deutschland verschlechtert. Der skizzierte Lösungsansatz basiert auf einer Flexibilisierung des Verhandlungsgeschehens, auf einer

Berücksichtigung weiterer verhandlungsrelevanter Faktoren (wie Kosten-Nutzen-Analyse der return on invest) und der Möglichkeit, bereits im Verhandlungsverfahren mengenbegrenzende Strukturen zu schaffen.“

Regulatory possibilities and obstacles in new health technologies - disclosure of data and new diseases

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Technology is vital and exciting – but it is just one part of a picture that includes patient care pathways, business and revenue models, data analytics and more. Connected health consolidates information from many different spheres of one person’s world to give a more complete picture of their health. This includes biological, genetic, medical, lifestyle and sentiment/mood data.

Data and data protection are crucial and the most important issue in process of connecting and consolidating information. Today despite the existing regulation on EU level we are facing numerous obstacles and "grey zones" which enable disclosure of data.

Macroeconomic environment and the development of personalized medicine

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One of the key characteristics of personalised medicine is a different relationship between the user (patient) and the provider of health care services. The service is tailor-made to a specific user. Service differentiation and market segmentation bring services that are under the umbrella of personalised medicine closer to some of the properties and issues of orphan drugs. Authors use the case of orphan drugs to discuss some important macroeconomic concerns relevant for personalised medicine.

The authors begin by addressing the challenges of using contemporary economic evaluation methods (cost-benefit analysis or related methods for full economic evaluation) for justifying the implementation of personalised medicine. Such services undoubtedly create large individual benefits. However, the issue of whether a positive net benefit from a social perspective can be attained is also easily questioned. Personalised medicine is creating a larger gap between individual and social effects of services. Interestingly, contrary to majority of health care services individual effects are overpowering the social effects.

The authors build on these challenges related also to assuring access and sustainable funding of personalised medicine and discuss how social effects can be accentuated. A theoretical conclusion has practical implications in the EU as it refers to the creation of a wider European health care system. Development of personalised medicine will intensify the need to move closer to the single European health care market with a transnational network of health care providers and joint funding and transfer payments between countries to prevent accessibility

differences. Such a development of a common health care system could also prove to be an effective way of eliminating macroeconomic disparities between countries that are currently threatening the existence of the EU and EMU.

Mechanism design and local regulation: the case of welfare and aid policies (Helping the poor as a repeated game)

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The escalating crisis public budget has dramatically changed the available options for welfare policies, calling for a better use of aid funds. The presentation inserts itself into the debate on how money could be better spent in helping the poor and disadvantaged people, a significant burden for public budgets and, indirectly, health systems and financial equilibria.

In particular, the attention is devoted to a fresh rethinking on the way money is used to help the poor and the disadvantaged in developed countries with conditional schemes. The paper presents a game between a giver and a recipient of welfare benefits with conditions attached, showing that a particular institutional setting of giver's goals could misalign incentives and hinder conditionality in term of recipient's willingness to change behavior and to increase human capital. Simple simulations in not repeated and repeated contexts, with and without information extraction with inspections are developed to check if sensitive conclusion can be reached.

Outcomes suggest first to design policies in a more asset building-oriented setting and second to enforce game-repetition with inspections as a way to spread positive common knowledge among the recipients on the foreseeable future moves of the giver.

Changing giver's incentives and payoffs, could drive to more effective help toward individuals and families in dire times, with direct and indirect benefits to welfare budget and social capital.

Actuarial challenges in personalized medicine

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The developments in personalized medicine represent a turning point in the approach and development of drugs and medical practice. Among the many expected benefits, the most noticeable is the development and production of safer and more effective cures for specific diseases. However, in order to fully reach this advantage, there are many obstacles that ought to be surpassed such as the creation of new and/or adaptation of existing public policies, institutional and regulatory constraints, insufficient insurance levels not covering prevention and many others.

This research aims to identify the potential challenges of actuarial science in the context of the *new* era of personalized medicine. Namely, based on the analysis of the input data nowadays used in calculations of insurance premiums and current actuarial methods, the authors attempt to anticipate potential factors that should be taken into account in future life insurance calculations. In addition to more complex actuarial calculations, future issues in calculating premiums, when personalized medicine is concerned, will include moral dilemmas and constraints related to confidential medical data that the policy holder *wishes* and the relevant medical institution needs to withhold.

Personalized medicine and personalized pricing: Four degrees of price discrimination

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Economics developed a set of three degrees of price discrimination dependent on whether the seller targets individuals or groups, and whether buyers wish to use quantity rebates. The seller's reason to price discriminate is to capture as much of the buyers utility surplus. Price discrimination is deemed unfair and immoral, and this is especially so in the market for pharmaceutical therapies. But, sometimes it can indeed be socially useful to price discriminate as the practice, under circumstances, enhances efficiency and social welfare.

The market for pharmaceuticals is a non-typical market as irreversible costs of research and development form the brunt of the cost structure. As pharmaceutical companies are driven by the profit motive and bounded by patent expiration dates, discriminatory pricing schemes are necessary to recover investment costs of research and development as quickly as possible. The first degree of price discrimination consists of perfect, individually targeted, price/quality combinations that fully extract consumers' surplus. The second degree price discrimination consists of quantity rebates. The third degree of price discrimination is based on group targeting according to the group average willingness to pay. This is a problem for low income EU member states as prices of pharmaceuticals are formed according to the dominant market average willingness to pay.

In this paper, we introduce a fourth degree of price discrimination based on qualitative features of pharmaceuticals on a market for antiviral drugs. The main qualitative feature of an antiviral drug is its Sustained Virological Response (SVR). We conjecture the SVR to be the primary cause of price differentials for antiviral pharmaceutical therapies on the market. The fourth type of discrimination would be of particular interest to the pharmaceutical industry and health management organisations as it introduces nonlinear price-quality combinations. Since budgetary constraints prevent the less wealthy EU member states to acquire all the newest and extremely effective drugs that are getting to the market, some new types of contracts and confidential risk-sharing agreements are being envisaged.

Evolution paths of business models in personalized medicine

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A new personalized health care system is emerging, and old roles, rules and positions are changing while new players are taking places. In order to understand new sources of power (and surpluses) it is necessary to map designing elements of an emerging system.

Therefore, this paper focuses on detecting alternative designing paths for institutionalization of personalized medicine into health care systems and analyzing possible business models to meet both business, social and ethical challenges of health care systems in the future.

Models as conceptual representatives of some complex ideas or systems; comprised of elements, carry more or less explanatory power. The same holds truth for business models. Essentially, our design of a business model represents a description of (dynamic) power relations that may evolve in the personalized medicine sector.

Every system has its own power relations and in time of change old players will struggle to keep system as it is and they will resist to change as long as they have critical mass. The power of actors in the industry sector is based on their influence on designing rules and defining roles for entities (players) within the system. The ultimate aim of the players is in exerting benefits from the structure (system) and preserving or enhancing their position on the market.

Actors considered in our design are medicament and pharmaceutical sector, insurance industry, IT industry, education, regulatory institutions, agencies and bodies, NGO-s, etc.

Keywords: business model, organizational design, personalized medicine

Health Care and EU Law: The Role of Solidarity?

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The presentation will address the role of EU law in the field of health care. While respecting the competence of the Member States for the definition of their health policy and for the organisation and delivery of the health services and medical care, the European Union is increasingly getting involved in the promotion of the personalised medicine concept through various initiatives. Among other topics, the question of access of patients to innovative forms of diagnostic, treatment and pharmaceuticals raises particular concern. The implementation of the personalised medicine approach in various Member States may put a strain on one of the fundamental features of all health care systems: the principle of solidarity. The reconstruction of the health care systems to accommodate the new paradigm is inevitable. The question is, how will it affect the core values and principles which lie at the foundations of health care?

The focal point of this discussion will therefore revolve around the main challenges and possible directions for integration of personalised medicine models in clinical practice.

Antitrust issues in the European pharmaceutical market – the latest developments

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The presentation will discuss the major EU competition law developments in the pharmaceutical sector. Decisions in *Lundbeck, Servier* and *J&J/Novartis* provide a guidance on how the European Commission approaches intellectual property and regulatory issues that delay generic entry. Special attention is on the novel concept of "abusive denigration", of which there is no mention in the Treaty on the functioning of the European Union and no decisions by the European Commission.

After a brief discussion of intellectual property rights in pharmaceuticals, EU competition rules and practices, in particular pricing strategies of innovative pharmaceutical companies and their impact on competition, emphasis will be on the legality of national measures that limit parallel trade. It will be shown that the Court of Justice of the EU has adopted a compromise whereby pharmaceutical companies may not block all parallel trade but may take reasonable and appropriate measures in order to protect their legitimate commercial interests.

Intellectual property issues in medical application of 3D printing

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New developments of 3D printing reveal its potential to be even stronger than initially perceived. In the medical field, the uses of 3D technology range from diagnostic or treatment to education and clinical testing. Be it the bioprinting of organs or model organs or printing drugs, the legal risks related to 3D printing are inescapable. In particular, the risk of infringement of intellectual property rights held by third parties. The infringement may concern various intellectual property rights, specifically, patents, copyrights, designs or trademarks. Simply put, 3D printing is a new way of manufacturing, but without the organisational, logistic or other costs related to a traditional factory. The less expensive the 3D printing systems, the wider the category of the potential infringers. In addition to the 3D printer, the infringer only needs the respective CAD file. Expectedly, they are now available through file-sharing internet sites without the permission of the right-holders. This paper is intended to investigate the legal bases available for the protection of the intellectual property rights in the 3D printed items of medical uses.

Because medical products and/or processes for their production are usually protected by patents, the question is whether the same is true for the corresponding CAD file. This is very unlikely given the scope of the protection afforded by patents. The discussion about revisiting the traditional legal model of patent infringement is being heated up. It is of course a challenging exercise to conceptually fit into the existing patent system the idea of extending

the patent protection to creating and/or copying a CAD file. Because it is about copying, a further question might be as to whether the copyright may subsist in the CAD file. The discussion revolves around the fact that the CAD file is as its name suggests a computer-aided design and might lack originality. There are also confusing accounts mistaking the CAD file for software or giving weight to the fact that it takes the form of 3D digital data. Even if in principle the CAD file is copyrightable, it will probably not be so in all cases. Thus, the proposition is put forward by some to rely on the design right, focusing rather on the object printed than the file as depicting it.

The legal framework for genetic testing in the workplace in Germany

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Genetic tests could lead to improvement in occupational health and safety. However, there is a risk that some companies knowing their genetic constitution, could keep "vulnerable" workers away from certain activities rather than improving occupational conditions.

On April 24th, 2009, the German Federal Parliament passed the Genetic Diagnosis Act [Gesetz über genetische Untersuchungen bei Menschen, GenDG] regulating the use of genetic tests. The Act entered into force on February 1st, 2010. It applies to genetic tests for medical purposes as well as to genetic tests in insurance industry and in working life.

As a general rule, genetic tests in the workplace are not allowed. In the author's opinion, the legislative framework currently in force in Germany is an impediment to improvement of occupational health and safety.

Contextualizing bodily privacy in preimplantation genetic testing procedures

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“Preimplantation genetic testing” includes preimplantation genetic screening and preimplantation genetic diagnostic procedures. While genetic screening is primarily used to increase the viability of pregnancies, especially in older women, genetic diagnostic techniques allow medical professionals to detect inheritable conditions. Both procedures are used in the course of assisted procreation treatments in order to analyse the genetic makeup of embryos, allowing for the selection of a genetically most appropriate embryo that is then implanted into the uterus. Moreover, an innovative technology, CRISPR/Cas9 allows that embryo’s genetic composition be edited and has recently been approved for further research in the United Kingdom.

These developments in assisted procreation require us to discuss the extent of one’s bodily privacy, particularly the right to decide what to do with one’s own genetic material. The matter is especially current as, with our increasing understanding of the human genome, it will be possible to detect and, possibly, alter many of the embryo’s genetic features. The law is called upon to determine the boundaries of this, possibly expanding right. In Croatia, where there is a continuous backlash against the right to terminate a pregnancy, the possibility of using genetic testing technologies is extremely under-regulated and insufficiently discussed.

Against such a background, this presentation will examine the current state and challenges of bodily privacy in a comparative perspective.

Doping in sports: legal and other aspects

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The issue of doping is always a very interesting topic in the modern sport. On the other hand doping is interesting from the medial but also from the legal point of view. To comprehend the complexity of doping, from the legal point of view, firstly it is important to define doping and give the legal sources and the legal framework from the international but also from the national perspective.

The definition given by the State Law, but also from autonomous legal sources given by the international and national sports federations autonomous legal is of essential importance for the future legal implementation, for prevention and finally for legal prosecution with potential criminal and/or sports sanctions. There will be analysed some of the most interesting "doping" cases which happened in Croatia.

Key-words: Doping, sports, law, international, national, Croatia.