ABSTRACT BOOK

15th Balkan Congress of Human Genetics and 3rd Alpe Adria Meeting of Human Genetics

October 09-11, 2025
"Rikli Balance" Hotel
Bled, Slovenia

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Welcome Address

Dear Colleagues, dear Friends,

On behalf of the Scientific and Organizing Committee and the Slovenian Association of Medical Genetics, we would like to warmly welcome you to the **15th Balkan Congress of Human Genetics and 3rd Alpe Adria Meeting of Human Genetics** with international participation.

We sincerely hope this joint meeting will present you with an opportunity to meet, share ideas, and form new collaborations with colleagues from the field of Genetics from the Balkans, the Alpe-Adria region and beyond.

In addition to lectures on the newest genomics technologies and an overview of regional applicative and research genetics, we hope to address our common challenges and solutions via the Genetic Medicine in Balkan Countries roundtable as well as to set up a Strategy for Future Genomic Medicine via the International genomic forum roundtable. We sincerely hope you will enjoy our Workshops and that they will be the first of many more.

Finally, we hope our initiatives will encourage you to join existing platforms aiming to unify practice guidelines and services in the region, and to further advance contemporary medical genetics approaches to help your patients. We kindly invite you to join us in discussing and defining the future of genomic medicine.

We warmly welcome you at Bled!

Nina Vodnjov, Anja Kovanda and Aleš Maver

General information

Venue:
Arnold Hall
Hotel "Rikli Balance"
Cankarjeva cesta 4,
4260 Bled
Slovenia

Registration desk
Reception desk is organized the lobby of the Hotel "Rikli Balance" and will be open for information and registration from 7:30 every day of the congress.

Language:
The official language of the Congress is English.

Oral presentations
Facilities will be available for presenting Microsoft PowerPoint slides in 16:9 ratio in PPTX or PPT format. Speakers are kindly requested to either bring the USB stick to the presentation computer no latest than 90 minutes before the respective session or uploading their presentation before the conference starts via provided link. Please, take in consideration the allocated time for effective presentation of your presentation.

Poster presentations
The poster presentations will be presented on digital displays in front of the lecture rooms, in 7 Poster sessions, according to the program. Each presenter will be given 4 minutes to present their work using the PowerPoint slides and 1 minute for discussion. There will be a moderator and an assistant at each poster session that will help presenters with everything in terms of the presentation.

Registration Fee
The registration fee covers the programme, access to the scientific sessions, a welcome drink and get-together on Thursday, the conference dinner on Friday, coffee breaks, and Friday's lunch. PDF version of the Abstract book is available on the event web-site. A certificate of attendance will be provided on site.

Congress programme

DAY 1 Thursday 9th of October 2025

8:00-13:00	**WS.01**	**Workshop: Interpretation of NGS data**	**A. Maver**	
13:00		**Lunch break**		
14:00-15:40	**P1**	**Welcome address and plenary lectures *(B. Peterlin, D. Plaseska-Karanfilska)***		
	W.01.P 45 min	Using genomic medicine to make drug prescription safer and more effective	**W. Newman**	**United Kingdom**
	W.02.P 45 min	Gamechanger in rare disease research and diagnosis: the role of 3D facial gestalt scanning technology	**M. Macek**	**Czech Republic**
15:40-16:50	**S1**	**Session 1: Advances in rare disease diagnostics *(W. Newman, K. Writzl)***		
	S1.01.I 20 min	Long-read sequencing for rare disease research and diagnostics	**B. Van der Sanden**	**Netherlands**
	S1.02.I 20 min	AI-Assisted Genome Diagnostics with Long Reads	**S. Ossowski**	**Germany**
	S1.03.I 10 min	Structural variants in rare disease	**A. Kovanda**	**Slovenia**
	S1.04.O 10 min	Rapid Intraoperative Classification of Central Nervous System Tumours Using Real-Time Nanopore Sequencing	**S. Petrin**	**Slovenia**
	S1.05.O 10 min	The contribution of reanalysis of whole exome sequencing data to diagnosis rate	**H. Bas**	**Turkey**
16:50		**Coffee break**		
17:20-18:50	**S2**	**Session 2: What is new in Mendelian disorders *(M. Macek, L. Lovrečić)***		
	S2.01.P 20 min	Beyond Chromosomes: The Monogenic Causes of Early Pregnancy Loss	**D. Plaseska-Karanfilska**	**North Macedonia**
	S2.02.I 20 min	Chromatin remodeling disorders - challenging path to diagnosis and management	**L. Odak**	**Croatia**
	S2.03.O 10 min	Reporting Beyond the Primary Diagnosis: Actionable Additional Findings in WES/WGS	**B. Golob**	**Slovenia**
	S2.04.O 10 min	3D Facial Gestalt Analysis of Individuals with Mutated PKD1 Genes in Polycystic Kidney Disease Patients	**M. Mihulová**	**Czech Republic**
	S2.05.O 10 min	Uncovering Dual Diagnoses through Trio-Based Whole Exome Sequencing (WES): Incidence and Clinical Implications	**F. Perino**	**Italy**
	S2.06.O 10 min	Resolving diagnostic challenges in skeletal dysplasia – a clinical overview of a ten years' experience of a single genetic center in Serbia	**M. Mijović**	**Serbia**
	S2.07.O 10 min	Genetic basis of female protective effect in neurodevelopmental disorders and beyond	**D. Perović**	**Serbia**
18:50	**S3-R**	**Roundtable: Genetic Medicine in Balkan countries: Challenges and solutions**		
18:50-20:00	**S3.01.I** 10 min	Balkan Journal of Medical Genetics (BJMG): Gateway to publishing quality research	**D. Plaseska Karanfilska**	**North Macedonia**
	S3.02.I 10 min	The importance of European Reference Network in rare disease diagnosis and management: Slovenia's experience	**I. Babič Božović**	**Slovenia**
	S3.03.I 10 min	Competences of health professionals in genomic counselling	**N. Kregar Velikonja**	**Slovenia**
	S3.04.P	Maturity level of National Genomic Systems 10 min / Discussion 30 min	**B. Peterlin**	**Slovenia**
20:00		**Welcome drink and get together**		

DAY 2 - Morning Friday, 10th of October 2025

08:00-09:30	**S4**	**Genetics of neurologic and neurodevelopmental disorders** *(O. Miljanović, M. Đurišić)*		
	S4.01.P 20 min	The contribution of genomic diagnostics to the elucidation of neurodevelopmental disorders	**O. Miljanović**	**Montenegro**
	S4.02.O 10 min	The FMR1 Premutation in Patients with Late-Onset Movement Disorders and Family Members of Fragile X Syndrome Patients: A Diagnostic Opportunity	**M. Pesić**	**Serbia**
	S4.03.O 10 min	Routine molecular genetic testing of GAA-FGF14-Related Ataxia and RFC1 CANVAS Spectrum Disorder	**H. Jaklič**	**Slovenia**
	S4.04.O 10 min	Monogenic Causes of Early-Onset Dementia: Evidence from Whole Exome Sequencing	**E. Shukarova Stefanovska**	**North Macedonia**
	S4.05.O 10 min	Expansion and contraction of CGG repeats in FMR1 gene within one family	**B. Pejović**	**Serbia**
	S4.06.O 10 min	ERBB4 exonic deletions in patients with intellectual disability and speech developmental delay	**M. Rasić**	**Serbia**
09:10	**S4.06.S**	**How to Combine Genomics, Deep Phenotyping, and AI to Diagnose Patients with Rare Diseases**		**Genomize**
09:30-10:30	**S13 ARNOLD 1**	**Quality assurance in Balkan countries** ***(L. Lovrečič)*** (concurrent with P1 and P2 poster sessions) **How to obtain regulatory compliance for in-house in vitro devices (IH-IVD's)?** *(H. Podgornik, UMCL, Slovenia)* 20 min **The challenge of persistent poor performance in external quality control** *(W. Gutowska-Ding, EMQN, UK)* 20 min Virtual		
09:30-10:30	**P1 ARNOLD 2**	**Concurrent Poster viewing session – Cancer** 5 min per poster	**P001-P010, P067** ***(H. Butz, V. Šetrajčič Dragoš)***	
	P2 ROSA	**Concurrent Poster viewing session - Regional healthcare** 5 min per poster	**P011-P016, P068, P070-P072** ***(A. Marjanovic, A. Maver)***	
09:30		**Coffee break**		
10:30-11:50	**S5**	**Advances in cancer diagnosis** *(V. Stegel, D. Primorac)*		
	S5.01.P 20 min	A New Era of AI and Whole Genome Sequencing (WGS) for Cancer Diagnosis and Treatment Strategies	**D. Primorac**	**Croatia**
	S5.02.O 10 min	Increased Identification of PARP Inhibitor-Eligible Patients in Epithelial Ovarian Cancer through HRD Testing at the Institute of Oncology Ljubljana	**V. Stegel**	**Slovenia**
	S5.03.O 10 min	Chaperone-Mediated Autophagy in Glioblastoma: A Multi-Omics Perspective	**Ö. Yildirim**	**Turkey**
	S5.04.O 10 min	Better diagnosis of liver cancer with the use of Xenium spatial transcriptomics	**U. Prosenc Zrmzljak**	**Slovenia**
	S5.05.O 10 min	Genes associated with higher mutational burden in tumors and improved response to checkpoint immunotherapy	**G. Kungulovski**	**North Macedonia**
	S5.06.O 10 min	Clinical verification of plasma cell immunoselection for FISH analysis in multiple myeloma	**H. Podgornik**	**Slovenia**
	S5.07.O 10 min	Computational Identification of Potential Therapeutic Agents Targeting the MUC16 Gene in Glioblastoma	**R. Kalkan**	**Northern Cyprus, Turkey**
	S5.08.O 10 min	Immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome in a large exome dataset: Identification of novel variants in DNMT3B, ZBTB24, and CDCA7 genes	**F. Dereli Devrez**	**Turkey**
12:00		**Lunch break**		

DAY 2 Afternoon Friday 10th of October 2025

13:00-14:30	**S6**	**Concurrent session - Room Arnold 1 - Prenatal and preventive genomics** ***(S. Hadjidekova, M. Xhetani)***		
	S6.01.P 20 min	Recurrent Pregnancy Loss and Genetics: Exploring the Genetic Factors Behind Pregnancy Complications	**M. Xhetani**	**Albania**
	S6.02.P 20 min	Enhancing Prenatal Diagnosis of Fetal Congenital Anomalies Through Next-Generation Sequencing	**F. Burada**	**Romania**
	S6.03.I 20 min	Prenatal Genomic Testing - Current position and future directions	**L. Lovrečić**	**Slovenia**
	S6.04.I 20 min	Foetal radiation risk. Role of geneticists in biodosimetry service and genetic counselling	**J. Pajić**	**Serbia**
	S6.05.O 10 min	Familial Cases Show Higher Prevalence of Rare Predicted Pathogenic Variants in 56 Novel Genes Associated with Spontaneous Preterm Birth	**T. Mladenić**	**Croatia**
	S6.06.O 10 min	Preliminary serum metabolomics analysis highlighting tryptophan pathway alterations in spontaneous preterm birth	**S. Dević Pavlić**	**Croatia**
13:00-14:30	**S7**	**Concurrent session - Room Arnold 2 - Oncogenetics - the current state and challenges in the region** ***(H. Podgornik, A. Patocs)***		
	S7.01.P 20 min	Role of clinical and laboratory geneticists in precision cancer medicine	**A. Patocs**	**Hungary**
	S7.02.I 20 min	OncoOrigin: The Future of Precision Oncology through Integration of Machine Learning and Tumor Genomics for Identifying Primary Tumor Site	**P. Brlek**	**Croatia**
	S7.03.I 20 min	Challenging interpretation of germline variants in hereditary breast and ovarian cancer	**H. Butz**	**Hungary**
	S7.04.O 10 min	Spectrum of germline BRCA pathogenic variants in ovarian cancer patients from North Macedonia	**S. Kiprijanovska**	**North Macedonia**
	S7.05.O 10 min	Germline Screening for Hereditary Cancer Predisposition in the Bulgarian Population: Insights from 2024	**N. Valcheva**	**Bulgaria**
	S7.06.O 10 min	Exploring attitudes towards nutritional advice amongst individuals affected by Lynch Syndrome in the UK	**I. Rennocks**	**United Kingdom**
	S7.07.O 10 min	Genetic Factors and Acute Kidney Injury: Influence on Cancer Treatment Strategies	**M. Imeraj**	**Albania**
14:30-15:30	**P03 Arnold 1** **P04 Arnold 2** **P05 Rosa**	**Concurrent Poster viewing session – Case reports and Series** 5 min per poster	**P017-P026** ***(A. Kovanda, K. Writzl)*** **P027-P035** ***(J. Pajić, I. Babič Božović)*** **P038-P046** ***(O. Antonova, F. Burada)***	
15:30-16:30	**S8**	**Screening and prevention programmes in the Balkan countries** ***(T. Bahsi, F. Burada)***		
	S8.01.P 20 min	PGT and hereditary breast cancer - can and should we break the chain?	**S. Hadjidekova**	**Bulgaria**
	S8.02.P 20 min	Combating Rare Diseases - Preconception and newborn screening programs in Turkey	**T. Bahsi**	**Turkey**
	S8.03.O 20 min	Facing Uncertainty in Prenatal Screening: Personal and Social Resources for Psychological Resilience	**J. Jakerlová**	**Czech republic**
16:30-17:40	**S9**	**Advanced treatments for genetic disorders and cancer** ***(D. Biskup, P. Gasparini)***		
	S9.01.P 30 min	On the way to personalized tumor vaccines	**D. Biskup**	**Germany**
	S9.02.P 30 min	Drug repurposing for inherited disease	**P. Gasparini**	**Italy**
	S9.03.O 10 min	The U-PGx project and PREPARE study in Slovenia: lessons learned on implementation of pharmacogenomics testing	**V. Dolžan**	**Slovenia**
17:40	**S9.04.S**	**PARPe Diem: Drawing Lessons from Experience to Shape Tomorrow**		**Astra Zeneca**
18:10-19:10	**S10-R**	**Roundtable: International genomic forum: Strategy for Future Genomic Medicine** ***(O. Miljanović, D. Primorac, P.Gasparini, B. Peterlin)***		
20:00		**Conference Dinner -** Grand Hotel Toplice		

DAY 3 Saturday 11th of October 2025

08:00-09:50	**S11**	**Genetics of complex diseases and functional genomics** *(I. Babić Božović, V. Vidović)*		
	S11.01.I 20 min	APOE, APP, and PSEN1 Mutation Screening in Alzheimer's Disease: A 15-Year Experience in Serbia	**A. Marjanović**	**Serbia**
	S11.02.I 20 min	Frequency of common variants predisposing to estrogen positive diseases in the Bulgarian population	**O. Antonova**	**Bolgaria**
	S11.03.I 20 min	Role of SIRT1 and SIRT3 Genetic Polymorphisms in the Risk of Acute Myocardial Infarction among Patients from the Republic of Srpska	**V. Vidović**	**Bosna and Herzegovina**
	S11.04.O 10 min	Genetic risk factors for anaphylaxis: Insights from somatic KIT p.D816V variant and Hereditary α-tryptasemia	**M. Rijavec**	**Slovenia**
	S11.05.O 10 min	Pediatric multiple sclerosis cases burdened with rare, predicted pathogenic variants in iron metabolism genes	**A. Turk**	**Slovenia**
	S11.06.O 10 min	Long-Read Sequencing in the Human Genome's Repetitive Landscape: Challenges and Clinical Opportunities	**T. Tesovnik**	**Slovenia**
	S11.07.O 10 min	Identifying patterns of differential methylation in multiple sclerosis by positional integration approach and their functional characterization	**N. Mele**	**Slovenia**
	S11.08.O 10 min	Connecting the Dots: Genetics, Diet, and Microbiome in Endometriosis (EM)	**A. Santin**	**Italy**
	S11.09.O 10 min	Severe Clinical Phenotype in Alport Syndrome Due to Two COL4A4 Exon Skipping Events	**A. Zupan**	**Slovenia**
10:00	**S11.10.S**	**NGS solutions for Human genetics**		**Agilent**
10:20-11:20	**P06 ARNOLD 1**	**Concurrent Poster viewing session – complex and functional genomics** 5 min per poster	**P047-P056** *(L. Odak, A. Kovanda)*	
	P07 ARNOLD 2	**Concurrent Poster viewing session – diagnostics** 5 min per poster	**P058-P066, P069** *(T. Pajič, M. Rijavec)*	
11:20-13:00	**S12**	**Expanding the genotype-phenotype landscape of genetic disorders in the Balkans** *(S. Bertok, A. Marjanović)*		
	S12.01.P 20 min	Write according to the rules, read between the lines	**M. Djurišić**	**Serbia**
	S12.02.O 10 min	Genetics of porphyria. Efforts to associate specific mutations with clinical manifestations	**T. Todorov**	**Bulgaria**
	S12.03.O 10 min	Expanding the Genotypic Spectrum of Epidermolysis Bullosa: A Case Series	**E. H. Ceylan**	**Turkey**
	S12.04.O 10 min	Genotype-Phenotype Correlation in TTN Gene Variants	**M. B. Yilmaz**	**Turkey**
	S12.05.O 10 min	Challenges and Rewards in Diagnosing Diamond-Blackfan Anaemia: A Case Series from Cooperating Regional Tertiary Care Centres	**T. Pajič**	**Slovenia**
	S12.06.O 10 min	Body mass index is an overlooked confounding factor in clustering studies of 3D facial scans of children with autism spectrum disorder	**M. Schwarz**	**Czech republic**
	S12.08.O 10 min	Hereditary Myopathies in 45 Turkish Patients: Genetic Spectrum and Diagnostic Outcomes	**S. Demir**	**Turkey**
	S12.09.O 10 min	Biomolecular characterization of hereditary transthyretin amyloidosis in Bulgaria	**A. Todorova**	**Bulgaria**
13:00-13:20		**Closing sessions**		
		Best poster and oral presentation award winners announcement Closing remarks and thanks		
13:20		**Lunch break**		
14:00-16:00	**WS.02**	**Workshop: Translational research on rare diseases**	**M. Stojiljkovic**	

Workshops/symposia

October 9, 2025 (Thursday)

8:00-13:00	WS.01 Arnold 2 Hall	**Workshop: Interpretation of NGS data**	A. Maver

8:00 – 9:05 **SESSION 1 - Things to do before the start of NGS diagnostics**

Presentations WS-NGS-1 to WS-NGS-4

8:00 - 8:05 ***WS-NGS-1 – Introduction***

Aleš Maver, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

The next generation sequencing workshop is the first edition of the NGS-themed workshop series we will be organizing in the region. It aims to empower the participants to engage in the interpretation process of comprehensive sequencing approaches. The workshop is tailored to colleagues that work with results and reports of clinical next-generation sequencing, including clinical geneticists, clinical laboratory scientists and trainees at the beginning of their career.
The goal is to primarily focus on clinical examples encountered in routine diagnostic process and try to provide guidance to handle the edge clinical cases and harmonize the interpretation and analysis approaches used by laboratories in the region.

8:05 - 8:20 ***WS-NGS-2 - The significance of correct interpretation - examples of how an incorrect classification may lead to medical errors and how to prevent them (what have we learned)***

Aleš Maver, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

8:20 - 8:45 ***WS-NGS-3 - How to ensure appropriate quality of data before starting the interpretation - gender matching, het/hom ratios, trio QC, special situations***

Tadej Pajič, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Whole Exome Sequencing (WES) is a multi-stage analytical process, with each phase containing essential quality control (QC) checkpoints to ensure data integrity, accuracy, and clinical relevance. Proper QC is fundamental to avoiding misinterpretation and achieving reliable variant detection. One of the most critical factors is coverage, as low sequencing depth or uneven coverage may result in missed variants or false conclusions. B-Allele Frequency (BAF), Copy Number Variation (CNV), Region of Homozigosity (RoH) plots reveal evidence of structural variants and inheritance patterns. All these plots give us a broader view of the genome than single nucleotide analysis (SNV) analysis alone. A gender check serves as a straightforward QC step that helps detect potential sample swaps, labeling errors, or rare biological discrepancies. Trio-based QC plays a vital role in confirming familial relationships, validating inheritance

patterns, and identifying de novo variants. In clinical cases, clonal structural variants may mask hereditary findings, emphasizing the need for repeat testing from alternative non-blood tissues and the inclusion of genetic counseling. Furthermore, clinical and reproductive history must be carefully considered when interpreting WES results, as these factors can significantly affect variant interpretation. We believe that these QC procedures represent the minimum requirements that must be completed before proceeding to variant interpretation. The integration of these QC checks—coverage assessment, structural variant visualization, gender verification, and family-based validation—ensures robust, reproducible, and clinically meaningful WES results.

8:45 - 9:05 ***WS-NGS-4 - Blind spots - The caveats and limitations of the NGS technology in a diagnostic setting***

Vid Velepec, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

NGS (Next Generation Sequencing) technology is indispensable for the rapid and efficient diagnosis of hereditary diseases, but the data we receive from it is not always as intuitive as one would hope.

We must pay special attention to compound heterozygotes, as pathogenic recessive variants can still cause diseases if there is another variant on the opposite allele in the same gene, but the location of the variant on the alleles is often difficult to determine without further tests precisely because of the short NGS transcripts. These transcripts can also cause problems with pseudogenes and genes that occur in multiple copies, as they cause difficulties in accurately mapping the genome from the transcripts due to homologous segments. When classifying variants, we must also pay attention to genes with incomplete penetrance and hypomorphic alleles, as they may often appear in population databases despite their pathogenicity, as well as to genes that may cause variable clinical pictures depending on the type of mutation. Moreover, there will always be mutations that are difficult to determine with data alone, such as variants that have a different effect on various transcripts of the same gene.

In summary, NGS technology enables efficient treatment of genomes in diagnostics, as long as we are mindful of the imperfect mappability of the shorter reads in NGS, consider the phenotypic impact of different transcripts and understand the corelation of various mutations in relation to variant population frequencies.

9:05 – 10:20 **SESSION 2 - Tips and tricks for variant interpretation**

Presentations WS-NGS-5 to WS-NGS-7

9:05 - 9:30 ***WS-NGS-5 - When loss of function is not as pathogenic as it seems - interpreting loss of function variants***

Nina Vodnjov, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Loss-of-function (LoF) variants result in a reduction or complete loss of normal protein function. They are most commonly annotated as nonsense, frameshift, intragenic deletion or duplication, or insertion/deletion (indel). These variants typically disrupt the open reading frame, resulting in premature termination codons being located in the mRNA before their usual position and triggering nonsense-mediated mRNA decay (NMD).

However, not all predicted LoF variants are actually medically relevant. Firstly, LoF variants should only be considered in genes where the loss of the gene's protein product is recognised as a pathomechanism of the disease. Secondly, variants in the final exon and the final 50 nucleotides of the penultimate exon may escape NMD, having no or minimal effect on the gene's protein product. Thirdly, the variant must affect the gene's biologically relevant transcripts and exons. Furthermore, many annotation tools may select the variant predicted to have the most deleterious effect, regardless of whether the transcript is biologically relevant. The ACMG criterion used for classifying LoF variants is PVS1. A decision tree has been proposed to help select the most appropriate level of this criterion.

In summary, the most accurate interpretation of LoF variants is achieved by considering the pathomechanism of the affected gene, the variant's location within the gene and the relevant transcript, while adhering to the PVS1 guidelines.

9:30 - 9:55 *WS-NGS-6 - Prudent use of population frequency evidence*

Urška Kotnik, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Population databases provide genomic data from unaffected control individuals, allowing us to examine the population frequency of variants in the general population and identify extremely rare, possibly pathogenic variants. Still, the presence of a variant in a control population does not necessarily ensure its irrelevance in the context of genetic disease.

Several challenges may be considered during variant interpretation, as they can result in the presence of pathogenic variation in control databases.First, osme databases contain individuals with phenotypes, not purely healthy controls. Second, the age of control individuals matters, asmany genetic diseases have late onset; therefore, pre-symptomatic individuals, believed to be healthy, may be included in the databases. Third, many genetic diseases, show reduced penetrance; therefore, a presence of a low number of pathogenic variants is expected in population databases. Fourth, somatic mosaicism can be present in population databases. Finally, consider the differences between populations. Population-specific databases are valuable for the detection of benign variants specific to certain groups that can be absent from general non-specific population databases. Such databases can help identify true pathogenic variants as well as establish the frequency of pathogenic variants in specific populations.

To sum up, while population frequency databases present an invaluable source of information for variant interpretation, the presence of a variant in those databases doesn't always rule out its relevance. Careful consideration of the variation and disease properties must be given before classifying the variant as benign due to its presence in population databases.

9:55 – 10:20 ***WS-NGS-7 - Appropriate use of evidence from familial studies in variant classification - the PS2/PM6 and PP1 criteria***

Barbara Golob, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

ACMG and ClinGen guidelines for variant interpretation recognize two types of evidence from family-based segregation analysis: de novo occurrence of a variant and its cosegregation with the phenotype. The first, de novo assessment, corresponds to the PS2/PM6 criterion. PS2 is applied when both parental relationships have been confirmed, either through trio exome/genome sequencing or with a panel of informative genetic markers. PM6 is used when the variant is absent in both parental samples, but parentage has not been confirmed. PS2 and PM6 can only be applied if the patient's phenotype is consistent with the gene–disease association. To strengthen this criterion, the ClinGen Sequence Variant Interpretation group has developed a points-based system for variants proven to have arisen de novo in multiple probands with varying levels of phenotypic specificity. The second criterion, PP1, considers cosegregation of a genetic variant with disease with either a dominant or recessive model of inheritance. Quantitative guidelines by Jarvik and Browning provide cut-offs for pathogenicity based on the probability that the observed segregation occurred by chance rather than true association. When counting meioses, both the inheritance model and penetrance must be considered.

10:45 – 12:00 **SESSION 3 - Advanced issues in variant interpretation**

Presentations WS-NGS-8 to WS-NGS-10

10:45 - 11:10 ***WS-NGS-8 - Critical assessment of evidence from the literature and databases - appropriate weighing of PM3 and PS4 evidence***

Maja Štalekar, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

The most natural approach when encountering a variant in a gene associated with a disease that could potentially explain a patient's symptoms is to search databases and scientific literature for previously reported findings of the same variant in similar patients. Reported cases provide valuable information, as they offer evidence of pathogenicity that can support the application of the PS4 criterion in dominant disorders or PM3 in recessive disorders. However, such cases must be critically assessed.

This session will focus on key considerations for the confident application of these criteria. Importantly, the variant must be sufficiently rare to justify its non-arbitrary presence in an affected individual. While large case-control studies are often unavailable, we propose a simple yet stringent strategy: counting individual, independent cases to support PS4. Similarly, the weight of PM3 relies on counting independent cases, but also requires consideration of variant classification and the cis/trans phase of the second detected variant.

Intriguing examples of literature assessment will be showcased.

11:10 - 11:35 ***WS-NGS-9 - The curse of missense variants - using predictors, and constraint data to facilitate the interpretation of your variant***

Nina Vodnjov, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Missense variant result from a single nucleotide aminoacid change, causing an alternative amino acid residue to be incorporated into the encoded protein. Pathogenic missense variants most commonly impact the functional, structural, or signalling domains of a protein, causing disease via loss- or gain-of-function, dominant-negative and other pathomechanisms. Although functional studies would provide the most accurate information about their biological effect, they are often not performed as they are outside the scope of everyday clinical practice.

However, there are several strategies that can help us in determining the medical significance of missense variants. Firstly, it should be determined whether missense variants in that gene are an established cause of a given disease by using the literature or databases. Secondly, many in silico prediction tools have been developed to assist in determining whether a variant will have a pathogenic or neutral impact. Thirdly, examining the variant's surroundings in detail using genome browsers helps us to establish whether the region is a mutational hotspot, an essential functional domain, or an important motif. The presence of any of these features would suggest that the variant is likely to have a pathogenic effect and a possible medical impact. Finally, using gene-specific guidelines wherever possible assists with assigning the most accurate and harmonized classification to the variant.

To sum up, the most accurate estimate of the effect of the missense variant is achieved by considering gene-specific pathologic mechanism, in silico prediction models and a careful survey of surrounding variants, alongside the use of gene-specific guidelines where possible.

11:35 – 12:00 ***WS-NGS-10 - The non-coding genome - interpretation of splice variants and functional studies***

Polina Tsygankova, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

The interpretation of splice variants represents a critical challenge in the era of clinical next-generation sequencing (NGS), particularly as a substantial proportion of disease-associated variants occur in non-coding regions. This workshop focused on the principles of splicing biology, available computational prediction tools, and functional validation strategies for accurate variant classification. We first reviewed exon–intron structure and the key cis and trans elements that regulate pre-mRNA splicing, highlighting canonical donor and acceptor sites as well as splicing enhancers and silencers. The categories of splice mutations were introduced, followed by an overview of commonly used in silico predictors such as SpliceAI and MaxEntScan. Practical aspects of input formatting, score interpretation, and thresholds for pathogenicity assessment were discussed in detail.

To address the limitations of prediction tools, functional assays remain essential. Methods such as RNA analysis from patient-derived tissues, minigene reporter systems, and fibroblast cultures were presented, with emphasis on their strengths, challenges, and applicability to clinically relevant genes with tissue-specific expression. Case studies, including variants in SUPV3L1, PC, and PSAP, illustrated how combined

in silico and experimental approaches improve variant interpretation, support ACMG/AMP classification (e.g., PVS1, PP3), and directly impact patient care.

Participants engaged in small tasks to apply prediction tools and evaluate functional evidence, thereby consolidating theoretical knowledge with practical skills. By integrating computational and experimental strategies, the workshop demonstrated a structured approach for interpreting splice variants, aiming to improve diagnostic yield and inform clinical decision-making in genomic medicine.

12:00 – 13:25 **SESSION 3 - Going beyond the basic analysis of NGS**

Presentations WS-NGS-11 to WS-NGS-15

12:00 – 12:25 ***WS-NGS-11 - Tips and tricks for efficient CNV analysis in NGS data***

Gaber Bergant, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Structural variants (SVs), including copy number variants (CNVs), represent a major source of human genetic variability while also representing a variant type commonly causing human disease. With next-generation sequencing (NGS) permeating diagnostic and research settings in human genetics, the ability to reliably detect and interpret SVs and CNVs has become essential. This workshop aims to provide participants with practical strategies to interpret SVs and CNVs called from NGS data, as well as to understand and optimize SV analysis workflows in both exome and genome sequencing.

In the introduction of the workshop, we briefly review the biological and clinical relevance of SVs and CNVs, highlighting their contribution to both monogenic disorders and microdeletion/microduplication syndromes. In the core of the workshop, we will explore the technical principles of leading tools for SV/CNV detection, such as ExomeDepth, CoNIFER, MANTA, and others, through the analysis of their strengths, weaknesses, and ideal use cases. Emphasis is placed on workflow design to maximize accuracy while minimizing false positives. Additionally, the importance of strict application of the ACMG/ClinGen technical standards for CNV classification is also addressed in the workshop, emphasizing consistent and evidence-based variant interpretation. Finally, interactive case studies will allow participants to apply theoretical knowledge to real-world data. By the end of the workshop, participants will have a basic understanding of how to integrate SV/CNV detection into NGS pipelines and produce clinically meaningful variant reports.

12:25 – 12:40 ***WS-NGS-12 - Extended data analysis methods - expansions, breakpoints and homozygosity analysis***

Gaber Bergant, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Next-generation sequencing (NGS) has become a foundational tool in the diagnosis of rare genetic conditions; however, many patients remain undiagnosed following the conventional analysis, focusing on single-nucleotide variants (SNVs) and small indels. In this hands-on workshop, we will present further

strategies, apart from structural variant analysis, that unlock additional diagnostic insight from existing NGS data.

This workshop will introduce several additional variant types and analysis methods that can be used in NGS data and which contribute to the diagnostic yield of NGS: (i) tandem repeat expansions, (ii) genomic breakpoints with an emphasis on using exome sequencing datasets, (iii) homozygosity mapping, (iv) B-allele frequency plot analysis, and others.

The workshop session will briefly cover the theory and implementation of each method, including algorithmic approaches, filtering strategies, and pitfalls in interpretation. Additionally, trade-offs between increased sensitivity and added interpretive burden will be covered and discussed. Through guided exercises on real datasets, participants will learn to integrate these analyses into diagnostic pipelines and recognize even the rare disease-causing variant types. By the end of the workshop, the participants will be able to recognize tandem repeat expansions, breakpoints, as well as recognize aberrations in homozygosity profiles and B-allele frequency plots, and to apply additional diagnostic methods in pursuit of the suggested diagnostic hypothesis.

12:40 – 13:00 ***WS-NGS-13 - Long read sequencing - the basics and practical guidance in clinical diagnostics***

Jernej Kovač, University Medical Centre Ljubljana, University Children's Hospital, Clinical Institute of Special Laboratory Diagnostics, Ljubljana, Slovenia

13:00 – 13:20 ***WS-NGS-14 - Essential role of data sharing in the process of routine NGS data analysis***

Barbara Golob, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

Data sharing has underpinned many exciting and transformative discoveries, driving the expansion of human genetics. These advances were only possible once certain data became publicly and freely available. Today, large open-access public databases are an essential part of daily clinical laboratory genetic diagnostics – a resource we all greatly appreciate – and they provide sufficient information for interpreting the vast majority of variants. However, in about 10% of NGS cases, we still identify variants of uncertain significance (VUS), which require additional evidence for conclusive classification. Moreover, in some cases, we encounter variants in genes of uncertain significance (GUS). For both VUS and GUS, additional evidence and/or similar reported cases are necessary. This highlights the value of internal variant databases maintained by genetic laboratories worldwide, which often remain inaccessible to the wider genetics community but could play a critical role in resolving the pathogenicity of variants or genes of interest. To address this gap, platforms under the umbrella of the Matchmaker Exchange were established to connect cases with similar genetic variants and/or phenotypes. At KIGM, we routinely use GeneMatcher for data sharing and as a tool to connect with other genetics groups in the search for causative variants. Our matchmaking success rate is 12.3%.

13:20 – 13:25 ***WS-NGS-15 - Closure and plans for next workshops***

Aleš Maver, University Medical Centre Ljubljana, Clinical Institute of Genomic Medicine, Ljubljana, Slovenia

October 11, 2025 (Saturday)

14:00-16:00 | **WS.02 Arnold 2 Hall** | **Workshop: Translational research on rare diseases** | **M. Stojiljkovic**

14:00 – 14:20 ***WS-TRRD-1 - BRIDGING-RD project: Advancing Research and Innovation Through Collaboration***

Maja Stojiljkovic, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

There are over 330 million people living on the planet affected by one of over 6,000 identified genetic rare diseases (RD). They urgently need timely diagnosis and development of specific treatments. Although Europe leads the way in RD research, there is a clear gap in research and innovation (R&I) between countries. To bridge this gap, networking and knowledge sharing between IMGGE (Institute of Molecular Genetics and Genetic Engineering, Serbia) and 3 world-class counterparts at EU level - KI (Karolinska Institutet, Sweden), CNAG (National Center for Genomic Analysis, Spain) and UAM (Autonomous University of Madrid, Spain) has started. BRIDGING-RD's objectives are: (1) upgrade the IMGGE RD Biobank to reach full interoperability of genetic and phenotypic data in order to increase participation in transnational research and innovation projects related to human health; (2) upgrade bioinformatics pipelines specific to RD to increase the rate of solved RD cases in IMGGE's RD Biobank; (3) upgrade capacity for modelling of metabolic diseases as well as capacity to test small molecule drugs, in order to increase the number of translational studies; (4) upgrade research support offices in order to increase success in obtaining funds from research and/or innovation agencies, industry, foundations etc. Crucially, an exploratory R&I project, engaging all partners will focus on identifying an innovative drug for a selected metabolic RD. BRIDGING-RD will have impact by significantly improving the scientific excellence and innovation capacity of IMGGE.

This work was supported by Horizon Europe Project BRIDGING-RD, HORIZON-WIDERA-2023-ACCESS-02, No 101160079.

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14:20 – 14:40 ***WS-TRRD-2 - The Role of Next-Generation Sequencing for Application of Available Gene and Cell Therapy***

Kristel Klaassen, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

Next-Generation Sequencing (NGS) has completely revolutionized the diagnostics of patients with rare diseases through the identification of disease-causing genes and variants, and it also led to the development of specific treatments (such as gene and cell therapy) that target the underlying pathophysiology. NGS facilitates the discovery of specific genetic alterations for which gene therapies can

be directed, thus improving their precision and effectiveness. For cell therapy, NGS enables the classification of cell populations, therefore accelerating the transition of these therapeutic approaches from bench to bedside. In Serbia, NGS has been used for genetic analysis of rare diseases for more than a decade, and it has allowed for the selection of patients eligible for available gene therapies. For patients with inherited retinal diseases, NGS facilitated the identification of biallelic pathogenic variants in the RPE65 gene, thus qualifying them for treatment with Luxturna (voretigene neparvovec-rzyl). For patients with dystrophic epidermolysis bullosa, NGS enabled the use of the first topical gene therapy, Vyjuvek (beremagene geperpavec-svdt), which delivers the normal COL7A1 gene to the wounds. In the era of precision medicine, NGS will continue to progress and integrate into clinical practice in order to offer tailored treatments for more patients with rare diseases.

This work was supported by Horizon Europe Project BRIDGING-RD, HORIZON-WIDERA-2023-ACCESS-02, No 101160079.

Kristel Klaassen, Marina Andjelkovic, Anita Skakic, Milena Ugrin, Jovana Komazec, Sonja Pavlovic, Maja Stojiljkovic

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14:40 – 15:00 *WS-TRRD-3 - Prime editing for rare disease – a case study on CTNNB1 syndrome*

Vida Forstnerič, Center for the Technologies of Gene and Cell Therapy and Department of Synthetic Biology and immunology, National Institute of Chemistry, Slovenia

CTNNB1 syndrome is a rare monogenic neurodevelopmental disorder caused by heterozygous loss-of-function mutations in the CTNNB1 gene, which encodes β-catenin, a key effector of the Wnt signaling pathway. There is currently no targeted therapy for this condition. Here, we explore the application of CRISPR Prime Editing as a precision genome-editing strategy to correct pathogenic CTNNB1 mutations without inducing double-stranded DNA breaks.

We designed and screened multiple prime editing (PE) guide RNAs (pegRNAs) targeting two clinically relevant CTNNB1 point mutations. Editing efficiency and fidelity were evaluated in vitro using a reporter system. We further improved the system via coiled-coil based tethering of the nickase and reverse transcriptase subunits of the PE system and showed improved function with several tested pegRNAs. To facilitate screening on a relevant cell model, we additionally developed and characterized lipid nanoparticle (LNP) formulations functionalized for efficient uptake by human induced pluripotent stem cells (iPSCs). Delivery of mRNA via functionalized LNPs resulted in successful cellular uptake and nuclear localization, supporting their potential use in stem cell-based disease modeling and correction.

Our findings highlight the feasibility of Prime Editing for allele-specific correction of CTNNB1 mutations and establish a foundation for the development of a non-viral, clinically scalable delivery platform for therapeutic genome editing in neurodevelopmental disorders.

Vida Forstnerič[1,2], Jure Bohinc[1], Duško Lainšček[1,2], Greta Junger[1], Špela Miroševič[3,4], Damjan Osredkar[5,6], Mojca Benčina[1,2], Roman Jerala[1,2]

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15:00 – 15:20 ***WS-TRRD-4 - The Importance of In Vitro Models in Developing Novel Therapeutic Strategies for Rare Hepatic Diseases: iPSC-Derived Hepatocytes and CRISPR-Based Approaches***

Anita Skakic, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

Rare hepatic diseases present significant challenges due to their genetic heterogeneity, low prevalence, and limited treatment options. Understanding the mechanisms underlying disease development and identifying effective treatments require model systems that are both physiologically relevant and genetically accurate. Traditional models, such as primary hepatocytes and animal studies, have provided valuable insights but are often limited by interspecies differences, poor scalability, and restricted access to human disease-relevant tissue. Recent advances in induced pluripotent stem cell (iPSC) technology have enabled the generation of patient-derived hepatocyte-like cells that closely mimic liver function and carry the genetic background of the disease. When combined with CRISPR/Cas9 genome editing, these models enable the precise investigation of disease-causing variants, functional studies, and the development of isogenic controls. Moreover, iPSC-derived hepatocytes are increasingly used in high-throughput drug screening platforms, supporting the discovery of novel therapeutic strategies. Together, these technologies highlight the critical role of iPSC- and CRISPR-based in vitro models in advancing our understanding of rare hepatic metabolic disorders and accelerating the identification of new treatments.

This work was supported by Horizon Europe Project BRIDGING-RD, HORIZON-WIDERA-2023-ACCESS-02, No 101160079.

Anita Skakic, Marina Parezanovic, Marina Andjelkovic, Nina Stevanovic, Milena Ugrin, Maja Stojiljkovic

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15:20 – 15:40 ***WS-TRRD-5 - Advanced in vitro model for pulmonary diseases: In vivo validation, therapeutic testing, and innovation readiness***

Marina Andjelkovic, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

Mucociliary clearance (MCC), a vital process for airway maintenance, is impaired in acute, chronic, and genetic respiratory diseases affecting over a billion people worldwide. Key causes include thick mucus accumulation and impaired ciliary motility. This study aimed to develop an in vitro MCC model system, evaluate small molecules with potential therapeutic effects, and validate findings in vivo.

Primary NHBE cells were cultured in an air–liquid interface (ALI) system to induce differentiation into multiciliated and goblet cells. The model was validated using confocal microscopy, qRT-PCR for ciliogenesis and differentiation markers, and Western blot analysis. Two small molecules were selected based on known and hypothesized roles in MCC.

An in vitro MCC model was successfully established, and small molecules were applied. A preclinical study was performed in healthy mice using intranasal administration to confirm therapeutic potential and validate in vitro results. Upon demonstrating efficacy, the innovation reached Technology Readiness Level 5, and a national patent application was submitted.

This study established a reproducible in vitro MCC model and identified potential therapeutics that enhanced MCC. Selected small molecules showed efficacy in vitro and were validated in vivo, confirming therapeutic potential. The innovation's advancement to TRL5 and patent submission marks a key step toward translational application in respiratory medicine.

This work was supported by Horizon Europe Project BRIDGING-RD, HORIZON-WIDERA-2023-ACCESS-02, No 101160079.

Marina Andjelkovic, Anita Skakic, Nina Stevanovic, Marina Parezanovic, Jovana Jasnic, Maja Stojiljkovic

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Invited Lecturers

CVs and Abstracts

WS.01

Assist. Prof. Aleš Maver, MD, PhD

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Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
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In my professional career, I have been working in the field of rare and complex human disease genetics. I have been mostly involved in the application of high-throughput sequencing approaches for clinical diagnostics and research.

Currently, my work is focused on diagnostics based on exome, genome and RNA sequencing. I am particularly enthusiastic about finding novel approaches to improve genome-level clinical variant interpretation, create resources of national variation and to increase use of data sharing to facilitate the diagnosis of rare genetic disorders.

I am also interested in the application of novel computational approaches to improve the diagnosis and novel gene discovery.

Since 2002, I have been involved in various research projects in the fields of rare and complex genetic disorders, neurodegenerative disorders and immune disorders.

Title / Abstract:
WORKSHOP: INTERPRETATION OF NGS DATA

W.01.P

Prof. William Newman MD, PhD

University of Manchester, Manchester, UK
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Dr Newman is a Clinical Senior Lecturer at the University of Manchester, and Honorary Consultant in Genetic Medicine since 2004. He studied Medicine at Manchester University and completed professional training in Clinical Genetics undertaking a PhD as a Wellcome Trust Fellow on the genetics of skeletal development. Bill moved to Toronto to undertake a Fellowship with Professor Kathy Siminovitch where he worked on genetic studies in rheumatoid arthritis and inflammatory bowel disease. His research is now primarily focussed on pharmacogenetics (response to medication), especially in cancer treatment. His clinical work is increasingly directed to working with families with inherited heart problems.

Title / Abstract:

USING GENOMIC MEDICINE TO MAKE DRUG PRESCRIPTION SAFER AND MORE EFFECTIVE

Over the past decades many genetic variants have been identified that alter individuals' responses to their medication resulting in ineffective treatment or adverse drug reactions. In England, through the NHS Network of Excellence in Pharmacogenomics, we have developed an implementation science program to adopt pharmacogenomics into routine clinical use in primary care. This has focused on the type of genetic test, the way that the data is transferred into an actionable format for the clinician and determining the clinical outcomes of this intervention.

In this talk, I will discuss the clinical context of pharmacogenomics for adoption – the clinical settings in primary and hospital care.

I will emphasise how a new way of presenting genomic data is required for adoption at scale that is acceptable to both patients and health professionals. I will present the use of point of care genetic testing in time critical scenarios and the challenges in moving to a fully pre-emptive testing model to improve medicines optimisation.

W.02.P

Prof. Milan Macek Jr., MD, DSc

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Professor Milan Macek Jr. MD, DSc leads the largest academic medical/molecular genetics institution in the Czech Republic – Department of Biology and Medical Genetics of Charles University Prague-2nd School of Medicine and Motol University Hospital and the National Coordination Centre for Rare Diseases (www.nkcvo.cz; NKCVO). He chairs the National Rare Disease Taskforce at the Ministry of Health and coordinates Orpha.net nationally. As NKCVO chairman, he ensured Czechia's top EU13 ranking in European Reference Networks for rare diseases since 2017. He is a past President of the European Society of Human Genetics (www.eshg.org; 2010-2011 ESHG) and serves as the ESHG liaison for European National Human Genetics Societies. Under his leadership, medical genetics became an official EU specialty in 2011. He collaborated with the Council of Europe on the Additional protocol on genetic testing for health purposes to the Oviedo convention (2019). Prof. Macek was a board member of the European Cystic Fibrosis Society (ECFS.eu; 2007-2014) and is on the European Cystic Fibrosis Registry board. Within the European Society of Human Reproduction and Embryology (www.eshre.eu; ESHRE), he was responsible for joint position statements of ESHG and ESHRE in reproductive genetics. Prof. Macek is the president of the Czech Society of Medical Genetics and Genomics (www.slg.cz) and was the chief government advisor of the CZ EU Council presidency, under which the EU Council recommendation on rare diseases was adopted in 2009. During the second CZ EU Council presidency in 2022, he facilitated implementation for the Call for Action for rare diseases (www.mzcr.cz/towards-a-new-european-policy-framework-building-the-future-together-for-rare-diseases/). His citation index is over 24,000x, and he has an H-index of 60.

Title / Abstract:

”GAMECHANGER” IN RARE DISEASE RESEARCH AND DIAGNOSIS: THE ROLE OF 3D FACIAL GESTALT SCANNING TECHNOLOGY

S2.01.P and 3.01.I

Prof. Dijana Plaseska-Karanfilska, MD, PhD

Research Center for Genetic Engineering and Biotechnology “Georgi D. Efremov”, Macedonian Academy of Sciences and Arts, Skopje, Republic of North Macedonia
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Dijana Plaseska-Karanfilska graduated from the Faculty of Medicine in Skopje, Republic of Macedonia, and earned her PhD from the Medical Faculty of Limburg University in Maastricht, the Netherlands. She currently serves as Head of the Research Centre for Genetic Engineering and Biotechnology "Georgi D. Efremov" at the Macedonian Academy of Sciences and Arts, Skopje.

She has made significant contributions to the molecular characterization of various monogenic diseases in Macedonia and has successfully translated numerous molecular genetic tests into clinical practice. She has coordinated several research projects, including an infrastructural project funded by the European Commission, which has enhanced national research capacities in genomics and proteomics. Her research interests focus on reproductive genetics, breast cancer, and rare diseases. She has published 190 papers in peer-reviewed journals and has delivered over 250 presentations at scientific events.

Dijana Plaseska-Karanfilska is a member of Academia Europaea and a Corresponding Member of the Macedonian Academy of Sciences and Arts. She is the Editor of the Balkan Journal of Medical Genetics and Section Editor of the EuroBiotech Journal. Additionally, she serves as President of the Macedonian Society of Medical Genetics and the Macedonian Association of Medical Editors, Coordinator of the Macedonian ORPHANET team, Macedonia’s Coordinator in the European Biotechnology Thematic Network Association, and Member of the Advisory Board for Rare Diseases at the Ministry of Health, Republic of North Macedonia.

Title / Abstract:

S2.01.P - BEYOND CHROMOSOMES: THE MONOGENIC CAUSES OF EARLY PREGNANCY LOSS

Early pregnancy loss (EPL), particularly when recurrent, remains a deeply distressing and emotional event for many couples. While chromosomal abnormalities have long been recognized as the predominant cause of EPL, many cases, particularly those involving euploid embryos, remain unexplained. Emerging data, including our own findings, suggest that monogenic alleles may play a substantial role in recurrent, unexplained EPLs. These genetic alterations may involve lethal variants that are incompatible with early development, often resulting in embryonic or fetal demise. Additionally, some alleles associated with rare but non-lethal disorders may contribute to loss through subtle effects on organogenesis or placental function. Advances in next-generation sequencing (NGS), particularly whole exome sequencing (WES) of products of conception, have enabled the identification of such monogenic defects, highlighting the need to integrate this approach into the diagnostic workup of recurrent pregnancy loss when standard investigations are inconclusive. Identifying monogenic causes of EPL not only deepens our understanding of early human development but also opens new pathways

for genetic counseling, carrier screening, and potential use of reproductive options such as preimplantation genetic testing for monogenic defects (PGT-M).

Title / Abstract:

3.01.I - BALKAN JOURNAL OF MEDICAL GENETICS: GATEWAY TO PUBLISHING QUALITY RESEARCH

The Balkan Journal of Medical Genetics (BJMG) is an international, peer-reviewed, open-access journal dedicated to advancing knowledge in human and medical genetics, with a particular focus on the Balkan region. Since its establishment in 1998, BJMG has served as a platform for disseminating high-quality original research, reviews, and case reports, fostering scientific exchange among researchers, clinicians, and genetic professionals. The journal is indexed in leading international databases, including PubMed, Scopus, and Web of Science, ensuring broad visibility and accessibility.

This presentation will outline the journal's mission, editorial standards, indexing achievements, and its commitment to ethical publishing and adherence to international reporting guidelines. Emphasis will be placed on BJMG's role in strengthening regional scientific output and supporting researchers by providing a recognized gateway for publishing high-quality research from the Balkans. Looking ahead, future directions include the implementation of enhanced digital submission and manuscript processing platforms, the expansion of the Editorial Board, an increase in the number of submissions and published articles, and further growth in international recognition and impact.

S3.04.P

Prof. Borut Peterlin, MD, PhD

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Borut Peterlin is a clinical geneticist and neurologist, head of the Clinical Institute of Genomic Medicine, University Medical Center Ljubljana. He is a professor of Human Genetics at the Medical faculty in Ljubljana and visiting professor at the Medical faculties in Beograd, Rijeka and Osijek. He is board member and past president of the European Society of Human Genetics and Chair of the Professional Committee of the Slovenian Association for Medical Genetics. His research interests are discovering new genes and mechanisms of human disorders and implementing novel genomic technologies in rare diseases, public health and personalized medicine in health systems.

Title / Abstract:
MATURITY LEVEL OF NATIONAL GENOMIC SYSTEMS

S4.01.P

Prof. Olivera Miljanović, MD, PhD

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Olivera Miljanović, MD, PhD, pediatritian, clinical geneticist, is full professor in pediatrics, medical and clinical genetics, bioethics and biomedicine at the Medical Faculty University of Montenegro. At the same institution she serves as the head of the Center for Scientific Research, and the president of the Committee for Medical Ethics and Bioethics. She was the Vice-dean for educational affairs (2013 – 2018).

Professor Miljanovic is a head of the Center for Genomic medicine and Immunology at Clinical Center of Montenegro, which is founded upon her leadership in 2000. She was director of the Clinical Center of Montenegro and director of the Institute for Children's Diseases Clinical Center of Montenegro. Her main current professional and research interest includes identifying the genomic contribution to the development of congenital anomalies and neurodevelopmental disorders in children.

She is a member of the Medical Research Committee of the Montenegrin Academy of Sciences and Arts, the International Teachers' Forum (IFT) of the UNESCO Chair in Bioethics, the Bioethics Committee of the Council of Europe, the Council of the Association of Preventive Pediatrics of Montenegro, the MC board of COST – MINDDS Action, the Advisory Board of STREAMLINE project, Horizon (2022-2025); partner in PharmGenHUB project, Horizon (2022-2025).

She is the author of over 150 articles in indexed journals, chapters in monographs, a handbook, published keynote lectures and presentations at international conferences. She is the editor-in-chief of Medical Essays and a member of the editorial board of Medical Data.

Professor Miljanović received her undergraduate, academic, and specialist education at the Universities of Belgrade and Zagreb.

Title / Abstract:

THE CONTRIBUTION OF GENOMIC DIAGNOSTICS TO THE ELUCIDATION OF NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders (NDDs) affect more than 3% of children worldwide, with only ~30% of cases attributable to known genetic risk, making them an issue of public concern. This highly heterogeneous group of early-onset neurological disorders includes autism spectrum disorders (ASD), intellectual disabilities (ID), attention deficit hyper¬activity disorder, language disorders and epileptic encephalopathies.

Over the past decade, significant scientific progress in the research of synaptic functions, transcriptional and epigenetic regulation, as well as the design of monogenic, oligogenic, polygenic and omnigenic models has enabled a better understanding of NDDs` genetic architecture.

A recognizable genetic etiology has been identified in 15–53% of NDDs, depending on the specific presentation and test used. Mutations in over 1000 risk genes have been discovered by whole-exome/genome sequencing, as the underlying mechanism for NDDs. Rare genetic mutations (de novo

and inherited) in autosomal or X-linked mental retardation genes are causative in ~11% of simplex ASD cases, with FMR1 gene identified as one of the most common monogenic causes of ID and ASD in male patients. Rare CNVs and mutations were identified in 3% of patients with idiopathic epilepsy and epileptic encephalopathies.

This lecture will discuss the role of advanced genetic diagnostics in determining the etiology of NDDs, as a prerequisite for early therapeutic interventions, along with a review of our patients with NDDs and the interpretation of their genetic testing results in a clinical context.

S5.01.P

Prof. Dragan Primorac, MD, PhD

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Professor Dragan Primorac, M.D., Ph.D., is a pediatrician, geneticist, and forensic expert witness. According to one of the leading world publishers, Elsevier BV, Prof. Primorac has been on the list of the top 2% of world scientists for career-long and single-year impact for the last four years. He became the first recipient of the title "Global Penn State University Ambassador" since the University was established in 1855. Currently, he serves as a professor at Eberly College of Science, The Pennsylvania State University, and the University of New Haven in the United States, as well as at medical schools in Split, Rijeka, and Osijek, and REGIOMED Medical School in Germany. He has authored nearly three hundred scientific papers, abstracts, and thirty books or book chapters. Prof. Primorac has been invited to give lectures at 150 conferences worldwide. His work has been published in the most cited journals, including Science and Nature. So far, his papers have been cited 10,200 times (Google Scholar).

In the early '90s, with colleagues from the USA, he pioneered DNA identification of skeletal human remains found in mass graves. During the same period, his group from UConn described the molecular mechanism of Osteogenesis Imperfecta Type I caused by splicing mutations at the donor (5') site. In 2000, as a member of an international consortium, he published a Science paper describing a genetic perspective of human history in Europe, analyzing 22 binary markers of the non-recombining Y chromosome. In 2017, he authored a Nature paper describing the early and largely extinct expansion of anatomically modern humans (AMHs) out of Africa by analyzing human genomes from 148 populations worldwide. In 2017, his research team, for the first time, showed (by using delayed contrast-enhanced MRI of cartilage (dGEMRIC)) the molecular impact of micro-fragmented adipose tissue containing MSCs on hyaline cartilage regeneration. As one of the pioneers in the field, Prof. Primorac currently applies the personalized medicine paradigm (pharmacogenomics, whole genome sequencing, mesenchymal stem cell treatment, etc.) in routine clinical practice.

In 1997, Prof. Primorac co-founded The International Society of Applied Biological Sciences. So far, more than 6,000 scientists and 700 invited speakers (including ten Nobel laureates) from 75 countries have participated in ISABS conferences held every two years in Croatia in partnership with Mayo Clinic. He founded the "Nobel Spirit".

Prof. Primorac currently serves on the Executive Committee of the International Consortium for Personalized Medicine (IC PerMEd), established by the European Commission. He is also the President of the International Regenerative Medicine Experts Society (IARMES), the Croatian Society for Human

Genetics, the Croatian Society for (Precision) Personalized Medicine, and he is a member of the Croatian Prime Minister's Scientific Committee. In 2011, he founded St. Catherine Specialty Hospital, the European center of excellence in personalized medicine. Prof. Primorac has received more than 30 domestic and international awards.

Title / Abstract:

A NEW ERA OF AI AND WHOLE GENOME SEQUENCING (WGS) FOR CANCER DIAGNOSIS AND TREATMENT STRATEGIES

S6.01.P

Assoc. Prof. Merita Xhetani, MD, PhD

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Dr. Merita Xhetani is Associate Professor, member of University of Tirana, and Head of the Center for Molecular Diagnostics and Genetic Research, University Hospital Obstetrics and Gynecology "Queen Geraldine".

She leads a research working group affiliated with the Academy of Sciences, dedicated to studying biomarkers associated with rare genetic diseases.

Recently, she founded a high-complexity laboratory dedicated to advanced genomic testing, particularly exploring genetic factors linked to recurrent pregnancy loss through the application of genomic techniques. In addition to her research, Prof. Xhetani actively provides genetic counseling, supporting patients and their families in understanding and managing genetic conditions.

In addition to her academic engagement, Prof. Xhetani serves as the President of the Albanian Society of Human Molecular Genetics (ASHMG), playing a key role in promoting and developing genetics in Albania.

Title / Abstract:

RECURRENT PREGNANCY LOSS AND GENETICS: EXPLORING THE GENETIC FACTORS BEHIND PREGNANCY COMPLICATIONS

Recurrent pregnancy loss (RPL), commonly defined as the occurrence of two or more consecutive miscarriages, is a multifactorial condition that affects 5-10% of couples of reproductive age. Genetic abnormalities, particularly chromosomal aneuploidies, represent one of the leading causes of early miscarriage, yet their frequency and patterns remain strongly influenced by maternal age and other biological factors. Pregnancy loss in the first trimester (≤12 weeks) is a frequent and distressing complication, with genetic abnormalities playing a central role in its pathogenesis. In this study, we examined uncontaminated early pregnancy loss specimens to determine the frequency and spectrum of fetal chromosomal abnormalities and associated genetic factors.

During this talk, our findings and data will be shared to demonstrate that chromosomal aneuploidies are the leading contributors to early pregnancy loss, with a clear age-related increase in frequency, particularly for trisomies. The co-occurrence of mutations in coagulation, immune, and developmental pathways underscores the multifactorial etiology of miscarriage and highlights the importance of integrated genetic testing for risk assessment, counseling, and potential preventive strategies. While chromosomal aneuploidies remain the leading cause of early and recurrent pregnancy loss, our findings also highlight the importance of non-chromosomal biomarkers in understanding and managing this condition. The incorporation of additional biomarkers, such as those related to inflammation, vascular function, and metabolic regulation, may improve risk stratification and provide earlier, more personalized interventions for affected women. This broader perspective underscores the

need for integrated multi-omics approaches in both research and clinical practice, paving the way for novel diagnostic tools and potential therapeutic strategies to reduce the burden of pregnancy loss.

S6.02.P

Prof. Florin Burada, MD, PhD

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Professor Florin Burada is Head of the Department of Medical Genetics at the University of Medicine and Pharmacy of Craiova and Coordinator of the Regional Centre for Medical Genetics Dolj (RCGM Dolj), Romania. In 2023, Dr. Florin Burada was elected President of the Romanian Society of Medical Genetics (RSMG). He has extensive experience in cytogenetic and molecular genetic testing, including conventional karyotyping, real-time PCR, QF-PCR, MLPA, array CGH, and sequencing. His main areas of interest include prenatal screening and diagnosis, genetics of infertility, chromosomal disorders, and congenital anomalies.

Title / Abstract:

ENHANCING PRENATAL DIAGNOSIS OF FETAL CONGENITAL ANOMALIES THROUGH NEXT-GENERATION SEQUENCING

Florin Burada[1,2], Cristina Comanescu[3], Razvan Plesea[1,2], Andreea Iordache[1,2], Mihai Cucu[1,2], Ioana Streata[1,2], Madalina Barbu[3], Dominic Iliescu[3], Alexandru Comanescu[3]

Fetal structural anomalies are identified in about 3-4% of pregnancies. Chromosomal microarray (CMA) is recommended for prenatal diagnosis in cases with one or more fetal structural abnormalities identified by ultrasonography and it is used to detect aneuploidies and copy number variations. In recent years, next-generation sequencing (NGS), especially exome sequencing (ES), is being increasingly used to identify potential monogenic disease in prenatal setting. The diagnostic yield depends on many factors including selection of cases by a multidisciplinary team, the type or number of malformations, and whether trio analysis is performed. Although whole-genome sequencing (WGS) has a higher diagnostic capability than ES due to its ability to detect pathogenic CNVs, as well as intronic variants, repeat expansions or structural variants there are concerns related to the cost-effectiveness of WGS and the interpretation of findings. We present several cases with fetal structural abnormalities detected by ultrasonography referred to our centre. The genetic testing was performed after genetic counseling, including CMA and either targeted gene panels or ES from amniotic fluid or fetal tissue samples. CMA results were normal in all cases, while NGS identified variants associated with autosomal recessive disorders. Our findings support the use of NGS in cases with nondiagnostic CMA and highlight the importance of offering expanded carrier screening to all couples planning a pregnancy.

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S7.01.P

Prof. Attila Patocs, MD, PhD

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Currently he is Head of Department of Molecular Genetics and Clinical Laboratory at National Institute of Oncology and Head of HUN REN Oncogenomics Research Group. Formerly, he was Head of Endocrine Genetics Laboratory at Semmelweis University and Head of MTA-SE "Momentum" Hereditary Endocrine Tumors Research Group as well. His research activities engage in various topics such as: genetic background of endocrine tumors, glucocorticoid resistance and hereditary breast and ovarian cancer. Furthermore, mitochondrial tumor suppressor genes and their roles in the pathogenesis of tumors and the role of microRNAs in the pathogenesis of pituitary and adrenal tumors.

Prof. Attila PATOCS graduated in General Medicine (MD) from Semmelweis University in Hungary. Afterwards, he earned a degree as a biological engineer (MSC) from the Technical University of Budapest. Later on, he completed his PhD at Semmelweis University Doctoral School, where he was an associate professor between 2008-2019. Moreover, he spent 18 months in Genomic Medicine Institute Cleveland Clinic, Lerner Research Institute as post-doctoral fellow. Additionally, he received a Board Certification in Laboratory Medicine and Molecular Genetic Diagnostics and Clinical Laboratory Genetics. He has won several merit awards from Semmelweis University, two Bolyai János fellowship awards and in 2024 the Hungarian Academy Prize.

He has published over 260 scientific publications, with IF over 1000, and has over 7000 citations. At present, he holds leadership positions of two Hungarian Societies: Secretary of the Hungarian Cancer Society, and president of Hungarian Society of Genetics and Genomics.

Moreover, he acts as Principal Investigator for four ongoing grants (Genomic Data Infrastructure (GDI) project, Precision Cancer Medicine for all European Citizens (PCM4EU) Hungarian Academy of Sciences, HUN-REN NIO-TTK-HCEMM Oncogenomics Research group; National Tumorbiology Laboratory).

Title / Abstract:

ROLE OF CLINICAL AND LABORATORY GENETICISTS IN PRECISION CANCER MEDICINE

S8.01.P

Prof. Savina Hadjidekova, MD, PhD

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Prof. Dr. Savina Hadjidekova is Head of the Department of Medical Genetics at Medical University of Sofia. She is the Chair of the Board of the Bulgarian Society of Human Genetics and Genomics, a member of the European Society of Human Genetics, and a member of the Bulgarian Medical Association. Within the academic community, she serves on the Faculty Council of the Faculty of Medicine at MU-Sofia and the Academic Council of MU-Sofia. She is a genetic consultant at Nadezhda Hospital and heads the Genetic Laboratory at the same institution. Under her leadership, Bulgaria witnessed a groundbreaking advancement in 2008 with the introduction of preimplantation genetic testing for chromosomal and monogenic diseases. Her commitment to scientific inquiry is demonstrated through her participation as a leader or co-investigator in 20 scientific projects. Her research contributions include 113 original publications and 285 citations in the Scopus database.

Title / Abstract:

PGT AND HEREDITARY BREAST CANCER - CAN AND SHOULD WE BREAK THE CHAIN?

Background: Hereditary breast cancer, primarily associated with pathogenic variants in *BRCA1* and *BRCA2*, poses a significant lifetime risk of breast and ovarian cancer. Preimplantation Genetic Testing (PGT) offers an opportunity for at-risk individuals to prevent the transmission of these mutations to their offspring through in vitro fertilization (IVF). The genetic testing process involved embryo biopsy, targeted mutation analysis, and selection of embryos free from pathogenic variants.

PGT demonstrated high accuracy in detecting pathogenic variants, with unaffected embryos available for transfer in approximately 50–70% of cases. Psychological benefits included reduced anxiety regarding hereditary cancer risk in offspring.

While PGT allows families to reduce the transmission of cancer predisposition genes, challenges include the emotional burden of IVF, the ethical debates surrounding genetic selection and the need for comprehensive genetic counseling

Conclusion: PGT for hereditary breast cancer provides an effective reproductive option for mutation carriers seeking to reduce cancer predisposition in future generations. While the procedure offers significant benefits, comprehensive genetic counseling remains essential to address medical, ethical, and emotional considerations.

S8.02.P

Prof. Taha Bahsi, MD, PhD

Genetics Department, Memorial Healthcare Group, Istanbul, Turkey

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Prof. Bahsi serves as the Director of the Genetics Department at Memorial Healthcare Group, one of the largest chain health groups in Türkiye. He is also the President of the Turkish Medical Genetics Association. He also serves as a founding member and vice president of the Turkish Hereditary Cancer Association. He has been working on cancer genetics for about 10 years and is a member of the Turkish Ministry of Health Rare Diseases Commission, TÜSEB Biotechnology Institute and Cancer Institute scientific board. He established the first genetic screening program in Türkiye, the preconception and newborn SMA screening laboratory. He has chaired many national and international scientific meetings.

Title / Abstract:

COMBATING RARE DISEASES - PRECONCEPTION AND NEWBORN SCREENING PROGRAMS IN TURKEY

S9.01.P

Dirk Biskup, PhD

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Dirk Biskup (PhD) co-founded the human diagnostics company CeGaT GmbH with his wife, Saskia Biskup (MD, PhD). CeGaT was among the first companies worldwide to leverage high-throughput sequencing (NGS) to comprehensively identify genetic mutations causative for various diseases, including cancer. For this pioneering work, CeGaT received several awards. Today, CeGaT is fully owned by the founder family and ranks among the largest sequencing and genetic diagnostics labs in Europe.

Dirk also founded Cenata GmbH, a leader in non-invasive prenatal testing in Germany, and CAG GmbH (now Generatio GmbH), one of the country's largest animal genetic testing laboratories. He currently also serves as managing director of the MVZ Tübingen GmbH, an outpatient clinic specializing in oncology and gastroenterology care.

Dirk is co-founder and managing director of cecava GmbH, actively driving the company's strategic development. cecava is dedicated to advancing cancer treatment with personalized and hence more effective immunotherapies. A first phase I clinical trial addressing glioblastoma patients will start in 2026.

Previously, Dirk held senior leadership roles at Bertelsmann AG, serving as Senior Director in the M&A department, where he contributed to numerous company acquisitions. He also served as CFO at Berryville Graphics, Bertelsmann's largest U.S. printing facility, and as European CFO of AEG Electric Tools, overseeing its European subsidiaries and holding companies as managing director.

He holds a Master's degree and a PhD in Business Administration from the University of Hamburg and the University of Bielefeld, Germany, respectively.

Title / Abstract:
ON THE WAY TO PERSONALIZED TUMOR VACCINES

Over the past decades, it has been shown that each tumor has unique properties and structures (so-called neoepitopes) on its surface, distinguishing it from other tumors and healthy tissues. Hence, to improve the effectiveness of current cancer therapies, more personalized treatment approaches are required, individually directed against the novel neoepitope targets on the tumor.

Each tumor acquires novel mutations during its development, leading to alterations in the sequence of proteins. Parts of such proteins (peptides) are presented on the tumor cell surface. If these peptides carry tumor mutation-derived alterations (neoepitopes), they may be sensed as foreign by immune cells (T cells). Upon recognition, these T cells can kill such tumor cells. Neoepitopes are not only highly tumor-specific but also new to the immune system, making them highly immunogenic and, therefore, ideal targets for cancer immunotherapies.

For immunization, the patient-individual set of tumor mutation-derived neoepitope-like synthetical peptides is injected into the skin of the patient, triggering the immune system specifically. This approach of personalized tumor vaccines has been applied to more than 800 patients. Results on 173 glioblastoma patients and 52 *IDH1*-mutant glioma patients have recently been published.

In my talk I will elaborate on the original idea and the mode of action of personalized tumor vaccines. I will present how these personalized tumor vaccines are manufactured and administered. And I will present our findings with respect to median overall survival. And lastly, I will give an outlook on a phase I GBM study we plan to start beginning of 2026.

S9.02.P

Prof. Paolo Gasparini, MD, PhD

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Prof. Paolo Gasparini got the degree in Medicine and residencies in Haematology and Medical Genetics. He is professor of Medical Genetics at the University of Trieste, Head of Medical Genetics Service and Head of the Department for Advanced Diagnostics and Clinical Trials at IRCCS Mother Child Hospital Burlo Garofolo, in Trieste. He is member of the CAT (Committee for Advanced Therapies) and CHMP (Committee Human Medicinal Products) of the European Medicine Agency (EMA) and current President of the Italian Society of Human Genetics (SIGU). He has a longstanding experience in studying genetic basis of inherited diseases as well genetics risk factors for complex traits and diseases, in addition to genetics of senses, such as genetics of hearing loss, taste and food preferences, and their implication on health status.

Title / Abstract:
DRUG REPURPOSING IN INHERITED DISEASES

Drug repurposing is the process of finding new therapeutic indications for existing drugs. It is a solid alternative to traditional drug discovery and development being faster, less expensive and safer for patients. It is estimated that de novo pharmaceutical studies take between 10 and 17 years to develop, while drug repurposing can shorten the process to 3-to-8 years. Also, the overall drug-related risk is reduced, as often repurposing candidates already have well-characterized safety and pharmacokinetic profiles obtained from previous preclinical studies and clinical trials. The discovery of new indications can nowadays largely benefit from in silico methods, as computational pharmacology, high-throughput screening assays and artificial intelligence.

Drug repurposing could be the most successful strategy to find new treatments for Rare Diseases (RDs). Due to limited understanding of the disease and the complexity of designing effective multi-step trials for a small cohort of patients, development of novel orphan drugs can be challenging, resulting in more than 95% of RDs lacking in licensed treatment. Most patients have only access to symptomatic or palliative therapy, resulting in a substantial decrease in quality of life or early mortality. RDs affect up to 300 million people worldwide being a relevant social and health problem. Some examples of drug repurposing in inherited diseases will be here presented and discussed

S12.01.P

Marina Djurišić, PhD

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Marina Đurišić, molecular biologist and physiologist with 30 years of work in the field of medical genetics. She is a highly qualified and experienced geneticist with expertise in various laboratory methods and techniques. Marina is the president of the Medical Genetics Section of the Serbian Genetics Society and for 10 years has been the head of the Laboratory of Medical Genetics, The Institute for Health Care of Mother and Child of Serbia Dr. Vukan Čupić, in Belgrade. In the laboratory, she is also responsible for monitoring quality assurance/quality control indicators, training associates, and implementing laboratory practice for students of the Faculty of Biology.

Title / Abstract:
WRITE ACCORDING TO THE RULES, READ BETWEEN THE LINES

Misinterpretation of genetic test results is a problem that has existed for a sometime, but has been increasingly discussed in recent years. Problems can arise at different levels and in different segments. Everyone in the line: laboratory geneticist - clinician – patient – can share responsibility of misinterpretation of the test. It is important that the laboratory minimize the risk of misunderstanding. It is possible by using appropriate guidelines and manuals, communicating with colleagues from other laboratories, communicating with clinicians, participating in quality control schemes, actively writing articles, instructions, lectures.

S1.01.I

Bart van der Sanden, PhD

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Bart van der Sanden is a postdoctoral researcher in the Genomic Technologies research group of Prof. Alexander Hoischen at Radboudumc in Nijmegen. He obtained his PhD from Radboudumc, where he investigated hidden variants and non-coding variation. In his postdoctoral research, he focuses on advancing genomic technologies for rare disease diagnostics, with an emphasis on long-read sequencing and optical genome mapping. Additionally, he is involved in the ERDERA project, which seeks to advance rare disease research in Europe, including the integration of long-read technologies.

Title / Abstract:

LONG-READ SEQUENCING FOR RARE DISEASE RESEARCH AND DIAGNOSTICS

PacBio HiFi long-read genome sequencing (lrGS) is now the most comprehensive technology for germline rare disease genetic testing. lrGS simultaneously delivers accurate detection of all variant classes including single nucleotide substitutions, indels, structural variants (SVs), copy number variants (CNVs), and short tandem repeats (STRs) in a single experiment. In addition, it enables accurate variant phasing and direct methylation analysis.

Unlike short-read sequencing, lrGS identifies clinically relevant variants in even the most complex genomic regions. Across 145 clinically relevant and technically challenging variants, HiFi sequencing detects 93%, including repeat expansions and variants in homologous regions, and does so robustly even at reduced coverage. This demonstrates that one platform is sufficient for capturing the full spectrum of pathogenic variation.

HiFi genomes scale seamlessly into clinical practice. In 1,000 prospectively sequenced patients, HiFi lrGS delivered 96.4% concordance with current multi test standard of care workflows while providing additional or improved diagnoses in 3.4% of cases. Variants were missed only in two rare instances of mosaicism or low coverage. Integrated methylation analysis directly complemented genetic findings in additional patients. An lrGS-first approach streamlines workflows, shortens diagnostic turnaround, and maintains manageable laboratory workload, making it superior to existing fragmented pipelines.

Most critically, HiFi lrGS also resolves previously unsolved cases. In 100 neurodevelopmental disorder trios unresolved by trio-based exome sequencing, HiFi genomes revealed pathogenic variants in 7% and strong candidates in another 10%. These included indels, deep intronic splice mutations, SVs, and STR expansions that were invisible to prior testing. By directly uncovering the full landscape of de novo mutations, HiFi genomes achieve meaningful diagnostic uplift even in the most challenging cohorts.

HiFi long-read sequencing has redefined rare disease genomics. It replaces the need for multiple specialized assays, uncovers all classes of pathogenic variants, accelerates diagnostics, and provides answers for previously unresolved patients. It is not a future prospect, it is the new standard.

As part of ERDERA, a European initiative to advance rare disease research and diagnostics, WP8 will extend access to long-read sequencing and complementary technologies to underrepresented countries. By building local pipelines, training laboratories, and integrating approaches such as lrGS, optical genome mapping and multi omics, WP8 will develop the most innovative diagnostic approach for rare diseases. This will accelerate accurate diagnoses for patients and families across Europe and ensure that the benefits of long-read sequencing are shared more equitably.

S1.02.I

Prof. Stephan Ossowski, PhD

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Prof. Dr. Stephan Ossowski leads the Genome Informatics Group at the University of Tübingen. He obtained his PhD from the Max Planck Institute for Developmental Biology (2006–2010), where he developed novel next-generation sequencing (NGS) methods for plant genome analysis. From 2010 to 2017, as a group leader at the Centre for Genomic Regulation (CRG) in Barcelona, he expanded his research to human disease and cancer genomics, pioneering the use of emerging long-read sequencing technologies. Since joining Tübingen in 2017, his group has focused on developing advanced NGS analysis methods and AI-driven clinical decision support systems for rare disease and cancer diagnostics. Currently, the Ossowski Lab is at the forefront of applying long-read whole-genome sequencing (LR-GS) in clinical research, contributing to several European initiatives, including Genomes of Europe, Solve-RD, ERDERA, lonGER, and ELRIN.

Title / Abstract:

AI-ASSISTED GENOME DIAGNOSTICS WITH LONG READS

Reconstructing complex genomic regions such as segmental duplications, repeat expansions, and structural variants remains challenging with short-read sequencing, often leaving disease-causing variants undetected in rare disease cases. Nanopore long-read genome sequencing (LR-GS) offers a powerful solution by resolving complex regions, revealing structural variants and repeat expansions, enabling haplotype phasing, and integrating methylome analysis. To accelerate its clinical adoption, we launched the European Long-Read Innovation Network (ELRIN) to assess the diagnostic value of Nanopore sequencing, establish sustainable workflows, and provide shared SOPs, bioinformatics tools, and training for genetic testing laboratories.

While LR-GS improves variant detection, interpreting the resulting data remains a bottleneck. Identifying causal variants in rare disease (RD) patients is time-intensive and requires expert review. To address this, we developed aiDIVA, an AI-driven decision support platform that integrates genomic and phenotypic data to prioritize causal variants. aiDIVA combines random forest and evidence-based models with clinical metadata (e.g., HPO terms) to generate pathogenicity scores, applies phenotype similarity matching, and uses large language models to refine top candidates. A meta-AI model integrates all results into a final ranking.

In benchmarking with over 3,000 diagnostically solved RD cases from the University Clinics Tübingen, aiDIVA identified the correct causal variant among the top three candidates in 97% of cases and provided interpretable explanations for each. Together, ELRIN and aiDIVA are advancing rare disease diagnostics by merging long-read sequencing and artificial intelligence.

S1.03.I

Assist. Prof. Anja Kovanda, PhD

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Assist. Prof. Anja Kovanda, Ph.D., Clinical Laboratory Geneticist

I'm working in diagnostics and research at the Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Slovenia, and in education at the Faculty of Medicine and the Biotechnical Faculty, University of Ljubljana, Slovenia.

The main focus of my work are rare diseases and prenatal/preventive genetics, optical genome mapping (OGM), long-read sequencing (LRS), solving hard-to-amplify regions with PCR, special DNA and RNA structures and mutations, expansion disorders, FSHD, Parkinson's disease, microbiology, virology, infection-related cancers, host-pathogen interactions, drug resistance, and evolution.

Title / Abstract:
STRUCTURAL VARIANTS IN RARE-DISEASE

Structural genetic variants may range in size from a few bases to several Mb pairs and come in many different types, such as duplications, amplifications, and deletions that represent copy number variants, as well as insertions, balanced translocations, and inversions that appear copy number neutral. SV are increasingly found as causative variants in rare-disease, however, many remain potentially undetected using the current routine technologies such as microarrays and short-read sequencing. Optical genome mapping (OGM) is based on image acquisition of single, labeled, high-molecular-weight DNA molecules and their assembly and comparison with the genomic reference. By using OGM we can detect structural genomic variants such as translocations, inversions, insertions, deletions, duplications, and complex structural rearrangements in many size ranges. We aim to present the four years of experience with OGM at the Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Slovenia. In rare disease patients in whom the cause could not be identified using other methods, OGM helped us identify causative large inversions, insertions/pathogenic expansions, small one or two-exon deletions that may be missed by exome sequencing, etc. In addition to showing the advantages of this technology, we aim to also highlighting the remaining technical limitations as well as the complexity of diagnostic results in rare disease cases.

S2.02.I

Assist. Prof. Ljubica Odak, MD, PhD

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Assistant Professor Ljubica Odak, MD,PhD is a pediatrician and Head of Department of Medical and Laboratory Genetics, Endocrinology and Diabetology with daily care unit at Children's Hospital Zagreb. She graduated at Zagreb University School of Medicine, where she also received her PhD degree. Dr. Odak has a long-term clinical experience in medical genetics. In 2023, elected as an assistant professor at University of Zagreb, Faculty of Education and Rehabilitation Sciences.

From the beginning of her career, she is actively participating in research projects and trainings dedicated to medical genetics. Her main clinical and research interests are genetics of neurodevelopmental disorders, epidemiological and genetic aspects of congenital anomalies and genetic syndromes, connective tissue disorders, implementation and application of genetic testing methods in clinical practice. She is an author/co-author of more than 40 research articles in indexed journals (Current Contents/PubMed) and more than 80 congress abstracts and a reviewer in several journals. She is a Secretary General of the Croatian Society of Human Genetics.

She is actively involved in university medical genetics teaching at the Zagreb University School of Medicine. She is a member of the Committee for the implementation of medical genetics specialists training in Croatia of the Ministry of Health and official UEMSA-e delegate for Medical Genetics Section.

Dr. Odak is involved in activities of Zagreb EUROCAT registry of congenital anomalies, initially as an associate for data collection and analysis and since 2023 as a registry leader. She is a Children’s Hospital Zagreb coordinator for ERN-ITHACA network.

Title / Abstract:

CHROMATIN REMODELING DISORDERS - CHALLENGING PATH TO DIAGNOSIS AND MANAGEMENT

Purpose: Mutations in chromatin remodeling genes are a significant cause of complex neurodevelopmental disorders with overlapping clinical features and a heterogeneous genetic basis. The aim of this study is to evaluate diagnostic approach in patients whose clinical features and genetic testing results were suggestive of chromatin remodeling disorders (CRDs).

Method: We retrospectively analyzed clinical and molecular genetic data from 49 patients with suspected CRDs. Clinical evaluation included clinical examination and description of clinical features using specific Human Phenotype Ontology terms. In parallel, previously obtained genomic data were reviewed: exome sequencing (ES) using NextSeq Illumina and chromosomal microarray (CMA) using Agilent 60K oligonucleotide. Variants were classified according to the ACMG/AMP guidelines. Variant

interpretation utilized databases and tools including the DECIPHER, ClinVar, PubMed, VarSome, OMIM and UCSC Genome Browser.

Results: In 31 out of 49 patients, ES confirmed a CRD diagnosis; in 29 at initial evaluation, two after reevaluation. Seven patients had previously undescribed de novo pathogenic/likely pathogenic variants in CRD-related genes. Additionally, three patients had chromosomal microdeletions encompassing CRD genes. Variants of uncertain significance were initially reported in 15 patients; six of these were reclassified as likely benign/benign upon reevaluation.

Conclusion: Our study emphasizes integrated clinical and molecular approach in diagnosing CRDs. Periodic reevaluation of genomic data enhances variant classification and contributes to precise diagnoses. Notably, this patient cohort enriched the mutational spectrum by identifying several previously undescribed de novo pathogenic/ likely pathogenic variants in CRD-related genes. High percentage of inconclusive data requires use of additional genetic testing methods and expertise.

S3.02.I

Ivana Babić Božović, MD, PhD

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Ivana Babić Božović, MD, PhD is a clinical geneticist at the Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana in Slovenia and an Assistant Professor at the Department of Biology and Medical Genetics at the University of Rijeka. She is the Head of Slovenian national Hub for European Reference Network and a member of the Slovene Association of Medical Genetics Board. Her work is dedicated to clinical evaluation, diagnosis, research and education in the field of rare diseases. Within institutional cross-border collaboration, she is also working as clinical geneticist at the Clinical Hospital Centre Rijeka in Croatia, mainly focused on building genomic services for clinical needs.

Title / Abstract:

THE IMPORTANCE OF EUROPEAN REFERENCE NETWORK IN RARE DISEASE DIAGNOSIS AND MANAGEMENT: SLOVENIA'S EXPERIENCE

Ivana Babić Božović, Luca Lovrečić, Borut Peterlin

European Reference Networks (ERNs) are cross-border virtual platforms connecting European Union (EU) healthcare providers (HP) to improve care for patients with rare and complex diseases. Currently 24 ERNs operate across EU addressing the challenges posed by low prevalence, the limited knowledge and treatment options of rare diseases (RD), whereas over 70% of those are of genetic origin. The complex clinical presentation of RD demands highest level of expertise and multidisciplinary approach, involving several medical specialists, which are experts in their field yet commonly unaware of RD complexities. Therefore, the clinical geneticists are in position to play the central role for RD patients management within the ERNs as they are well aware of RD presentation.

Slovenian healthcare institutions have successfully joined ERNs, and formed the ERN hub for coordination of activities within ERNs, reflecting strong national commitment and expertise. This enabled exchange of knowledge and expertise with specialists across Europe on specific diagnostics and therapeutic options, trough virtual case discussions and cross-border expert panels. ERNs facilitate the establishment of clinical practice guidelines, standardization of treatment, ensuring uniformed, evidence-based care for patient across EU. Data sharing, collaborative research and educational activities, enhance the skills and knowledge of healthcare professionals involved in the care of patients with RD, particularly in the field of clinical genetics.

As platforms for clinical excellence, innovation, and collaboration, ERNs represent a strategic opportunity for healthcare professionals and their patients with RD, whereas the clinical geneticists are in position to play the central role, particularly in small healthcare systems like Slovenia.

Clinical Institute of Genomic Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia

S3.03.I

Assoc. Prof. Nevenka Kregar Velikonja, PhD

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Assoc. Prof. Nevenka Kregar Velikonja is a molecular and cell biologist. She began her postgraduate research at the Department of Medical Genetics of the Gynecology Clinic at University Medical Centre Ljubljana, the predecessor of today's Clinical Institute of Genomic Medicine. Her early work focused on diseases caused by trinucleotide repeat sequences, an area that has significantly contributed to the understanding of genetic mechanisms underlying rare disorders.

Currently, she is Dean of the Faculty of Health Sciences at the University of Novo mesto. Within her academic and professional career, she has been dedicated to fostering the academic and professional development of future healthcare professionals in the field of genomics. In this role, she actively promotes the integration of molecular biology and genomics into healthcare education and practice, bridging the gap between advanced scientific knowledge and clinical application.

She has also coordinated the development of the Genomic Counselling Training Programme, designed specifically for graduate nurses and other healthcare professionals. This program equips participants with the knowledge and skills necessary to understand, interpret, and communicate genomic information in clinical settings.

Title / Abstract:
COMPETENCES OF HEALTH PROFESSIONALS IN GENOMIC COUNSELLING

With the advent of widespread whole genome sequencing, personalized medicine, prenatal screenings, and predictive health technologies, genomic counseling has rapidly evolved into a mainstream healthcare discipline. As genetic insights increasingly influence clinical decisions—from oncology to cardiology and rare disease management—the demand for well-trained genomic counselors is growing globally. It also requires improvement of genetic literacy of healthcare workers on all levels of health care system.

Recognizing this, Slovenia launched a dedicated continuous education program "Genomic Informing" to equip healthcare workers with specialized skills for participating in multidisciplinary team dealing with patients that undergo genomic diagnostics and counceling.

To date, two generations of participants finished the programe. Programe evaluation shows that participants express high satisfaction rate. All prescribed programe competences are rated over 4 on scale 1-5, in terms of importance as well as gaining of the competences during programme. The highest rated competence is 'awareness of the need to improve, complement, deepen and update their own professional knowledge', which is essential for health professional to keep in touch with the rapidly advancing field of genomic medicine.

S6.03.I

Assoc. Prof. Luca Lovrečić, MD, PhD

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I first realized I wanted to become a human geneticist after a high school lecture on the genetics of bean colors - a moment that became my lifelong spark. This passion led me to study medicine and biology, dedicating my professional life to clinical evaluation, diagnostics, and research in the field of rare diseases. Motivated by this interest, I completed training in both clinical genetics and laboratory medical genetics. Today, I work with patients while also leading diagnostic laboratories at the Clinical Institute of Genomic Medicine, UMC Ljubljana, and my daily motivation comes from delivering the highest standards of care and best practice in the field of rare disease genomics.

In addition to my clinical and laboratory work, I serve on several national and international advisory boards, coordinate Orpha.net at the national level, and had the honor of serving as president of the Slovene Association of Medical Genetics.

I am currently an Associate Professor of Human Genetics at the Faculty of Medicine, University of Ljubljana, and mentor geneticists in training and young researchers. Guiding and empowering the next generation of geneticists is both my greatest responsibility and meaningful privilege, and it continues to shape the purpose of my professional life.

Title / Abstract:

PRENATAL GENOMIC TESTING - CURRENT POSITION AND FUTURE DIRECTIONS

Prenatal genetic diagnostics is celebrating 65 years this year with the first documented and published amniocentesis performed due to the increased risk of genetic disease in the fetus in 1960. The constantly evolving field of medical genetics and genomics is the reflection of both technological and bioinformatic advances, as well as the availability of population-scale national and international genomic databases, joining normal and pathological variation. Genetic testing methods with the potential to identify different types of pathological genetic changes have been constantly emerging and the approaches to fetal cells acquisition are moving from invasive testing with increased risk for pregnancy loss towards the ability to detect fetal DNA changes in maternal blood.

With the overarching aim to have a »one-size-fits-all« test with the results within a few days, prenatal genome-wide testing has its own challenges. Despite becoming technically possible with the rapid whole-genome sequencing and sophisticated bioinformatics, there are still significant scientific, logistical, and ethical dilemmas. Professional societies guidelines and recommendations determine the minimal requirements that should be provided in the routine daily prenatal genetic diagnostics. Yet, we all too often face a situation where technological advances and knowledge overtake and set boundaries not only in research settings but also in routine prenatal genetic diagnostics.

The obvious challenges in prenatal setting are time pressure to reach final results, the incidental findings in the parents and/or fetus, the variants of unknown significance, and ad-hoc multidisciplinary

team formation, depending on the indication for testing in the first place. Another important issue that needs to be addressed and accounted for is the evolving US-detectable fetal phenotype and the need of urgent gene panel adaptation and data re-analysis during ongoing pregnancy.

While exome and genome sequencing are powerful and are being implemented as a diagnostic test in the routine use for fetuses with congenital anomalies, testing of all pregnancies cannot currently be supported due to the lack of validation and knowledge about its benefits and pitfalls.

S6.04.I

Jelena Pajić, PhD

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Jelena Pajić, doctor of medical sciences, research associate in genetics, with 20 years of work in medical practice. She works in the Laboratory for Biodosimetry and Cytogenetics in the Serbian Institute of Occupational Health "Dr. Dragomir Karajović", accredited by the national accreditation body for in vitro cytogenetic tests of human blood. She is skilled in diagnostics of abnormalities of genetic material under the influence of ionizing radiation at the cytogenetic level (Dicentric test and cytokinesis block micronucleus test). Since 2014, she's been the head of the Center for Radiation Protection. She did her PhD (Faculty of Medicine, University of Belgrade) in the field of molecular medicine and the Post Master program-specialist studies "Human genetics" (Faculty of Biology, University of Belgrade) in the field of genotoxicology. In addition to the Society of Geneticists of Serbia, she is also a member of the Society for Radiation Protection of Serbia and Montenegro, as well as a permanent member of the European Radiation Dosimetry Group and the BioDoseNet Group of the World Health Organization.

Title / Abstract:

FOETAL RADIATION RISK. ROLE OF GENETICISTS IN BIODOSIMETRY SERVICE AND GENETIC COUNSELLING

Foetal radiation risk is subject of special interest in radiation protection. It refers to a few scenarios of exposure during pregnancy (planned, accidental, occupational) and exposures of woman of reproductive capacity. Foetal radiation risk includes deterministic effects, such as miscarriage, growth restriction, and malformations (above a dose threshold), and stochastic effects, such as childhood cancer (with a probability that increases with dose) or genetic risks.

Factors influencing risks are gestational age: Risks are highest during organogenesis (weeks 2-7) and the first trimester and decrease during the second and third trimesters and radiation dose: Risk increases with higher radiation doses.

Thousands of pregnant women are exposed to ionizing radiation each year.

An appropriate risk evaluation should be made in order to avoid probably unnecessary termination of pregnancies

The justification principle of radiation protection should always be based upon individual circumstances for both decision: to expose pregnant woman and to advise termination of the pregnancy after the exposure.

S7.02.I

Petar Brlek, MD, PhD Candidate

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Dr. Petar Brlek is a physician, inventor (patent holder), and the founder and president of the Youth Section of the Croatian Society for Human Genetics. He is also a member of the European Society of Human Genetics (ESHG) and the International Society for Applied Biological Sciences (ISABS). He received Croatia's national "Oscar of Knowledge" award for academic excellence and the Rector's Award (2020) for his bioinformatics research on genetic and molecular alterations in the EGFR-PI3K-AKT-mTOR signaling pathway in diffuse brain gliomas.

Dr. Brlek graduated with honors from the University of Zagreb School of Medicine in 2021 and joined the Center of Excellence for Personalized Medicine at St. Catherine Specialty Hospital, where from 2023 to 2025 he coordinated a landmark clinical study integrating artificial intelligence and whole-genome sequencing in personalized medicine. In 2022 and 2023, he advanced his expertise through training at leading international genetic laboratories in whole-genome sequencing under the mentorship of world-renowned experts.

At the invitation of the Centers of Excellence, the Croatian Pediatric Society, and the Croatian Academy of Medical Sciences, he has delivered numerous invited lectures on the clinical application of whole-genome sequencing in oncology, pediatrics, and personalized medicine. In November 2023, he was appointed the first medical genetics resident in the history of Croatia, marking a milestone in the nation's healthcare system.

In addition to his clinical work, Dr. Brlek has been actively engaged in applying artificial intelligence to personalized medicine, a field in which he has delivered numerous lectures nationally and internationally. In 2025, he became the patent holder of an innovative AI model that harnesses whole-genome sequencing data to predict the risk of multifactorial diseases and guide personalized treatment strategies.

Title / Abstract:

ONCOORIGIN: THE FUTURE OF PRECISION ONCOLOGY THROUGH INTEGRATION OF MACHINE LEARNING AND TUMOR GENOMICS FOR IDENTIFYING PRIMARY TUMOR SITE

Cancers of unknown primary (CUPs) account for approximately 3–5% of all malignancies and represent one of the greatest diagnostic and therapeutic challenges in oncology. Despite advances in imaging and histopathology, determining the tissue of origin often remains inconclusive, limiting therapeutic decision-making.

In this presentation, we will introduce OncoOrigin, a machine learning (ML) model we developed to predict the primary site of malignancy using tumor genomic and transcriptomic data. The model was trained on more than 20,000 tumor samples from the cBioPortal database, integrating somatic variant data from over 600 cancer-associated genes, together with clinical parameters such as patient age and sex. The XGBoostClassifier-based model demonstrated excellent predictive performance, achieving a top-2 accuracy of 0.91 and an ROC-AUC of 0.97, outperforming other tested approaches.

To support clinical implementation, we developed a graphical user interface (GUI) that allows clinicians to upload sequencing results and receive interpretable predictions of the most probable primary site, along with visualization of gene-level feature importance.

By integrating machine learning and tumor genomics, OncoOrigin bridges computational modeling with real-world oncology practice. This approach illustrates the emerging role of AI in precision oncology, providing valuable decision support in CUP diagnostics and expanding opportunities for personalized cancer care.

S7.01.I

Henriett Butz, MD, PhD

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Dr. Henriett Butz, MD, PhD works as a clinical geneticist and molecular diagnostics specialist with extensive expertise in hereditary cancer syndromes and tumorigenesis. She earned her medical degree and PhD in Clinical Medical Sciences from Semmelweis University, where she later specialized in medical laboratory diagnostics, molecular genetic diagnostics, and clinical genetics. She completed post-doctoral training in the The Keenan Research Centre for Biomedical Science of St. Michael's Hospital, Toronto, and in the Department of Laboratory Medicine and Pathobiology, University of Toronto.

Dr. Butz currently serves as the head of the Biobank Centre for Oncology at the National Institute of Oncology and is a chief physician in clinical genetics and molecular genetic diagnostics. She is also a senior research fellow at the Oncogenomics Research Group (HUN-REN) and a principal investigator at Semmelweis University's Department of Laboratory Medicine. Her research focuses on genetic and epigenetic mechanisms in cancer, the role of non-coding RNAs, and translational applications of next-generation sequencing.

Through her research, teaching, and clinical contributions, Dr. Butz continues to advance precision oncology, bridging molecular research with patient care.

Title / Abstract:

CHALLENGING INTERPRETATION OF GERMLINE VARIANTS IN HEREDITARY BREAST AND OVARIAN CANCER

Hereditary breast and ovarian cancers account for ~5–10% of breast cancer cases. With expanding therapeutic indications and next-generation sequencing, germline testing is offered to more patients, yet gene panels vary widely and interpretation remains challenging.

We aim to (i) summarise which genes should be tested and in which patients, and (ii) highlight major challenges in genetic testing.

Applying evidence-based criteria and restricting analysis to seven genes with proven impact on cancer-specific mortality improves diagnostic yield and reduces the burden of variants of uncertain significance (VUS). Broader panels raise VUS rates, increasing stress for patients and clinicians without clear benefit.

Real-world data show that up to 35% of germline variants are missed by tumour sequencing, while some tumour-detected variants are absent in the germline. As therapy eligibility (e.g., PARP inhibitors), surveillance, and family screening require germline confirmation, reflex testing is essential.

Finally, not all pathogenic variants imply inherited risk. Mosaicism and clonal hematopoiesis, increasingly identified with deep sequencing, can mimic germline findings but require different interpretation and follow-up.

Therefore, accurate interpretation including gene-specific interpretation demands integrating clinical context, family history, and biological mechanisms to avoid misclassification and guide precision prevention and care.

S11.01.I

Ana Marjanović, PhD

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Dr. Marjanović is a Research Associate at the Faculty of Medicine, University of Belgrade. She is currently engaged in the Laboratory for Molecular Genetic Diagnostics of Neurological Diseases at the Neurology Clinic, University Clinical Center of Serbia, bringing over 10 years of expertise in the genetics of neurological disorders.

She completed her graduate and doctoral studies at the Faculty of Biology, University of Belgrade. Her PhD research focused on the prevalence of hexanucleotide repeat expansions in the *C9orf72* gene in patients presenting predominantly motor and cognitive-behavioral symptoms. Her earlier scientific work was dedicated to the application of diagnostic techniques in neurogenetics, particularly fragment analysis of hexanucleotide repeats in the *C9orf72* gene.

Dr. Marjanović has contributed to three research projects funded by the Ministry of Science, Technological Development, and Innovation, as well as one project supported by the Serbian Academy of Sciences and Arts. She is currently a participant in the International Genetic Frontotemporal Dementia Initiative (GENFI), a collaborative project aimed at advancing the understanding of the genetic basis of frontotemporal dementia.

Title / Abstract:

***APOE*, *APP*, AND *PSEN1* MUTATION SCREENING IN ALZHEIMER'S DISEASE: A 15-YEAR EXPERIENCE IN SERBIA**

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder clinically manifested as cognitive decline, impaired daily functioning, neuropsychiatric symptoms, and behavioral changes. In late onset AD (>65 years) *APOE* ε4 is considered as a major risk factor, while in patients with early onset, around 80% of pathogenic variants have been found in gene Presenilin 1 (*PSEN1*), 15% in Amyloid precursor protein (*APP*), and only 5% in the gene Presenilin 2 (*PSEN2*). Materials and methods: The patients were recruited at the Memory Center, Neurology Clinic, University Clinical Center of Serbia from 2010 to 2025. After the informed consent, the patient's DNA was extracted using standard protocols. *APOE* genotyping was performed by real-time PCR using assays rs429358 and rs7412. Sanger sequencing was applied to analyze exons 16 and 17 of *APP*, and all the coding regions of *PSEN1*. Results: Among 707 genotyped patients with clinically possible AD, the most common *APOE* genotype was ε3/ε3 (53.3%), followed by ε3/ε4 (31.8%) and ε4/ε4 (7.8%).Total of 438 patients were tested for the presence of mutations in the *APP*, and 125 patients for mutations in *PSEN1*. Two pathogenic variants (p.T714I and p.V717I) were identified in *APP* in 3 patients. In *PSEN1*, 8 patients had pathogenic or likely pathogenic variants (p.M139T, p.Y159C, p.G206D, p.P267T and p. R269H). Conclusion: This study represents a comprehensive genetic analysis of Alzheimer's disease among patients in Serbia.

S11.02.I

Assist. Prof. Olga Antonova, MD, PhD

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Dr. Olga Antonova is a specialist in Medical Genetics, Nutrition and Dietetics and Nutrigenetics with over 15 years of clinical experience. She has completed internships and specialized training at leading genetic institutes in Tübingen and Jena (Germany), Nicosia (Cyprus), as well as Manchester, and London (UK). Her professional interests are in the field of preventive and precision medicine and include integrating knowledge of individual genetic information, with nutrition, environmental factors and the level of medical care in the field. This covers issues of reproductive medicine, oncogenetics, sports genetics, etc. Since 2020, Dr. Olga Antonova is a member of the Governing Board of the European Society of Human Genetics (ESHG), a Board member of the Bulgarian Society of Human Genetics and Genomics, member of the Policy and Ethics committee (PEC, ESHG), member of the International Society of Nutrigenetics & Nutrigenomics (ISNN), member of the Bulgarian Medical Association and of the Bulgarian Society of Nutrition and Dietetics. Dr. Antonova is an Assist. Prof. in the the Department of Medical Genetics at Medical University of Sofia. Her commitment to scientific inquiry is demonstrated through her participation as a leader or co-investigator in more than 15 local and international scientific projects. Her research contributions include 41 publications indexed in Web of Science and 183 citations in WOS database.

Title / Abstract:

FREQUENCY OF COMMON VARIANTS PREDISPOSING TO ESTROGEN POSITIVE DISEASES IN THE BULGARIAN POPULATION

Olga Antonova[1,2], Boryana Gerasimova[1], Viktoria Spasova[1,2], Savina Hadjidekova[2], Vesela Karamisheva[3]

Background: Estrogen-positive diseases, including breast, endometrial and gynecological disorders, are influenced by genetic variants involved in estrogen metabolism and detoxification. Variant distribution differs between populations and may underlie ethnic-specific risk profiles, yet data on the Bulgarian population remain limited.

Objectives: To assess the frequency of selected polymorphisms implicated in estrogen-related disease susceptibility in a Bulgarian cohort.

Methods: Common variants in metabolic genes were analyzed: *CYP1A1* (Msp1 T>C, Ile462Val), *CYP1B1* (Val432Leu), *CYP17A* (34T>C), *MnSOD* (Ala16Val), *GSTM1* (Ins/Del), *GSTT1* (Ins/Del), *COMT* (Val158Met), *MTHFR* (677C>T), *SULT1A1* (Arg213His), *NQO1* (609C>T), and *F5* (G1691A, Factor V Leiden). DNA was extracted from peripheral blood samples of 50 unrelated Bulgarian individuals. Genotyping was performed using PCR-based assays. Participants completed a questionnaire evaluating dietary, epidemiological, and occupational risk factors that may interact with genetic variants to influence disease risk.

Results: Preliminary analysis of 45 patients revealed distinct susceptibility patterns. 13% carried *CYP17A* and *GSTT1* risk variants, and 22% the unfavorable *COMT* allele. *GSTM1* deletion was

detected in 62% of individuals, with 13% showing a combined *GSTM1/GSTT1* deletion. The majority (95.6%) retained wild-type *F5*. 18% carried three of twelve high-risk polymorphisms, 6.7% carried three high-risk plus four moderate-risk variants, and 16% carried five to seven intermediate-risk polymorphisms, cumulatively impairing estrogen detoxification.

Conclusion: These findings provide the first dataset on estrogen-related susceptibility in Bulgarians. Thise observed cumulative genetic burden may shape individual and population-level risk profiles, highlighting the need to integrate genetic and environmental data in future studies.

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S11.03.I

Assist. Prof. Vanja Vidović, PhD

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Assist. Prof. Dr. Vanja Vidović completed her undergraduate studies in Natural Sciences, major in Biology at Austin Peay State University, USA. She pursued her Master's and Doctoral degrees at the University of Belgrade, where she began her research at the Institute of Human Genetics at the Faculty of Medicine, University of Belgrade. Her early research focused on the role of various genetic variants in metabolic parameters that contribute to the development of atherosclerosis. Currently, Dr. Vidović serves as an Assistant Professor at the Faculty of Medicine, University of Banja Luka, where she holds a position at the Department of Human Genetics and the Center for Biomedical Research. Her primary research interests are centered on the genetics of cardiovascular diseases and pharmacogenetics. She is also the head of the English-language Medicine study program for international students. Dr. Vidović is the author of numerous scientific articles published in indexed journals, as well as various educational publications used in different forms of teaching.

Title / Abstract:

ROLE OF *SIRT1* AND *SIRT3* GENETIC POLYMORPHISMS IN THE RISK OF ACUTE MYOCARDIAL INFARCTION AMONG PATIENTS FROM THE REPUBLIC OF SRPSKA

SIRT1 and *SIRT3* are key regulators of cellular stress responses, inflammation, and metabolic homeostasis, all of which are critical in the pathophysiology of acute myocardial infarction. This case-control study included a total of 292 participants: 192 patients diagnosed with acute myocardial infarction (AMI) and 100 healthy control subjects. No statistically significant differences were observed between *SIRT1* rs7069102 and *SIRT3* rs1229334 genotypes in relation to mean values of total cholesterol (TC), HDL, LDL, triglycerides (TG), C-reactive protein (CRP), calcium, troponin, or ejection fraction (EF). Also, no direct association between *SIRT1* or *SIRT3* genotypes and overall AMI risk was observed. However, among AMI patients, carriers of the *SIRT1* CC+CG genotypes showed a significantly higher prevalence of hypertension compared to GG carriers ($p = 0.03$). No significant association was found between *SIRT1* genotypes and diabetes mellitus prevalence. For *SIRT3*, individuals with the CC genotype exhibited a significantly higher proportion of elevated LDL levels ($\chi^2=9.128$, $p=0.010$), while the rare CT genotype was more frequently observed in the borderline LDL group. Additionally, CT carriers had significantly higher triglyceride levels, with 60% presenting elevated TG values compared to CC carriers ($p = 0.033$), indicating a link between *SIRT3* polymorphisms and lipid metabolism. *SIRT1* CC genotype carriers had significantly lower CRP levels compared to CG+GG carriers ($p = 0.028$), suggesting a reduced inflammatory response. Patients with STEMI AIM were younger ($p = 0.045$), and more frequently smokers (76.3% vs. 23.7%, $p = 0.003$) compared to NSTEMI patients. Overweight/obese hypertensive patients carrying the *SIRT1* CC+CG genotypes had a higher likelihood of ST-segment elevation myocardial infarction when adjusted for age and smoking status ($p = 0.045$). These findings suggest that genetic variations in *SIRT1* and *SIRT3* contribute to individual differences

in cardiometabolic risk and inflammatory status, potentially impacting the clinical course of myocardial infarction.

S13.01.I

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Weronika Gutowska-Ding is a Scientific Program Manager and Quality Manager at EMQN, one of the leading global providers of external quality assessment (EQA) in molecular genetics and pathology. She oversees the development and delivery of international EQA schemes, supporting laboratories in maintaining high standards of diagnostic accuracy and clinical reporting.

Weronika plays a key role in ensuring EMQN's compliance with ISO 17043 and leads initiatives focused on continuous improvement, stakeholder engagement, and scientific integrity. Her work spans program coordination, quality system implementation, and strategic planning, contributing to the global harmonization of genetic testing standards.

She is actively engaged in EuroGentest, where she collaborates with European partners to promote best practices in genetic testing and laboratory quality. As part of her commitment to improving performance across the sector, Weronika co-founded the Joint Committee on Poor Performance, bringing together experts from multiple organizations to address recurring issues in laboratory quality and support underperforming labs through targeted interventions and education.

Her work reflects a deep commitment to improving patient outcomes through robust quality systems and international collaboration. At the Balkan Congress of Human Genetics, Weronika brings valuable insights into the role of EQA in shaping the future of genetic diagnostics across Europe.

Title / Abstract:

BEYOND COMPLIANCE: EUROGENTEST INITIATIVES AND EVIDENCE FOR THE ROLE OF EXTERNAL QUALITY ASSESSMENT IN DRIVING LABORATORY IMPROVEMENT

Weronika Gutowska-Ding[1,2], Gert Matthijs[1], Simon Patton[2]

External Quality Assessment (EQA) plays a central role in ensuring accuracy, reliability, and clinical utility in genomic testing, while also providing a mechanism for continuous improvement. Within EuroGentest, the Joint Committee on Poor Performance (JCPP) was established to address inconsistencies in how poor performance is defined and managed across Europe. Bringing together major EQA providers, including Equalis, Instand, ERNDIM, GenQA, and EMQN CIC, the JCPP is working to harmonise criteria, thresholds, and corrective action strategies to create a transparent, standardised framework for assessing underperformance. This initiative aims to reduce confusion for participating laboratories, foster comparability of data, and ultimately raise diagnostic standards across Europe. Beyond harmonisation, the committee is also exploring effective intervention strategies for persistently underperforming laboratories, including guidance for corrective action, enhanced training, and greater collaboration with regulatory bodies.

Complementing this policy-level work of JCPP, a longitudinal study of EQA data from ten genomic testing schemes was performed, each with at least a decade of consistent data and participation

from more than fifty laboratories per cycle. Results demonstrate measurable improvements in both genotyping and interpretation accuracy over time, with interpretation showing the most pronounced gains. Importantly, the rate of critical errors declined steadily with increased participation, indicating that sustained engagement in EQA directly supports quality enhancement rather than serving only as a compliance exercise. A small subset of laboratories displayed persistent performance fluctuations, underlining the importance of targeted support and intervention. Together, these findings highlight that EQA serves not only as an accreditation tool but also as a driver of lasting quality improvement.

By combining harmonisation efforts through EuroGentest with evidence of impact from longitudinal analyses, we demonstrate the dual value of EQA in promoting excellence, comparability, and patient safety across genomic laboratories in Europe.

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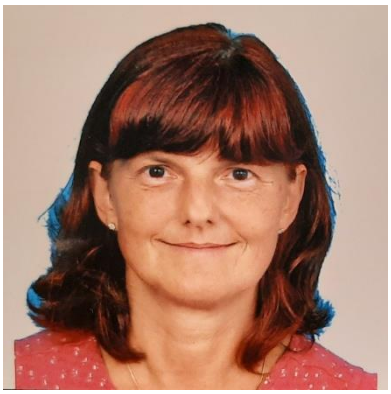
S13.02.I



Assoc. prof. Helena Podgornik, PhD

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After completing her undergraduate studies in chemical engineering, Assoc. Prof. Dr. Helena Podgornik earned her PhD in Biochemistry from the Faculty of Chemistry and Chemical Technology at the University of Ljubljana. After a decade working in biotechnology and bioremediation, she moved to the field of laboratory hematology in 2003. From 2007 she is a specialist in clinical biochemistry (EuSpLM) and from 2015 a specialist in medical laboratory genetics (ErCLG).

Assoc. prof. Helena Podgornik, PhD, is the head of the Specialized Hematology Laboratory at the University Medical Centre Ljubljana and a professor of clinical biochemistry and laboratory medicine at the Faculty of Pharmacy, University of Ljubljana. The Specialized Hematology Laboratory is the only institution in Slovenia dedicated to laboratory hematology and the diagnosis of various hematological diseases. Her main focus is the implementation and integration of different laboratory techniques to obtain comprehensive diagnostic and prognostic information. She has collaborated on national and international research projects related to hematological malignancies. In the last two decades, she has contributed to over 30 scientific publications in this field, some of which are the result of multicentre international collaboration.

She has been a member of national and international associations and has led the working group for laboratory hematology at the Slovenian Society for Clinical Chemistry and Laboratory Medicine since 2014.

Title / Abstract:

HOW TO OBTAIN REGULATORY COMPLIANCE FOR IN-HOUSE IN VITRO DEVICES (IH-IVD'S)?

The primary purpose of the In Vitro Medical Devices Regulation (EU) 2017/746 (IVDR) is to enhance patient safety by ensuring the safety of medical devices. The regulation allows healthcare institutions to manufacture their own diagnostic tests (IH-IVDs) under the conditions specified in Article 5.5. Points b and c of this article require that the laboratory have a quality system compliant with the ISO 15189 standard. This international standard specifies the requirements for the quality and competence of medical laboratories. Accreditation according to this standard therefore also ensures greater patient safety.

The implementation of the IVDR has accelerated the adoption of quality standards in clinical laboratories by approximately 10%, which is a positive effect. However, the remaining points of Article 5.5 have resulted in unnecessary bureaucracy, increased costs, unreasonable restrictions on test performance—especially for rare diseases—reduced availability of reagents, and decreased flexibility and competitiveness. Manufacturing and use of IH-IVDs are common in most diagnostic disciplines; however, genetics and rare disease diagnostics rely primarily on this category of tests. Therefore, genetic laboratories are particularly interested in changes to the regulation. The European Commission has opened a ‘Call for Evidence’ on the future of the IVDR. The revision aims to simplify, streamline, and

optimize the regulatory framework, while maintaining the overall structure of the regulations and keeping public health and patient safety at its core. Proposals have been prepared to remove all points of Article 5.5 except b and c, thus enabling European laboratories to focus on what we are trained and competent to do. However, compliance with ISO 15189 requirements will undoubtedly be expected of all European genetic laboratories.

Oral presentations

Session: S1.04.O

RAPID INTRAOPERATIVE CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMOURS USING REAL-TIME NANOPORE SEQUENCING

Sara Petrin, Špela Kert, Alenka Matjašič, Miha Jerala, Matic Bošnjak, Jože Pižem, Andrej Zupan

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DNA methylation profiling has emerged as a robust method for classifying central nervous system (CNS) tumours. Shallow methylation profiles can be rapidly generated using nanopore sequencing, which provides a convenient platform for real-time data generation and analysis. This can be utilized for a faster diagnosis and application in an intra-operative setting. During surgery, neurosurgeons need to find balance between maximum tumour removal and preservation of neurological function. Therefore, knowledge of the tumour type could direct the extent of resection. Our aim was to establish a standard procedure for the intraoperative CNS tumour classification. We performed the study on sixteen fresh-frozen tumour samples collected during neurosurgery. We isolated the DNA, performed library preparation using the Rapid Sequencing Kit, sequenced on Minion with R10 flow-cells, and performed data analysis using two methylation-based classification tools: Sturgeon and nanoDx. The average time from sample collection to final result was two hours. Our analysis showed promising results; fourteen out of sixteen cases matched the neuropathologist's final diagnosis. Further histopathological and molecular investigations are underway for the two discordant cases. This novel approach of CNS tumour classification during surgery could allow neurosurgeons to make a more informed decision about the extent of tumour resection, which could potentially reduce neurological morbidity and improve clinical outcomes.

***Topic**: Advances in rare disease diagnostics*

Session: S1.05.O

THE CONTRIBUTION OF REANALYSIS OF WHOLE EXOME SEQUENCING DATA TO DIAGNOSIS RATE

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Purpose: Whole-exome sequencing (WES) is widely used to diagnose genetic disorders. Advances in gene discovery and variant interpretation have enabled the reanalysis of previously inconclusive WES data, leading to new diagnoses. This study evaluates the diagnostic yield of WES reanalysis in unresolved cases.

Method: Patients with suspected genetic disorders and no diagnosis from initial WES were re-evaluated. Library preparation and exome enrichment were performed using the TWIST Human Comprehensive Exome kit, and sequencing was conducted on the MGI T7 platform. Variant interpretation followed ACMG and ClinGen guidelines. Family studies were used to confirm findings. Pathogenic/likely pathogenic variants were considered definitive diagnoses, while variants of uncertain significance (VUS) were classified as suspected diagnoses. The time between initial and repeat analyses, and reasons for previously missed variants, were recorded.

Results: Fifty reanalyses have been reviewed to date. Most patients had neurodevelopmental delay, though indications also included epilepsy and immunodeficiency. The interval between analyses ranged from 2 to 56 months. A definitive diagnosis was made in 3 cases (6%): one due to a newly established gene-disease association, and two due to previously overlooked variants. An additional 7 cases (14%) had VUS potentially related to the phenotype—2 linked to emerging gene-disease associations and 5 due to relaxed interpretation thresholds. No findings were identified in the remaining 40 cases.

Conclusion: Even in this early dataset, WES reanalysis proves valuable, revealing new diagnoses through updated gene knowledge and improved variant detection. We aim to present data from over 400 cases at the upcoming congress.

***Topic**: Advances in rare disease diagnostics*

Session: S2.03.O

REPORTING BEYOND THE PRIMARY DIAGNOSIS: ACTIONABLE ADDITIONAL FINDINGS IN WES/WGS

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Purpose: During WES and WGS interpretation, pathogenic variants are often identified that do not explain the referred clinical presentation but may relate to medically actionable conditions. In line with ACMG v3.3 guidelines, we report such variants in 84 actionable genes. At the Clinical Institute of Genomic Medicine (CIGM), these additional findings are routinely reported to adult patients with signed consent and to minors only if the condition can manifest in childhood. This study reviews all additional findings reported over the past four years.

Method: We retrospectively reviewed all variants reported as additional findings in WES and WGS at CIGM.

Results: We reported 127 variants in 50 genes as additional findings. Of these, 23 genes are part of the ACMG v3.3 list and 27 are not. Most variants (85%) were linked to cardiovascular or cancer phenotypes (59 and 49, respectively). Reported genes not on the ACMG list included *ABCC8*, *ACADM*, *ALG8*, *ALPK3*, *ATM*, *BCHE*, *CALR*, *CDH1*, *CDKN2A*, *CFTR*, *CHEK2*, *CLCN1*, *COL4A1*, *DDX41*, *DICER1*, *DMD*, *DNM2*, *FHOD3*, *G6PD*, *IDH2*, *KRAS*, *PKD2*, *POT1*, *PRRT2*, *RAD51C*, *SDHA*, and *SERPINC1*.

Conclusion: Additional findings are not rare. Gene selection for reporting should consider clinical actionability, disease severity, penetrance, and the impact or burden of treatment or screening.

***Topic**: What is new in Mendelian disorders*

Session: S2.04.O

3D FACIAL GESTALT ANALYSIS OF INDIVIDUALS WITH MUTATED *PKD1* GENES IN POLYCYSTIC KIDNEY DISEASE PATIENTS

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Introduction: Molecular genetic analysis of PKD patients (predominantly caused by variants in *PKD1* and *PKD2* genes) is often intricate, necessitating innovative diagnostic approaches. We studied association of *PKD1* pathogenic variants with 3D facial gestalt.

Materials and Methods: We enrolled 39 PKD cases (28 females, mean age 33y, 11 males, mean age 33y, all with *PKD1* mutation) and conducted facial scanning (3dMD Facial system), editing (Geomagic Wrap 2021) and analyzed (CPD-DCAthe Morphome3cs software) by comparing patients to average 3D facial models.

Results: In males, significant retrusion in the lateral supraorbital arches and nasal tip was observed, with non-significant retrusion in the medial forehead, nasal dorsum, philtrum, and lower lip. A notably receding chin and prominent zygomatic and lateral cheek areas further characterized the male phenotype. In females, non-significant prominence was found in the medial forehead, nasal dorsum, and lower lip, while significant features included retrusion of the lateral supraorbital arches and prominence in the zygomatic area and chin tip. Shared traits in both sexes included retrusion of the lateral supraorbital arches and zygomatic prominence.

Conclusions: Our findings suggest the existence of a distinct 3D facial gestalt in PKD patients with *PKD1* pathogenic variants, which may serve as a diagnostic aid or facilitate risk stratification in presymptomatic cases.

Supported by grant 44120 from The Charles University Grant Agency.

***Topic**: What is new in Mendelian disorders*

Session: S2.05.O

UNCOVERING DUAL DIAGNOSES THROUGH TRIO-BASED WHOLE EXOME SEQUENCING (WES): INCIDENCE AND CLINICAL IMPLICATIONS

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Background and Purpose: WES has revolutionized the diagnosis of rare diseases, increasing the number of patients diagnosed with multiple molecular alterations. This study investigates the incidence of dual molecular diagnoses and their clinical correlations with patients' phenotypes.

Methods: We analysed trio-based WES performed between 2020 and 2025 in patients with suspected monogenic disorders. Patients with two molecular diagnoses were classified into three groups: (1) patients with overlapping phenotypes caused by pathogenic variants (PVs) in two genes; (2) patients with distinct phenotypes, each linked to separate PVs; (3) patients with one molecular diagnosis and one incidental finding (IF).

Summary of Results: Among 1043 WES, the diagnostic yield was 42%, with dual diagnoses identified in 26 patients (2.5%). Of those, five patients (19%) were in group (1), including a child with neurodevelopmental disorder and PVs in *ASH1L* and *SPTBN1*; 13 patients (50%) in group (2), including a girl with *SCN1A*-related epilepsy and *MMP21*-related heterotaxy; and eight patients (31%) in group (3), including a girl with *LZTR1*-related RASopathy and *BRCA2* PV.

Conclusion: This study highlights the value of WES in revealing multiple PVs in a subset of patients, consistent with previous literature, and emphasizes the need of accurate reverse phenotyping. Establishing genotype-phenotype correlations, particularly in patients with complex presentations, is crucial for guiding prognosis, clinical management, preventive strategies for IFs and recurrence risk.

***Topic**: What is new in Mendelian disorders*

Session: S2.06.O

RESOLVING DIAGNOSTIC CHALLENGES IN SKELETAL DYSPLASIA – A CLINICAL OVERVIEW OF A TEN YEARS' EXPERIENCE OF A SINGLE GENETIC CENTER IN SERBIA

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Background: Genetic skeletal dysplasia is heterogeneous group of 771 disorders affecting the skeleton, often with overlapping phenotypes.

Material and methods: We analyzed 552 probands from the skeletal dysplasia database of Department of Clinical Genetics, University Children's Hospital, Belgrade, Serbia, registered from 2014 to 2024. We have conducted a clinical overview of tested probands with analysis of the diagnostic approach.

Results: Out of 252 probands, 217 were tested using next-generation sequencing (clinical exome sequencing or whole exome sequencing in the first step, and whole genome sequencing in the second step for selected negative probands) and 35 were tested using targeted gene/mutation analysis. Next generation sequencing showed a high detection rate of the causative gene variant(s) of 61.21% (131/217). Additionally, in 5.52% (12/217) of a non-diagnosed probands gene variant(s) of unknown significance were identified. In the targeted tested group, result was positive for 75.67% (27/35) of them.

Conclusion: We have achieved high diagnostic rate by combination of next generation sequencing and gene/mutation targeted testing for probands with skeletal dysplasia.

Through this study, we analyzed the diagnostic challenges, provided clinical insight for the utility of genetic testing and identified the potential benefits of an accurate diagnosis in future treatments and management of affected patients with skeletal dysplasia.

***Topic**: What is new in Mendelian disorders*

Session: S2.07.O

GENETIC BASIS OF FEMALE PROTECTIVE EFFECT IN NEURODEVELOPMENTAL DISORDERS AND BEYOND

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There is increasing awareness of sex bias in various diseases, particularly those that begin early in development, such as congenital anomalies (CA) and neurodevelopmental disorders (NDD). In NDD, male-to-female ratio can exceed 4 to 1. It is suggested that females may require a greater genetic/ environmental risk to exhibit the same phenotype, leading to the "female protective effect" hypothesis. Recent genomic data supports this concept by identifying rare and common sex-biased variants. However, the effects of structural variations from sex chromosomes or autosomes in NDD and CA are still under-researched. Here, we explore sex disparities in phenotype prevalence and copy number variation (CNV) detection rates in 1 412 patients referred for chromosomal microarray. Agilent oligonucleotide platforms were used. In our cohort, the male-to-female ratio was 1.6 to 1; most patients had NDD with comorbidities. Despite being outnumbered, females had significantly higher diagnostic yield (DY): 20,3% (110/542) compared to 13,4% in males (117/870); p=7x10-4. Although females exhibited more complex phenotypes, the difference was significant only in groups with ≤2 comorbidities. Higher DY showed congenital heart disease, urogenital anomalies, and autism spectrum disorders, all of which are more prevalent in males. This pattern suggests a higher threshold liability in females. Greater pathogenic CNV burden in females required to express the same phenotype supports the female protective effect hypothesis.

***Topic**: What is new in Mendelian disorders*

Session: S4.02.O

THE *FMR1* PREMUTATION IN PATIENTS WITH LATE-ONSET MOVEMENT DISORDERS AND FAMILY MEMBERS OF FRAGILE X SYNDROME PATIENTS: A DIAGNOSTIC OPPORTUNITY

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Introduction: Nucleotide repeat expansions are a well-recognized cause of neurological disorders, though their clinical manifestations can be highly heterogeneous. One notable example is the CGG trinucleotide repeat within the 5′ untranslated region (UTR) of the *FMR1* gene on the X chromosome. Depending on repeat size and sex, this expansion is associated with three distinct conditions: fragile X syndrome (FXS) when >200 CGG repeats (full mutation); fragile X-associated tremor-ataxia syndrome (FXTAS) and fragile X-associated primary ovarian insufficiency (FXPOI) in carriers of the premutation range (PM, 55–200 CGGs).

This study aimed to assess the frequency of FMR1 PM in individuals with late-onset movement disorders of unknown etiology, and to investigate the presence of the PM among relatives of individuals with confirmed FXS.

Methods: Genetic screening for *FMR1* CGG repeat expansions was performed using an AmplideX PCR kit.

Results: We screened 122 consecutive patients with late-onset movement disorders, and 69 relatives from 27 families with confirmed FXS. The *FMR1* PM was identified in 5 movement disorder patients (4.1%), enabling a conclusive diagnosis. Among the FXS families, 52 relatives (75.4%) were confirmed as PM carriers.

Conclusion: Although rare, *FMR1* PM may underlie a subset of late-onset movement disorders with previously unknown genetic cause. Routine screening in such cases should be

considered. Furthermore, cascade genetic testing in families with FXS is critical — particularly to inform reproductive counseling and guide neurological surveillance.

***Topic**: Genetics of neurologic and neurodevelopmental disorders*

Session: S4.03.O

ROUTINE MOLECULAR GENETIC TESTING OF GAA-*FGF14*-RELATED ATAXIA AND *RFC1* CANVAS SPECTRUM DISORDER

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Background: Ataxia is a neurological symptom caused by damage to the cerebellum and/or nerves controlling movement, and can occur because of acquired or genetic causes. Currently the diagnostic yield of genetic testing can identify the cause in approximately 40% of patients, leaving 60% undiagnosed. Recently, a pentanucleotide expansion in *RFC1* has been found to cause cerebellar ataxia, neuropathy, and vestibular areflexia (CANVAS) syndrome – an autosomal recessive form of ataxia, while a trinucleotide expansion in *FGF14* has been found to cause an autosomal dominant late-onset spinocerebellar ataxia 27B.

Aim: Our aim was to improve clinical patient care, by applying testing for these novel causes of genetic ataxia to routine genetic care.

Methods: We performed *RFC1* and *FGF14* expansion testing by using an in house PCR and RP-PCR method based on dual-labelled reactions (Jaklič et al., 2024), or a modified version of the original testing method (Jaklič et al., unpublished). Both methods have been streamlined to fit the routine genetic laboratory workflow and equipment and to minimize cost, by applying a simple, sensitive, specific, and fast screening step based on fluorescent fragment length analysis detection, to the expansion testing.

Results: By testing a cohort of 100 previously undiagnosed ataxia patients, we were able to determine the presence of *FGF14* pathogenic expansion in 7% of patients, while we found bialelic pathogenic CANVAS associated repeats in *RFC1* in 7% of patients.

Conclusion: Including novel genes in routine testing of ataxia can considerably improve the yield of genetic testing and improves patient care.

***Topic**: Genetics of neurologic and neurodevelopmental disorders*

Session: S4.04.O

MONOGENIC CAUSES OF EARLY-ONSET DEMENTIA: EVIDENCE FROM WHOLE EXOME SEQUENCING

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Background/Objectives: Early-onset dementia (EOD), defined as dementia with onset before age 65, accounts for fewer than 10% of all dementia cases. The most common subtypes are Alzheimer's disease (AD) and frontotemporal dementia (FTD). Genetic causes can be identified in approximately 10% of EOD cases.

Methods: Whole exome sequencing (WES) was performed in 39 patients: 29 with AD (median age 58.97; range 37–68) and 10 with FTD/motor neuron disease (MND) (median age 60.6; range 55–67). A virtual panel of 41 dementia-associated genes was analyzed, and variants were classified according to ACMG guidelines. *C9orf72* repeat expansions were assessed using F-PCR and TP-PCR in FTD cases.

Results: Pathogenic variants were identified in four AD patients (13.8%): two in APP (both with c.2158T>G) and two in *PSEN1* gene (c.497T>A and c.1309A>G). Among FTD patients, two carried *C9orf72* expansions and two were heterozygous for *OPTN* c.403G>T pathogenic variant. Variants of uncertain significance (VUS) were found in 11 patients across eight genes (*ABCA7*, *CHMP2B*, *GRN*, *GCH1*, *DNMT1*, *NOTCH3*, *SQSTM1*, *TREM2*). The *APOE* ε4/ε4 genotype was detected in two AD patients; ε3/ε4 in 13 AD and one FTD patient; and ε2/ε4 in one FTD patient. The ε4 allele frequency was notably higher in AD (29.3%) than in FTD (10%).

Conclusion: Pathogenic variants in AD-associated genes were detected in 13.8% of AD cases, while 20% of FTD cases were attributable to C9orf72 expansions. The *APOE* ε4 allele is a significant risk factor for early-onset as well as late-onset AD.

***Topic**: Genetics of neurologic and neurodevelopmental disorders*

Session: S4.05.O

EXPANSION AND CONTRACTION OF CGG REPEATS IN *FMR1* GENE WITHIN ONE FAMILY

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Background: Fragile X syndrome (FXS) is trinucleotide repeat disease caused by expansion of CGG repeats in 5' untranslated region of *FMR1* gene to full mutation (>200 repeats). Premutation alleles (55-200 repeats) are highly unstable predominantly leading to expansion of repeats in next generation; nevertheless, contraction events are also possible.

Purpose: To present the case of an unstable premutation allele in one family and highlight the importance of monitoring its transmission from one generation to another.

Method: The number of CGG repeats was assessed in DNA samples extracted from the peripheral blood of a mother, her affected and unaffected son using CGG Repeat Primed PCR (AmplideX® PCR/CE FMR1 Reagents (Asuragen, USA)).

Results: Molecular genetic testing of the affected son revealed the presence of a full mutation (>200 repeats) in hemizygous state, confirming the clinical diagnosis of FXS. The mother was heterozygote for one premutation allele in mosaic form (91-96±3 repeats) and one normal allele (29±1 repeats), while her unaffected son was shown to have a premutation (62±1 repeats) in hemizygous state.

Conclusion: This case demonstrates that both expansion and contraction of CGG repeats of the same premutation allele can occur within the same family, indicating that changes in number of CGG repeats are unpredictable and may occur in either direction (increase or decrease). Therefore, prenatal diagnostics is strongly recommended for female carriers of premutation.

***Topic**: Genetics of neurologic and neurodevelopmental disorders*

Session: S4.06.O

ERBB4 EXONIC DELETIONS IN PATIENTS WITH INTELLECTUAL DISABILITY AND SPEECH DEVELOPMENTAL DELAY

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Purpose: The *ERBB4* gene, located on chromosome 2q34, encodes a receptor tyrosine kinase of the ErbB family that is crucial for brain development and function. This receptor mediates signaling pathways through interactions with neuregulins and other growth factors. Deletions or loss of *ERBB4* have been associated with neurodevelopmental disorders, particularly intellectual disability and epilepsy, likely due to disruption of neuronal signaling and connectivity.

Method: From a cohort of 2,275 patients who underwent chromosomal microarray analysis (CMA) in our laboratory between 2018 and 2025, utilizing Agilent oligonucleotide 8x60K or 4x180K+SNP microarrays, individuals with deletions involving the *ERBB4* gene (MIM 600543) were identified and selected for further analysis.

Summary of results: We identified five individuals from two unrelated families with deletions on chromosome 2q34, each involving the single protein-coding gene *ERBB4*. In the first family, siblings, a sister and brother, with a 753 kb deletion encompassing exons 1 and 2 of *ERBB4*, both presented with hyperactivity, intellectual disability, and severe speech developmental delay. In the second family, a female patient, with a 425 kb deletion affecting the proximal region and exon 1 of *ERBB4*, exhibited speech developmental delay and behavioral disorders. The deletion was inherited maternally. Both her mother and grandmother have intellectual disabilities, with the mother also experiencing psychiatric symptoms.

Conclusion: Our findings highlight the involvement of *ERBB4* deletions in neurodevelopmental abnormalities, including intellectual disability and speech impairment, underscoring the gene's critical role in brain development and function.

***Topic**: Genetics of neurologic and neurodevelopmental disorders*

Session: S5.02.O

INCREASED IDENTIFICATION OF PARP INHIBITOR-ELIGIBLE PATIENTS IN EPITHELIAL OVARIAN CANCER THROUGH HRD TESTING AT THE INSTITUTE OF ONCOLOGY LJUBLJANA

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Introduction: Homologous recombination deficiency (HRD) in tumors is an important predictive biomarker in epithelial ovarian cancer (EOC) patients for response to PARP inhibitors in different treatment settings. HRD can be caused by pathogenic variant (PV) in *BRCA1* and *BRCA2* genes, *BRCA1* promoter hypermethylation (phm*BRCA1*) or PV/defects in other DNA repair genes involved in homologous recombination (HR). According to ESMO recommendations, HRD testing of EOC tumor includes genotyping of *BRCA1/2* genes, detection of phmBRCA1 and assessment of HRD genomic instability score (HRD-GIS) through detection of HRD genomic scars on DNA.

Methods: Since 2019, EOC tumor samples at the Institute of Oncology Ljubljana have been subjected to molecular genotyping, initially focusing exclusively on the genotyping of *BRCA1/2* genes. In 2024, the diagnostic workflow was substantially expanded to incorporate assessment of phmBRCA1, genotyping of additional non-*BRCA* HR genes, and evaluation of HRD using HRD-GIS. In 2024, a total of 120 EOC tumor samples were analyzed using this extended protocol.

Results: PV in *BRCA1* or *BRCA2* gene were detected in 26% of tested EOC tumors. PhmBRCA1 was detected in 8% of tested EOC tumors. PVs in non*BRCA* HR genes were detected in 8% of cases, only one third of these were HRD-positive as determined by the HRD-GIS test. Overall, HRD was detected in more than one third of EOC tumors.

Conclusion: Expanded molecular characterization of EOC tumors—incorporating phmBRCA1 analysis, genotyping of non-*BRCA* HR genes, and HRD-GIS assessment—resulted in a 40% increase in the detection of HRD-positive tumors, and subsequently patients who may benefit from PARP inhibitor therapy, compared to *BRCA1/2* genotyping alone.

***Topic**: Advances in cancer diagnosis*

Session: S5.03.O

CHAPERONE-MEDIATED AUTOPHAGY IN GLIOBLASTOMA: A MULTI-OMICS PERSPECTIVE

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Glioblastoma (GB) is the most aggressive primary brain tumour in adults, with limited treatment efficacy and poor patient survival. This study aimed to explore the contribution of chaperone-mediated autophagy (CMA) to GB pathogenesis through transcriptomic and proteomic analyses.

Method: The study included 14 glioblastoma tissue samples and 15 control brain tissues. Total RNA was extracted and subjected to RNA sequencing for transcriptomic profiling. In parallel, proteins isolated from the same samples were analysed using Western blotting to assess the expression of six CMA-related proteins.

Results: Differential gene expression analysis revealed a marked downregulation of genes related to synaptic signalling (e.g., *PRKCG*, *DDN*, *RAB3A*) and upregulation of genes involved in autophagy and cellular stress (e.g., *MSH5*, *ATG5*, *SPOCD1*). Gene ontology (GO) and KEGG pathway enrichment confirmed suppression of neuronal communication and activation of immune and metabolic pathways. Western blotting showed decreased expression of molecular chaperones (Hsc70, Hsp70, Hsp90) and increased levels of autophagy markers (ATG5, LC3A) in GB samples compared to controls.

Conclusion: These findings suggest that CMA dysregulation supports tumour cell survival and contributes to glioblastoma progression. Targeting autophagy-related pathways may provide novel therapeutic opportunities in GB.

***Topic**: Advances in cancer diagnosis*

Session: S5.04.O

BETTER DIAGNOSIS OF LIVER CANCER WITH THE USE OF XENIUM SPATIAL TRANSCRIPTOMICS

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The liver is a favored site of metastasis in the body. Metastatic pancreatic ductal adenocarcinoma and primary cholangiocarcinoma are morphologically very similar and therefore challenging to distinguish in liver biopsies. The distinction is important because surgical management and prognosis differ significantly. The traditional diagnostic approach employs immunohistochemical stains to exclude a metastatic carcinoma. Cholangiocarcinoma has been considered a diagnosis of exclusion, and extensive clinical and imaging work-up has been necessary before this diagnosis can be made.

We used tissue array from different types of liver cancer and performed the in-situ gene expression analysis with Xenium analyzer and Human Multi-Tissue and Cancer Gene Expression panel and Multiodal Cell Segmentation Kit, which enables the sub-cellular detection of 377 different gene transcripts. With the pathological annotation of just 9 different clusters, we could easily discriminate primary cholangiocarcinoma from metastatic pancreatic cancer biopsies. With further bioinformatic analysis, we selected 4 potential biomarkers that are specifically up-regulated in primary cholangiocarcinoma, but not in metastatic pancreatic cancer, and 4 potential biomarkers that are expressed in metastatic pancreatic cancer but not in primary cancers.

New tools enable faster discoveries of new biomarkers that could significantly improve liver cancer management and directly treat patients better.

***Topic**: Advances in cancer diagnosis*

Session: S5.05.O

GENES ASSOCIATED WITH HIGHER MUTATIONAL BURDEN IN TUMORS AND IMPROVED RESPONSE TO CHECKPOINT IMMUNOTHERAPY

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Cancer has long been associated with genetic defects in oncogenes and tumor suppressors. However, recent research has uncovered mutations in a broader range of genes whose roles in cancer are still being explored. In this study, we investigated a subset of these mutated genes across tens of thousands of genetic maps from various cancer types.

We analyzed genomic datasets from cBioPortal, including TCGA, MSK-MET, MSK-ICI, PCAWG, and OrigiMed, using WES, WGS, and panel sequencing. Statistical methods like Kruskal-Wallis tests, Cox proportional hazards models, Kaplan-Meier curves, and Pearson correlation were employed. Additionally, machine learning techniques were applied to explore complex relationships between gene mutation patterns, tumor mutational burden (TMB), and immune checkpoint inhibitor (ICI) response.

Our analysis revealed that a specific set of genes, identified through machine learning, is associated with high TMB. Mutations in multiple genes further increased TMB. We also found a strong link between these mutations and improved ICI responses, similar to those observed in cancers with deficiencies in canonical DNA repair pathways.

This study highlights a group of genes as potential predictive markers for TMB and ICI response. Their mutations were significantly associated with elevated TMB and better ICI outcomes across various cancers, offering insights into novel biomarkers and therapeutic strategies for cancer immunotherapy.

***Topic**: Advances in cancer diagnosis*

Session: S5.06.O

CLINICAL VERIFICATION OF PLASMA CELL IMMUNOSELECTION FOR FISH ANALYSIS IN MULTIPLE MYELOMA

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Purpose: Cytogenetics is crucial for predicting poor outcome in multiple myeloma (MM). The minimum set of three probes (17p, IGH, 1p/1q) should be used for FISH analysis, preferably with 1-2 additional probes (hyperdiploidy, MYC). Plasma cells (PC) should be isolated for FISH, as the infiltration rate does not allow the direct use of bone marrow (BM). Immunoselection is the most widely used method, but FISH is unsuccessful in at least one tenth of samples because no PCs are present. It remains questionable whether the lack of material is due to insufficient infiltration or insufficient isolation. To answer this question, we performed this retrospective analysis.

Methods: We analysed data from 1072 samples submitted for FISH MM between 2019 and 2024. PCs were isolated manually or automatically by immunoselection. Cytomorphology and flow cytometry (FC) results were also recorded and compared with the success of FISH and the number of probes used.

Results: With automated isolation, the proportion of successful FISH analyses increased by 13 % and the proportion of the wider probe set by 20 %. Successful FISH analysis correlated strongly with a confirmed diagnosis of MM by either cytomorphology or FC. FISH was successfully performed when the diagnosis of MM was confirmed, regardless of whether PC isolation was manual or automated. However, with automated immunoselection, FISH was performed on a greater proportion of samples and a greater amount of PC has been isolated, allowing a broader range of aberrations to be tested.

***Topic**: Advances in cancer diagnosis*

Session: S5.07.O

COMPUTATIONAL IDENTIFICATION OF POTENTIAL THERAPEUTIC AGENTS TARGETING THE *MUC16* GENE IN GLIOBLASTOMA

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Glioblastoma multiforme (GBM) is one of the most resistant malignancies of the central nervous system, marked by intratumoral heterogeneity, invasiveness, and resistance to conventional therapies. This study proposes a robust computational framework for the identification of candidate small-molecule inhibitors that target *MUC16* in glioblastoma (GBM). Transcriptomic datasets from The Cancer Genome Atlas (TCGA) were mined to identify frequently mutated genes associated with GBM. Co-expression and protein–protein interaction (PPI) network analyses using STRING and Cytoscape, identified key *MUC16*-associated oncogenic pathways. These findings support *MUC16* as a druggable target in GBM and offer a prioritized list of molecules for experimental validation, enhancing the potential for *MUC16*-targeted therapies in glioblastoma.

In silico screening tools were used to determine whether *MUC16* inhibitors might be useful in GBM therapy. Gene2drug assists in silico screening, ranking 609 compounds by their ability to dysregulate *MUC16*. PRISM viability assays on 68 cell lines analysed DepMap data for the antitumor activities of these drugs and their target gene. Candidate drug similarity was generated using DSEA, with compound rankings based on P values; only compounds with P < 1E–05 were relevant. Interaction with the *MUC16* gene was shown using Expression Public 24Q2, while Prism Reporposing Public evaluated in DepMap. Glioblastoma cell lines were sensitive to doxycycline (4.00E-5). We used SwissTargetPrediction to identify alternative targets for doxycycline, obtaining significant results with high probability scores. Integrating in silico insights with biological knowledge and conducting tissue-specific analyses with experimental biologists can enhance understanding.

***Topic**: Advances in cancer diagnosis*

Session: S5.08.O

IMMUNODEFICIENCY-CENTROMERIC INSTABILITY-FACIAL ANOMALIES (ICF) SYNDROME IN A LARGE EXOME DATASET: IDENTIFICATION OF NOVEL VARIANTS IN *DNMT3B*, *ZBTB24*, AND *CDCA7* GENES

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ICF syndrome is a very rare autosomal recessive disorder, with approximately 100 reported cases, characterized by immunodeficiency, centromeric instability, and facial anomalies. It is caused by pathogenic variants in *DNMT3B*, *ZBTB24*, *CDCA7*, and *HELLS*. This study aimed to characterize the clinical and genetic profiles of ICF patients evaluated at our center. In addition to previously diagnosed individuals, we reanalyzed 20,000 exome sequencing datasets to identify additional cases with biallelic variants in ICF-associated genes. Variants were classified using ACMG guidelines and ClinGen recommendations. For a subset of patients, cytogenetic analyses were performed to investigate ICF-specific chromosomal features. Biallelic variants in *DNMT3B*, *ZBTB24*, or *CDCA7* were detected in 10 individuals, totaling 11 variants. No variants were found in *HELLS*. Among these, six were novel: one splice-site, one nonsense, one frameshift, and one missense variant were classified as likely pathogenic. Centromeric instability was observed in two patients carrying VUS, supporting their potential pathogenicity. Clinical phenotypes were heterogeneous. Two additional novel missense variants were classified as variants of uncertain significance (VUS). This study expands the clinical and genetic spectrum of ICF syndrome and underscores the diagnostic utility of large-scale exome sequencing for detecting rare recessive conditions, even in the absence of a definitive clinical diagnosis.

***Topic**: Advances in cancer diagnosis*

Session: S6.05.O

FAMILIAL CASES SHOW HIGHER PREVALENCE OF RARE PREDICTED PATHOGENIC VARIANTS IN 56 NOVEL GENES ASSOCIATED WITH SPONTANEOUS PRETERM BIRTH

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Spontaneous preterm birth (sPTB) is a leading cause of neonatal morbidity and mortality, with evidence suggesting a heritable component, particularly through the maternal lineage. The aim of this study was to investigate whether genetic variants in the maternal genome contribute to the risk of sPTB. The study focussed particularly on rare predicted pathogenic variants (RPP), hypothesizing that they are more prevalent in familial cases of sPTB.

Whole-exome sequencing was performed on 188 participants (59 sporadic and 31 familial and sPTB cases, and 98 controls) to assess the distribution of RPP variants within a panel of candidate genes identified through systematic review and meta-analysis, as well as across the entire exome to discover novel genes. A genetic association study was subsequently conducted on 573 participants focusing on the candidate genes.

The analysis identified 56 novel candidate genes associated with sPTB. These novel genes were enriched for RPP variants in familial cases compared to sporadic ones (P=0.037). Among them, *PRUNE2* emerged as a strong candidate, with shared RPP variants identified in two unrelated families. Pathway analysis of the novel genes revealed significant enrichment in pyrimidine metabolism (Padj=0.002). Moreover, a common variant (rs2963463) in the EBF1 gene was significantly associated with a reduced risk of sPTB (Padj=0.03) in genetic association study.

The study confirmed a key role of maternal genomic variability in sPTB, particularly in familial cases, and identified 56 novel candidate genes.

***Topic**: Prenatal and preventive genomics*

Session: S6.06.O

PRELIMINARY SERUM METABOLOMICS ANALYSIS HIGHLIGHTING TRYPTOPHAN PATHWAY ALTERATIONS IN SPONTANEOUS PRETERM BIRTH

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The heterogeneous nature of spontaneous preterm birth (sPTB) suggests multiple underlying mechanisms, with emerging evidence pointing to disruptions in tryptophan–serotonin pathway, given serotonin's role in immune regulation and inflammation during pregnancy. This study aimed to determine whether serum metabolomic profiling could distinguish metabolic signatures in women with sPTB compared to full-term controls and to assess whether genetic variation in serotonin-related genes contributes to these differences.

Whole exome sequencing was performed on a cohort of 188 individuals, including 31 familial cases (defined by a positive personal and family history of sPTB), 59 sporadic cases (defined by a positive personal history of sPTB), and 98 controls (term birth). A burden analysis was conducted on 41 genes involved in serotonin metabolism. In addition, a cross-sectional analysis was carried out using serum samples from 10 participants—comprising 5 sPTB cases (2 sporadic and 3 familial) and 5 full-term controls. Serum metabolomics, both targeted and untargeted, were conducted using LC-MS/MS to identify metabolic differences between the group.

Metabolomic profiling revealed a significant reduction in serum serotonin levels in sPTB cases (p=0.024), with no changes in other tryptophan pathway metabolites, suggesting selective disruption in serotonin biosynthesis. Burden analysis showed no significant enrichment of rare variants in serotonin-related genes (combined: P=0.603; familial: P=0.409; sporadic: P=0.465), indicating a likely metabolic rather than genetic cause. Elevated phenylalanine (P=0.012), phenylethanolamine (p=0.015), and D-sphingosine (p=0.046) were also observed, pointing to broader metabolic shifts. These findings support a role for metabolic dysregulation in sPTB and highlight potential biomarkers for further investigation.

***Topic**: Prenatal and preventive genomics*

Session: S7.04.O

SPECTRUM OF GERMLINE *BRCA* PATHOGENIC VARIANTS IN OVARIAN CANCER PATIENTS FROM NORTH MACEDONIA

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Background: Genetic screening for *BRCA* mutations has significantly improved preventive strategies and enabled targeted therapies in women with ovarian cancer (OC). While the spectrum of germline *BRCA1/2* pathogenic variants (PVs) in breast cancer (BC) has been previously described in North Macedonia, data on PVs in OC remain limited.

Methods: We analyzed germline *BRCA1/2* variants using next-generation sequencing (NGS) in 125 patients with epithelial OC, enriched for early-onset disease and/or family history. The *BRCA* mutation profiles were compared between OC and BC patients.

Results: PVs were identified in 27 of 125 unrelated OC patients (21.6%). BRCA1 mutations predominated (74.1%), contrasting with BC patients, where *BRCA2* mutations were more frequent (55.9%). Among OC cases, eight distinct *BRCA1* PVs were detected; the most common was c.1102G>T (45%), followed by c.5266dupC (20%). This distribution differs from BC, where 18 different *BRCA1* PVs were identified with c.3700_3704del5 (23.3%) and c.181T>G (18.3%) being most prevalent. No recurrent *BRCA2* mutation was seen in OC; seven different PVs were identified in seven patients. In comparison, 33 distinct *BRCA2* PVs were found in BC patients, with c.7879A>T (17.6%) and c.8317_8330del14 (13.5%) being most frequent. Our previously designed SNapShot assay for 14 recurrent *BRCA* mutations among BC patients detects even higher percentage of OC (77.7%) than BC *BRCA* carriers (63.5%).

Conclusions: This is the first comprehensive analysis of *BRCA1/2* mutations in OC patients from North Macedonia. The findings support the use of a rapid, targeted first-step *BRCA* screening approach as a cost-effective strategy to identify carriers among epithelial OC patients.

***Topic**: Oncogenetics - the current state and challenges in the region*

Session: S7.05.O

GERMLINE SCREENING FOR HEREDITARY CANCER PREDISPOSITION IN THE BULGARIAN POPULATION: INSIGHTS FROM 2024

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Germline mutations in cancer predisposition genes play a critical role in oncogenesis and have direct implications for risk assessment, prevention, and clinical management. This study presents data from last year of germline testing in the Bulgarian population using next-generation sequencing (NGS) panels for Hereditary cancer. Three panels were applied amongst patients with different family histories. The first, targeting 26 genes associated with hereditary breast and ovarian cancer (HBOC), included 78 female patients; pathogenic or likely pathogenic (P/LP) variants were identified in 13 of them (16.7%), primarily in *BRCA1* and *CHEK2*. The second panel, comprising 85 genes related to multi-systemic oncological risk in women, included 93 patients, with 19 of them (20.4%) carrying P/LP variants, most frequently in *BRCA1* and *CFTR*. The third panel, designed for oncological risk in males (90 genes), was used in 25 patients; 11 of which (44%) harbored P/LP variants, predominantly in *NF1*, *MUTYH*, *BRCA1*, and *ATM*. These findings demonstrate a substantial diagnostic yield, particularly in the male cohort, and underscore the importance of NGS-based germline testing in identifying individuals shown with elevated hereditary cancer risk. Integration of such testing into routine oncological practice in Bulgaria may enhance early detection and prevention in risk patients, family screening and it is potential to improve clinical decision-making.

***Topic**: Oncogenetics - the current state and challenges in the region*

Session: S7.06.O

EXPLORING ATTITUDES TOWARDS NUTRITIONAL ADVICE AMONGST INDIVIDUALS AFFECTED BY LYNCH SYNDROME IN THE UK

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Purpose: Lynch Syndrome is an inherited condition associated with increased lifetime risks of colorectal, upper gastrointestinal, endometrial, ovarian, and prostate cancers. While diet and lifestyle recommendations exist to help reduce cancer risk, limited research explores how individuals with Lynch Syndrome receive and implement this advice. This study investigated opinions and attitudes towards nutritional guidance.

Method: Eighteen participants diagnosed with Lynch Syndrome were recruited via the Lynch Syndrome UK Facebook page. In-depth, semi-structured virtual interviews were conducted, and transcripts were analysed using thematic analysis.

Results: Two major themes emerged: Trust and Barriers. Subthemes under Trust included Frustration, Knowledge and Understanding, and Journey to Balance. Barriers included Finance, Time and Convenience, and Willpower. Participants expressed frustration over the lack of trustworthy, specialist nutritional guidance. There was a desire for more personalised support and education tailored to Lynch Syndrome, particularly for managing symptoms like early menopause following risk-reducing surgery. Dietary adherence was influenced by factors such as nutritional knowledge, perceived cancer risk, and quality of life.

Conclusion: This study highlights how trust in advice and personal barriers affect dietary adherence. Creating personalised, Lynch-specific nutritional resources may help individuals make sustainable changes to reduce cancer risk.

***Topic**: Oncogenetics - the current state and challenges in the region*

Session: S7.07.O

GENETIC FACTORS AND ACUTE KIDNEY INJURY: INFLUENCE ON CANCER TREATMENT STRATEGIES

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Background: Genetic variations in *BRCA1/2* and *HER2* overexpression play a fundamental role in determining cancer treatment strategies. The presence of acute kidney injury (AKI) complicates treatment selections, as many of these therapies are nephrotoxic. This study aims to explore how genetic factors and kidney impairment determine the selection of cancer treatment regimens, ultimately contributing to precision oncology.

Methods: In this retrospective cohort study, we evaluated 100 oncology patients (58 female, 42 male) treated at a tertiary care center. Among the female patients, 28 had breast or ovarian cancer, and 80% had a family history of malignancy, indicating the possibility of a *BRCA* mutation or hereditary cancer syndrome. All patients were assessed for drug regiments based on frequency, nephrotoxicity, and relevance to genetics status as well as the incidence of AKI, defined according to standard KDIGO criteria.

Results: AKI occurred 21% of all patients and 24% of females , most frequently with cisplatin- and bevacizumab-based treatment. Regimens with lower nephrotoxicity were more commonly used in patients with *BRCA1/2* and *HER2*-positive profiles. Olaparib was not used in this cohort possibly due to safety concerns or limited availability despite genetic indications.

Conclusion: This study highlights the clinical challenge of balancing integrated genetic therapy and kidney function assessment in the treatment of breast and ovarian cancer. Due to the occurrence of AKI, oncologic regimens were often modified, particularly in genetically predisposed patients. Further prospective studies are needed to evaluate kidney-adapted strategies, particularly in *BRCA*-mutant populations.

***Topic**: Oncogenetics - the current state and challenges in the region*

Session: S8.03.O

FACING UNCERTAINTY IN PRENATAL SCREENING: PERSONAL AND SOCIAL RESOURCES FOR PSYCHOLOGICAL RESILIENCE

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First-trimester aneuploidy screening is a standardized procedure in prenatal care in developed countries. While the majority of screenings yield negative results, approximately 5% to 10% of pregnancies are identified as screen-positive, indicating an increased risk for chromosomal abnormalities. These cases may require further prenatal diagnostics, which can ultimately confirm a genetic abnormality in the fetus. Although the technical aspects of aneuploidy screening are well established under the guidelines of the Fetal Medicine Foundation, less attention has been given to the psychological distress experienced by pregnant women during this process. Uncertainty surrounding the health of the fetus is a significant stressor that prompts various coping mechanisms and personal strategies aimed at maintaining well-being despite the circumstances. Since distress is often intensified in unpredictable and uncontrollable situations, where problem-solving strategies are not applicable, personal and social resources may serve a vital role in adaptation and copying efficiency. In our work we qualitatively explore the importance of personal and social resources that enhance the effectiveness of coping strategies when facing uncertainty in health-related contexts. We aim to create a basis for possible psychological interventions. This knowledge will facilitate genetic and psychological counseling in the clients of prenatal centers.

***Topic**: Prenatal and preventive genomics*

Session: S9.03.O

THE U-PGx PROJECT AND PREPARE STUDY IN SLOVENIA: LESSONS LEARNT ON IMPLEMENTATION OF PHARMACOGENOMICS TESTING

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The Ubiquitous Pharmacogenomics (U-PGx) project and the PREPARE study implemented pre-emptive, panel-based pharmacogenetic (PGx) testing across seven European countries, Slovenia included, to generate robust scientific evidence on the impact of PGx-guided therapy on patient outcomes.

The PREPARE study demonstrated that current genotyping technologies allow for rapid and reliable analysis of pharmacogenetic variants, with turnaround times sufficient to inform timely, evidence-based prescribing. A clinical decision support (CDS) system was successfully developed, but was not integrated into electronic health records (EHRs) in all participating countries due to the diversity in their health care IT infrastructures. In Slovenia, alternative solutions such as printed reports or portable PGx documentation (e.g., "safety code" cards or pharmacogenetic passports) provided effective solution for delivering PGx information. In Slovenia, in total 716 PGX reports have been delivered to the referring physicians and patients. In the study arm, 317 PGx reports were delivered with a median turnaround time 4.45 days from the sample collection. Approximately 95 % of the patients had at least one PGx variant linked to drug treatment recommendations reported, while 26.8 % of patients in the study arm and 29.3 % of patients in the control arm carried a PGx variant linked to recommendations for the treatment with the drug prescribed at inclusion (index drug).

The PREPARE study offered critical insights into the design, execution, and interpretation of future clinical implementation studies in pharmacogenomics. It identified key barriers to implementation in diverse healthcare settings, including Slovenia and provided enabling tools and solutions to support clinical implementation.

***Topic**: Advanced treatments for genetic disorders and cancer*

Session: S11.04.O

GENETIC RISK FACTORS FOR ANAPHYLAXIS: INSIGHTS FROM SOMATIC *KIT* P.D816V VARIANT AND HEREDITARY α-TRYPTASEMIA

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Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction, mostly triggered by food, drugs, or insect stings. While mast cells play a key role, the contribution of clonal mast cell-related disorders (cMCD), marked by activating somatic missense variant in the *KIT* gene, p.D816V (c.2447A>T), and hereditary α-tryptasemia (HαT), caused by increased α-tryptase–encoding *TPSAB1* copy number, to anaphylaxis caused by different triggers, is not fully understood.

1444 individuals with insect sting (*Hymenoptera* venom allergy, HVA) or drug-induced hypersensitivity and 183 controls with large local reactions (LLRs) or asymptomatic HV sensitisation, underwent examination for *KIT* p.D816V in peripheral blood leukocytes (PBL) using a highly sensitive qPCR and tryptase genotyping by droplet digital PCR.

KIT p.D816V was found in 21.6% of HVA cases, especially those with severe reactions (33.9% vs. 11% with milder symptoms; $p<0.0001$), but in only 1.3% of LLR and none with asymptomatic sensitization. Most *KIT*-positive patients had normal baseline tryptase (BST) (69%). HαT was the main cause of elevated BST and was associated with severe HVA (8.7%) and drug-induced anaphylaxis (14%), especially by antibiotics and biologics (24%). Concomitant HαT and *KIT* p.D816V conferred the highest risk for severe HVA (OR = 3.8; $p< 0.01$).

These findings highlight a high prevalence of cMCD and HαT in severe HVA and an important role of HαT in antibiotics- and biologics-induced anaphylaxis.

***Topic**: Genetics of complex diseases and functional genomics*

Session: S11.05.O

PEDIATRIC MULTIPLE SCLEROSIS CASES BURDENED WITH RARE, PREDICTED PATHOGENIC VARIANTS IN IRON METABOLISM GENES

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Multiple sclerosis (MS) is a multifactorial, immune-mediated demyelinating disease affecting the central nervous system (CNS). While most disease cases are adult-onset MS (AOMS), approximately 3-5% of cases have paediatric-onset MS (POMS). Recently, two iron-deficient POMS cases were reported with potentially causative variants in iron metabolism genes, suggesting a significant role of the iron metabolism genes and their variants in POMS. We hypothesized that rare, predicted pathogenic (RPP) variants iron metabolism-associated genes could represent a risk factor for POMS. For this purpose, we used whole exome sequencing data to investigate the proportion of individuals with RPP variants and conduct an RPP variant burden analysis in 27 iron metabolism-associated genes from the PanelApp England database in 46 POMS cases versus 3827 controls. We also assessed the role of RPP variants in an independent cohort of 215 AOMS cases. RPP variants were identified in 17.4% POMS cases (8/46), whereas 7.87% of controls (301/3827) and 7.9% of AOMS cases (17 of 215) carried RPP variants in genes associated with iron metabolism disorders. Our results showed that the proportion of individuals with RPP variants was significantly different between the POMS and control cohorts (p-value: 0.02697). Our results also showed that, compared to controls, three genes were significantly burdened with RPP variants in the POMS cohort - *CDAN1* (p-value: 5.63×10^{-10}), *HEPH* (p-value: 2.96×10^{-14}) and *STAB1* (p-value: 1.31×10^{-38}). Thus, the results show that POMS cases carry RPP variants in iron metabolism-associated genes more frequently than controls and AOMS cases, and that *CDAN1, HEPH* and *STAB1* could represent risk factors for POMS. The results of the present study suggest a possible role of rare variants in iron metabolism genes in MS aetiology.

***Topic**: Genetics of complex diseases and functional genomics*

Session: S11.06.O

LONG-READ SEQUENCING IN THE HUMAN GENOME'S REPETITIVE LANDSCAPE: CHALLENGES AND CLINICAL OPPORTUNITIES

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More than half of the human genome consists of repetitive sequences and regions with high homology. Although many of these are located in non-coding or structural regions, a subset of sequences with high homology includes genes and their pseudogenes. These regions are prone to homologous recombination and structural rearrangements, leading to deletions, insertions, gene conversions, and single-nucleotide variants (SNVs).

High sequence similarity in these loci makes accurate detection of pathogenic variants especially difficult. This issue is most acute in clinically relevant genes. PCR-based methods can improve the specificity of SNV detection but lack scalability and the ability to comprehensively detect structural variants. By contrast, targeted or genome-wide short-read sequencing technologies often fail to resolve these regions due to limited read lengths and ambiguous alignments, which can lead to miscalled or missed variants. Furthermore, bioinformatics pipelines must be tuned to separate true positives from artefactual calls in these homologous loci.

Long-read sequencing platforms, which generate reads spanning entire repetitive loci, offer a promising solution for accurate SNV and structural-variant detection and for resolving gene–pseudogene ambiguity. Our experience demonstrates their effectiveness in clinical diagnostics, particularly for genes with homologous sequences, such as *STRC* and *OTOA*, which are associated with hearing loss. As these technologies continue to evolve, they hold significant potential to enhance diagnostic precision and improve our understanding of genetic disorders associated with complex genomic regions.

***Topic**: Genetics of complex diseases and functional genomics*

Session: S11.07.O

IDENTIFYING PATTERNS OF DIFFERENTIAL METHYLATION IN MULTIPLE SCLEROSIS BY POSITIONAL INTEGRATION APPROACH AND THEIR FUNCTIONAL CHARACTERIZATION

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Purpose: In the past decade, several studies explored global methylation profiles in multiple sclerosis (MS), revealing differentially methylated regions (DMRs) with limited consensus. To identify convergent DMRs, we integrated resulting data with a position-based integration approach.

Methods: Systematic review identified eight methylome studies, reporting 19,982 significant DMRs. Using a rank sum method developed by our group, we assessed the results across studies. DMRs were mapped to genomic intervals of 10kbp. Significant DMR accumulation in each region was assessed via permutation test (N=1000) and bootstrapping (α=0.05). Significant coding and non-coding regions were annotated using gene ontology.

Results: We identified 172 significant regions ($p<0.05$): 2 regions with DMRs overlapping across four studies (*HLA-DRB1* region), 56 across three, and 114 across two. In non-coding regions, we detected DMRs in *TRAJ* cluster and lncRNAs linked to T-cell development and neuroinflammation. Hypomethylated DMRs near protein-coding genes were enriched in immune system regulation, vitamin D signalling, ion transport, and DNA expression regulation pathways. Hypermethylated DMRs are involved in immune and nervous system development, cell invasion, and ion transport.

Conclusion: By integrating methylation signals across multiple MS studies we identified consistent DMRs in coding and non-coding genomic regions, associated with T-cell function, immune system development, and ion transport.

***Topic**: Genetics of complex diseases and functional genomics*

Session: S11.08.O

CONNECTING THE DOTS: GENETICS, DIET, AND MICROBIOME IN ENDOMETRIOSIS (EM)

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Introduction: EM is a multifactorial disease, whose severity is shaped by diet and microbiome in a still unclear way. Regarding genetics, despite rare variants are emerging in complex disorders, their role in EM is unknown. Hence, we explored: 1) rare variants in EM, 2) diet and 3) gut microbiome's role in EM symptoms.

Methods: 146 EM cases were enrolled at IRCCS "Burlo Garofolo" (Italy), collecting clinical, genetic, and diet data.

1) WES prioritized rare predicted-damaging variants in 47 EM-genes to be tested with functional assays. Genotype-phenotype correlations were explored.

2) Regression models tested associations between diet and symptoms.

3) Rectal swabs from 50 cases underwent microbiome analyses; statistical models assessed associations with clinical data and symptoms.

Results: 1) WES detected 66 variants in 28 genes in 54 cases.

Variants in *SYNE1/SYNE2* genes, previously linked to severe EM pain, were found in 10 cases; 9/10 reported severe symptoms. Notably, endometrial cells from four carriers showed higher migratory capacity vs controls.

2) Protein-rich food was linked with lower dyspareunia severity ($p=0.03$), legumes with severe dysmenorrhea ($p=0.02$).

3) Fusobacteriota were enriched in EM-infertility, Prevotellaceae in dyspareunia, and Bacteroidota in dysmenorrhea cases.

Conclusions: This study details rare variants' role in EM and reveals links among symptoms, diet, and dysbiosis, offering insights into inflammatory mechanisms and highlighting possible therapeutic targets.

***Topic**: Genetics of complex diseases and functional genomics*

Session: S11.09.O

SEVERE CLINICAL PHENOTYPE IN ALPORT SYNDROME DUE TO TWO *COL4A4* EXON SKIPPING EVENTS

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Alport syndrome (AS) is a genetically heterogeneous disorder caused by mutations in *COL4A3*, *COL4A4*, or *COL4A5*, leading to progressive renal dysfunction. While genetic screening has advanced, many cases remain undiagnosed due to deep intronic splice site variants. We report a male patient diagnosed with autosomal recessive AS, characterized by hematuria, proteinuria, and chronic kidney disease progression. Initial kidney biopsy at age 10 revealed GBM thinning and focal sclerosis, while targeted DNA sequencing failed to detect pathogenic variants. Over 15 years, renal function declined, and a second biopsy showed severe glomerular basement membrane (GBM) abnormalities with multilamellated structures. Whole-transcriptome sequencing revealed two events of exon skipping, specifically at exons 27 and 38 of the *COL4A4* gene, which were verified by exon-specific PCR and Sanger sequencing. Evaluation of intronic regions revealed two heterozygous variants in non-canonical splice site regions of the skipped exons, though their role in aberrant splicing remains uncertain. Immunofluorescence analysis confirmed disrupted α3α4α5(IV) heterotrimer assembly. This is the first documented case of dual exon-skipping events in *COL4A4*, highlighting their contribution to disease severity. Our findings emphasize the need for RNA-based diagnostics to detect aberrant splicing events and raise questions about potential benefit of exon-skipping therapy in autosomal recessive AS.

***Topic**: Genetics of complex diseases and functional genomics*

Session: S12.02.O

GENETICS OF PORPHYRIA. EFFORTS TO ASSOCIATE SPECIFIC MUTATIONS WITH CLINICAL MANIFESTATIONS

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Porphyria refers to inborn errors of heme biosynthesis. This metabolic pathway requires eight enzymes and each them might be affected. This results in accumulation of porphyrins in different parts of the body. There are two major types of porphyria: acute porphyria affecting the nervous system and cutaneous porphyria affecting the skin. In addition, there are rare types of porphyria with mixed phenotype. Both autosomal dominant and autosomal recessive inheritance is possible. The symptoms include abdominal pain, polyneuropathy and psychological disturbances.

If the clinical diagnosis of porphyria is suspected, a panel of nine genes needs to be tested in the patient. This requires next generation sequencing and MLPA analysis for deletions/duplications detection.

Here we report 5 cases with different genetic variants in the genes *CPOX*, *PPOX* and *HMBS*. The first case is a 63 years old female diagnosed with muscular dystrophy and adrenal hyperplasia, who carries the variant *CPOX*:c.81G>C, p.Trp27Cys, classified as VUS. The second case is a child of 4 years with generalized developmental delay and VUS *PPOX*: c.987+5G>T. Furthermore, three females at the age 27, 45 and 28 have been clinically diagnosed with porphyria and all of them carry variants in the *HMBS* gene: c.499-15A>C (VUS); c.718_721dup; p.Pro241ArgfsTer11 (pathogenic) and c.-109C>T (VUS).

Genetic variants in heme biosynthesis pathway show different age of onset and clinical manifestation. The genetic diagnosis is crucial due to emerging therapeutic needs and the approaching RNA interference and gene replacement therapies, as well as enzyme replacement and chaperons administration treatments.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkans*

Session: S12.03.O

EXPANDING THE GENOTYPIC SPECTRUM OF EPIDERMOLYSIS BULLOSA: CASE SERIES

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Introduction: Epidermolysis bullosa (EB) is a rare group of inherited skin disorders characterized by blister formation following minimal trauma due to structural fragility at the dermoepidermal junction. EB is classified into four main subtypes: epidermolysis bullosa simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome. Each subtype is associated with mutations in specific genes encoding proteins involved in skin integrity.

Purpose: The aim of this study is to present the genetic analyses of 7 patients diagnosed with EB and to contribute to the understanding of genotype-phenotype correlations in EB.

Methods: Genomic DNA was isolated from peripheral blood samples .Next-generation sequencing (NGS) was performed using the Illumina NovaSeq platform with the SOPHiA™ Clinical Exome Solution (CES) V3 kits.

Results: 7 patients (four males, three females; aged 16–43 years) were included. Six distinct variants were identified: one large exonic deletion in *COL7A1*, and six single nucleotide variants. Two of the variants were novel: KRT5 c.556-2A>T, and *COL7A1* c.7523G>T p.(Gly2508Val). Four variants—*KRT14* c.612T>A p.(Tyr204*) and *COL7A1* c.6016G>A p.(Gly2006Ser) , *KRT5* c.499G>A p.(Glu167Lys), *ITGB4* c.1642G>A p.(Gly548Arg)—had previously been reported with EB in ClinVar Database.

Conclusion: This study contributes to the expanding genotypic spectrum of EB by identifying novel pathogenic variants in *KRT5* and *COL7A1*. These findings support the utility of comprehensive molecular testing in confirming EB subtypes and improving patient care through genotype-phenotype correlation and appropriate genetic counseling.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkans*

Session: S12.04.O

GENOTYPE-PHENOTYPE CORRELATION IN *TTN* GENE VARIANTS

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Objective: The TTN protein plays a key role in muscle tissue and both monoallelic and biallelic pathogenic variants in the *TTN* gene have been linked to diverse phenotypes.Despite the gene's large size, a clear genotype-phenotype correlation for *TTN*-related disorders remains unclear.This study retrospectively analysed patients with homozygous or compound heterozygous *TTN* variants to evaluate genotype-phenotype correlations in recessive cases.

Methods: Patients who underwent exome sequencing at our genetic centre were screened for biallelic *TTN* variants.The clinical significance of variants was assessed following ACMG criteria.The relationship between variant location, predicted effect and clinical severity was examined.

Results: Twenty patients with 26 biallelic *TTN* variants were identified: 10 missense, 8 splice-site, 4 nonsense, 3 frameshift and 1 deletion.Most variants were in the terminal region beyond exon 300, with fewer between exons 100 and 200. Loss-of-function variants near the terminal region were linked to childhood-onset phenotypes, while more proximal function-impairing variants were seen in prenatal onset cases.

Conclusion: Homozygous or compound heterozygous *TTN* variants strongly correlate with muscle disease phenotypes. Despite limited case numbers this study adds to the clinical understanding of *TTN* variants. Including heterozygous cases in future research may clarify genotype-phenotype relationships. Larger cohorts will further improve clinical interpretation.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkans*

Session: S12.05.O

CHALLENGES AND REWARDS IN DIAGNOSING DIAMOND-BLACKFAN ANAEMIA: A CASE SERIES FROM COOPERATING REGIONAL TERTIARY CARE CENTRES

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Background: Diamond-Blackfan anaemia (DBA) is an infrequent congenital bone marrow failure disorder characterised by erythroid hypoplasia, congenital anomalies, and an increased risk of hematologic and solid tumour malignancies. DBA is often challenging to diagnose due to a broad and variable phenotypic spectrum. The presentation ranges from mild cases diagnosed in adulthood to severe presentations with prenatal onset of nonimmune hydrops fetalis. We aimed to characterise a case series of DBA diagnosed at multiple tertiary centres, highlighting the diagnostic challenges and the role of genetic testing.

Methods: Three individuals with adult-onset DBA, aged 33, 41, and 55 years, four children DBA, aged 8, and 1 year (three pts), at the time of diagnosis, and one foetal case with generalised foetal hydrops, were included in the study. Clinical, haematological features, and treatment regimens were collected. Whole-exome sequencing was performed on DNA isolated from peripheral blood or foetal tissue samples, followed by investigation of genes associated with congenital anaemia.

Results: In adult DBA patients, two novel pathogenic loss-of-function (LoF) variants in the previously known DBA-associated gene *RPL11* and one novel strong variant of uncertain clinical significance (strong VUS) in the novel candidate gene *RPL23A* with the predicted splice donor loss were identified. In children, previously published pathogenic LoF variants in the genes *RPS26* and *RPS28* and a missense variant in *RPS29* were observed. In addition, one LoF variant in the known DBA-associated *RPL5* gene was not published before. A strong VUS, not previously reported, with the predicted splice acceptor loss in the *RPS19* gene was identified in the foetal tissue sample.

Conclusion: The availability of genetic testing and improved clinical recognition offer a means to establish a diagnosis and further enhance the

care of DBA patients. The novel identified variants in the previously known DBA-associated genes, and a novel DBA candidate gene (*RPL23A*) expand the list of DBA-associated variants and genes, respectively.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkans*

Session: S12.06.O

BODY MASS INDEX IS AN OVERLOOKED CONFOUNDING FACTOR IN CLUSTERING STUDIES OF 3D FACIAL SCANS OF CHILDREN WITH AUTISM SPECTRUM DISORDER

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Cluster analyzes of facial models of autistic patients aim to clarify whether it is possible to diagnose autism on the basis of facial features and further to stratify the autism spectrum disorder. We performed a cluster analysis of sets of 3D scans of ASD patients (116) and controls (157) using Euclidean and geodesic distances in order to recapitulate the published results on the Czech population. In the presented work, we show that the major factor determining the clustering structure and consequently also the correlation of resulting clusters with autism severity degree is body mass index corrected for age (BMIFA). After removing the BMIFA effect from the data in two independent ways, both the cluster structure and autism severity correlations disappeared. We also performed correlation analysis which showed that the only correction used in the existing clustering studies - dividing the facial distance by the average value within the face - is not eliminating correlation between facial distances and BMIFA within the facial cohort.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkans*

Session: S12.08.O

HEREDITARY MYOPATHIES IN 45 TURKISH PATIENTS: GENETIC SPECTRUM AND DIAGNOSTIC OUTCOMES

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Purpose: Hereditary myopathies are a heterogeneous group of conditions resulting from pathogenic variants in genes that encode proteins essential for maintaining muscle integrity and function. Diagnosis remains challenging, requiring multimodal approaches including clinical evaluation, electromyography (EMG), histopathology, and molecular genetic testing. This study presents a Turkish cohort of 45 patients with hereditary myopathies, emphasizing genetic diversity and diagnostic utility of advanced techniques.

Methods: We retrospectively analyzed patients (2020–2025) with muscle weakness, elevated CK levels, EMG abnormalities, and confirmed molecular diagnoses. Next-generation sequencing (NGS) panels targeting myopathy-related genes and multiplex ligation-dependent probe amplification (MLPA) for large deletions/duplications were employed. Variants were classified per ACMG guidelines.

Results: Among 45 patients (37 male, 8 female), pathogenic/likely pathogenic variants were identified in *SGCA*, *DYSF*, *DMD*, *RYR1*, *CAPN3*, and others. Key findings included: *DMD* hemizygous deletions (46%, 21/45), predominantly affecting exons 45–55. Recurrent variants: *SGCA* c.226C>T (p.Leu76Phe) in 3 familial cases and *DYSF* c.334C>T (p.Gln112Ter) in 2 unrelated patients. Additional pathogenic/likely pathogenic variants were identified in the *RYR*, *CAPN3*, and *COL6A1* genes.

Conclusion: Our cohort underscores the genetic heterogeneity of hereditary myopathies in Türkiye, with *DMD* deletions being the most prevalent. Combined NGS/MLPA proved essential for accurate diagnosis, enabling tailored management and genetic counseling. These findings highlight the need for population-specific studies to refine variant interpretation and improve diagnostic pipelines.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkan*

Session: S12.09.O

BIOMOLECULAR CHARACTERIZATION OF HEREDITARY TRANSTHYRETIN AMYLOIDOSIS IN BULGARIA

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Hereditary transthyretin amyloidosis (ATTRv) is an autosomal dominant genetic disorder caused by amyloidogenic pathogenic variants in the TTR gene. Clinical phenotypes vary from sensorimotor and autonomic neuropathy to cardiomyopathy.

The genetics of ATTRv in Bulgaria shows the presence of an endemic region for the Glu89Gln variant. However, the genetic diversity for ATTRv in the country is high, with eight pathogenic variants found so far. The clinical heterogeneity and age of onset require good biomarkers for early disease detection. The ubiquity of neurofilaments in axons explains the elevated release of neurofilaments light chain (NfL) following axonal damage. However, the accuracy of NfL has never been studied in detail in *TTR* mutation-specific cohorts.

Serum levels of NfL were measured five times over a 12-month period in 38 asymptomatic Glu89Gln carriers and 68 stage 1 polyneuropathy ATTRv Glu89Gln patients.

Proximity Extension Assay was used to run Olink Target 96 Neuro Exploratory protein biomarker panel in the tested cohort.

The results show statistically significant difference between the NfL levels in the two studied cohorts with higher mean level in the patient group. However, the overtime tracking of NfL levels do not show significant change over the period of one year. This could mean that longer period for testing is needed to ensure the accurate tracking of the disease progression.

ATTRv is highly prevalent in Bulgaria, which requires reliable diagnostics with practical applicability. The implementation of new reliable biomarkers for the prognosis and monitoring of ATTRv will enable more precise disease management and treatment evaluation.

***Topic**: Expanding the genotype-phenotype landscape of genetic disorders in the Balkans*

Poster presentations

Poster presentations list

October 10, 2025 (Friday - morning)			
09:30-10:30	P1 Arnold 2	Concurrent Poster viewing session – Cancer	P001-P010, P067 *(H. Butz, V. Šetrajčič Dragoš)*
	P2 Rosa	Concurrent Poster viewing session - Regional healthcare	P011-P016, P068, P070-P072 *(A. Marjanovic, A. Maver)*

P001 Špela Kert et al., Slovenia
Uncovering Immunogenic Gene Fusions in Glioblastoma for Personalized Immunotherapy

P002 Sandra Šućurović et al., Slovenia
Germline Mutations in Myeloid Malignancies in Slovenia

P003 Tjaša Korošec et al., Slovenia
Incidence of Multiple Malignancies in Patients with Triple-Negative Breast Cancer

P004 Gašper Klančar et al., Slovenia
Overview of Referral Diagnoses for Tumor Genotyping by Next-Generation Sequencing at the Institute of Oncology Ljubljana

P005 Borislav Crnojević et al., Serbia
Molecular and Cytogenetic Analyses of AML In Pediatric Patients in the Last Five Years- One Center Study

P006 Kiril Pakovski et al., North Macedonia
FGFR3 Expression and Tumour Size in Urothelial Carcinoma

P007 Perica Vasiljević et al., Serbia
Assessment of Complete Cytogenetic Response in Chronic Myeloid Leukemia Patients Treated with Tyrosine Kinase Inhibitors in Southern and Eastern Serbia

P008 Žiga Doljak et al., Slovenia
Association Between Genetic HIF1A Variants and the Efficacy of Cisplatin In Malignant Mesothelioma

P009 Špela Stangler Herodež et al., Slovenia
Xpert NPM1 Mutation Diagnostic Test Fort Monitoring of NPM1 mRNA Transcripts in Patients with Acute Myeloid Leukemia (AML)

P010 Bledi Kreka et al., Albania
ALK Positive Mutation in a Female Diagnosed with Pulmonary Adenocarcinoma

P067 Dimitar Ugrinovski et al., North Macedonia
Gene Variants in Urothelial Bladder Cancer Analyzed by Sequencing

P011 Helena Jakopič et al., Slovenija
Collaboration on Hereditary Angioedema with C1-Inhibitor Deficiency in South-Eastern Europe: Building a Regional Genetic Variant Landscape

P013 Sanja Ćirković et al., Serbia
Assessing Complex Paediatric Cases via Chromosomal Microarray and Multidisciplinary Team Collaboration

P015 Nataša Debeljak et al., Slovenia
Genetic Background of Hereditary Erythrocytosis in Slovenian Population

P016 Blerta Laze et al., Albania
Trends in Breast Cancer Incidence and Histopathologic Patterns in a Regional Hospital Center: "Implications for BRCA1/2 Genetic Screening"

P068 Marina Stratrova Tzimourakas et al., North Macedonia
Variants in the TP53 Gene in Patients with Urothelial Bladder Cancer Detected with Next-Generation Sequencing

P070 Ivana Grubiša et al., Serbia
Polygenic Risk Score and Genetic Markers in Alcohol-Related Cirrhosis

P071 Branka Zukić et al., Serbia
Pharmacogenomic Landscape of the Serbian Population

P072 Funda Kökali et al., Turkey
Humanitarian Genetics: Reflections From a Pediatric Geneticist in Kabul, Afghanistan

October 10, 2025 (Friday - afternoon)			
14:30-15:30	P03 Arnold 1	Concurrent Poster viewing session – Case reports and Series	P017-P026 *(A. Kovanda, K. Writzl)*
	P04 Arnold 2		P027-P035 *(J. Pajić, I. Babič Božović)*
	P05 Rosa		P038-P046 *(O. Antonova, F. Burada)*

P017 Emine Ikbal Atli et al., Turkey
Genetic Analysis of a Poirier–Bienvenu Neurodevelopmental Syndrome Caused by a De Novo Variant in CSNK2B

P018 Hakan Gürkan et al., Turkey
De-novo, Novel Likely Pathogenic Variant in SMC1A Gene in a Patient with Intellectual Disability and Seizures History

P019 Vida Živec, Slovenia
Case report: a hemizygous DMD:c.958c>t variant with splicing rescue and attenuated clinical presentation

P020 Elena Sukarova-Angelovska et al., North Macedonia
Phenotypic Spectrum in Patients with Copy Number Variations

P021 Júlia Martinková et al., Czech Republic
Duplication of the SOX3 Gene in an SRY-negative Boy with 46,XX Karyotype: a Case Report and a Literature Review

P022 Selma Kozarić et al., Bosna and Hercegovina
Prevalence of HLA-DQ2 and HLA-DQ8/DR4 Haplotypes and Their Association with Clinical Manifestations in Patients from Bosnia and Herzegovina

P023 Kristel Klaassen et al., Serbia
Mitochondrial Myopathy Caused by MT-ND5 Variant: Integrating WES and Mitochondrial DNA Analysis

P024 Deniz Kirac et al., Turkey
The Role of MTNR1A and MTNR1B Variations in Chronic Insomnia

P025 Treisi Goxhaj et al., Albania
Morbus Gaucher a Diagnostic Challenge

P026 Matevž Jus et al., Slovenia
Spectrum of NF1 Variants in a Patient Cohort from North-Eastern Slovenia

P027 Cekdar Kapazan et al., Turkey
A Multigenerational Nonsyndromic Hypopituitarism Family Associated with a Novel GLI2 Variant

P028 Korab Ukella et al., Kosovo
Frequency of ABCB1 C3435T and C1236T Polymorphisms in the Kosovo Population

P029 Ibrahim Kara et al., Turkey
Expanding the Clinical and Molecular Landscape of Pseudoxanthoma Elasticum with a Novel ABCC6 Variant

P030 Zornitsa Pavlova et al., Bulgaria
Differential Diagnostic Obstacles for Harel-Yoon Syndrome

P031 Ranka Rolović Nešković et al., Montenegro
A Case Report of a Patient with Neurodevelopmental Disorder with Hypotonia, Stereotypic Hand Movements, and Impaired Language – a Novel Variant in MEF2C Gene

P032 Vedat Yuce et al., Turkey
X-Linked Legacy: Multigenerational Expression of Aarskog-Scott Syndrome in a Single Family

P033 Beyza Karaca Doğan et al., Turkey
Rare Double Strike in Hypothalamic Signaling: A Case of Severe Pediatric Obesity Explained by MC3R and NMUR2 Variants

P034 Ivana Škrlec et al., Croatia
MTNR1B Polymorphisms and Circadian Phenotypes in Hashimoto's Disease

P035 Sahra Acir et al., Turkey
The Fifth Known Case of SASH3-Associated Immunodeficiency: Novel Variant and Severe Inflammatory Phenotype

P038 Engin Atli et al., Turkey
A Case Series on Suspected Bainbridge-Ropers Syndrome with a Two Novel Variation in ASXL3 Gene

P040 Sara Veleska et al., North Macedonia
A Case of Pallister-Killian Syndrome in a Newborn

P041 Şevval Yurt et al., Turkey
De Novo Ring Chromosome 20 in a Male Infant with Suspected Epilepsy

P042 Onur Hanoğlu et al., Turkey
Two Cases of Rare Pycnodysostosis Syndrome with CTSK Missense Variants

P043 Freshta Jurat et al., Turkey
Schuurs-Hoeijmakers Syndrome: Expanding the Phenotype of a Rare Disorder with a Recurrent PACS1 Variant

P044 Lenka Stojadinović et al., Serbia
Clinical Exome Sequencing Identifies Pathogenic SQSTM1 Variant in a Patient with Chorea and Gaze Palsy

P045 Milka Grk et al., Serbia
Analysis of the Association Between Collagen Gene Polymorphisms and Clinical Manifestations of Systemic Lupus Erythematosus

P046 Martina Mia Mitić et al., Serbia
Unravelling the Cause of Recurrent Venous Thrombosis in a Dabigatran-Treated Patient

October 11, 2025 (Saturday)			
10:20-11:20	P06 Arnold 1	Concurrent Poster viewing session – complex and functional genomics	P047-P056 *(L. Odak, A. Kovanda)*
	P07 Arnold 2	Concurrent Poster viewing session – diagnostics	P058-P066, P069 *(T. Pajič, M. Rijavec)*

P047 Nina Stevanović et al., Serbia
Pulmonary In Vitro Model System Enables Exploration of Innovative Treatment Strategies for Rare Respiratory Diseases

P048 Marina Parezanović et al., Serbia
Establishing In Vitro Models for Glycogen Storage Disease Type Ib: A Platform for Therapeutic Investigations

P049 Aleša Kristan et al., Slovenia
Functional Analysis of Novel EGLN1 and EPAS1 Variants in Hereditary Erythrocytosis

P050 Vesna Spasovski et al., Serbia
Establishment of an In Vitro Insulin Resistance Model in HepG2 Cells Through Glucose and Insulin Co-treatment

P051 Jadranka Vraneković et al., Croatia
Methylation Levels and Genetic Variants of MTHFR Gene Are Not Risk Factors for Congenital Heart Defect in Down Syndrome

P052 Ina Marku et al., Albania
Molecular Diagnosis of Sexually Transmitted Infections Related to Infertility: The Efficiency of Multiplex PCR Panels

P053 Aysegul Sahbaz et al., Turkey
Effects of HLA-DRA, HLA-DQA1, and IL-6 Gene Variations to Multiple Sclerosis

P054 Ina Marku et al., Albania
The Importance of HPV Genotyping in Albania: a First-of-its-kind Study at GeniusLab

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Session: P001

UNCOVERING IMMUNOGENIC GENE FUSIONS IN GLIOBLASTOMA FOR PERSONALIZED IMMUNOTHERAPY

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Gene fusions can create chimeric proteins with strong tumour specificity and high immunogenic potential. Although they are usually not driver mutations in glioblastoma, they can serve as a valuable source of neoantigens as they are described as more immunogenic than somatic mutations. Our aim was to investigate gene fusions in glioblastomas as potential neoantigen sources for personalized cancer vaccines. RNA sequencing was performed on 79 FFPE glioblastoma tissue samples. Fusion events were identified using STAR-Fusion, Arriba and FusionCatcher. We considered only fusions that were detected by at least two tools, supported by ≥ five junction reads, and showed protein-coding potential. Immunogenic potential was predicted with pVACfuse based on patient-specific *HLA* profiles obtained with OptiType. Peptides with a predicted IC50 < 500 nM were classified as immunogenic. Gene fusions were detected in 29 of 79 samples, with multiple fusions detected in eight cases. A total of 47 fusions were identified, of which 16, were predicted to generate immunogenic peptides. Notably, the fusions were diverse and non-recurrent, highlighting their patient-specific nature. Our findings suggest that gene fusions are present in a considerable fraction of glioblastoma cases and may lead to immunogenic neoantigens. These fusion-derived neoantigens could support the development of individualized vaccine strategies and expand the therapeutic landscape for glioblastoma.

***Session topic**: Cancer*

Session: P002

GERMLINE MUTATIONS IN MYELOID MALIGNANCIES IN SLOVENIA

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Germline mutations in genes associated with myeloid malignancies are increasingly recognized as significant contributors to disease pathogenesis and clinical course, especially in acute myeloid leukemia (AML). Identifying hereditary predispositions has important implications for patient management, particularly when evaluating candidates for allogeneic hematopoietic cell transplantation (HCT), where related donors may carry the same mutations.

Method: In a cohort of 1,020 patients with myeloid malignancies, over the last six years next-generation sequencing (NGS) was performed. DNA was extracted from mononuclear cells obtained from bone marrow or peripheral blood and analyzed using a targeted NGS approach. An amplicon-based panel (Archer, IDT) was employed, covering 37 genes, including *CEBPA*, *RUNX1*, *GATA2*, and *DDX41*, all of which are associated with hereditary hematologic malignancies. Variant annotation and classification followed the ACMG guidelines.

Results: We identified pathogenic or likely pathogenic germline variants in the above-mentioned genes. With the exception of *GATA2*, most of them were found in patients with AML: *CEBPA* (5/5), *RUNX1* (5/6), *GATA2* (1/8), and *DDX41* (4/6). These germline variants were confirmed either during remission or in related family members who were potential donors for allogeneic HCT. Several germline variants of uncertain significance (VUS) were also detected in the aforementioned genes. In two families with *CEBPA* and *RUNX1* mutations, the disease was confirmed in several members.

Conclusion: Patients harboring germline mutations tended to present at a younger age and often reported a family history of hematologic malignancies. These findings underscore the importance of genetic screening in myeloid malignancies, not only for accurate diagnosis and prognosis but also for appropriate familial counseling and donor selection.

***Session topic**: Cancer*

Session: P003

INCIDENCE OF MULTIPLE MALIGNANCIES IN PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER

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Background: Breast cancer (BC) survivors have a 3.6% lifetime risk of developing a second malignancy. Triple-negative BC (TNBC) is frequently associated with germline BRCA and other homologous recombination (HR) gene mutations, potentially increasing this risk.

Aim: To determine the incidence and types of additional malignancies in TNBC patients and explore associations with germline mutations in HR-related genes.

Methods: We retrospectively analyzed 301 female TNBC patients diagnosed between April 1995 and May 2018 at the Institute of Oncology, Ljubljana.

Results: Sixty-four patients (21%) developed at least one additional malignancy; six (2%) had two, and one had three. The most frequent second malignancy was BC (29/64; 45%), followed by gynecological cancers (13/64; 20%). Other malignancies included skin, gastrointestinal, lung, and urological cancers, and lymphomas. Among 58 patients with genetic data, 34 (58.6%) had *BRCA* mutations and 6 (10.3%) had mutations in other HR genes. We found no significant correlation between the presence of germline mutations in genes involved in HR and the occurrence of multiple malignancies in patients with TNBC (Hi-square 0.0, p 1.0).

Conclusion: TNBC patients exhibit a high incidence of multiple primary malignancies, regardless of HR gene mutation status. Vigilant long-term surveillance, preventive measures, and comprehensive genetic evaluation are essential for early detection and improved outcomes in this high-risk group.

***Session topic**: Cancer*

Session: P004

OVERVIEW OF REFERRAL DIAGNOSES FOR TUMOR GENOTYPING BY NEXT-GENERATION SEQUENCING AT THE INSTITUTE OF ONCOLOGY LJUBLJANA

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Introduction: Tumor tissue testing provides valuable insights into disease diagnosis, prognosis, treatment response, and supports the implementation of personalized medicine. Therefore, incorporating such testing into diagnostic workflows is essential for optimal patient care. The aim of this study was to provide an overview of referral diagnoses for tumor genotyping using next-generation sequencing (NGS).

Methods: We analyzed 3,089 tumor samples referred to our laboratory for NGS-based genotyping between 2022 and 2024, with a focus on referral diagnoses and descriptive statistical evaluation.

Results: The most common referral diagnoses were colorectal cancer (769; 24.9%), ovarian cancer (472; 15.3%), and prostate cancer (408; 13.2%). Other frequent referrals included melanoma (303; 9.8%), endometrial cancer (205; 6.6%), and sarcomas (190; 6.2%). Breast (110; 3.6%), urothelial (86; 2.8%), and lung cancers (83; 2.7%) were also represented. Less frequent referrals included cholangiocarcinoma, tumors of unknown origin, gastrointestinal stromal tumors and gastric cancer, pancreatic and thyroid cancers, lymphomas, suspected hereditary cancer syndromes, and renal cancer. Variants with strong clinical significance were identified in over one-third of the cases.

Conclusion: These results demonstrate the broad range of clinical indications for tumor genotyping in routine diagnostics, highlighting its relevance across both common and rare tumor types.

***Session topic**: Cancer*

Session: P005

MOLECULAR AND CYTOGENETIC ANALYSES OF AML IN PEDIATRIC PATIENTS IN THE LAST FIVE YEARS - ONE CENTER STUDY

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Acute myeloid leukemia (AML) represents 20% of pediatric acute leukemia. At diagnosis, karyotype associated with FISH and molecular analyses were performed to enable prognosis and risk stratification.

The study aimed to present cytogenetic, FISH and molecular analysis results in patients with AML diagnosis in last 5 years.

From January 2019 to December 2024 bone marrow samples of 23 AML pediatric patients were analyzed in the Laboratory of Medical Genetics. In all samples simultaneously karyotype and RT-PCR assay for AML recurrent fusion transcripts t(15,17), t(8;21), inv(16) were used. Some patients were analyzed for *FLT3-ITD* and also using FISH for *MLL* rearrangements.

5 patients were positive for t(15,17) fusion, 1 for t(8,21) and 3 for inv(16). 3 patients were positive for *FLT3-ITD*. 9 karyotypes were normal and 14 were aberrant. List of aberrant karyotypes: 45,XX,der(1)t(1;1)(p36;q11),add(9)(p?1),-15,
46,XY,t(11;15)(p15;q11.2)c,
47,XY,add(5)(p15),inv9(p12q13)c+21,
46,XY,add(8)(q24),-16+mar,inc.,
87-92hr/46,XX,
46,XY,t(10;11)(12;q23),
47,XY,+8,-15,+mar1/48,XY,+8,-15,+mar1,+mar2/46,XY,
46,XX,t(15;17)(q24;q21),
46,XX,t(5;9)(q13;q34)/46,XX,
46,XX,t(9;11)(p21;q23),
47,XX,t(1;7)(p34;q36),del(12)(p13)+19,46,XY,del(5)(q?),
46,XX,inv(9)(p12q13)c,add(21)(q22),inc.,
46,XX,t(6;9)(p22;q34)/46,XX.

Three patients were positive for the *MLL* rearrangement and 2 of them had *MLL-MLLT3* fusion.

Combining all methods above allows better risk stratification and adequate treatment of the disease.

***Session topic**: Cancer*

Session: P006

FGFR3 EXPRESSION AND TUMOUR SIZE IN UROTHELIAL CARCINOMA

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Fibroblast growth factor receptor 3 (FGFR3) is implicated in the development and progression of various malignant neoplasms, including urothelial carcinoma (UC). This research aimed to analyse *FGFR3* gene expression in patients with histologically confirmed UC. A total of 80 fresh-frozen tissue samples were used in the study. Total RNA was extracted from each sample, and quantitative real-time PCR was used to assess *FGFR3* expression levels.

The analysis revealed a statistically significant correlation between elevated *FGFR3* gene expression and smaller tumour size, specifically tumours measuring less than 3 cm in diameter ($p = 0.0013$). This inverse relationship indicates that higher *FGFR3* expression is linked to a less aggressive tumour phenotype, characterised by reduced invasiveness and smaller dimensions.

These findings reinforce the role of FGFR3 as an important prognostic biomarker in UC, associated with more favourable clinical features. Elevated *FGFR3* expression appears to predict lower tumour invasiveness, reduced aggressiveness and, as shown here, smaller tumour size at diagnosis. Consequently, *FGFR3* expression profiling may help stratify patients according to clinical risk and support clinicians in tailoring more precise therapeutic and follow-up strategies.

***Session topic**: Cancer*

Session: P007

ASSESSMENT OF COMPLETE CYTOGENETIC RESPONSE IN CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH TYROSINE KINASE INHIBITORS IN SOUTHERN AND EASTERN SERBIA

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm primarily characterized by a distinct cytogenetic abnormality, the Philadelphia chromosome (Ph). The resulting *BCR-ABL1* fusion gene encodes a constitutively active tyrosine kinase. Tyrosine kinase inhibitors (TKIs) have significantly improved the clinical outcomes of CML patients; however, these are suboptimal in low socioeconomic countries. This study aimed to evaluate the effectiveness of TKIs in achieving complete cytogenetic response in CML patients, with a specific focus on gender and age in Southern and Eastern Serbia. Bone marrow aspirates from 69 patients with confirmed CML, treated with TKIs and referred to the University Clinical Center Niš between 2020 and 2023, were cytogenetically evaluated for the presence of the Ph. The cohort consisted of 55.62% female and 44.38% male patients. The frequency of CML diagnosis correlated positively with age: 8.7% of patients were younger than 44, 36.2% were 44 - 65, and 55.1% were older than 65 years. A major cytogenetic response, defined as the absence of the Ph chromosome, was achieved in 47.62% of patients after 12 months of TKI therapy. Therapy-resistant women were mostly middle-aged, whereas resistant men were primarily from the older age group. Our findings align with studies conducted in other geographic regions. Nevertheless, further investigations are necessary to ascertain whether meaningful differences in clinical outcomes exist within this population.

***Session topic**: Cancer*

Session: P008

ASSOCIATION BETWEEN GENETIC *HIF1A* VARIANTS AND THE EFFICACY OF CISPLATIN IN MALIGNANT MESOTHELIOMA

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Background: Malignant mesothelioma (MM) is a rare, aggressive malignancy of the pleura and peritoneum most commonly associated with asbestos exposure. Despite multimodal therapeutic approaches, the prognosis remains poor, mainly due to the late diagnosis and limited chemosensitivity of the tumour. Standard first-line chemotherapy usually includes cisplatin in combination with pemetrexed or gemcitabine. Chemosensitivity of mesothelioma cell spheroids was shown to be influenced by their ability to survive under hypoxic conditions. Hypoxia increases the level of hypoxia-inducible factor 1A (HIF-1A), which may promote the resistance to cisplatin-based therapies. The aim of this study was to investigate the association between *HIF1A* gene polymorphisms and response to chemotherapy in Slovenian patients with MM.

Methods: This retrospective study included 234 patients with histologically confirmed MM treated with cisplatin/pemetrexed or cisplatin/gemcitabine doublet chemotherapy at the Institute of Oncology in Ljubljana. Three *HIF1A* polymorphisms (rs11549465, rs11549467 and rs2057482) were genotyped by competitive allele-specific PCR. The association between these genetic variants and response to chemotherapy, progression-free survival (PFS) and overall survival (OS) was investigated using logistic regression, non-parametric tests and the Cox proportional hazards model.

Results: No significant association was found between the *HIF1A* rs11549467 and rs2057482 and the response to cisplatin-based treatment. However, carriers of the rs11549465 CT genotype showed a modest but statistically significant reduction in response to chemotherapy after adjustment for weight loss and C-reactive protein (CRP) ($p = 0.044$).

Conclusions: Among the investigated *HIF1A* polymorphisms, only rs11549465 showed a modest effect on the response to cisplatin-based chemotherapy in MM.

***Session topic**: Cancer*

Session: P009

XPERT NPM1 MUTATION DIAGNOSTIC TEST FORT MONITORING OF *NPM1* MRNA TRANSCRIPTS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

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Purpose: Acute Myeloid Leukemia (AML) represents about 80% of acute leukemia in adults and is known to have various *NPM1* exon 12 mutations. Guidelines for treating AML patients include the evaluation of molecular response (MR) based on determination of *NPM1* in defined time points. The aim of this study was to introduce the Xpert cartridge-based *NPM1* mutation detection into routine molecular monitoring of AML Slovenian patients from north-eastern region.

Method: Xpert NPM1 Mutation Assay (Cepheid, USA) is an automated test for quantifying the amount of mutant *NPM1* mRNA transcripts (type A, B and D) in exon 12 as the percent ratio of *NPM1* Mutation/*ABL1* with high sensitivity using real-time PCR and nested PCR in one automated cartridge.

Results: In the first year of Xpert NPM1 Mutation Assay use, we tested 17 blood samples. Six of them were positive in the dynamic range between 500% to 0,030% *NPM1* mutation/*ABL*, two samples were positive with clinically demonstrated limit of detection (LoD) of 0.030% and the remaining nine were negative.

Conclusion: From clinical aspect, Xpert NPM1 Mutation Assay can be considered as a useful and very fast clinical tool for the molecular follow up of AML patients which allows the early prediction of a relapse to be quickly identified and monitor the treatment and care effectiveness. The MR results obtained with Xpert NPM1 Mutation Assay are available in just three hours following sample reception, which is the main advantage of this method.

***Session topic**: Cancer*

Session: P010

ALK POSITIVE MUTATION IN A FEMALE DIAGNOSED WITH PULMONARY ADENOCARCINOMA

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Background: The combination of immunohistochemistry markers can be used to differentiate between various chest tumors Genetic profiling of Lung cancer is an essential part of treatment

ALK is a rare mutation which stands for anaplastic lymphoma kinase Most ALK-positive cancers are in non-small cell lung cancer (NSCLC).and have a good responsiveness to Alk inhibitor treatment

Methods: A 65 year old female patient. She complained of pain in left hemithorax. She was nonsmoker and had no comorbidities . Chest CT Scan showed a left heterogenous malignant pleural thickening. Trans parietal biopsy and immunochemistry examination was done.

The first result in Immunohistochemistry showed: TTF-1 (-), CK 5/6 (-), WT -1(-) CK 20(-)

A(+), Napsin (+). This suggested that the patient may have carcinomatous metastasis form a gastro intestinal cancer, but colonoscopy did not find any pathologic changes.

The second Immunochemistry report showed: TTF -1 (+), CK 7 (+), CD 19(+), CD X2 ¬? This suggested pulmonary adenocarcinoma after which a genetic testing of tumor was ordered resulting ALK positive.

Results: PET-CT revealed a nodus in left lung with FDG pathological uptake, and pathologic lymph nodes in abdomen.Treatment with an ALK inhibitor Alectinib was recommended . She continued the treatment and regular clinical and imaging evaluation of disease status showed a very good response to treatment. There were no changes in PET-CT (only atelectasis and fibrosis). After 5 years she is still under treatment with Alectinib.

Conclusions: The identification of an ALK-positive mutation in this case highlights the critical role of molecular profiling in diagnosis and personalized treatment of pulmonary adenocarcinoma. Targeted therapy offers promising outcomes, underscoring the need for routine genetic testing in lung cancer patients , offering them optimal therapeutic strategies and improved prognosis,

***Session topic**: Cancer*

Session: P011

COLLABORATION ON HEREDITARY ANGIOEDEMA WITH C1-INHIBITOR DEFICIENCY IN SOUTH-EASTERN EUROPE: BUILDING A REGIONAL GENETIC VARIANT LANDSCAPE

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Hereditary angioedema (HAE) is a rare, autosomal dominant disorder marked by recurrent episodes of angioedema affecting the skin, gastrointestinal tract, and airways. Most cases are due to deficiency or dysfunction of C1 esterase inhibitor (C1INH), encoded by the *SERPING1* gene. In recent years, several South-Eastern European countries have collaborated to better understand the genetic basis of HAE-C1INH in the region.

This study analysed clinical and molecular data from 169 patients with confirmed HAE-C1INH from Bosnia and Herzegovina (n=7), Croatia (n=64), Serbia (n=58), Slovenia (n=25), and North Macedonia (n=15). The objective was to identify shared and country-specific *SERPING1* variants and explore potential founder effects.

Genetic testing was performed at the University Clinic Golnik, where a comprehensive genetic analysis of 169 clinically well-characterised HAE-C1-INH patients from 88 unrelated families was conducted. This included Sanger and next-generation sequencing of the *SERPING1* gene, along with MLPA to identify copy number variations.

Most patients had HAE-C1INH type I (n=149), while a smaller subset had type II (n=20). Across all countries, 57 known pathogenic or likely pathogenic variants were identified. Notably, twelve novel variants were discovered, including one region-specific frameshift mutation in Croatia (c.74_75delAT in exon 3, p.(Asn25SerfsTer32)). This variant was found in four families (18 patients in total).

This is the most extensive genetic study of HAE-C1INH in the South-Eastern European countries, providing a foundation for improved diagnostics and research.

***Session topic**: Regional healthcare*

Session: P013

ASSESSING COMPLEX PAEDIATRIC CASES VIA CHROMOSOMAL MICROARRAY AND MULTIDISCIPLINARY TEAM COLLABORATION

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Chromosomal microarray (CMA) is a cornerstone of genomic medicine, detecting structural copy number variants (CNVs) that underlie rare genetic disorders. Interpreting CMA findings can be challenging, particularly when two or more pathogenic CNVs are identified or when variants smaller than 200 kb—typically excluded from routine reporting—are detected.

This study explores the clinical relevance of such CNVs in three patients with unexplained developmental/intellectual delay (DD/ID), dysmorphic features, and other anomalies, evaluated at the Mother and Child Health Care Institute of Serbia "Dr Vukan Cupic" from June to November 2024. CMA was performed on DNA samples using the high-resolution Agilent SurePrint G3 Human CGH 4x180k kit at the Laboratory of Medical Genetics.

Notable cases include Patient 1, with two pathogenic variants: a 185 kb complex gain at Xq28 and a 546 kb gain at 16p11.2, correlating with overlapping features of K/L-mediated Xq28 duplication syndrome and 16p11.2 microduplication syndrome. Patient 2 exhibited a likely pathogenic 67 kb loss at 2p16.3, associated with NRXN1-complex neurodevelopmental disorder, alongside a 602 kb gain at Xp22.31 of uncertain significance, challenging standard diagnostic criteria. Patient 3, the youngest, presented with DD and a likely pathogenic 161 kb gain at 2q33.1, corresponding to SATB2-associated syndrome.

Our work highlights the diagnostic power of CMA in identifying concurrent structural variants and underscores the need for detailed phenotypic assessment in clinical dysmorphology. These cases demonstrate the value of a multidisciplinary approach in interpreting complex genomic findings, offering critical insights for genetic counselling and personalised care.

***Session topic**: Regional healthcare*

Session: P015

GENETIC BACKGROUND OF HEREDITARY ERYTHROCYTOSIS IN SLOVENIAN POPULATION

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Purpose: Hereditary erythrocytosis (ECYT) is a rare haematological genetic disorder characterised by an increased red blood cells mass that can lead to thrombotic complications. The purpose of the study was to identify clinically important rare genetic variants in a national cohort of erythrocytosis patients.

Methods: A three-step diagnostic algorithm for non-clonal erythrocytosis was developed to screen patients with idiopathic erythrocytosis. Patients were referred for genetic testing using targeted NGS with genes related to erythropoiesis or iron metabolism. Genetic variants were addresses by various functional tests.

Summary of results: National screening identified 65 patients, including two families. Genetic testing identified a known pathogenic *EPAS1* variant in one patient and several variants of unknown significance (VUS) in 6 patients, including one family (Table 1). In silico structural analysis showed localisation of *EGLN1* and *EPAS1* VUS in domains effecting protein function. *In vitro* functional tests confirmed effect on protein level, however further analysis are needed confirm their contribution to the ECYT development.

Conclusion: The genetic cause of erythrocytosis is suggested in 7 out of 65 patients. The low diagnosis rate suggests that additional genes contribute to the development of the disease.

Table 1: Rare variants identified in Slovenian patients (N) with erythrocytosis

Gene	DNA change	Protein change	N	Classification (ACMG/AMP)
EPAS1	c.1609G>A	p.(Gly537Arg)	1	Pathogenic, ECYT4
EGLN1	c.1124A>G	p.(Glu375Gly)	1	VUS
EGLN1	c.1072C>T	p.(Pro358Ser)	2	VUS
EPAS1	c.2120A>C	p.(Lys707Thr)	1	VUS
JAK2	c.1767C>A	p.(Asn589Lys)	1	VUS
SH2B3	c.901G>A	p.(Glu301Lys)	1	VUS

***Session topic**: Regional healthcare*

Session: P016

TRENDS IN BREAST CANCER INCIDENCE AND HISTOPATHOLOGIC PATTERNS IN A REGIONAL HOSPITAL CENTER: "IMPLICATIONS FOR *BRCA1/2* GENETIC SCREENING"

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Background: Based on a large number of studies, *BRCA 1* and *BRCA 2* are two tumour suppressor genes considered polymorphic with approximately 70.000 variants, causing an increased risk in breast and ovaries cancer. The Regional Hospital in Fier city was identified with the highest breast cancer incidence in Albania between 2015 and 2019.

Aim of the Study: This study aims to analyze trends in breast cancer incidence and histopathologic patterns, and to assess the implications for *BRCA1/2* genetic screening, with particular attention to identifying familial cancer risk.

Methodology: Data is collected from the medical records of the Oncology Department of Regional Hospital in Fier city, for 75 women diagnosed with breast cancer between 2022 and 2024.

Results: The majority of breast cancer cases occurred in women over 45 years old (94.7%), with a high prevalence of hormone receptor positivity, particularly ER+ in 69.3 %, PR+ in 65.4 %, Her2+ in 8 % of patients. TN and non-TN breast cancer were identified respectively in 4% and in 66.7% of patients. Infiltrating ductal carcinoma was the most common subtype, observed in 81.3% of patients, while invasive metaplastic carcinoma, a rare and aggressive form, was diagnosed in 1.3% of patients, 14.4% (11/75) subjects were identified with a family history of cancer.

Conclusion: The presence of a family history of cancer in 14.4% of cases highlights the potential role of hereditary factors and supports the consideration of genetic counseling and testing, especially for patients with a strong familial background.

***Session topic**: Regional healthcare*

Session: P017

GENETIC ANALYSIS OF A POIRIER–BIENVENU NEURODEVELOPMENTAL SYNDROME CAUSED BY A *DE NOVO* VARIANT IN *CSNK2B*

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A heterozygous mutation of *CSNK2B* (OMIM*115441) causes Poirier–Bienvenu neurodevelopmental syndrome (POBINDS, OMIM #618732), a rare autosomal dominant neurologic illness that was initially described by Poirier et al. (2017). The 7 exons of *CSNK2B*, which has a genomic size of 3988 bp and codes for 215 amino acids, are found at 6p21.33. It is interesting to note that *CSNK2B* encodes a regulatory subunit (β) of casein kinase II (CK2) that is involved in synaptic transmission, neuronal growth, and development (Di Stazio et al., 2023).

In this study, *CSNK2B* variant heterozygous NM_001320.7(*CSNK2B*):c.497T>G (p.Met166Arg) *de novo* novel variant and was detected using WES in a 12-years-old Turkish boy with POBINDS who mainly presented with generalized seizures, intellectual disability. The variant c.497T>G (p.Met166Arg) is a novel variant that is not included in HGMD and Clinvar databases and has not been reported in the literature. Another patient was 1 year old and applied to the clinic with a history of afebrile seizures. According to the patient's WES result, Heterozygous, NM_001320.7(*CSNK2B*):c.139C>T (p.Arg47Ter) variation was detected. The patients' karyotype, array CGH and fragile X results were normal.

A heterozygous variant of *CSNK2B* causes the rare autosomal dominant neurologic disorder known as Poirier–Bienvenu neurodevelopmental syndrome (POBINDS), which is typified by early onset epilepsy, hypotonia, varying degrees of intellectual disability (ID), developmental delay (DD), and facial dysmorphism.

The novel variant broadens the range of *CSNK2B* variations, offering recommendations for early clinical diagnosis, genetic counseling, and family treatment.

***Session topic**: Case reports and series*

Session: P018

DE NOVO, NOVEL LIKELY PATHOGENIC VARIANT IN *SMC1A* GENE IN A PATIENT WITH INTELLECTUAL DISABILITY AND SEIZURES HISTORY

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Objective: An 8 years and 9 months old girl presented to us with complaints of ıntellectual disability and seizures history. The patient is the second child of an unrelated couple. She was born at term, by cesarean section, weighing 3670 g. Head stiffness occurred at the age of 8 months, sitting without support at the age of 12 months and walking at the age of 18 months. The patient had her first seizure at the age of 7 years in the form of convulsions. Dysmorphic findings: microcephaly, brachycephaly, wide forehead, long facial structure, flat eyebrows, mild synmorphia, deep-set eyes, low-set ears, prominent filtrum, thin lips and short neck.

Methods: Chromosome analysis of the patient was 46,XX, arrayCGH and Fragile X analyses were normal. As a result of WES analysis, the heterozygous NM_006306.4(*SMC1A*):c.1114-1G>A variant detected in the patient was a novel variant not identified in the databases. The variant detected in the patient was not detected in the genomic DNA of the patient's parents and was considered as *de novo*. Considering this result, the relevant variant was re-evaluated by giving a PM6 score in the in-silico prediction program according to the ACMG-2015 guidelines and was accepted as “likely pathogenic” by us.

Conclusion: In the OMIM database, *SMC1A* gene is associated with Cornelia de Lange syndrome 2 and Developmental and epileptic encephalopathy 85, with or without midline brain defects phenotypes showing XLD inheritance. Our patient was evaluated as compatible with the phenotype of developmental and epileptic encephalopathy 85, with or without midline brain defects based on physical examination findings.

***Session topic**: Case reports and series*

Session: P019

CASE REPORT: A HEMIZYGOUS *DMD*:c.958C>T VARIANT WITH SPLICING RESCUE AND ATTENUATED CLINICAL PRESENTATION

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Pathogenic variants in the dystrophin gene (*DMD*; NM_004006.2), located on the X chromosome, are associated with Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and X-linked dilated cardiomyopathy (XLCM). Disease severity correlates with the "reading frame rule", whereby out-of-frame mutations typically lead to the severe Duchenne phenotype, while in-frame mutations are associated with the milder Becker form.

We report the case of a 48-year-old male who, despite elevated creatine kinase levels (352 U/L; normal <190 U/L), exhibited no clinical features of muscular disease. He was found to carry a hemizygous likely pathogenic nonsense variant in the *DMD* gene (*DMD*:c.958C>T) during familial testing prompted by his daughter's Whole Exome Sequencing (WES) for suspected Juvenile Myoclonic Epilepsy. The same variant was identified in a heterozygous state in his 21-year-old daughter and is associated with X-linked cardiomyopathy (XLCM) in females.

Although the variant has not been previously reported in the literature in connection with human disease, it is recorded in ClinVar in two entries: one from a patient with DMD and another from a patient with dystrophin defects. Functional analysis indicated that the variant leads to exon 9 skipping, resulting in an in-frame deletion in approximately 56% of transcripts (DOI: 10.1101/2024.01.31.578175). This allows partial preservation of the reading frame and likely prevents degradation of transcripts by nonsense-mediated decay (NMD), which may explain the milder clinical phenotype.

This case highlights the importance of transcript-level analysis for accurate interpretation of nonsense variants in the DMD gene.

***Session topic**: Case reports and series*

Session: P020

PHENOTYPIC SPECTRUM IN PATIENTS WITH COPY NUMBER VARIATIONS

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Objective: New molecular technologies are a powerful tool in diagnostics of neurodevelopmental disorders (NDD) in children. There is no single approach to the molecular testing of the patients. Unnecessary investigations burdens the laboratory itself, consumes significant resources, and distracts the attention of parents. The aim of the study is optimization of indications for the microarray analysis.

Materials and methods: 340 patients with a NDD were enrolled for detecting CNVs. The cohort was divided according the positive result for CNV. A genotype-phenotype study was performed including several phenotypic descriptors – presence of developmental delay, neurologic disorders, seizures, dysmorphic characteristics, anthropometric status and other congenital anomalies.

Results: The group of patients in whom a CNV change was detected showed a significant difference compared to the group without CNV in the following phenotypic descriptors: delay in motor development, the presence of dysmorphic features, current neurological abnormalities, as well as the presence of associated anomalies of other organs. Other phenotypic parameters were rarely present.

Conclusion: The detection rate of CNV in patients with NDD is variable. In our study the percentage was higher - 57%, due to the strict criteria for referral. The results indicate that the diagnostic yield is higher when several phenotypic descriptors such as motor delay, dysmorphia, neurologic anomalies and organ malformations are present. There is a need for standardized algorithm of phenotypic parameters in patients.

***Session topic**: Case reports and series*

Session: P021

DUPLICATION OF THE *SOX3* GENE IN AN *SRY*-NEGATIVE BOY WITH 46,XX KARYOTYPE: A CASE REPORT AND A LITERATURE REVIEW

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Background: 46,XX testicular disorder/difference of sex development (DSD), also known as XX male syndrome, is a rare condition in which an individual with a 46,XX karyotype develops a male phenotype. In 90% of cases, the syndrome is caused by a translocation of the *SRY* gene, located on the Y chromosome, to the X chromosome or an autosome. The remaining 10% of cases are characterised by the absence of the *SRY* gene. We report an *SRY*-negative 3-year-old boy with normal male secondary characteristics, despite a 46,XX karyotype.

Methods: Exome sequencing, array CGH and quantitative methylation sensitive QF-PCR were performed.

Results: We identified a 723 kb duplication of the Xq27.1q27.2 region, encompassing the *SOX3* gene. An imbalance in the methylation of one X chromosome was observed, with a ratio of 5:1. Exome sequencing was negative for pathogenic variants (SNVs) associated with DSD. Furthermore, the patient's mother was found to be a carrier of the duplication.

Conclusion: The duplication of the *SOX3* gene has been previously reported in 11 *SRY*-negative male patients, 9 of whom exhibited various stages of genital development disorders, including hypospadias, cryptorchidism, and bifid scrotum. In accordance with the present case, only 2 patients with normal male genitalia (albeit infertile due to the absence of the azoospermia factor region) have been reported. The present case report further supports the hypothesis that the overexpression of the *SOX3* gene in the developing gonads is likely to induce testis development, thereby compensating for the loss of *SRY* gene function in 46,XX male patients.

***Session topic**: Case reports and series*

Session: P022

PREVALENCE OF *HLA-DQ2* AND *HLA-DQ8/DR4* HAPLOTYPES AND THEIR ASSOCIATION WITH CLINICAL MANIFESTATIONS IN PATIENTS FROM BOSNIA AND HERZEGOVINA

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Celiac disease is a chronic inflammatory disorder of the small intestine, triggered by gluten ingestion in genetically predisposed individuals. Patients with this lifelong disease may experience various symptoms, such as abdominal pain, vomiting, headache, and constipation. The *HLA-DQ2* and *HLA-DQ8* are recognized as critical genetic markers strongly associated with the development of celiac disease. The aim of this study was to evaluate the presence of *HLA-DQ2* and *HLA-DQ8/DR4* haplotypes in a group of 94 patients in Bosnia and Herzegovina and to gather data on most common symptoms associated with these haplotypes. Peripheral blood samples were collected and processed for DNA extraction. Genotyping for *HLA-DQ2* and *HLA-DQ8/DR4* was conducted with the geneMAP™ Celiac (DQ2, DQ8, DR4) Detection Kit. Genotyping was performed on a MicPCR system (Bio Molecular Systems, Australia).The analysis revealed that 39 of the tested patients were positive for *HLA-DQ2* or *HLA-DQ8/DR4* alleles. Specifically, 20 patients were identified as carrying the *HLA-DQ2* haplotype, while 17 were positive for the *HLA-DQ8/DR4* haplotype. Approximately 40% of the patients identified with one of these two haplotypes reported symptoms. The *HLA-DQ8* haplotype was slightly less common than *HLA-DQ2*. This study is the first in Bosnia and Herzegovina to examine the prevalence of HLA-DQ2 *and HLA-DQ8/DR4* haplotypes and their clinical implications for disease susceptibility.

***Session topic**: Case reports and series*

Session: P023

MITOCHONDRIAL MYOPATHY CAUSED BY *MT-ND5* VARIANT: INTEGRATING WES AND MITOCHONDRIAL DNA ANALYSIS

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Mitochondrial disorders caused by pathogenic variants in mitochondrial genome represent a heterogeneous group of disorders, including mitochondrial myopathy, Leigh syndrome, MELAS and others. We report a patient with mitochondrial myopathy caused by a pathogenic variant in the *MT-ND5* gene. The patient is a male child born after an uneventful full-term pregnancy from healthy nonconsanguineous parents. He presented with failure to thrive with psychomotor delay and recurrent infections. Neurologic examination at 11 months revealed axial hypotonia with limb hypertonia, hyperreflexia, head tremor, weak supporting and postural responses, hypomimic face, bilateral eyelid semiptosis, convergent strabismus and inability to visually track objects. Elevated serum lactate prompted further metabolic analyses which indicated a defect in oxidative phosphorylation. Whole exome sequencing (WES) analysis aimed at nuclear-encoded mitochondrial genes was negative, but the analysis of mitochondrial DNA revealed a pathogenic variant c.758T>C (p.Val253Ala) in the *MT-ND5* gene, with a heteroplasmy level of 54%. Variant was confirmed by Sanger sequencing, while the analysis of maternal sample showed that the variant arose *de novo*. This study highlights the importance of integrating mitochondrial DNA analysis with WES to enable precise diagnosis and treatment of different mitochondrial disorders.

***Session topic**: Case reports and series*

Session: P024

THE ROLE OF *MTNR1A* AND *MTNR1B* VARIATIONS IN CHRONIC INSOMNIA

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Purpose: Chronic insomnia is a prevalent sleep disorder characterized by difficulty in initiating or maintaining sleep, or early morning awakenings, persisting for at least three times per week over a three-month period and impairing daily functioning. Melatonin, a key regulator of circadian rhythms, acts through the *MTNR1A* and *MTNR1B* receptors. Genetic variations in these receptor genes may influence susceptibility to insomnia. Therefore this study aims to investigate the association between two specific gene polymorphisms rs2119882 in *MTNR1A* and rs4753426 in the *MTNR1B* with chronic insomnia.

Methods: A total of 200 participants were enrolled, including 100 patients diagnosed with chronic insomnia and 100 healthy controls. Genomic DNA was isolated from peripheral blood samples. Genotyping of the rs2119882 and rs4753426 polymorphisms were performed by using real-time polymerase chain reaction(RT-PCR). Results were evaluated statistically.

Results: There was no statistically significant difference in the distribution of *MTNR1A* rs2119882 polymorphisms between patients and controls; however, the homozygous mutant genotype(CC) was more prevalent among patients. For the *MTNR1B* rs4753426 polymorphism, the homozygous mutant genotype(CC) was found statistically high in the patient group. The C allele of rs4753426 was significantly more frequent in patients. Demographic analysis also showed that chronic insomnia was significantly more common among retirees and unemployed individuals.

Conclusion: The findings suggest that the *MTNR1B* rs4753426 polymorphism, particularly the CC genotype, may be associated with an increased genetic predisposition to chronic insomnia. This study highlights the potential of melatonin receptor gene variants in the pathogenesis of insomnia and may inform future gene-targeted therapeutic approaches.

***Session topic**: Case reports and series*

Session: P025

MORBUS GAUCHER A DIAGNOSTIC CHALLENGE

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Purpose: Morbus Gaucher is the most prevalent lysosomal storage disorder, caused by an autosomal recessive deficiency of the enzyme β-glucocerebrosidase. This enzymatic defect leads to the accumulation of glucosylceramides within the reticuloendothelial system, predominantly affecting the spleen, liver, bone marrow, and occasionally the lungs. This study aims to highlight the importance of early recognition of Gaucher disease (GD) in patients with unexplained systemic symptoms, particularly splenomegaly and thrombocytopenia, and to assess a diagnostic algorithm that integrates basic hematological and biochemical parameters.

Method: We report the case of a 57-year-old male with type 2 diabetes, presented with chronic fatigue and longstanding bone pain previously misdiagnosed as generalized arthritis and treated with corticosteroids without improvement. Given the persistent symptoms and lack of definitive diagnosis, Gaucher disease was suspected, prompting enzyme and hematologic testing. This case was evaluated alongside a published diagnostic algorithm that uses platelet count, ferritin, and transferrin saturation to assess the likelihood of Gaucher disease.

Results: The patient presented with hepatosplenomegaly, anemia, thrombocytopenia, elevated ferritin, and transferrin saturation, along with chronic fatigue and bone pain. Abdominal ultrasound confirmed liver and spleen enlargement, while bone marrow biopsy revealed characteristic Gaucher cells with wrinkled cytoplasm and increased reticulin fibers, consistent with a lysosomal storage disorder. These clinical, laboratory, and histological findings supported the diagnosis of Gaucher disease.

Conclusion: Although Gaucher is the most common lysosomal deposition disease it remains rare and most cases present with a gradual installation of the clinic which explains the delay in diagnosis. It is very important to include Gaucher as a possible diagnosis in cases of splenomegaly and / or thrombocytopenia. GD is characterized by its clinical polymorphism.

***Session topic**: Case reports and series*

Session: P026

SPECTRUM OF *NF1* VARIANTS IN A PATIENT COHORT FROM NORTH-EASTERN SLOVENIA

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Background: Neurofibromatosis type 1 (NF1) is a genetically diverse disorder. Due to its variable presentation, especially in early childhood, molecular testing is often needed to confirm the diagnosis. We analyzed *NF1* variants detected in patients from North-eastern Slovenia.

Methods: Patients referred for *NF1* testing underwent NGS and Sanger sequencing; MLPA was used for copy number changes. Variants were classified per ACMG guidelines and correlated with clinical data when available.

Results: We identified more than 20 distinct *NF1* variants. These included frameshift (e.g., c.1756_1759del, c.6378_6384del), nonsense (c.2356C>T), splice-site (c.2851-6_2851-3del, c.480-2A>C), missense (c.1466A>G, c.4330A>G), and in-frame deletions (c.2070_2072del). Two multiexon deletions were found via MLPA: chr17:26580402-26616409 and chr17:29553443-29592368. Several variants were rare or novel. Truncating and splicing variants were the most common. Variant effects were interpreted in the context of available phenotype data.

Conclusion: Our findings confirm the wide spectrum of *NF1* variants in this small cohort, with a predominance of truncating and splicing variants. The results emphasize the need for comprehensive genetic analysis to support diagnosis and management and add valuable insight into the local molecular landscape of NF1.

***Session topic**: Case reports and series*

Session: P027

A MULTIGENERATIONAL NONSYNDROMIC HYPOPITUITARISM FAMILY ASSOCIATED WITH A NOVEL *GLI2* VARIANT

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Variants in *GLI2* have been associated with a spectrum of hypothalamic–pituitary axis defects, ranging from isolated growth hormone deficiency (IGHD) to classic Culler–Jones syndrome. However, milder or non-syndromic phenotypes have been increasingly reported. We present a multigenerational family carrying a novel pathogenic *GLI2* variant with variably expressive hypopituitarism and no syndromic features.

Clinical Exome Solution V3 next generation sequencing kit and Illumina NovaSeq system were used for DNA sequencing.

The proband was a male child with IGHD, subtle midline facial anomalies including a smooth philtrum and mildly depressed nasal bridge. There was no parental consanguinty. In family history the father had childhood-onset IGHD and mild hypotelorism; the paternal uncle exhibited combined pituitary hormone deficiency, intellectual disability and mild hypotelorism; a grandson of a different paternal uncle also had combined pituitary hormone deficiency. No affected family members showed major syndromic features. Pituitary MRI of the proband and affected relatives was normal. Genetic testing revealed a heterozygous novel *GLI2* c.2524del p.(Ser842Profs*53) pathogenic variant. The variant was confirmed by Sanger sequencing in the proband, his father, and uncle's grandson.

Our *GLI2* related familial hypopituitarism report expands the *GLI2* phenotypic spectrum and supports its inclusion in diagnostic panels even in the absence of syndromic features or midline anomalies.

***Session topic**: Case reports and series*

Session: P028

FREQUENCY OF *ABCB1* C3435T AND C1236T POLYMORPHISMS IN THE KOSOVO POPULATION

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Introduction: P-glycoprotein is an efflux transporter, encoded by the *ABCB1* gene, that regulates drug absorption, distribution and elimination. Polymorphisms C1236T and C3435T may alter its activity, contributing to interindividual variability in pharmacokinetics, pharmacodynamics, drug response and therapeutic effectiveness. This study aimed to evaluate the frequencies of these polymorphisms in the Kosovo population in order to contribute to the understanding of genetic factors that influence drug response.

Methods: A total of 384 individuals from the Kosovo population were enrolled in the study. Genomic DNA was isolated from whole blood samples using the Nextractor NX-48s system. Genotyping was performed using TaqMan SNP genotyping assays (C1236T rs1128503; C3435T rs1045642) on Real-Time PCR following the manufacturer's protocol. The results were subsequently analyzed by the allele discrimination method using the MxPro software.

Results: The observed allele frequencies of the *ABCB1* polymorphisms in the Kosovo population were C = 0.57, T = 0.43 for C1236T (exon 12) and C = 0.52, T = 0.48 for C3435T (exon 26). The corresponding genotype distributions were 30% CC, 53% CT, and 16% TT for C1236T, and 25% CC, 53% CT, and 22% TT for C3435T. Genotype frequencies at both loci were in agreement with Hardy–Weinberg equilibrium, suggesting genetic stability.

Conclusion: This is the first study to report the distribution of *ABCB1* C1236T and C3435T polymorphisms in the Kosovo population. The observed allele and genotype frequencies are consistent with those reported in other European populations. The data underscore the importance of considering *ABCB1* genetic variants in pharmacogenetic research and may support future efforts toward personalized drug therapy in this population.

***Session topic**: Case reports and series*

Session: P029

EXPANDING THE CLINICAL AND MOLECULAR LANDSCAPE OF PSEUDOXANTHOMA ELASTICUM WITH A NOVEL *ABCC6* VARIANT

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Background: Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disorder caused by mutations in the *ABCC6* gene and is predominantly characterized by progressive calcification and fragmentation of elastic fibers, affecting the skin, eyes, and cardiovascular system. In this study, we report a PXE case harboring one novel and one recurrent *ABCC6* variant to explore the genotype–phenotype correlation of these identified mutations.

Methods: Genomic alterations were investigated using mini clinical exome sequencing (CES) panel including 1493 genes, which of 46 are related to corneal dystrophies.

Case and Results: A 33-year-old woman, initially referred due to corneal dystropy, who was subsequently found to manifest additional abnormalities consistent with PXE, including yellowish papular skin lesions on her neck and buccal mucosa lesions. In *ABCC6* gene c.2248-1G>A and c.3341G>A variants were identified in compound heterozygous state. The c.2248-1G>A variant was novel and classified as “likely pathogenic” according to ACMG guidelines (PVS1, PM2, PP3). Analysis of genes associated with corneal dystrophies revealed no additional pathogenic or likely pathogenic variants.

Conclusions: This case report expands the mutational spectrum of *ABCC6* in PXE and underscores the complexity of genotype–phenotype relationships in this disorder. Although corneal involvement is atypical in PXE, the presence of corneal abnormalities in this patient suggests that such ocular findings may occasionally coexist, either as part of the disease spectrum or as incidental phenomena. These insights highlight the importance of comprehensive clinical and genetic evaluation to guide accurate diagnosis and personalized management in PXE.

***Session topic**: Case reports and series*

Session: P030

DIFFERENTIAL DIAGNOSTIC OBSTACLES FOR HAREL-YOON SYNDROME

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ATAD3A-related genetic conditions encompass a wide clinical spectrum caused by pathogenic variants in the *ATAD3A* gene. *ATAD3A* is a nuclear encoded mitochondrial regulator with role for the maintenance of the mitochondrial genome. Rare cases with confirmed pathogenic variants in the *ATAD3A* gene have been described as autosomal-dominant and autosomal-recessive Harel-Yoon syndrome, which could present with neurologic, muscular, cardiac and sensory symptoms.

Here we present a case of 4 years old female with epilepsy and developmental delay, who was initially referred for whole exome sequencing (WES) and DNA microarray for copy number variations at laboratory Genoks, Turkey. Both reports were negative. Later the WES data files were provided by the patient's parents to our laboratory for wider scope bioinformatic analysis using GeneSearchNGS software. The potential pathogenic variants were confirmed and segregated in the family via direct Sanger sequencing with BigDye Terminator Sequencing Kit on ABI3130 genetic analyzer.

The results showed a *de novo* missense variant c.1148C>T, p.(Pro383Leu) in the *ATAD3A* gene, which we classified as variant of uncertain significance. After discussion with the referring clinicians and patient's parents, we concluded that the detected variant c.1148C>T, p.(Pro383Leu) in the *ATAD3A* gene is the most probable cause for the observed clinical symptoms in the patient, who turned out to manifest also with hypotonia.

Harel-Yoon syndrome is a very rare disease with a wide phenotypic spectrum overlapping many other diagnoses, so it is important to be included in the diagnostic pipelines of pediatric cases with epilepsy and developmental delay of unknown origin.

***Session topic**: Case reports and series*

Session: P031

A CASE REPORT OF A PATIENT WITH NEURODEVELOPMENTAL DISORDER WITH HYPOTONIA, STEREOTYPIC HAND MOVEMENTS, AND IMPAIRED LANGUAGE – A NOVEL VARIANT IN *MEF2C* GENE

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Background: *MEF2C* gene is associated with neurodevelopmental disorder with hypotonia, stereotypic hand movements and impaired language – NEDHSIL. Main characteristics are: global developmental delay with hypotonia, limited walking, intellectual disability, poor or absent speech and stereotypic hand movements. About 80% of patients develop seizures. Some patients have dysmorphic features, cardiac manifestations, strabismus and abnormalities on brain MRI (enlarged cerebral ventricles, thin corpus callosum).

We report a case of two year old female patient with global developmental delay and intractable epilepsy. There was no abnormalities in her natal and familiar history. She presented motor delay (unstable short-term sitting, no standing and walking) with hypotonia, refractory epilepsy and voicing only single voices. She expressed dismorphic features: depressed nasal bridge, anteverted nares and short neck. Brain MRI showed hypoplastic corpus callosum.

Material and methods: First step was cytogenetic analysis. Then, WES analysis performed on Illumina NovaSeq6000 according to the protocol TwistExomev5_0_CNV.

Result: Cytogenetic analysis showed a karyotype with triple X, which couldn't explain the child`s phenotype. WES analysis identified a heterozygous likely pathogenic variant c.946C>T, p.(Gln316*); NM_ 001193347.1 in the *MEF2C* gene. This variant has not yet been reported in association with human diseases in the biomedical literature, however the following lines of evidence favor its pathogenicity: the variant is absent from control populations in gnomAD and the variant is anticipated to result in the loss of function in *MEF2C* (an established mechanism of pathogenicity).

Conclusion: Our case represents a novel (not yet reported) likely pathogenic variant in *MEF2C* gene and shows genotype-phenotype correlation.

***Session topic**: Case reports and series*

Session: P032

X-LINKED LEGACY: MULTIGENERATIONAL EXPRESSION OF AARSKOG-SCOTT SYNDROME IN A SINGLE FAMILY

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Aarskog-Scott syndrome (AAS) is an X-linked genetic disorder characterized by short stature, facial anomalies, skeletal deformities, and genitourinary malformations.

This study seeks to investigate the range of phenotypic differences and the varying ways genetic traits are expressed within a single family. We aim to better understand how the same genetic factors can lead to diverse physical characteristics and manifestations, even among closely related individuals.

We evaluated one family through detailed medical history, pedigree analysis, physical examination, laboratory tests and imaging studies. After DNA isolation from the patients' peripheral blood, the exon and exon-intron boundary regions of the *FGD1* gene were analyzed using next-generation sequencing (NGS).

In this study, we identified a novel hemizygous c.1451del p.(Lys472Argfs*36) frameshift variant located in exon 7. The variant was classified as likely pathogenic (PVS1, PM2) according to ACMG criteria. Pedigree analysis revealed multiple affected individuals with variable features including dysmorphic facial traits, short stature, and premature birth. Segregation confirmed the presence of the variant across three generations with different clinical manifestations.

This report demonstrates the clinical utility of combining genomic analysis with comprehensive family evaluation in the diagnosis of AAS. The findings highlight the phenotypic variability of *FGD1*-associated disorders and the need for a multidisciplinary approach in suspected familial cases.

***Session topic**: Case reports and series*

Session: P033

RARE DOUBLE STRIKE IN HYPOTHALAMIC SIGNALING: A CASE OF SEVERE PEDIATRIC OBESITY EXPLAINED BY *MC3R* AND *NMUR2* VARIANTS

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Monogenic obesity is a rare form of obesity caused by single gene mutations that disrupt key pathways regulating energy balance and appetite, typically manifesting with early onset and severe clinical consequences. We report a non-syndromic obesity case in an 11-year-old male with hyperphagia starting at age 3 and an 8-year obesity history. The patient's prenatal and developmental history was unremarkable, and birth parameters were within normal limits. Although there was no consanguinity, several maternal family members had undergone bariatric surgery for obesity. Laboratory evaluation revealed insulin resistance without other significant metabolic disturbances. Whole Exome Sequencing identified two rare heterozygous variants in evolutionarily conserved regions of the leptin-melanocortin pathway: *MC3R*: c.634C>T (p.Leu212Phe) and *NMUR2*: c.858dupT (p.Asp287*). Neither variant has been previously associated with monogenic obesity in the literature, but both were classified as likely pathogenic (LP) according to ACMG guidelines. Functionally, the *MC3R* missense variant is expected to impair receptor signaling by altering transmembrane structure, while the *NMUR2* nonsense variant likely results in premature protein truncation and mRNA degradation through nonsense-mediated decay. Together, these variants are predicted to disrupt sequential signaling within the leptin-melanocortin axis, weakening hypothalamic appetite control and reducing energy expenditure. This dual impairment provides a molecular explanation for the patient's severe early-onset obesity and supports its classification within the mono-oligogenic obesity spectrum. Moreover, these findings suggest potential responsiveness to targeted therapies involving *NMUR2* agonists or *MC3R*-based interventions. This case contributes novel candidate variants for obesity pathogenesis and supports precision medicine approaches.

***Session topic**: Case reports and series*

Session: P034

MTNR1B POLYMORPHISMS AND CIRCADIAN PHENOTYPES IN HASHIMOTO'S DISEASE

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Circadian rhythm disruption is recognized as a disorder of the endocrine system. Melatonin, the most crucial circadian hormone, promotes sleep and regulates biological rhythms. Its deficiency can lead to dysregulation of the immune system, as melatonin influences the immunity of immune cells via the MTNR1B receptor. Disturbances in melatonin–MTNR1B signalling pathway can contribute to autoimmune diseases. This study investigated the association of *MTNR1B* gene polymorphisms with chronotype and daytime sleepiness in patients with Hashimoto's thyroiditis (HT). A total of 115 HT patients were included. Chronotype was assessed using the reduced Morningness-Eveningness Questionnaire (rMEQ) and daytime sleepiness with the Epworth Sleepiness Scale (ESS). The rMEQ categorized patients into evening vs. neither + morning chronotypes, and the ESS into normal vs. increased daytime sleepiness. Three *MTNR1B* polymorphisms: rs10830963, rs1387153, and rs4753426, were genotyped using TaqMan assays on QuantStudio5. We found no association between these polymorphisms and chronotype in HT. However, rs10830963 was associated with increased ESS. The GCC haplotype (rs10830963, rs1387153, rs4753426) was also associated with increased ESS. In addition, the CT genotype of rs1387153 was associated with increased ESS. These results suggest that *MTNR1B* polymorphisms may influence daytime sleepiness in HT and thus offer the potential for personalized therapeutic approaches.

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***Session topic**: Case reports and series*

Session: P035

THE FIFTH KNOWN CASE OF *SASH3*-ASSOCIATED IMMUNODEFICIENCY: NOVEL VARIANT AND SEVERE INFLAMMATORY PHENOTYPE

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Background: *SASH3* encodes a lymphocyte-specific adaptor protein crucial for T-cell receptor signaling. Loss-of-function variants have recently been linked to a novel X-linked primary immunodeficiency characterized by immune dysregulation, recurrent infections, and inflammatory features. To date, only four affected individuals have been described worldwide.

Case Presentation: We report an 8-year-old boy, born to consanguineous parents, who presented with recurrent empyema, three episodes of pneumothorax, pustular skin lesions, and allergic asthma. Family history was notable for allergic rhinitis and asthma in a sibling. Immunologic evaluation revealed hypogammaglobulinemia with low serum IgG and IgA, elevated IgE, and normal IgM levels. Lymphocyte subsets were within normal ranges: CD3+ T cells 67.5%, CD4+ 41.4%, CD8+ 26.6%, CD19+ B cells 21.9%, and NK cells 9.7%. Marked eosinophilia was present. Despite low total IgG (22.7%), specific antibodies to rubella and measles were detectable, suggesting partial humoral immunity.

Whole-exome sequencing identified a novel hemizygous missense variant in *SASH3* (c.578C>T) within the conserved SH3_2 domain. This variant is absent from population databases and HGMD. The patient's mother was heterozygous, supporting X-linked inheritance. Clinical and molecular findings suggest the variant is likely pathogenic.

Conclusion: This case represents the fifth reported patient with *SASH3*-related immunodeficiency, reinforcing the gene's role in immune regulation. The combination of recurrent infections, allergic features, and immune dysregulation expands the known phenotype and highlights the need to consider X-linked causes in atypical male immunodeficiency cases.

***Session topic**: Case reports and series*

Session: P038

A CASE SERIES ON SUSPECTED BAINBRIDGE-ROPERS SYNDROME WITH A TWO NOVEL VARIATION IN *ASXL3* GENE

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Background/Objectives: Bainbridge-Ropers syndrome (BRPS), which was identified in 2013, is caused by functional *de novo* variations that occur during egg and sperm development in the *ASXL3* gene located on chromosome 18. Clinical features include characteristic skeletal abnormalities with dysmorphic facial features, learning and speech difficulties, postnatal growth delays, autistic traits, hypotonia and feeding problems.

Methods: Whole Exome Sequencing was studied in a total of 7 patients who presented with clinical findings of ASD, hypotonia, ID and seizure. Segregation analyses in the family were performed with Sanger sequencing.

Results: Two different novel *de novo* frameshift variations were detected in patients. The relevant variations were evaluated as Likely pathogenic according to the ACMG classification. NM_030632.3(*ASXL3*):c.2213C>T variation, which was evaluated as uncertain significance according to ClinVar, was detected in 2 of the patients. Segregation analysis showed paternal inheritance. Two of the other 3 variations were missense and one was a splice site change. As a result of the segregation analysis, it was concluded that these 3 variations showed paternal inheritance and that they were not expected to have an effect on the patients clinics.

Conclusion: Although Bainbridge-Ropers syndrome is rare it is rapidly increasing in patients reported today with the developing NGS analyses. The clinical phenotype of Bainbridge-Ropers syndrome is further expanded with the *de novo* novel frameshift *ASXL3* variations that are likely to have pathogenic effects that we detected as a result of WES.

***Session topic**: Case reports and series*

Session: P040

A CASE OF PALLISTER-KILLIAN SYNDROME IN A NEWBORN

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Background: Pallister–Killian syndrome (PKS) is a multisystem developmental disorder caused, by mosaic state of isochromosome 12p. Usually it is represent by supernumerary marker chromosome with different percentage in variable tissues. The clinical manifestations of PKS include characteristic craniofacial dysmorphism, pigmentary skin anomalies, limb differences, congenital heart defects, congenital diaphragmatic hernia, hypotonia, intellectual disabilities, and epilepsy.

Materials and methods: We report a case of a male infant, with hypotonia, significant craniofacial dysmorphisam and sparse hair above ears. Furthermore anomalies in skin pigmentation were present. The baby experienced feeding difficulties due to the pronounced motor incapacity.

Blood sample was taken and both karyotype and microarray were performed using standard procedures.

Results: Conventional karyotyping revealed a low-grade mosaicism with an extra marker chromosome, i(12p). Microarray CGH confirmed the presence of mosaic tetrasomy of chromosome 12p. arr[hg38] 12p13.33q1 2(64,620-38 ,621,326)x2-3

Conclusion: Clinical presentation and severity of the developmental delay mostly depend on the degree of mosaic cell line in the blood and other tissues. Follow up of our patient showed profound developmental delay, so we assume existence of higher degree of mosaicism it other tissues. However, we were unable to perform genetic evaluation of fibroblasts so far. The combined use of karyotyping and array CGH increase the sensitivity for the detection of low-rate mosaicism.

***Session topic**: Case reports and series*

Session: P041

DE NOVO RING CHROMOSOME 20 IN A MALE INFANT WITH SUSPECTED EPILEPSY

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Purpose: This case report aims to present a rare *de novo* ring chromosome 20 [r(20)] and a 1732 kb deletion involving 46 OMIM genes at 20q13.33, detected in an infant with clinical suspicion of epilepsy, in order to contribute to the understanding of genotype-phenotype correlations in chromosomal epilepsies and to highlight the relevance of chromosomal anomalies in early-onset neurodevelopmental disorders.

Method: A 9-month-old male infant was referred due to suspected seizure activity. Karyotype analysis revealed a ring chromosome 20. To further investigate, chromosomal microarray analysis (array-CGH) was performed.

Results: Array-CGH revealed a 1732 kb heterozygous deletion at 20q13.33 involving 46 OMIM genes. Among these, two genes (*CHRNA4* and *KCNQ2*) are directly associated with epilepsy. Parental chromosome results are normal, confirming the variant as *de novo*. The patient is under ongoing neurological evaluation. Genetic counseling has been provided to the family, and follow-up continues to monitor developmental progress.

Conclusion: This case highlights the diagnostic value of combining karyotype and array-CGH in patients with early neurological symptoms. The identification of a *de novo* ring chromosome 20 and epilepsy-related gene deletion provides a strong genetic explanation for the phenotype and underscores the need for early genetic testing in infants with unexplained neurodevelopmental findings.

***Session topic**: Case reports and series*

Session: P042

TWO CASES OF RARE PYCNODYSOSTOSIS SYNDROME WITH *CTSK* MISSENSE VARIANTS

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Introduction: Pycnodysostosis is a rare genetic disorder characterized by short stature, short limbs, distinctive facial dysmorphism, and osteosclerosis associated with increased bone fragility.The genetic basis of the syndrome is due to biallelic pathogenic variants in the CTSK gene.

Method: After obtaining a comprehensive medical history, constructing a pedigree, and performing a thorough clinical evaluation, DNA was isolated from peripheral blood samples of the patients using Zeesan Lab-Aid 824s Blood Isolation Kit. The SOPHIATM Clinical Exome Solution (CES) V2 next generation sequencing kit covering 5400 genes and Illumina NovaSeq system were used for DNA sequencing.

Case: Two patients, one male and one female, presented with history of spontaneous fractures, frontal and occipital prominence, a prominent nose, and dental anomalies .The female patient was currently 20 years old and had a history of 15 spontaneous bone fractures. Scaphocephaly observed in the male patient is a clinical feature that is rarely seen in this syndrome.Genetic analysis identified a novel missense variant, c.238G>T (p.Asp80Tyr), located in exon 3 of the *CTSK* gene, as well as the previously reported c.3G>A (p.Met1?) variant, respectively.

Discussion: In this study, the clinical features and genetic findings of two patients diagnosed with pycnodysostosis were evaluated, and a novel mutation identified in one of the cases adds to the existing literature.

***Session topic**: Case reports and series*

Session: P043

SCHUURS-HOEIJMAKERS SYNDROME: EXPANDING THE PHENOTYPE OF A RARE DISORDER WITH A RECURRENT *PACS1* VARIANT

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Background: Schuurs-Hoeijmakers syndrome (SHS) is a rare autosomal dominant neurodevelopmental disorder characterized by distinctive facial dysmorphisms, developmental delay, and congenital heart defects. Pathogenic variants in the *PACS1* gene, which plays a critical role in neuronal development and intracellular trafficking, are causative. This case report aims to contribute to knowledge on Schuurs-Hoeijmakers syndrome by describing the phenotypic spectrum.

Case Presentation: We report a 2-year-old male patient presenting with dysmorphic features including plagiocephaly, hypertelorism, bilateral epicanthal folds, flat philtrum, low-set ears, long eyelashes, downslanting palpebral fissures, a bulbous nasal tip, and a thin upper lip. He was born at 34 weeks' gestation via cesarean section with a birth weight of 2630 g, length of 45 cm, and head circumference of 34 cm. Due to prematurity, he was admitted to the neonatal intensive care unit for 20 days. His motor milestones were delayed. He has ventricular septal defect (VSD), patent ductus arteriosus (PDA), and hypotonia. Bilateral cryptorchidism was also noted. Cranial MRI revealed a cavum pellucidum variation. Karyotyping and chromosomal microarray, yielded normal results. Whole-exome sequencing identified a heterozygous missense variant in *PACS1*, c.607C>T (p.Arg203Trp), which has been previously reported as likely pathogenic.

Conclusion: Although the *PACS1* variant identified in this patient is not novel, our case further expands the phenotypic spectrum of SHS, a rare neurodevelopmental disorder with limited reports in the literature. The recognition of its characteristic abnormalities, combined with the implementation of comprehensive genetic testing, is essential for accurate diagnosis, personalized care, and appropriate support for affected children and their families.

***Session topic**: Case reports and series*

Session: P044

CLINICAL EXOME SEQUENCING IDENTIFIES PATHOGENIC *SQSTM1* VARIANT IN A PATIENT WITH CHOREA AND GAZE PALSY

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Introduction: Childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy (NADGP) is a progressive, autosomal recessive disorder characterised by gait ataxia, dysarthria, gaze palsy, dystonia, and cognitive impairment. The condition is highly uncommon with approximately 30 cases described. Clinical onset typically occurs in late childhood or early adolescence, most frequently between the ages of 6 and 12 years. The disease is caused by biallelic pathogenic variants in the *SQSTM1* gene, which encodes the ubiquitin-binding protein p62 (sequestosome-1), a key mediator in cellular signaling, apoptosis, and autophagy.

Methods: Clinical exome sequencing (CES) was performed using the TruSight One panel on the Illumina MiSeq platform in a 33-year-old patient with childhood-onset slowly progressive gait abnormalities, slurred speech, chorea, horizontal gaze palsy, as well as cognitive and behavioral disturbances. Prior diagnostic testing for Huntington's disease, Friedreich's ataxia, and chorea-acanthocytosis were negative.

Results: CES identified a homozygous nonsense variant in the *SQSTM1* gene: NM_003900.5:c.286C>T (p.Arg96Ter), classified as pathogenic. This variant has previously been associated with NADGP, and the very low allele frequency (f = 0.0000103) is supporting its rarity. The NADGP phenotype associated with this pathogenic variant aligns fully with the patient's clinical presentation, further substantiating the variant's pathogenicity.

Conclusion: To our knowledge, this is the first patient diagnosed with NADGP in Serbia. This case underscores the clinical utility of exome sequencing in elucidating the complex genetic etiology of chorea and related movement disorders.

***Session topic**: Case reports and series*

Session: P045

ANALYSIS OF THE ASSOCIATION BETWEEN COLLAGEN GENE POLYMORPHISMS AND CLINICAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune dysregulation, the production of diverse autoantibodies, and the involvement of multiple organ systems. Autoantibodies against type I and V collagen have been detected in many patients, suggesting a potential link between structural protein variants and disease phenotype. We aimed to analyze the association between *COL1A1* and *COL5A1* gene polymorphisms and clinical manifestations in SLE patients.

Method: The study included 100 SLE patients diagnosed and treated at the Clinic of Allergy and Immunology, University Clinical Center of Serbia. Genotypisation for *COL1A1* rs1800012 and *COL5A1* rs12722 polymorphisms was performed using TaqMan assays.

Results: This study included 100 patients with SLE. Genotyping of the *COL1A1* rs1800012 polymorphism showed that 63 (63%) patients harboured CC genotype, 31 (31%) had CA genotype, and 6 (6%) patients had AA genotype. For *COL5A1* rs12722 polymorphism 21 (21%) patients had CC genotype, 52 (52%) carried CT, and 27 (27%) patients had TT genotype. Oral ulcerations were observed in 26 (26%) patients. The analysis showed a significantly higher frequency of oral ulceration in patients with TT genotype for *COL5A1* rs12722 polymorphism compared to carriers of the C allele (n=12 (44.4%) vs n=14 (19.2%); p=0.011).

Conclusion: The findings of this study suggest that *COL5A1* rs12722 polymorphism could be associated with SLE manifestations.

***Session topic**: Case reports and series*

Session: P046

UNRAVELLING THE CAUSE OF RECURRENT VENOUS THROMBOSIS IN A DABIGATRAN-TREATED PATIENT

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This study aimed to explore the cause of recurrent venous thrombosis in female patient treated with dabigatran.

The patient's first thrombotic event occurred at the age of 59, presenting as deep vein thrombosis with massive pulmonary embolism. Following heparin and one month of dabigatran, recurrent thrombosis occurred. The patient was switched to enoxaparin and acenocoumarol, used without complications for eight years. Haemostatic balance was assessed using the overall haemostatic potential (OHP) assay. Whole-exome sequencing was conducted. The coagulation-related genes were selected based on literature and STRING-DB database. Gene variants were identified using ClinVar, ACMG, UniProt, as well as MetaSVM, MetaLR, MetaRNN, REVEL, ClinPred, and AlphaMissense scores. AlphaFold were used to visualize impact of identified variants on protein structures. Dabigatran-related *ABCB1* and *CES1* variants were also explored.

Elevated OHP and the overall coagulation potential levels, accompanied by reduced the overall fibrinolysis potential levels, were observed. Highly damaging heterozygous variants in *THBS1* (p.Gln1089His) and *MYH9* (p.Arg1877Trp) genes were identified. The variant in *THBS1* was predicted to affect the protein structure. In addition, multiple mutations in *ABCB1* gene were observed.

Findings suggest a notable influence of underexplored genetic factors in case of RVT and further functional analyses.

***Session topic**: Case reports and series*

Session: P047

PULMONARY *IN VITRO* MODEL SYSTEM ENABLES EXPLORATION OF INNOVATIVE TREATMENT STRATEGIES FOR RARE RESPIRATORY DISEASES

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Introduction: Hundreds of rare pulmonary diseases have been identified, most of which involve impaired mucociliary clearance, a process essential for lung function. These progressive, life-threatening disorders lack effective treatments, with lung transplantation often being the only option. This study focuses on the molecular mechanisms of lung epithelial formation and aims to develop an *in vitro* model system for investigating novel therapeutic strategies.

Methods: NHBE cells were cultured in an air–liquid interface (ALI) system to induce differentiation into multiciliated and goblet cells. Validation included confocal microscopy (β-tubulin, *DNAI1*, *MUC5B*, *MUC5AC*), qRT-PCR of ciliogenesis markers (*TP63*, *NOTCH1*, *CP110*, *MCIDAS*, *GEMC1*, *CCNO*, *RFX3*), and differentiated cell markers (*FOXJ1*, *DNAI1*, *TFF3*, *MUC5B*, *MUC5AC*), along with Western blot (acetyl-α-tubulin, *DNAI1*, *TP63*).

Results: Ciliated cells appeared around day 12 post-ALI. By day 28, a fully differentiated pseudostratified airway epithelium was formed. Confocal imaging confirmed motile cilia and mucus, and protein analysis demonstrated the presence of key ciliary proteins.

Conclusion: The use of NHBE cells provides a reproducible, accessible, and standardized system, ideal for high-throughput drug screening targeting mucociliary clearance and other processes in the respiratory tract, while also reducing variability associated with patient-derived samples.

***Session topic**: Complex and functional genomics*

Session: P048

ESTABLISHING *IN VITRO* MODELS FOR GLYCOGEN STORAGE DISEASE TYPE IB: A PLATFORM FOR THERAPEUTIC INVESTIGATIONS

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Glycogen Storage Disease Type Ib (GSD Ib) is characterized by metabolic dysfunction as well as chronic endoplasmic reticulum (ER) stress and increased apoptosis, contributing to disease progression. The chemical chaperone 4-phenylbutyrate (4-PBA) has shown promise in reducing ER stress-mediated apoptosis. There is a pressing need for cost-effective, human-relevant *in vitro* models to enable screening of small molecules (SMs) with therapeutic potential for GSD Ib.

A G6PT-deficient Flp-In HEK293 cell line was generated using CRISPR/Cas9-mediated knockout of *SLC37A4* and validated at the genomic level. The expression of key unfolded protein response (UPR) markers (*ATF4*, *DDIT3*, *HSPA5*, *XBP1s*) and apoptotic genes (*BCL2/BAX*, *CASP3*, *CASP7*) was quantified by RT-qPCR in untreated and 4-PBA-treated cells.

Treatment with 1 mM 4-PBA significantly downregulated UPR-related transcripts and executioner caspases while increasing the BCL2/BAX ratio, suggesting a shift toward cell survival. These findings support the ability of 4-PBA to alleviate ER stress and apoptosis in G6PT-deficient cells.

The G6PT-deficient HEK293 model offers a robust, scalable platform for first-line screening of small molecules targeting ER stress and apoptosis in GSD Ib. Our findings support the therapeutic potential of 4-PBA and highlight the model's applicability in drug repurposing efforts for metabolic disorders.

***Session topic**: Complex and functional genomics*

Session: P049

FUNCTIONAL ANALYSIS OF NOVEL *EGLN1* AND *EPAS1* VARIANTS IN HEREDITARY ERYTHROCYTOSIS

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Hereditary erythrocytosis (HE) is a rare disorder characterised by increased red blood cell mass. Among its genetic causes are variants in *EGLN1* and *EPAS1*, genes involved in oxygen sensing. In Slovenian HE patients, three novel variants of uncertain significance (VUS) were identified: *EGLN1* c.1072C>T (p.Pro358Ser), c.1124A>G (p.Glu375Gly), and *EPAS1* c.2120A>C (p.Lys707Thr). This study investigated their potential pathogenicity through functional analysis. Variants were mapped to protein structures and domains obtained from databases and literature. HEK293 cells were transfected with wild-type or variant genes, and luciferase assays were used to assess effect on protein activity. Protein accumulation and stability were analyzed after cell lysis by western blot, with cyclohexamide added for stability assessment. Known benign and pathogenic variants served as controls. Structural mapping showed both *EGLN1* VUSs lie in the catalytic domain, while the *EPAS1* VUS is near the nuclear localization signal. *EGLN1* VUSs showed reduced protein accumulation but no significant changes in luciferase activity. Notably, p.Pro358Ser showed significant decreased stability ($P<0.01$). Preliminary results for *EPAS1* p.Lys707Thr showed increased luciferase activity, similar to the known pathogenic variant p.Gly537Arg. These findings suggest impaired protein stability for *EGLN1* variants and a potential gain-of-function effect for *EPAS1* p.Lys707Thr, warranting further investigation.

***Session topic**: Complex and functional genomics*

Session: P050

ESTABLISHMENT OF AN *IN VITRO* INSULIN RESISTANCE MODEL IN HepG2 CELLS THROUGH GLUCOSE AND INSULIN CO-TREATMENT

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Insulin resistance is a metabolic condition where the body's cells do not respond effectively to insulin, resulting in increased blood sugar levels. It plays a key role in the development of type 2 diabetes, which causes over 6.7 million deaths each year worldwide.

In vitro models of insulin resistance still represent a powerful tool for studying various aspects of this complex metabolic condition, despite well-known limitations. The HepG2 cell line preserves the insulin response pathways of hepatocytes, making it an ideal model for studying insulin resistance in liver cells.

Here we treated HepG2 cells with high concentrations of glucose (3, 4.5 and 10g/L) and various doses of insulin (10-5, 10-6, 10-7, 10-8M) in order to establish the model of insulin resistance. Cell viability was measured using MTT test, and the qPCR was used for determination of expression of *IRS1*, *GLUT2*, *AKT1* and *G6PC1* genes in treated cells.

Our results demonstrated a significant decrease in cell viability at the highest insulin concentration (10^{-5} M). Notably, neither insulin alone nor high glucose concentrations individually induced insulin resistance in HepG2 cells. However, the combined treatment with 4.5 g/L glucose and 10^{-6} M insulin lead to decreased expression of *IRS1*, *GLUT2*, and *AKT1* (0.4, 0.15, and 0.01 times lower than control, respectively) and increased expression of G6PC1 gene (2.0 times higher than control), which is expected in insulin resistance model. Cell viability was not affected with this treatment.

The established model of insulin resistance will be further used for drug screening studies.

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***Session topic**: Complex and functional genomics*

Session: P051

METHYLATION LEVELS AND GENETIC VARIANTS OF *MTHFR* GENE ARE NOT RISK FACTORS FOR CONGENITAL HEART DEFECT IN DOWN SYNDROME

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Aims: The main aim was to assess promoter methylation levels of the *MTHFR* gene in Down syndrome (DS) individuals, including those with congenital heart defects (DSCHD+), and those without (DSCHD-). The secondary aim was to investigate the association between *MTHFR* 677C>T / 1298A>C gene polymorphisms and MTHFR gene methylation levels.

Patients and Methods: The main aim was to assess promoter methylation levels of the MTHFR gene in DS individuals, including those with congenital heart defects (DS-CHD+), and those without (DS-CHD-), as well as control subjects. We also investigated if common MTHFR polymorphisms, namely 677C > T and 1298A > C correlate with MTHFR promoter methylation levels. Genomic DNA was extracted from peripheral blood. Methylation-sensitive high-resolution melting and PCR–RFLP were used to assess methylation and genotyping.

Results: Study presented a lower *MTHFR* gene methylation level in DSCHD- (58.26±15.26) than in DSCHD+ individuals (66.29±14.69) but statistical significance was not shown after correction for sex and age (p=0.38), SNPs (*MTHFR* 677C>T/1298A>C) have no impact on *MTHFR* methylation levels (p > 0.05)

Conclusion: Methylation levels of *MTHFR* gene promoter is not statistical different between DSCHD+ and DSCHD- individuals. Results suggests that there is no significance of analyzed SNPs on *MTHFR* methylation level and are not a risk factor for CHDs in DS.

***Session topic**: Complex and functional genomics*

Session: P052

MOLECULAR DIAGNOSIS OF SEXUALLY TRANSMITTED INFECTIONS RELATED TO INFERTILITY: THE EFFICIENCY OF MULTIPLEX PCR PANELS

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Sexually transmitted infections (STIs) are a significant yet often silent cause of infertility, especially in women. This study, conducted at GeniusLab, assessed the diagnostic performance of multiplex Real-Time PCR (RT-PCR) in detecting STI-related pathogens in 125 patients evaluated for infertility. Cervical and urethral swabs were analyzed for 10 pathogens: Chlamydia trachomatis, Gardnerella vaginalis, HSV-1/2, Neisseria gonorrhoeae, Mycoplasma genitalium, Mycoplasma hominis, Trichomonas vaginalis, Ureaplasma urealyticum, and Ureaplasma parvum. RT-PCR enabled simultaneous detection and quantification of multiple pathogens, outperforming conventional NAT which lacks sensitivity and provides only qualitative results. Positive cases were more frequent in females (68%), with co-infections found in 6 women and 1 man. Chlamydia trachomatis (29%) and Gardnerella vaginalis (21%) were the most prevalent. The study underscores the high rate of polymicrobial infections and their clinical relevance in infertility. RT-PCR offers detailed, reliable data essential for early, personalized treatment. Although limited by sample size and non-random selection, findings strongly support integrating multiplex RT-PCR into routine infertility diagnostics to improve reproductive health outcomes.

***Session topic**: Complex and functional genomics*

Session: P053

EFFECTS OF *HLA-DRA*, *HLA-DQA1*, AND *IL-6* GENE VARIATIONS TO MULTIPLE SCLEROSIS

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Purpose: Multiple sclerosis (MS) is among the most common autoimmune disorder characterized by inflammation and degeneration affecting central nervous system. Although the exact etiology of multiple sclerosis is unknown, it is thought to occur as a result of interactions between genetic and environmental factors. In this study, it was aimed to analyze the relationship between MS and HLA-DRA (rs3135388 and rs3135391), HLA-DQA1 (rs9272346) and IL-6 (rs1800795 and rs1900796) variations. Additionally, it was aimed to investigate the relationship between environmental factors such as vitamin D, vitamin B12 and B9 levels with MS.

Methods: A hundred healthy controls and 98 MS patients were enrolled into the study. After DNA was isolated from peripheral blood, rs3135388 and rs3135391 variations in *HLA-DRA*, rs9272346 variation in *HLA-DQA1*, and rs1800795 and rs1900796 variations in *IL-6* were analyzed by RT-PCR.

Results: The results showed a significant difference in *IL-6* (rs1800796) G/C between the patient and control groups when genotypes and allele distributions were analyzed. Any significant difference was not found between environmental factors, MS and genotype distributions.

Conclusion: There is evidence suggesting a significant association between *IL-6* (rs1800796) polymorphisms and MS. *IL-6* (rs1800796) GC genotype may be associated with disease susceptibility or risk. By increasing the number of patients, more meaningful results can be achieved in future studies.

***Session topic**: Complex and functional genomics*

Session: P054

THE IMPORTANCE OF HPV GENOTYPING IN ALBANIA: A FIRST-OF-ITS-KIND STUDY AT GENIUSLAB

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Human papillomavirus (HPV) is a leading cause of cervical cancer, with specific high-risk genotypes responsible for most cases. This study represents the first HPV genotyping initiative in Albania, conducted at Genius Laboratory, aiming to identify genotype distribution and inform national prevention strategies. A total of 466 clinical samples were tested using a 21-genotype panel via Real-Time PCR on the QuantStudio™ 7 Flex platform. DNA was extracted manually with the Sacace Genomic Column DNA Express kit. HPV DNA was detected in 61.64% of samples, indicating a high prevalence in the tested population. The most affected group was women under 30, while cases of squamous cell carcinoma were identified in women over 41, highlighting risks across age groups. HPV16 was the most common genotype (17.6%), followed by HPV18 (11.3%) and HPV31 (9.4%). Other high-risk genotypes, including HPV45, HPV52, and HPV58, were also detected. Low-risk types like HPV44 were less frequent. These findings confirm a high burden of high-risk HPV types and diverse genotype circulation in Albania. This first-of-its-kind effort demonstrates the feasibility of advanced molecular diagnostics in emerging healthcare settings and underscores the urgent need for national HPV vaccination, routine screening, and sustained public health awareness across all age groups.

***Session topic**: Complex and functional genomics*

Session: P055

DETECTION OF *HELICOBACTER PYLORI* IN STOMACH CANCER PATIENTS USING DPCR

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Gastric cancer is the fifth most common and the fourth leading cause of cancer-related death worldwide. A major risk factor is infection with *Helicobacter pylori* (*H. pylori*), bacteria that colonizes the gastric epithelium, induces chronic inflammation, and contributes to gastric cancer. Only pathogenic strains expressing the cagA virulence gene are strongly associated with cancer development. Conventional detection methods, invasive (histology) and non-invasive (stool antigen test), fail to distinguish between pathogenic and non-pathogenic strains. Digital PCR (dPCR) offers superior sensitivity and specificity to quantify specific gene targets in complex sample types. This study aimed to optimize a dPCR-based protocol for the detection of H. pylori and to differentiate between non-pathogenic (ureA, babA) and pathogenic (cagA) strains in gastric cancer tissue. DNA from 7 formalin-fixed paraffin-embedded H. pylori-positive controls and 127 frozen gastric cancer tissues was analysed using QuantStudio 7 Flex (qPCR) and Absolute Q (dPCR) platforms. Our results demonstrated that dPCR identified H. pylori gene targets in samples that were missed by qPCR due to low H. pylori level. In some cases, pathogenic cagA was detected in higher copy numbers than non-pathogenic markers. This highlights the improved sensitivity and strain specificity of dPCR. We conclude that dPCR is a reliable method for the detection and characterization of H. pylori infection in gastric cancer patients.

***Session topic**: Complex and functional genomics*

Session: P056

miRNA AND circRNA AS POTENCIAL BIOMARKERS FOR ALS

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Introduction: Identifying reliable biomarkers is crucial for enhancing early diagnosis, monitoring disease progression, and identifying potential molecular mechanisms for future therapeutic targets in ALS. Among the potential biomarker candidates, miRNAs and circRNAs have garnered significant attention.

Samples: Patients were diagnosed with ALS at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, Slovenia. A total of 180 ALS patients and 200 controls were included in the study. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia, and written informed consent was obtained from all participants.

Results: Using qPCR, we analyzed several miRNAs, including miR-206, miR-218, miR-132, miR-133b, miR-23a, miR-451a, miR-663a, let-7b-5p, miR-338, miR-638, and miR-206. We found the majority of selected miRNAs significantly upregulated in the blood of ALS patients. These miRNAs are implicated in key aspects of ALS pathophysiology, including stress granule formation, nuclear pore complex dysfunction, histone methyltransferase complex alterations, and MAPK signaling disruptions.

Microarray analysis of circRNAs in PBMC revealed several promising candidate circRNAs, which were further selected for analysis on the basis of the high level of conservation and genetic constraints of the host gene and their potential role in neurodegeneration. The hsa_circ_0000567, hsa_circ_0005218, hsa_circ_0023919, hsa_circ_0043138, hsa_circ_0063411, hsa_circ_0088036, hsa_circRNA_102111, hsa_circRNA_007448, hsa_circRNA_102732, hsa_circRNA_100548, hsa_circRNA_060762, were all found deregulated in our cohort of ALS patients compared to controls.

Conclusion: These findings advance our understanding of ALS pathogenesis and provide a foundation for developing miRNA- and circRNA-based diagnostic strategies. Further validation of these results is essential to improve ALS diagnosis and treatment possibilities.

***Session topic**: Complex and functional genomics*

Session: P057

COMPREHENSIVE TRYPTASE GENOTYPING AND βIII FRAME-SHIFTED ALLELE DETECTION EMPLOYING MULTIPLEX ddPCR

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Anaphylaxis is a life-threatening systemic hypersensitivity reaction. Accurate determination of the tryptase genotype—including copy number variation (CNV), isoforms, and frameshift variants—is essential for risk assessment and further research in anaphylaxis and other mast cell-related disorders. The aim of this study was to develop and optimize multiplex droplet digital PCR (ddPCR) assays for comprehensive tryptase genotyping, capable of quantifying α- and β-tryptase sequences and detecting the βIII frame-shifted allele (βIIIFS). The assays were validated using DNA samples from 114 patients with anaphylaxis referred to the University Clinic Golnik. Results from the multiplex ddPCR were fully concordant with the original duplex assays. βIIIFS was successfully detected in all relevant cases, and the results were confirmed by Sanger sequencing. Compared to separate duplex ddPCRs, these multiplex assays significantly reduce material costs and processing time. In addition to determining CNV—particularly for diagnosing hereditary α-tryptasemia (HαT)—they enable reliable βIIIFS detection, supporting future studies on the tryptase locus in mast cell-related diseases. The comprehensive and cost-effective nature of this approach makes it highly suitable for both clinical diagnostics and large-scale research studies. Integration into routine diagnostic workflows could significantly improve genetic screening for patients at risk of severe allergic reactions.

***Session topic**: Diagnostics*

Session: P058

OVERCOMING DIAGNOSTIC CHALLENGES IN *PKD1* GENE ANALYSIS

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Background: The *PKD1* gene is associated with the autosomal dominant form of polycystic kidney disease. Routine diagnostics for patients begin with WES (whole exome sequencing) analysis. Due to the numerous pseudogene regions of the *PKD1* gene, a series of different diagnostic methods is used to prove the variant in the active gene.

Methods: If the causal variant is clearly present in the active gene, the case is concluded after WES analysis. Otherwise, MLPA (multiplex ligation-dependent probe amplification) analysis or Sanger sequencing of the problematic regions follows.

Results: Our study included 56 probands with 12 pathogenic variants in the *PKD1* gene. The interpretation of the obtained results from WES was possible for only three variants. Considering the pseudogene regions in gene, the investigated pathogenic variants were not detected by MLPA. For the remaining nine variants, additional diagnostics with long-range PCR and Sanger sequencing was required.

Conclusion: Our results show that due to the large number of homologous sequences, it is not possible to provide a result in most cases using only WES. Therefore, the use of a combination of different diagnostic methods is essential to prove pathogenic variants in the *PKD1* gene.

***Session topic**: Diagnostics*

Session: P059

DIAGNOSIS OF NEUROFIBROMATOSIS TYPE 1 USING CES, CMA AND MLPA METHODS

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Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous tumour predisposition syndrome caused by mutations in the NF1 gene. Due to its overlapping clinical features with other genetic syndromes, accurate molecular diagnosis is essential for adequate patient surveillance. This study evaluates the diagnostic utility of combining clinical exome sequencing (CES) and comparative genomic hybridisation (CMA) in patients with suspected NF1.

Methods: Forty patients with a clinical suspicion of NF1 were analysed, 28 of whom also met the clinical criteria for NF1. CES, using the Illumina platform, was performed to identify pathogenic sequence variants. CMA, using Agilent 8x60K microarray and MLPA (Multiplex ligation-dependent probe amplification), was used to detect larger genomic or intragenomic deletions involving NF1.

Results: NF1 gene mutations were identified in 18 patients by sequencing, while CNVs were detected in 5 patients using CMA. Of these, three presented with large regional deletions, and two infants with isolated café-au-lait macules carried intragenic deletions within the NF1 gene.

Conclusion: These findings support the combined use of CES, CMA and MLPA in the diagnostic work-up of NF1, as this approach improves overall detection rates by identifying a wider range of genetic alterations. Early molecular confirmation enables personalised surveillance, and informed reproductive counselling, especially in patients presenting with isolated café-au-lait macules.

***Session topic**: Diagnostics*

Session: P060

APPLICATION OF QUANTITATIVE PCR FOR *SMN1* CARRIER DETECTION IN PRENATAL AND FAMILY PLANNING SETTINGS

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Spinal muscular atrophy (SMA) is a severe autosomal recessive neuromuscular disorder primarily caused by *SMN1* exon 7 deletion. Carrier detection is essential for identifying at-risk couples and offering reproductive options. This study aimed to determine the carrier frequency during prenatal screening and family planning. Genomic DNA was extracted from 1,230 blood samples and copy number analysis of *SMN1* exons 7 and 8 was performed using the Tianlong *SMN1* gene detection kit on the Gentier 96E real-time PCR system. Among the 1,230 individuals tested, 40 carriers of *SMN1* exon 7 and/or 8 deletions were identified, yielding an overall carrier frequency of 3.25%. This included 37 pregnant women (age range: 23–43 years; gestational age: 10–12 weeks), representing a carrier frequency of 3.01% (37/1,230). All male partners of these carrier pregnant women were tested; one was also identified as a carrier, constituting a 2.7% partner carrier rate (1/37). Additionally, two other carriers were found: one non-pregnant woman with a positive family history and one male partner (with a family history of SMA) whose female partner was not pregnant and not a carrier. These findings underscore the utility of quantitative PCR as a rapid and reliable tool for carrier screening in the prenatal setting. Early identification of carriers enables timely genetic counseling, partner testing, and informed decision-making, thereby supporting the integration of SMA screening into standard prenatal care.

***Session topic**: Diagnostics*

Session: P061

COMPARISON OF qPCR-HRM AND FRAGMENT ANALYSIS METHODS TO DETERMINE THE METHYLATION STATUS OF THE *MLH1* GENE PROMOTER IN TUMOR SAMPLES

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Background: Hypermethylation of the *MLH1* gene promoter is associated with the tumorigenesis of colorectal cancer (CRC) and endometrial cancer (EC), recognized as a useful tool to distinguish sporadic from inherited Lynch syndrome-related cancers. *MLH1* gene promoter methylation status is generally determined by methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), however the results are occasionally inconclusive. To address this, we aimed to optimize and validate an alternative method, a methylation-sensitive quantitative PCR high-resolution melting (qPCR-HRM, PMID: 29224163) method, and compare the results with those of the MS-MLPA.

Methods: We isolated DNA from 25 formalin-fixed paraffin-embedded tissue EC samples. The MS-MLPA method, already established and routinely used in the laboratory, was performed with the MRC Holland (the Netherlands) ME-011 kit according to the manufacturer's instructions. The qPCR-HRM method was performed using MeltDoctor® HRM Mastermix (Thermo Fisher Scientific, USA) and EpiMelt MLH1 test assay (MethylDetect ApS, Denmark) according to our optimised protocol, because this combination of the reagents was never used beforehand with QuantStudio™ 5 instrument (Thermo Fisher Scientific, USA).

Results: Using the MS-MLPA method, methylation status could be determined for all 25 samples (19 non-methylated samples, 6 methylated samples). The results of the qPCR-HRM analysis were completely consistent with the results of the MS-MLPA.

Conclusion: We proved that the *MLH1* promoter methylation status qPCR-HRM results could be obtained with the combination of MeltDoctor® HRM Mastermix and EpiMelt MLH1 test assay. The qPCR-HRM results of *MLH1* promoter methylation status were thus consistent with those from MS-MLPA, suggesting that the method could be used for validation for inconclusive MS-MLPA results.

***Session topic**: Diagnostics*

Session: P062

HAPLOTYPE ANALYSIS OF *MMP-9* GENE POLYMORPHISMS AND THEIR ASSOCIATION WITH HEMORRHAGIC RISK FOLLOWING THROMBOLYSIS IN ACUTE ISCHEMIC STROKE PATIENTS

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Purpose: Acute ischemic stroke (AIS) is among the leading causes of death and long-term disability worldwide. Intravenous thrombolysis is a well-established treatment that can improve neurological recovery, but it also carries a notable risk of intracranial hemorrhagic complications. Matrix metalloproteinase-9 (MMP-9) has been implicated in mechanisms that exacerbate brain injury post-stroke. Genetic polymorphisms within the *MMP-9* gene may affect its expression and influence an individual's susceptibility to hemorrhagic events following thrombolytic therapy. This study aimed to investigate the potential association between *MMP-9* haplotypes and the development of intracranial hemorrhagic complications in AIS patients.

Method: This study included 161 AIS patients treated with thrombolysis. All participants were monitored during hospitalization for the occurrence of intracranial hemorrhage. Genotyping of *MMP-9* polymorphisms (rs3918241, rs3918242, rs3918249) was performed using Real-Time PCR. Haplotype analysis was conducted using Haploview software.

Summary of results: The most frequent haplotypes were TCT (71.2%), TCC (14.9%), and ATC (11.4%). No significant correlation was found between these haplotypes and the risk of hemorrhagic transformation, symptomatic hemorrhage, or other types of intracerebral bleeding. These findings suggest no strong association between *MMP-9* haplotypes and hemorrhagic complications in AIS patients undergoing thrombolysis.

***Session topic**: Diagnostics*

Session: P063

IMPLEMENTATION OF *HLA-DQ2/DQ8* GENETIC TESTING FOR COELIAC DISEASE IN A CLINICAL LABORATORY

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Background: Coeliac disease (CD) is a complex systemic autoimmune disease of the small intestine with highly variable clinical presentation and influenced by both environmental and genetic factors. The prevalence of the disease in Europe and in Slovenia is around 1%. Among the genetic factors, *HLA-DQ2* and *HLA-DQ8* are known to contribute to CD, where more than 90% of CD patients are *HLA-DQ2* positive, around 10% of CD patients are *HLA-DQ8* positive, and around 2% of CD patients are *HLA-DQ2* and *HLA-DQ8* negative, respectively. Genetic testing is indicated in individuals with clinical suspicion of CD and/or in whom serological tests yield inconclusive results. We aimed to verify a qPCR Genvinset HLA Celiac Plus kit for diagnostic application in the adult population.

Methods: DNA was isolated from blood and buccal swab samples by using the chemagic DNA Blood 4k Kit H24 on the chemagic™ 360 (Revvity, USA). We tested 10 samples of subjects with known HLA genotype by using the Genvinset HLA Celiac Plus kit, according to the manufacturer's instructions. In all verification subjects, the genotype was previously determined at an independent laboratory, by using the same method. Next, 50 consecutive samples of subjects with an unknown HLA genotype were tested with the Genvinset HLA Celiac Plus kit to evaluate its performance under routine laboratory settings. 23 of the 50 subjects (46 %) had symptoms of CD.

Results: The HLA genotypes determined for the 10 samples were completely concordant between the two independent laboratories. The results of consecutive testing of clinical samples led to the identification of 21 risk genotypes (21/23) among the individuals with symptoms of CD. The most common genotype was DQB1*02 heterozygotes/DQA1*05 heterozygotes, followed by DQB1*02 homozygotes/DQA1*05 heterozygotes (both DQ2 positive).

Conclusion: Genvinset HLA Celiac Plus kit can be easily applied to the routine diagnostic testing. Expectedly, in our cohort, *HLA-DQ2* appears to be the most common type among CD patients, as previously reported (PMID: 20301720).

***Session topic**: Diagnostics*

Session: P064

VALIDATION OF THE AUTOMATIC DNA ISOLATION FROM VARIOUS HUMAN TISSUES AND OF BACTERIAL DNA FROM ORAL MUCOSA SWABS BY METHOD BASED ON MAGNETIC BEADS

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Background: Isolation of pure and high-quality DNA is crucial for further analyses, which are essential for diagnosing human genetic diseases and predicting and monitoring the impact of treatments. We wanted to verify whether the automated, magnetic-based isolation method using the ChemagicTM360 instrument is comparable to the established, laboratory methods (reference methods).

Methods: We studied 4 tissue types for human DNA and buccal swab samples for bacterial DNA isolation. The efficacy of DNA isolation was determined by fluorometric measurement of concentration and quantity, spectrophotometric DNA purity and concentration, quantity and integrity assessment based on amplification of short repetitive Alu sequences by quantitative PCR. Capillary electrophoresis was used to quantify the size of the resulting cell-free DNA. For bacterial DNA, we determined the amplification of region V3-V4 of gene 16S rRNA.

Results: Compared to the reference methods, the ChemagicTM360 showed similar or even better results for fluorometric quantification, spectrophotometric purity determination, qPCR-based DNA quantity, and integrity measurements. The sizes of cell-free DNA fragments and the presence of bacterial DNA signals on agarose gel were also comparable between the methods.

Conclusion: We concluded that the automated DNA isolation procedure is comparable to manual methods and therefore suitable for routine laboratory use with additional benefits of higher throughput and better reproducibility.

***Session topic**: Diagnostics*

Session: P065

MOLECULAR MULTITESTING – OVERVIEW OF KEY FACTORS FOR HIGH-QUALITY AND RAPID DIAGNOSTICS

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Purpose: PCR-based detection and genotyping of HPV allows differentiation between types with high oncogenic risk and those with low risk. Based on years of work with clinicians, Poliklinika Breyer has identified key factors that simplify and expedite the diagnostic process.

Methods: The optimal testing method was established through the evaluation of various transport media and molecular diagnostic platforms. The selected approach supports various sample types, enables room temperature stability and extended analysis upon clinicians' request, ensures pathogen inactivation, and allows for rapid, automated nucleic acid extraction and analysis. For samples with lower DNA concentration and possible inhibitors, the laboratory employs an alternative advanced processing method. These measures minimize the need for repeated sampling, improving patient comfort. Effectiveness was assessed via statistical analysis of internal data from Poliklinika Breyer (2023-2024).

Results: An increase was observed in both the total number of HPV-tested samples and the proportion of multitested samples. In 2024, sample heterogeneity expanded, and the frequency of samples requiring re-collection declined.

Conclusion: The use of a universal medium with simple storage, transport, multitesting capability, and automated processing has increased the number of total and multitested HPV samples. These results highlight the effectiveness of integrating advanced diagnostic technologies with a clinician-focused approach.

***Session topic**: Diagnostics*

Session: P066

VALIDATION OF BIOINFORMATIC TOOLS FOR PHARMACOGENOMIC ANALYSIS ON NGS DATA

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Purpose: Bioinformatic tools have been developed to extract pharmacogenomic information from sequencing data. The Pharmacogenomics Clinical Annotation Tool (PharmCAT) is currently the only tool that generates an interpretation report from genetic variants. However, it cannot detect structural variants, which can be clinically important. For instance, the no-function CYP2D6*5 (a gene deletion) occurs in 3–5% of the European population. Therefore, it is recommended to use tools like Stargazer alongside PharmCAT. Our goal is to assess the performance of various tools on both short- and long-read sequencing data and to develop a pipeline to generate clinically actionable recommendations.

Methods: Variant Calling Format (VCF) files from short-read sequencing reference samples (HG002, Genome in a Bottle) and later also files from long-read sequencing will be used to evaluate the capacity of PharmCAT, in combination with other tools capable of calling complex pharmacogenes (*CYP2D6*) to provide evidence-based drug treatment recommendations.

Results: We preliminary analysed a short-read single nucleotide variation VCF file of HG002 sample, aligned to the GRCh38 in PharmCAT (v3.0.0). We were able to accurately call 9 out of 18 genotypes: *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP3A5*, *CYP4F2*, *DPYD*, *RYR1*, *UGT1A1*, *VKORC1*. However, we were unable to call genotypes for *ABCG2*, *CACNA1S*, *CFTR*, *CYP2D6*, *CYP3A4*, *G6PD*, *NUDT15*, *SLCO1B1*, and *TPMT* due to missing data or gene complexity. PharmCAT by default does not call *CYP2D6* unless an external genotype file is provided.

Conclusion: We expect that by adjustment of the VCF file and using additional tools, we will be able to resolve complex sequencing information and provide recommendations for clinically relevant pharmacogenes. Long-read WGS data may be a better source for pharmacogenes harbouring structural variants.

***Session topic**: Diagnostics*

Session: P067

GENE VARIANTS IN UROTHELIAL BLADDER CANCER ANALYZED BY SEQUENCING

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Background: Urothelial bladder cancer (UBC) is one of the most commonly diagnosed malignant neoplasms in the world. Depending on the infiltration of the muscle layer of the bladder, UBC is classified into two main categories, non-muscle-invasive (NMIBC) and muscle-invasive bladder cancer (MIBC). There is a growing evidence suggesting that genetic mutations play a key role in the molecular etiopathogenesis of UBC.

Material and Methods: Tissue samples were obtained from 32 patients with UBC who underwent cystoscopy and transurethral resection of bladder tumor (TURBT). Genomic DNA was extracted from fresh frozen tissue samples. Only samples with >50 ng/μL DNA were analyzed. A targeted cancer panel of 95 genes was used for sequencing. Libraries were prepared with KAPA EvoPlus and sequenced on an Illumina NovaSeq 6000. Variants were analyzed with CLC Genomics Workbench. COSMIC, ClinVar, dbSNP, gnomAD, and GeneBee.

Results: Targeted sequencing using the selected gene panel showed that all tumor samples (n=32) had one or more somatic mutations. Of the 95 genes tested, a total of 157 gene variants were identified in 46 genes, which, based on clinical significance, were designated as pathogenic (P) variants (n=63), likely pathogenic (LP) variants (n=34), and variants of unknown significance (VUS) (n=60). In addition, 41 likely benign and 70 benign variants were detected, but these 111 changes were excluded from further analysis.

Conclusion: Mutations in certain genes are associated with UBC. Precise genetic stratification might improve the advanced medical treatment of patients with such malignancy.

***Session topic**: Cancer*

Session: P068

VARIANTS IN THE *TP53* GENE IN PATIENTS WITH UROTHELIAL BLADDER CANCER DETECTED WITH NEXT-GENERATION SEQUENCING

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Background: Urothelial bladder cancer (UBC) is the tenth most diagnosed cancer worldwide, affecting male with significantly higher frequency than the female. Generally, UBC is subdivided in muscle-invasive bladder cancer (MIBC) and non-muscle invasive bladder cancer (NMIBC). So far, different studies have shown positive correlation of many genes with this malignancy. The *TP53* gene is a key tumor suppressor gene that is extremely frequently mutated in most human malignant neoplasms, including in patients with UBC.

Material and Methods: Of the 32 patients included in the study, 13 were with MIBC and 19 with NMIBC. For extraction of DNA, fresh frozen tumor samples were used. The extraction was automatic, followed by sequencing on Illumina platform with customized panel of 95 genes.

Results: In total, we detected 18 somatic mutations in the *TP53* gene. Of those, 14 were missense mutations, 3 were nonsense mutations and one was in a splicing region. From all the variants found, 14 (77, 78%) were pathogenic, 1 (5,56%) was likely pathogenic, 2 (11,11%) were VUS and 1 (5,56%) was likely benign.

***Topic**: Regional healthcare*

Session: P069

A RETROSPECTIVE ANALYSIS OF THE DISTRIBUTION AND POSITIVITY RATES OF MOLECULAR PCR TESTS PERFORMED IN A TERTIARY CARE CENTER THROUGHOUT 2024

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Background: PCR-based molecular diagnostics are a cornerstone in the evaluation of hematologic, immunologic, and hereditary disorders. Analysing test distribution and positivity rates is essential for optimizing diagnostic workflows and laboratory resource allocation.

Materials and Methods: We retrospectively evaluated 2,491 PCR-based molecular tests performed between January and December 2024 in our outpatient clinic. Eight widely utilized assays were analysed alongside demographic and clinical data.

Results: The most frequently performed tests were *FMF* (n=664) and *JAK2* V617F (n=648), with positivity rates of 29.5% and 13%, respectively. Additional rates included *BCR-ABL1* (15%), *HLA-B51* (39.1%), *HLA-B27* (21.6%), and *PML-RARA* (4.3%). The celiac panel revealed *DQ2* (44%), *DQ8* (23%), and *DR4* (23%) allele positivity. In the thrombophilia panel, F2 variants were found in 14% heterozygous and 3.1% homozygous, while F5 (Factor V Leiden) mutations were present in 23.1% heterozygous and 4.7% homozygous cases.

Conclusion: Our findings demonstrate the effective application of PCR-based molecular tests in accordance with clinical indications across diverse disease contexts. The observed patterns and diagnostic yields provide actionable insights for refining test indications, improving workflow efficiency, and guiding molecular diagnostic strategies.

***Topic**: Diagnostics*

Session: P070

POLYGENIC RISK SCORE AND GENETIC MARKERS IN ALCOHOL-RELATED CIRRHOSIS

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Purpose: A minority of excess alcohol drinkers develop cirrhosis. Variants in patatin-like phospholipase domain-containing protein 3 gene (PNPLA3) and transmembrane 6 superfamily member 2 gene (TM6SF2) were previously identified as associated with alcohol-related cirrhosis (ALC). Aim of our study was to analyse variants in PNPLA3 and TM6SF2 genes and to develop and assess polygenic risk scores (PRS) for early risk stratification of excess alcohol drinkers at the most significant risk of developing ALC.

Methods: We enrolled 118 patients with ALC and 131 control subjects who were either abstainers or consumers of low levels of alcohol without evidence of liver disease. Genotyping was performed using PCR-RFLP and PRS based on independent allelic effect size estimates were computed from genotyped genetic loci and compared across the groups.

Summary of results: The development of ALC was associated with CG and GG PNPLA3 genotypes (P<0.001) and CT genotype of TM6SF2 (P=0.007). Patients with cirrhosis had significantly higher mean PRS than controls (0.32 vs. 0.167, adjusted p =1.8e-07). The odds ratios (ORs) and (95% CIs) between the group with the highest PRS score compared with the reference group were 6.707; 3.313-13.581, P<0.001. In ALC patients the PNPLA3 rs738409 and TM6SF2 rs58542926 variants were associated with an increased risk for ALC development. Additionally, PRS derived from these two variants facilitates risk stratification and may support earlier clinical interventions.

***Topic**: Regional healthcare*

Session: P071

PHARMACOGENOMIC LANDSCAPE OF THE SERBIAN POPULATION

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Purpose: Pharmacogenomics offers the opportunity to predict drug response by analyzing an individual's genetic profile. Highthroughput sequencing technologies facilitated identification and interpretation of variants in many pharmacogenes simultaneously. The integration of pharmacogenomics into clinical practice is still scarce. The aim of our study was to assess the most comprehensive pharmacogenomics landscape of the Serbian population so far.

Methods: Genomic data of 881 individuals from Serbia obtained by clinical and whole exome sequencing was used. Raw sequencing files were processed using an in-house pipeline. The PharmCAT and Stargazer tools were used for annotation of pharmacogenetics star alleles and determination of phenotypes. Star allele and phenotype frequencies were calculated and compared to worldwide and European populations.

Summary of results: The greatest differences in pharmacogenomic profiles were noted between the Serbian and worldwide populations. In the Serbian population, the most relevant pharmacogenes were *CYP2B6*, *NAT2*, *SLCO1B1*, *UGT1A1* and *VKORC1*. Significant differences in frequencies of pharmacogenetic phenotypes that influence response to several drug categories including statins and antidepressants indicate that pharmacogenomics testing would be beneficial in the Serbian population. Implementation of pharmacogenetic testing could be achieved through analysis of clinical and whole exome sequencing data.

***Topic**: Regional healthcare*

Session: P072

HUMANITARIAN GENETICS: REFLECTIONS FROM A PEDIATRIC GENETICIST IN KABUL, AFGHANISTAN

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My name is Dr. Funda Kökali, a pediatric geneticist from Türkiye. Between June 4–11, 2025, I joined a humanitarian medical mission in Kabul, Afghanistan, organized with Yeryüzü Doktorları, a non-governmental organization providing healthcare and nutritional support in underserved areas.

Our team delivered primary care in remote settings through mobile clinics, addressing acute illnesses, chronic conditions, and preventive needs. Common complaints included febrile illnesses, respiratory infections, gastrointestinal symptoms, dermatological conditions, anemia, and fatigue. We also offered basic health education to patients and caregivers.

A major challenge was the absence of diagnostic infrastructure for children with suspected genetic disorders. While we managed acute care, no referral or long-term evaluation pathways existed for rare or syndromic conditions.

One striking case involved two siblings in a nutrition program, both with dysmorphic features, microcephaly, and severe growth failure. Despite clear signs of a possible genetic disorder, they had never received formal evaluation. Many similarly affected dysmorphic children were seen during the mission.

Another case involved a child with craniosynostosis, polydactyly, and a bifid thumb. The family's question wasn't about acute illness, it was, "Why is our child like this?" In resource-limited settings, the lack of answers, not medicine, is often the deepest burden.

This experience reinforced that genetics is not a luxury but a human right. Recognizing syndromic patterns and validating families' concerns must become part of humanitarian care. Global health equity demands access to genetic evaluation, even in the most underserved contexts.

***Topic**: Regional healthcare*

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Prvi in edini zaviralec PARP odobren za 5 različnih lokalizacij tumorjev[1-5]

RAK JAJČNIKOV

Prvi zaviralec PARP odobren za vzdrževalno zdravljenje napredovalega raka jajčnikov v monoterapiji (v 1L pri bolnicah z mutacijo *gena BRCA1/2* in 2L) ali kombinaciji z bevacizumabom (pri bolnicah s HRD).[1-3, 5]

RAK TREBUŠNE SLINAVKE

Edini zaviralec PARP odobren za vzdrževalno zdravljenje bolnikov z zarodno mutacijo gena *BRCA1/2*, ki imajo razsejani adenokarcinom trebušne slinavke in jim bolezen ni napredovala po najmanj 16 tednih prvega reda zdravljenja s kemoterapijo na osnovi platine.[1-4]

RAK DOJK

Prvi zaviralec PARP odobren za zdravljenje, pri bolnikih z zarodno mutacijo gena *BRCA1/2*, ki imajo HER2-negativni zgodnji, lokalno napredovali ali razsejan rak dojk.[1-2, 4]

RAK PROSTATE

Edini zaviralec PARP odobren za zdravljenje bolnikov z razsejanim KORP v monoterapiji za bolnike z mutacijami gena *BRCA1/2*, ki jim je bolezen napredovala po zdravljenju z novim hormonskim zdravilom, in v kombinaciji z abirateronom ne glede na status mutacij.[1-4]

RAK ENDOMETRIJA

Prvi in edini zaviralec PARP odobren za vzdrževalno zdravljenje odraslih bolnic s primarno napredovalim ali ponovljenim rakom endometrija v kombinaciji z durvalumabom za bolnice, ki nimajo okvare popravljanja neujemanja pri podvojevanju DNA (pMMR), bolezen pa jim ni napredovala med zdravljenjem prve linije z durvalumabom v kombinaciji s karboplatinom in paklitakselom.[1-4,*]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

LYNPARZA 100 mg filmsko obložene tablete / LYNPARZA 150 mg filmsko obložene tablete

PARP – poli (ADP-riboza) polimeraza, **1L** – v prvem redu zdravljenja, **2L** – v drugem redu zdravljenja, **HRD** – pomanjkanje homologne rekombinacije, **KORP** – na kastracijo odporen rak prostate

SESTAVA: Ena filmsko obložena tableta vsebuje 100 mg olapariba ali 150 mg olapariba.

INDIKACIJE: Rak jajčnikov: 1) *zdravilo Lynparza je indicirano kot monoterapija za*:
• vzdrževalno zdravljenje odraslih bolnic z napredovalim (stadij III in IV po FIGO) epitelijskim rakom visokega gradusa jajčnikov, jajcevodov ali primarnim peritonealnim rakom z mutacijo gena *BRCA1/2* (germinalno in/ali somatsko), ki so v odzivu (popolnem ali delnem) po zaključeni prvi liniji kemoterapije na osnovi platine.
• vzdrževalno zdravljenje odraslih bolnic, pri katerih je prišlo do ponovitve epitelijskega raka visokega gradusa jajčnikov, jajcevodov ali primarnega peritonealnega raka, občutljivega na platino, ki so v popolnem ali delnem odzivu na kemoterapijo na osnovi platine.
2) *zdravilo Lynparza je v kombinaciji z bevacizumabom indicirano za:*
• vzdrževalno zdravljenje odraslih bolnic z napredovalim (stadij III in IV po FIGO) epitelijskim rakom visokega gradusa jajčnikov, jajcevodov ali primarnim peritonealnim rakom, ki so v popolnem ali delnem odzivu po zaključeni prvi liniji kemoterapije na osnovi platine v kombinaciji z bevacizumabom, pri katerih je rak povezan s pozitivnim stanjem pomanjkanja homologne rekombinacije (HRD – homologous recombination deficiency), opredeljenim z mutacijo gena *BRCA1/2* in/ali genomsko nestabilnostjo.
Rak dojk: *zdravilo Lynparza je indicirano kot:*
• monoterapija ali v kombinaciji z endokrinim zdravljenjem za adjuvantno zdravljenje odraslih bolnikov z germinalnimi mutacijami gena *BRCA1/2*, ki imajo HER2-negativnega zgodnjega raka dojk z velikim tveganjem in so bili predhodno zdravljeni z neoadjuvantno ali adjuvantno kemoterapijo.
• monoterapija za zdravljenje odraslih bolnikov z germinalno mutacijo gena *BRCA1/2*, ki imajo HER2-negativnega lokalno napredovalega ali metastatskega raka dojk. Bolniki morajo biti predhodno zdravljeni z antraciklinom in taksanom v okviru (neo)adjuvantnega zdravljenja ali zdravljenja metastatske bolezni, razen če za ti zdravljenji niso primerni. Pri bolnikih, ki imajo raka dojk s pozitivnimi hormonskimi receptorji (HR), je morala bolezen prav tako napredovati med predhodnim hormonskim zdravljenjem ali po njem, ali morajo bolniki veljati za neprimerne za hormonsko zdravljenje.
Adenokarcinom trebušne slinavke: zdravilo Lynparza je kot monoterapija indicirano za vzdrževalno zdravljenje odraslih bolnikov z germinalno mutacijo gena BRCA1/2, ki imajo metastatski adenokarcinom trebušne slinavke in njihova bolezen ni napredovala po najmanj 16 tednih zdravljenja s platino v shemi prve linije kemoterapije.
Rak prostate: *zdravilo Lynparza je indicirano:*
• kot monoterapija za zdravljenje odraslih bolnikov z metastatskim, na kastracijo odpornim rakom prostate (mKORP) in mutacijami gena *BRCA1/2* (germinalnimi in/ali somatskimi), pri katerih je bolezen napredovala po predhodni terapiji, ki je vsebovala novo hormonsko zdravilo.
• v kombinaciji z abirateronom in prednizonom ali prednizolonom za zdravljenje odraslih bolnikov z mKORP, pri katerih kemoterapija ni klinično indicirana.
Rak endometrija: Zdravilo Lynparza je v kombinaciji z durvalumabom indicirano za vzdrževalno zdravljenje odraslih bolnic s primarno napredovalim ali ponovljenim rakom endometrija, ki nimajo okvare popravljanja neujemanja pri podvojevanju DNA (pMMR), bolezen pa jim ni napredovala med zdravljenjem prve linije z durvalumabom v kombinaciji s karboplatinom in paklitakselom.

ODMERJANJE IN NAČIN UPORABE: Priporočeni odmerek zdravila Lynparza pri monoterapiji ali v kombinaciji z drugimi zdravili je 300 mg (dve 150 mg tableti) dvakrat na dan; to ustreza celotnemu dnevnemu odmerku 600 mg. 100 mg tablete so na voljo za zmanjšanje odmerka. Bolnice s ponovitvijo raka jajčnikov morajo začeti zdravljenje z zdravilom Lynparza najpozneje v 8 tednih po zadnjem odmerku sheme zdravljenja na osnovi platine. Če je zdravilo Lynparza uporabljeno v kombinaciji z bevacizumabom za prvo linijo vzdrževalnega zdravljenja po dokončanju prve linije zdravljenja na osnovi platine in z bevacizumabom, je odmerek bevacizumaba 15 mg/kg enkrat na 3 tedne. Glejte celotne informacije o zdravilu za bevacizumab. Za priporočeno odmerjanje partnerskega zdravila/partnerskih zdravil (zaviralec aromataze/antiestrogen in/ali LHRH) v kombinaciji endokrinega zdravljenja glejte celotne informacije o zadevnem zdravilu. Če je zdravilo Lynparza uporabljeno v kombinaciji z abirateronom za zdravljenje bolnikov z mKORP, je odmerek abiraterona 1000 mg peroralno enkrat na dan. Abirateron je treba dajati s 5 mg prednizona ali prednizolona peroralno dvakrat na dan. Glejte celotne informacije o zdravilu za abirateron. Če je zdravilo Lynparza uporabljeno v kombinaciji z durvalumabom za vzdrževalno zdravljenje odraslih bolnic s primarno napredovalim ali ponovljenim rakom endometrija brez okvare MMR (pMMR), ki jim bolezen ni napredovala med zdravljenjem prve linije z durvalumabom v kombinaciji s karboplatinom in paklitakselom, je odmerek durvalumaba 1500 mg na 4 tedne. Glejte celotne informacije o zdravilu za durvalumab. Prvo linijo vzdrževalnega zdravljenja napredovalega raka jajčnikov z mutacijo gena BRCA in prvo linijo vzdrževalnega zdravljenja HRD-pozitivnega napredovalega raka jajčnikov v kombinaciji z bevacizumabom je priporočljivo nadaljevati do radiološkega napredovanja bolezni ali nesprejemljive toksičnosti ali do največ 2 leti, če po 2 letih ni radioloških znakov bolezni. V primeru znakov bolezni po 2 letih, se lahko zdravljenje nadaljuje, če bi le to po mnenju zdravnika bilo koristno za bolnico. Glejte informacije o zdravilu bevacizumab za priporočeno celotno trajanje zdravljenja največ 15 mesecev, vključno z obdobji v kombinaciji s kemoterapijo in kot vzdrževalno zdravljenje. Pri adjuvantnem zdravljenju zgodnjega raka dojk je priporočljivo, da bolniki prejemajo zdravljenje do 1 leto ali do ponovitve bolezni ali do nesprejemljive toksičnosti, kar od tega se zgodi najprej. Zdravljenje ponovitve raka jajčnikov, raka dojk, adenokarcinoma trebušne slinavke,raka prostate in napredovalega ali ponovljenega raka endometrija je priporočljivo nadaljevati do napredovanja osnovne bolezni ali nesprejemljive toksičnosti. Učinkovitost in varnost ponovnega vzdrževalnega zdravljenja z zdravilom Lynparza po prvi ali poznejši ponovitvi bolezni pri bolnicah z rakom jajčnikov nista bili dokazani. Podatkov o učinkovitosti in varnosti ponovnega zdravljenja pri bolnicah z rakom dojk ni. Pri raku prostate je treba pri bolnikih, ki niso bili kirurško kastrirani, nadaljevati z medicinsko kastracijo z analogom luteinizirajočega hormona sproščajočega hormona. Če je zdravilo Lynparza uporabljeno v kombinaciji z abirateronom in prednizonom ali prednizolonom, je zdravljenje priporočljivo nadaljevati do napredovanja osnovne bolezni ali do nesprejemljivih toksičnih učinkov. Pri vseh bolnikih je treba med zdravljenjem še naprej uporabljati analoge GnRH (gonadotropin sproščajočega hormona) ali pa morajo bolniki pred tem opraviti obojestransko orhidektomijo. Glejte informacije o zdravilu za abirateron. Podatkov o učinkovitosti ali varnosti ponovnega zdravljenja z zdravilom Lynparza pri bolnikih z rakom prostate ni. Če je zdravilo uporabljeno v prvi liniji vzdrževalnega zdravljenja napredovalega ali ponovljenegaraka endometrija, ki nima okvare MMR (pMMR), v kombinaciji z durvalumabom je zdravljenje je priporočljivo nadaljevati do napredovanja osnovne bolezni ali do nesprejemljivih toksičnih učinkov. Glejte informacije o zdravilu za durvalumab. V primeru potrebe po zmanjšanju odmerka zaradi neželenih učinkov je priporočeno zmanjšanje odmerka na 250 mg dvakrat na dan (to ustreza celotnemu dnevnemu odmerku 500 mg). Če je potrebno še dodatno zmanjšanje odmerka, je priporočljivo zmanjšanje odmerka na 200 mg dvakrat na dan (to ustreza celotnemu dnevnemu odmerku 400 mg). Zdravljenje z zdravilom Lynparza mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil proti raku. Mutacijsko stanje *BRCA* in/ali genomsko nestabilnost morajo imeti bolniki potrjeno z validiranim testom. Pred uporabo zdravila Lynparza v kombinaciji z abirateronom in prednizonom ali prednizolonom za zdravljenje bolnikov z mKORP genomsko testiranje ni potrebno. Pri zdravljenju v prvi liniji vzdrževalnega zdravljenja napredovalega ali ponovljenega raka endometrija, ki nima okvare MMR (pMMR), v kombinaciji z durvalumabom je pred uvedbo zdravljenja treba z validiranim testom potrditi, da ima bolnica stanje tumorja brez okvare MMR (pMMR). Genetsko svetovanje bolnikom z mutacijami *BRCA* je treba opraviti v skladu z lokalnimi predpisi. Zdravilo Lynparza se lahko pri bolnikih z blago okvaro ledvic (očistek kreatinina 51 do 80 ml/min) uporablja brez prilagoditve odmerka. Pri bolnikih z zmerno okvaro ledvic (očistek kreatinina 31 do 50 ml/min) je priporočen odmerek 200 mg dvakrat na dan. Uporaba zdravila se pri bolnikih s hudo okvaro ali končno odpovedjo ledvic (očistek kreatinina ≤ 30 ml/min) ne priporoča, ker varnost in farmakokinetika pri tej skupini bolnikov nista bili raziskani. Zdravilo Lynparza se lahko daje bolnikom z blago ali zmerno okvaro jeter (klasifikacija Child-Pugh A ali B) brez prilagoditve odmerka. Uporabe zdravila Lynparza se ne priporoča pri bolnikih s hudo okvaro jeter (klasifikacija Child-Pugh C), ker varnost in farmakokinetika pri tej skupini bolnikov nista bili raziskani. Zdravilo Lynparza je za peroralno uporabo. Tablete zdravila Lynparza je treba pogoltniti cele in se jih ne sme gristi, drobiti, raztapljati ali lomiti. Lahko se jih jemlje ne glede na obroke. **KONTRAINDIKACIJE:** Preobčutljivost na učinkovino ali katero koli pomožno snov. Dojenje med zdravljenjem in en mesec po zadnjem odmerku. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** *Hematološki toksični učinki:* Pri bolnikih, zdravljenih z zdravilom Lynparza, so bili opisani hematološki toksični učinki, vključno s klinično diagnozo in/ali laboratorijskimi izsledki, na splošno blage ali zmerne (stopnja 1 ali 2 po CTCAE) anemije, nevtropenije, trombocitopenije in limfopenije. Če je bilo zdravilo Lynparza uporabljeno v kombinaciji z durvalumabom, so poročali o čisti aplaziji rdečih krvnih celic (PRCA) in/ali o avtoimunski hemolitični anemiji (AIHA). Bolniki ne smejo začeti zdravljenja z zdravilom Lynparza, dokler ne okrevajo po hematoloških toksičnih učinkih predhodnega zdravljenja proti raku. Preiskava celotne krvne slike je priporočljiva na začetku zdravljenja, potem vsak mesec prvih 12 mesecev zdravljenja in pozneje redno. Če se pri bolniku pojavijo hudi hematološki toksični učinki ali je odvisen od transfuzij krvi, je treba zdravljenje z zdravilom Lynparza prekiniti in uvesti ustrezno hematološko testiranje. Če krvne vrednosti ostanejo klinično nenormalne še 4 tedne po prekinitvi uporabe zdravila Lynparza, je priporočljivo opraviti preiskavo kostnega mozga in/ali krvno citogenetsko analizo. Če je PRCA ali AIHA potrjena, je treba zdravljenje z zdravilom Lynparza in durvalumabom prenehati. *Mielodisplastični sindrom/akutna mieloična levkemija (MDS/AML):* Celokupna pojavnost MDS/AML je bila pri bolnikih, ki so v kliničnih preizkušanjih prejemali monoterapijo z zdravilom Lynparza, vključno v obdobju dolgoročnega spremljanja preživetja, < 1,5 %, z večjo pojavnostjo pri bolnicah z *BRCA*m, pri katerih je prišlo do ponovitve na platino občutljivega raka jajčnikov, ki so predhodno prejele vsaj dve liniji kemoterapije s platino in so jih spremljali 5 let. Večina teh primerov je bila s smrtnim izidom. Če obstaja sum na MDS/AML, je potrebno bolnico napotiti na nadaljnje preiskave k hematologu, vključno z analizo kostnega mozga in odvzemom krvi za citogenetiko. Če se po preiskavi dolgotrajne hematološke toksičnosti potrdi MDS/AML, je treba uporabo zdravila Lynparza prekiniti in bolnico ustrezno zdraviti. *Venski trombembolični dogodki:* Med zdravljenjem z zdravilom Lynparza so poročali o venskih trombemboličnih dogodkih, predvsem o pljučni emboliji, vendar ti dogodki niso imeli kakšnega doslednega kliničnega vzorca. V primerjavi z drugimi odobrenimi indikacijami so opažali večjo pojavnost pri bolnikih z metastatskim, na kastracijo odpornim rakom prostate, ki so prejemali tudi androgeno deprivacijsko zdravljenje. Bolnike spremljajte glede kliničnih znakov in simptomov venske tromboze in pljučne embolije, ter jih zdravite kot je medicinsko ustrezno. Bolniki z anamnezo VTE imajo morda večje tveganje za njeno ponovitev in jih je treba ustrezno spremljati. *Pnevmonitis:* V kliničnih študijah je bil pnevmonitis, vključno s smrtnim izidom, opisan pri < 1,0 % bolnikov, ki so prejemali zdravilo Lynparza, spremljali pa so jih številni predispozicijski dejavniki. Če se pri bolniku pojavijo novi ali poslabšajo obstoječi dihalni simptomi, npr. dispneja, kašelj in zvišana telesna temperatura, ali je ugotovljen nenormalen radiološki izvid prsnih organov, je treba zdravljenje z zdravilom Lynparza prekiniti in takoj opraviti preiskave. Če je pnevmonitis potrjen, je treba zdravljenje z zdravilom Lynparza prekiniti in bolnika ustrezno zdraviti. *Hepatotoksičnost:* Če se pojavijo klinični simptomi ali znaki, ki kažejo na razvoj hepatotoksičnosti, je treba takoj izvesti klinično oceno bolnika in preiskave delovanja jeter. V primeru suma na z zdravilom povzročeno okvaro jeter (DILI - drug-induced liver injury) je treba zdravljenje prekiniti. V primeru hude DILI je treba razmisliti o ukinitvi zdravljenja, kot je klinično primerno. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Zdravilo Lynparza se uporablja kot monoterapija in ni primerno za uporabo v kombinaciji z mielosupresivnimi zdravili proti raku, vključno z zdravili, ki poškodujejo DNA. Sočasna uporaba olapariba s cepivi ali imunosupresivnimi zdravili ni raziskana. Za presnovni očistek olapariba so pretežno odgovorni izoencimi CYP3A4/5. Sočasna uporaba zdravila Lynparza z znanimi močnimi ali zmernimi zaviralci tega izoencima ni priporočljiva. Če je treba sočasno uporabiti močne ali zmerne zaviralce CYP3A, je treba odmerek zdravila Lynparza zmanjšati. Prav tako med zdravljenjem z zdravilom Lynparza ni priporočljivo pitje grenivkinega soka. Prav tako olapariba ni priporočljivo uporabljati z znanimi močnimi ali zmernimi do močnimi induktorji tega izoencima, ker obstaja možnost, da se učinkovitost zdravila Lynparza bistveno zmanjša. Olaparib *in vitro* zavira CYP3A4 ter *in vivo* predvidoma blago zavira CYP3A. Zato je potrebna previdnost pri sočasni uporabi olapariba z občutljivimi substrati CYP3A4 ali substrati, ki imajo ozko terapevtsko okno. Bolnike, ki sočasno z olaparibom prejemajo substrate CYP3A z ozkim terapevtskim oknom, je priporočljivo ustrezno klinično spremljati. *In vitro* so ugotovili indukcijo CYP1A2, 2B6 in 3A4, prav tako ni mogoče izključiti možnosti, da olaparib inducira CYP2C9, CYP2C19 in P-gp, zato lahko olaparib po sočasni uporabi zmanjša izpostavljenost substratom teh presnovnih encimov in prenašalne beljakovine. Učinkovitost nekaterih hormonskih kontraceptivov se lahko zmanjša, če so uporabljeni sočasno z olaparibom. *In vitro* olaparib zavira efluksni prenašaleca P-gp, zato je potrebno bolnike, ki sočasno prejemajo substrate P-gp, ustrezno klinično spremljati. *In vitro* olaparib zavira BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 in MATE2K. Še zlasti je previdnost potrebna, če se olaparib uporablja v kombinaciji s katerim koli statinom. Izvedli so klinično študijo za oceno kombinacije olapariba z anastrozolom, letrozolom in tamoksifenom, vendar klinično pomembnih medsebojnih delovanj niso opazili. **NEŽELENI UČINKI:** Zdravilo Lynparza je bilo povezano z neželenimi učinki, ki so bili na splošno blage ali zmerne resnosti (stopnja po CTCAE 1 ali 2) in na splošno niso zahtevali prekinitve zdravljenja. Če je zdravilo Lynparza uporabljeno v kombinaciji z bevacizumabom pri raku jajčnikov, v kombinaciji z abirateronom in prednizonom ali prednizolonom pri raku prostate, ali v kombinaciji z durvalumabom po zdravljenju z durvalumabom v kombinaciji s kemoterapijo na osnovi platine za raka endometrija, se varnostni profil na splošno sklada z varnostnim profilom vsakega posameznega zdravila. Na mostni profil tem elji na ium ulativnih podatkih 4499 bolnikov s solidnimi tumorji, ki so bili v kliničnih preskušanjih zdravljeni z monoterapijo z zdravilom Lynparza v priporočenem odmerku. *Zelo pogosti neželeni učinki:* anemija, nevtropenija, levkopenija, zmanjšanje apetita, omotica, glavobol, spremenjen okus, kašelj, dispneja, bruhanje, driska, navzea, dispepsija in utrujenost (vključno z astenijo). *Pogosti neželeni učinki:* limfopenija, trombocitopenija, zvišanje transaminaz, stomatitis, bolečine v zgornjem delu trebuha, izpuščaj, zvišanje kreatinina v krvi in venska trombembolija. Pri bolnicah, ki so prejemale zdravilo Lynparza v kombinaciji z durvalumabom po zdravljenju z durvalumabom v kombinaciji s kemoterapijo na osnovi platine, so se z večjo pogostnostjo pojavili neželeni učinki: trombocitopenija in izpuščaj (zelo pogosti) ter preobčutljivost (pogosti). Ugotovili so tudi dodatni neželeni učinek čiste aplazije rdečih krvnih celic. **PLODNOST, NOSEČNOST IN DOJENJE:** Ženske v rodni dobi ne smejo biti nosečе na začetku zdravljenja z zdravilom Lynparza in ne smejo zanositi med zdravljenjem in še 6 mesecev po prejetju zadnjega odmerka. Pri vseh ženskah v rodni dobi je potrebno pred zdravljenjem opraviti test nosečnosti in ga redno izvajati med celotnim zdravljenjem. Priporočljivi sta dve visoko učinkoviti in komplementarni obliki kontracepcije. Zaradi možnega medsebojnega delovanja olapariba s hormonsko kontracepcijo je treba razmisliti o dodatni nehormonski kontracepciji. Pri ženskah s hormonsko odvisnim rakom je treba razmisliti o dveh nehormonskih načinih kontracepcije. Zdravilo Lynparza je kontraindicirano med obdobjem dojenja in še en mesec po prejetju zadnjega odmerka. Moški bolniki morajo med zdravljenjem in še 3 mesece po prejetju zadnjega odmerka zdravila Lynparza med spolnimi odnosi z nosečo žensko ali žensko v rodni dobi uporabljati kondom. Tudi partnerke moških bolnikov morajo uporabljati visoko učinkovito kontracepcijo, če so v rodni dobi. Moški bolniki med zdravljenjem z zdravilom Lynparza in še 3 mesece po zadnjem odmerku tega zdravila ne smejo darovati sperme. **REŽIM PREDPISOVANJA IN IZDAJE ZDRAVILA:** Rp/Spec. **DATUM ZADNJE REVIZIJE BESEDILA:** 5.6.2025 (SI-4324) **IMETNIK DOVOLJENJA ZA PROMET**: AstraZeneca AB, SE-151 85 Södertälje, Švedska. Dodatne informacije so na voljo pri podjetju AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, 1000 Ljubljana, telefon: 01/51 35 600. **Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.**

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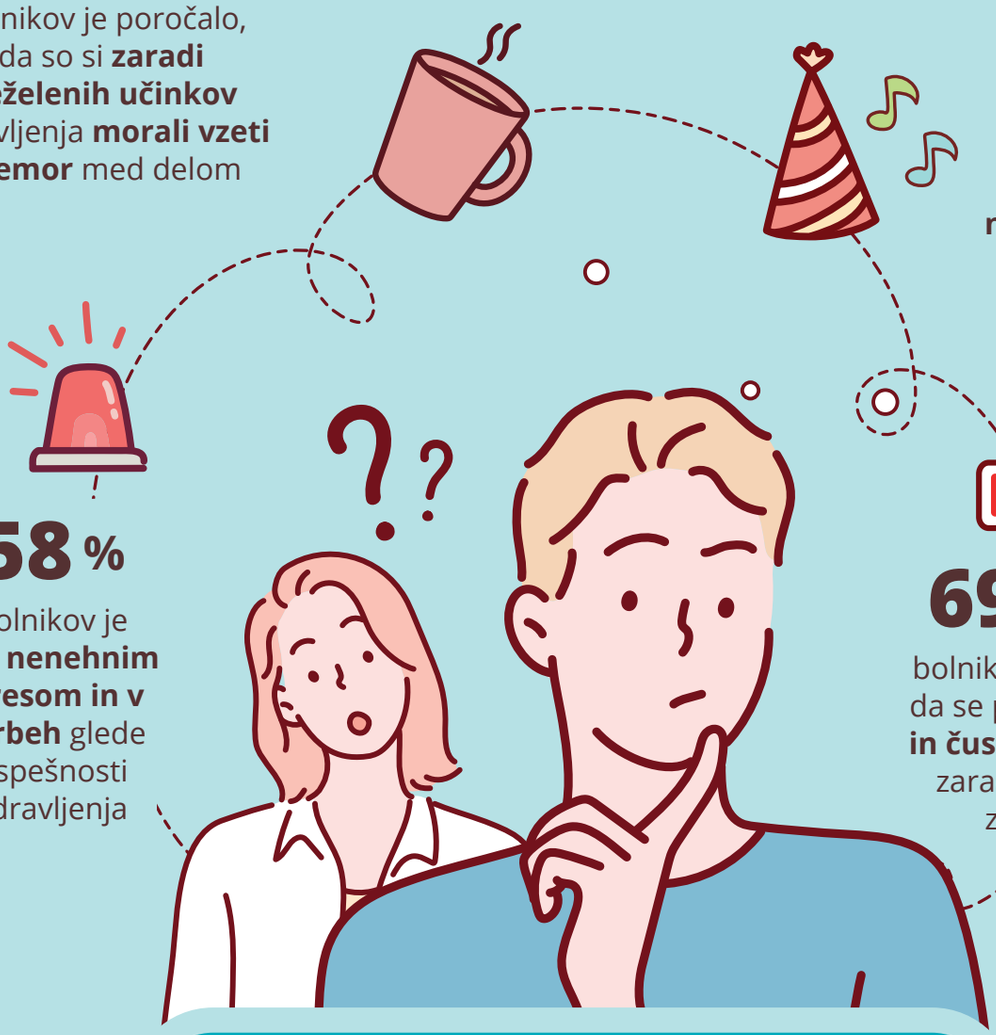

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KML; kronična mieloična levkemija. **Vira: 1.** Russo D, Malagola M, Polverelli N, Farina M, Re F, Bernardi S. Twenty years of evolution of CML therapy: how the treatment goal is moving from disease to patient. Ther Adv Hematol. 2023 Dec 22;14:20406207231216077. doi: 10.1177/20406207231216077. PMID: 38145059; PMCID: PMC10748527. **2.** Lang F, Pemberton-Whiteley Z, Clements J, et al. Chronic Myeloid Leukemia Survey on Unmet Needs (CML SUN): Balancing Tolerability and Efficacy Goals of Patients and Treatment Decision-Making. Presented at: EHA2023 Hybrid Congress; June 08-15, 2023; Frankfurt, Germany.

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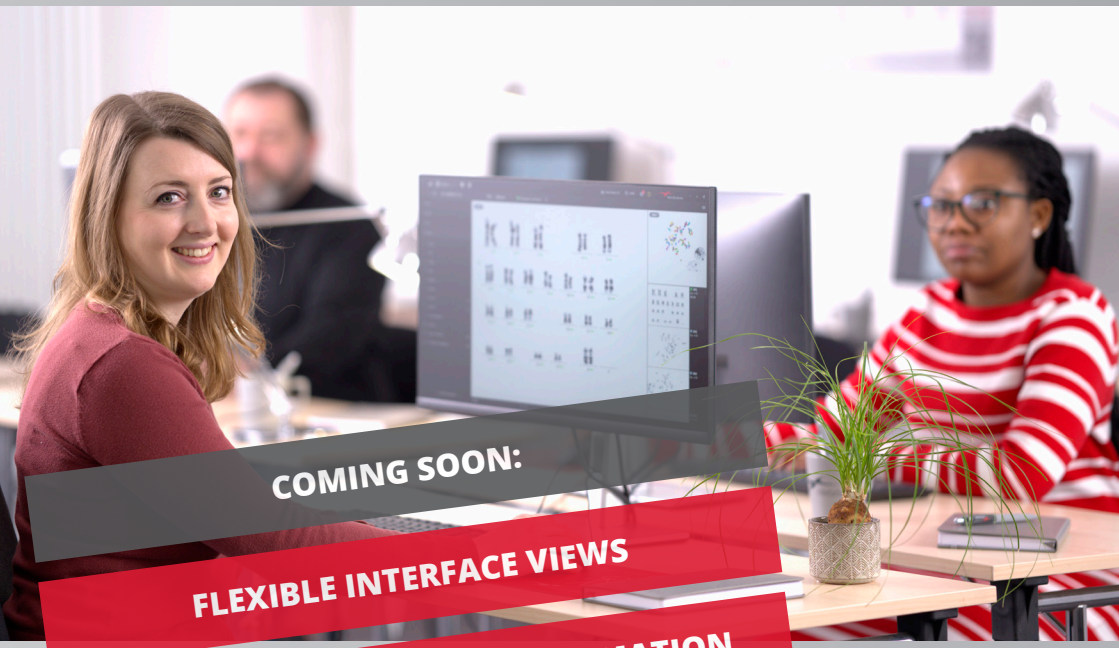

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