MENDEL'S LEGACY
– 150 YEARS OF THE GENIUS OF GENETICS

(Human Genetics from Mendel to the Present Day)

Professional events of Czech Society of Medical Genetics
and Mendel Museum of the Masaryk University in Brno

The event is part of celebrations of the anniversary of
150 years since the publication of Mendel's work.

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TURISTICKÉ INFORMAČNÍ CENTRUM MĚSTA BRNA

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HF-1

Gregor Johann Mendel – Man, Abbot and Scientist

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In 1865, exactly 150 years ago, Gregor Johann Mendel formulated the basic principles of heredity, that are still valid. Thanks to tireless work of this Augustinian monk, we can consider Czech Republic as the birthplace of genetics – science affecting all areas of life sciences.

The lecture will show Mendel as a complex personality – from which environment he originated and what influenced him. It will go through the most important milestones in his life from his childhood in a family working in agriculture, through his studies, entering the Augustinian Abbey in Old Brno, his scientific work till his death and later the rediscovery of his work. Other Mendel´s fields of interest like beekeeping and meteorology will be mentioned as well.

HF-2

The History of Medical Genetics in Brno From Phenotype to Genotype

Renata Laxová
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The Pediatric Research Institute was established in 1960 within the grounds of the Children's Hospital in Brno. It consisted of two existing wards with 20 children's beds in each and some 8 new labs, each with its own research agenda. Professor Otokar Teyschl was the original director, Prof. Zdeněk Brunecký, followed.

Two important issues faced the institute's future activities. First, we were located in Brno, in the city of Mendel's work and his discoveries.

Secondly, in 1948, two years after the end of World War II, our young, democratic and freedom loving Republic found itself under the influence of Stalin and the USSR. This affected our political climate, agriculture, industry, business, art and, of course science. Soviet political principles taught that change and progress occurred only through REvolution and through transmission of environmental characteristics.

In the area of medical genetics, we were woefully behind.

We decided we would try to catch up with the rest of the world who were using (and accused of abusing) new discoveries in human genetics. We would try to avoid some of the pitfalls experienced in e.g. the USA where specific population groups were protesting their designation as "at higher risk" for certain disorders like sickle cell disease in African Americans, or other haemoglobinopathies, in other ethnic populations.

Our goal was to evaluate the incidence and prevalence of some traits, e.g. blood types, and of diseases within our own population, their genetic, environmental or other provenance. We decided to attempt a study of our own surrounding population, that of the Southern Moravian Region, comprising some two million inhabitants.

A bright young ophthalmologist on our staff, Dr Milan Vrba, suggested that we initiate twin studies. That is what we did, for six weeks every summer, from 1961 through 1965.

The remainder of these comments will highlight evaluations of 600 pairs of mono- and dizygotic twins, aged 5 to 16 years and their (some) 600 pairs of parents, as well as other new (at the time) findings in areas of population genetics.

Finally, the newly recognized **genotype** of a familial syndrome, known only **phenotypically** since 1972, will conclude this presentation.

HF-3

Development of Medical Genetics in Czechoslovakia after 1945: Interwiews and Documentation

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Medical genetics was established in Czechoslovakia as an independent scientific field shortly after the WWII. Until early 1950s, medical genetics in Czechoslovakia continued in the tradition of reformist eugenic efforts of the second half of the 1930s. After the 1948 Communist takeover, however, classical genetics was gradually suppressed and forcefully replaced by Lysenkoism and Michurinian biology. This development significantly affected also on the situation in medicine. This state of affairs remained largely unchanged until the beginning of the 1960s.

Progressive development started, when especially the reception of the then latest discoveries made the time official doctrine of Lysenkoism obsolete. The final turning point was the Centenary International Mendel Symposium hold in Brno fifty years ago in 1965. A number of institutions, mostly related with paediatrician care, were created which focused on genetic counselling and prenatal care (Prague, Brno), on basic research in the area of immunogenetics and mutagenesis (Prague), and, somewhat later, also cytogenetics (Prague), which was originally covered by endocrinology. Faculties of medicine in Prague and Brno and the Czechoslovak Academy of Sciences played a key role in this process.

The historical project covers the following two topics: i. development of medical genetics by recording authentic testimonies/interviews of the generations reaching now their 80s and late 70s, ii. establishment of an independent documentary collection, which gathers materials and images which would otherwise be irretrievably lost.

The collection includes also approximately 400 items (books) incl. offprints and some rare issues.

HF-4

From genes to genomes in medical research and patient care Intellectual disability as a model disorder

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Rapid developments in genomics technologies now allow us to sequence all genes (the exome) or even the entire genome of thousands of patients in research and diagnostics. This is completely changing the way genetics studies are done, and allows us to take full advantage of the power of genomics in medicine. The identification of genetic variations is not a bottleneck anymore, we can now focus on the major remaining bottleneck; Interpretation of the enormous amount of genomic variation in the context of a clinically heterogeneous phenotype. Solving this will require a concerted clinical, biological and bioinformatics approach, international agreement on phenotype ontologies, sharing of clinical and genomic data, optimization of variant interpretation tools and the validation of these using relevant biological models. I will demonstrate the progress made in the last few years and discuss some of the remaining issues using severe intellectual disability as a model disorder. For this disorder we are making much progress and now have the opportunity to provide medically relevant genetic information to the majority of patients and families involved. De novo germline mutations and structural variations affecting ID genes are now recognized as the major cause of severe intellectual disability. We are using genome sequencing to learn more about the timing and distribution of de novo mutations throughout the genome. Novel areas of research involve the study of mutations outside of genes, mutations present in only a proportion of all cells, and more complex forms of inheritance. Also, we are studying the role of de novo mutations in other disorders and are investigating risk factors that increase the number of de novo mutations in the offspring.

References: Gilissen et al. Genome sequencing identifies major causes of severe intellectual disability. Nature 511: 344–7 (2014). de Ligt et al. Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability. New England Journal of Medicine 367: 1921–1929 (2012). Vissers et al. A de novo paradigm for mental retardation. Nature Genetics 42: 1109–12 (2010).

RD-1

Rare (Mendelian) Disorders: models for genetic testing, neonatal screening and mutation specific therapies

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There are increasing disparities in terms of the rapid production of biomedical data, by e.g. next generation sequencing technologies (NGS) in genetics/genomics and lagging clinical validity and utility of such data within the domain of health care. The falling price of DNA sequencing which now exceeds Moore´s law for semiconductors and the relative rapid increase in genetic testing outside of the traditional "germ line" diagnostic domain, e.g. tendency to use DNA sequencing in neonatal screening within second line tiers creates strong pressures on a) finite resources in all solidarity principle-based European health care systems and b) on proper interpretation of detected variants (i.e. detection of variants of unknown significance). We will present the challenges on the example of cystic fibrosis, whereby the locus specific CFTR2.org variant database has established "disease liability" of CFTR gene mutations in a small fraction of the overall allelic variation in the CFTR gene. Moreover, data on intragenic rearrangements, larger indels are mostly missing, majority of which could be identified by "deep sequencing". Utilisation of DNA sequencing in neonatal screening, be it classical (Sanger sequencing) or NGS leads to a substantial increase in costs and also increases the overall number of cases with equivocal diagnosis. Moreover, NGS enables sequencing of not only the CFTR gene itself, but also of the remainder of the human coding sequence (hence "exome"), which creates additional problems in terms of detection of unsolicited secondary findings (eg. in breast cancer genes BRCA1/BRCA2). Sequencing could be justified if the screened population is very heterogeneous (eg. due to sizeable non-European admixture). On the other hand specific panels of CF-causing mutations, accounting for at least 85 % of population specific alleles, provide maximum diagnostic utility and least "headache" in terms of uninterpretable results. Finally, we will present the role of sequencing together with expression studies in the development of novel therapies in cystic fibrosis targeted at specific molecular defects.

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RD-2

The Frambu model and supplementary services to persons with rare genetic disoders and their families in Norway

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Frambu is a centre of expertise for 120 rare genetic disorders and diagnostic groups. Frambu has many services for persons with these rare disorders, their families and involved professionals. Our courses are interdisciplinary, providing information about the disorders and news from studies and research. Participants also get to meet and share experiences and solutions with others with the same disorder. The user associations of persons with the different disorders are actively taking part in course planning. The objective of Frambu is to empower persons with a rare disorder to live with it in a more confident and constructive way.

RD-3

From exomes to genomes: Next generation clinical genetics

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Medical geneticists must adopt roles as multidisciplinary team members and clinical genomics experts in the emerging personalized-medicine focused health care system. This is illustrated by two examples: Whole-exome sequencing studies that identified a new and fairly common cause of intellectual disability with therapeutic potential,[1] and whole genome sequencing studies unraveling an unique and unexpected cause of congenital immune activation mimicking chronic infections with sedimentation rates > 100, a dominant but recessively inherited condition undiagnosed by WES or linkage analysis.

[1] Houge G, Haesen D, Vissers LE, et al.: B56δ-related protein phosphatase 2A dysfunction identified in patients with intellectual disability. J Clin Invest. 2015 Jul 13

RD-4

ČAVO – Czech Association for Rare Diseases
The role of patient organizations in improving care and quality of life for patients with rare diseases

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The motto of the Czech Association for Rare Diseases is: **Rare but strong together**. It effectively points out the importance of uniting and coordinating the individual efforts of patients and patient organizations with rare diseases. Considering that there are about 7,000 different rare diagnoses, the motto is especially apt.

ČAVO, the Czech Association for Rare Diseases, was founded in Spring 2013 and currently has 30 members representing patient organizations, as well as an additional 18 individual members. ČAVO's mission is to bring together the organizations serving people with rare diseases as well as individuals, to represent their interests and to strengthen awareness of rare disease issues among experts in health care, leaders of state and international institutions and the public.

ČAVO also works closely with European counterparts to exchange knowledge, best practices and experience in dealing with rare diseases and integrating work in the Czech rare disease field into the European system.

This presentation will provide an overview of the organization's activities, as well as to call for continued dialogue and integration of patient organizations into the overall health care strategy for patients with rare diseases.

RD-5

Rare dermatology diseases

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Department of Paediatric Dermatology (DPD) focuses on severe rare dermatology diseases (RD). 624 patients with RD are followed in the department. Interdisciplinary team for children and adult patients with RD was inicialised and is managed by the department stuff. DPD closely cooperates with the Centre of Molecular Biology and Gene Therapy and Department of Medical Genetics University Hospital Brno providing diagnostic of 86 genodermatoses genes mutations. Prenatal diagnostics and preimplantation genetic diagnosis is offered to the RD affected families. DPD collaborates with EB Clinet, DEBRA International and Genodermatoses network.

EB Centre University Hospital Brno was founded in 2001 (http://www.ebcentrum.cz) and DEBRA Czech Republic in 2004 (www.debra-cz.org). EB Centre provides a complex medical care and support for all patients with EB and their families (children and adults). EB Centre was established as centre of excellence by Ministry of Health Care in 2012. National EB registry managed by the EB centre contains all EB patients from the Czech Republic and partly from Slovakia (248 patients with EB in total, 39% dystrophic EB, 7% junctional EB, 54% simplex EB). EB Centre provides consulting and diagnostic for EB patients from Ukraine and Russia in demanded cases. The centre offers medical training for the medical stuff from Eastern Europe.

RD-6

DNA diagnostics of genodermatoses in the University Hospital Brno

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Genodermatoses are inherited skin disorders characterised by high clinical and genetic heterogeneity. We started DNA diagnostics of genodermatoses in 2005 when we introduced diagnostics of epidermolysis bullosa dystrophica (the COL7A1 gene) and epidermolysis bullosa simplex (the KRT5 and KRT14 gene). In subsequent years, DNA diagnostics was further extended and diagnostics of different types of ichthyoses were introduced (the FLG, STS, ALOX12B, ALOXE3, NIPAL4, CYP4F22, TGM1, KRT1, KRT10, KRT2 genes) together with diagnostics of acral peeling skin syndrome (the TGM5 gene). In 2014, we implemented the solution-based capture method SeqCap EZ Choice Library (Roche NimbleGen) and targeted resequencing. A custom capture array was designed to capture exons and adjacent intron sequences of 81 genes associated with selected inherited skin and connective tissue disorders. Using SeqCap- targeted resequencing and subsequent verification of discovered sequence changes by classical sequence analysis, we performed analysis of 94 patients, causal mutation(s) was identified in 56 of them (60%). Epidermolysis bullosa simplex, epidermolysis bullosa dystrophica, autosomal recessive congenital ichthyoses, epidermolytic hyperkeratosis, osteogenesis imperfekta, and Ehlers-Danlosova syndrome are the most frequent disorders diagnosed in our laboratory using the mentioned approach.

This study was supported by the project of the Internal Grant Agency of the Ministry of Health of the Czech Republic (NT/14585-3) and the project of the Technology Agency of the Czech Republic (TE02000058).

RD-7

Congenital ichthyoses

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Congenital ichthyoses are a very heterogeneous group of skin disorders manifested by dry, rough and puffing skin. Ichthyoses belong to the group of rare diseases – keratodermias.

In all forms of ichthyoses skin barrier is broken, thus causes a higher transepidermal water loss and reduce the ability to maintain sufficient water in the epidermis. Clinical manifestations of individual types of ichthyoses are caused by mutations in different genes.

The authors emphasize the importance of molecular genetic testing, which is in our center for various types genodermatoses available.

Currently we have examined a total of 120 patients with congenital ichthyosis: * Ichthyosis vulgaris 40%, Cong. icht. erytrodermia 35%, ichthyosis lamellaris 15%, X-linked CI 5% and keratinopathic ichthyosis 5%.

Diagnostics at the molecular level confirms histopathologic diagnosis and may determine prognosis, genetic prevention and comprehensive genetic counseling, which is a great benefit for parents of the patient and his relatives wide.

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RD-8

Famous Animal Experiments from Mendel to Watson & Crick A Historical Perspective

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During the 35 years between the time (1865) that Mendel presented his results and their rediscovery (1900) the essential features of cellular architecture and gametogenesis were described, thus setting the stage for validating Mendel´s seminal work. Not long after the rediscovery, it was generally accepted that Mendel´s Laws applied to animals as well as to plants.

We will present some of the early genetic studies using animals by Weisman, Galton, Bateson, Wright and Barr culminating in the use of mice by Avery, MacCleod & McCarty that unequivocally showed that nucleic acids constituted the genetic material, i.e. genes. This discovery was a necessary antecedent for Watson & Crick's detailed description of the conformational structure of DNA in 1953.

RD-9

Hereditary oncology diseases

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Cancer diseases are mostly polyfactorial and polygenic, but in 5–10% of cases mendelian inheritance is the major cause of the disease occurrence. Frequently genetic predisposition is found in breast, ovarian and colorectal cancer, but any type of cancer can be hereditary. So far we know about 200 different cancer genetic syndromes, most of them transmitted by autosomal dominant inheritance, but some rare syndromes are recessive diseases.

Diagnostic of these syndromes, calculations of possible cancer risks for carriers and specialized preventive care are very effective tools for diminishing of cancer burden in families and cancer death. Some preventive programs are very effective, but in some complicated syndromes there is still not much we can offer and research of preventive modalities is necessary.

Genetic testing is evolving very quickly. Genetic testing of cancer syndromes started more then 20 years ago and increased with the discovery of BRCA1 and BRCA2 genes for hereditary breast and ovarian cancer syndrome and several mismatch repair genes responsible for Lynch syndrome or hereditary nonpolyposis colorectal cancer. Many other important genes for other syndromes were discovered since. Genetic counseling is important first step for clinical suspicion for cancer syndrome and for genetic testing planning. For gene testing different methods are used, previously SSCP, heteroduplex analysis, PTT tests, DGGE, now more HRM, DHPLC and direct sequencing. Classical individual gene testing is now more and more replaced by next generation sequencing with multiple gene panels. There are several strategies in the use of panels. Many companies are offering panels of high risk genes with known clinical relevance. In some institutions clinical testing of significant genes is done together with research only genes and these data are collected for further analysis. How to explain the results for the clinical use is sometimes quite complicated. From these results we can clearly say that all cancer is a polygenic disease, almost all patients have several germline mutations or variants in different genes, which may play somehow important role in cancer etiology. We have to work together to elucidate the most important biological and clinical data and push our understanding of hereditary cancer further.

RD-10

Hereditary arrhythmic syndromes

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Hereditary arrhythmic syndromes are rare diseases of the heart with high risk of malignant arrhythmias. These arrhythmias could lead to syncope – short episode of unconsciousness – or even to sudden death. Often, the first manifestation occurs in young and previously healthy individuals.

These diseases are: the Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and above all the long QT syndrome (LQTS). According to the recent Italian study the prevalence of LQTS is at least 1:2500. Thus, LQTS has almost reached the threshold for rare diseases. Hereditary arrhythmic syndromes are caused by disorders of electric processes in heart cells. In substantial proportion of cases mutations of genes encoding cardiac ion channels and related proteins are found.

Clinical diagnostic of these disease can be difficult, while findings of routine cardiological investigation (including echocardiography) are normal. Only in limited number of cases some electrocardiographic signs are present (e.g. QT interval prolongation). More often these signs occur only during stress test – i.e. bicycle ergometry. Reliable recognition of a life-threatening disease enables a physician to apply proper therapy – either administration of a betablocking agent or implantation of a defibrillator. Genetic investigation plays an important role. Finding of a pathologic mutation can confirm the diagnosis in various proportion of patients, nevertheless association of particular mutation with pathologic phenotype is not always straightforward.

RD-11

Inborn errors of metabolism and newborn screening

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The concept of genetically determined chemical individuality was proposed by Sir Archibald Garrod in 1902. Using genealogical observations in patients with alkaptonuria Garrod applied Mendel's laws and coined the concept of inborn errors of metabolism (IEMs) as inherited disturbances in chemical individuality. At present IEMs represent a group of almost thousand diseases with known genetic defects and underlying molecular mechanisms, mostly resulting from deficient activity of enzymes. In clinical practice biochemical genetics enables to establish precise diagnosis and to provide genetic counseling in affected families and more importantly to treat a significant proportion of patients with IEMs.

Different approaches with varying efficacy have been developed to treat patients suffering from IEMs. The dietary treatments modulating the flux of metabolites in the affected pathway include restriction of specific components in the food (e.g. sugars) or of proteins with supplementation of amino acid mixtures, and provision of nutrients below the enzymatic block. Other common treatment modalities are targeting the appropriate enzyme (vitamins stabilize misfolded mutant proteins while enzyme replacement therapy provides parenterally the recombinant missing protein) while other therapies use different targets. Improved knowledge of molecular mechanisms leads to the exploration of innovative approaches such as small molecule chaperones, antisense oligonucleotides or chemical modification of mutant amino acid residues. In the presentation all current treatment modalities as well as novel diagnostic and therapeutic approaches will be demonstrated in homocystinuria due to cystathionine beta-synthase deficiency.

Recent technological advances-namely tandem mass spectrometry-enabled a worldwide expansion of newborn screening programs for treatable diseases. The newborn screening program in the Czech Republic was expanded in 2009 and targets 13 conditions-hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis and 10 IEMs. The detection rate for the past 5 years was 1:1,100 demonstrating that this type of secondary prevention can lead to a significant improvement of care for patients with rare diseases.

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RD-12

Usefulness and limitations of conventional and repeat-primed PCR based molecular testing of myotonic dystrophy type 1 and 2

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Both genetic types of myotonic dystrophy, DM1 and DM2, are caused by microsatellite expansions. The DM1 associated CTG tract in the DMPK gene is basically a simple repeat, while the CCTG repeat in the CNBP gene, associated with DM2, is a part of a complex repetitive motif $(TG)_n(TCTG)_n(CCTG)_n$, in which each of the elements are highly polymorphic. Repeat-primed PCR represents one of the commonly used techniques for the determination of the presence or absence of expanded DM1/DM2 alleles. However, as the structure of the two repeat motifs is different, there are features of repeat-primed PCR which are unique for each type of DM. Our contribution reviews our six year experience with PCR based (conventional and repeat-primed PCR) DM1/DM2 testing in Slovakia. Surrounding sequences and the purity of the repeat motif represent crucial features for the results of repeat-primed PCR applications. As we mentioned above, the DMPK CTG motif is generally pure, however, in rare cases sequence interruptions can be present and can modify both the conventional and repeat-primed PCR results. In opposite, the CNBP CCTG tract is generally interrupted while uninterrupted alleles are rather rare. Because of the complexity of the CNBP repeat motif and the generally presenting interruptions in the CCTG part, repeat-primed PCR reaction should be designed in a proper way – it is better to avoid amplification through the $(TG)_n(TCTG)_n$ part of the motif. Since our results suggest the potential benefit of the simultaneous use of conventional PCR and repeat-primed PCR performed in both directions, we have designed several multiplex reactions to parallelise the required testing reactions. Moreover, fluorescent labelling of both primers in conventional PCR may also improve the accuracy and reliability of the diagnostic assays based on these methods. Although the simultaneous dual-labelled conventional PCR and bidirectional repeat-primed PCR testing approach improves the DM diagnostic procedure it has also limitations which should be kept in mind during assay designs and results interpretations. Of course, modifications described in our contribution are not restricted only to DM testing and may also be useful in PCR/repeat-primed PCR testing of several other repeat expansion disorders. Our work was partially supported by grant VEGA_2/0115/15.

E-1

GATTACA here and now: from science fiction to reality

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GATTACA, a famous movie written directed by Andrew Niccol, was introduced in 1997 and raised both professional and public discussions about emerging ethical issues concerning DNA research, reproductive technologies, privacy and discrimination. GATTACA the movie is set in the "not-too-distant future" but it is usually understand as a pure sci-fi genre at the present day. Nevertheless, 18 years later, some of the described practices still remain the fiction, but the others already became the reality. In this presentation, the new technologies used for DNA diagnostics (both for medical and non-medical purposes) will be considered in the context of changed privacy perception.

E-2

Změna paradigmatu medicíny a její etická rizika

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V celých dějinách lékařství byl za pacienta považován ten, kdo začal trpět nějakou nemocí, nebo jehož tělo dlouhodobě nepracovalo správně a úsilí lékařů směřovalo k tomu, navrátit funkci jednotlivých orgánů do normy. Toto zadání nemocnic se v současnosti mění. V posledních několika letech dochází díky prudkému rozvoji molekulární genetiky ke kompletní změně paradigmatu medicíny. Díky možnostem sekvenování genomu člověka či provedení genetického profilu, který zajišťují soukromé firmy, začínají do nemocnic přicházet víc a více lidé, v tuto chvíli a podle všech kritérií zcela zdrávi, dožadující se kvůli získaným informacím různých preventivních zákroků. Slova „pacient" či „nemocnice" tak přestávají být lingvisticky přesné. Díky bezprecedentně prudkému poklesu sekvenování genomu člověka jsme dnes již schopni sekvenovat genom jedince v prenatálním stadiu, provádět široce pojaté testy embryí v rámci preimplantační diagnostiky a každým dnem jsme schopni vyčíst více informací z genomu člověka, což nositele může vést a reálně vede buď k častějším preventivním prohlídkám či k žádostem o preventivní zákrok. V přednášce budou zvažována etická rizika tohoto obratu, jakož i související a stále větší rizika novodobé eugeniky.