VILNIUS UNIVERSITY HOSPITAL SANTAROS KLINIKOS

RESEARCH AND INNOVATION

2022

Dear colleagues,

We invite you to explore the third issue of "Research and Innovation" – a yearly overview of the main R&D achievements at Vilnius University Hospital Santaros Klinikos. In 2022, Santaros Klinikos faced new challenges - we had a duty to help the victims of the shocking war in Ukraine. We can be proud that the doctors and nurses of Santaros Klinikos participated in the voluntary aid missions in Ukraine organised by the Ministry of Health of the Republic of Lithuania, counselled asylum seekers and aided Ukrainian specialists in their home country.

In 2022, Santaros Klinikos remained a strong regional clinical and research centre, with a growing number of newly initiated and long-term R&D initiatives. Specialists at Santaros Klinikos actively collaborate with foreign partners, implement projects funded by the European Horizon Programme, engage in international networks to improve the quality of both research and patient care, and conduct clinical trials. A consistent and focused activity of our specialists in most fields of medicine allows us to maintain the highest standard of healthcare and gives us the opportunity to explore new areas for the discovery of novel diagnostic and treatment methods. As we look forward to the richness and diversity of our research and innovation in 2022, I invite you to become inspired for new initiatives and overcome even the most difficult professional challenges.

Sincerely

Director General Prof. Feliksas Jankevičius

Contents

Biomedical Research Unit, Innovation and Technology Transfer Unit

Biomedical research and Research and Experimental Development (R&D) projects at Vilnius University Hospital Santaros Klinikos

Biomedical research

One of the many activities of Vilnius University Hospital Santaros Klinikos (VUH SK) is to conduct independent biomedical research. VUH SK continuously promotes the development of biomedical research, contributes to the formation of Lithuanian and European Union (EU) health policy, and implements EU joint actions and biomedical projects. In 2022, biomedical research at the hospital consisted of epidemiological, retrospective, prospective studies, clinical drug and medical device trials, R&D projects in collaboration with other scientific institutions, presentations at international conferences, research works of PhD and undergraduate students. Biomedical research is focused on drug and medical device clinical trials as well as investigation of chronic non-infectious and infectious diseases. VUH SK has a modern infrastructure for Phase I-IV clinical trials of drugs, medical devices and other biomedical research.

In 2022, 529 biomedical trials in various therapeutic areas were active at VUH SK – 236 scientific trials (48 initiated in 2022), 293 drug and medical device clinical trials (51 initiated in 2022) (Figure 1). 50 new preliminary contracts and 51 clinical trial contracts for medicinal products and medical devices have been signed, as well as 26 cooperation agreements with other Lithuanian and foreign scientific institutions for research purposes. In 2022, representatives of the Biomedical Research Unit of VUH SK prepared four presentations at international conferences[1-4] and published seven articles[5-11].

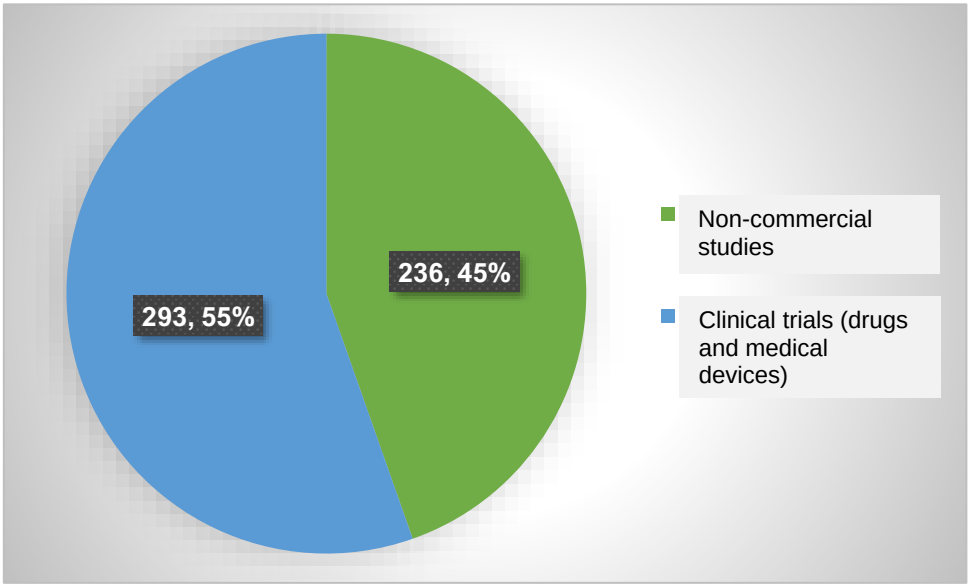

Figure 1. Biomedical research at VUH SK in 2022.

In 2022, the main areas of biomedical research at VUH SK were cardiology and angiology, obstetrics and gynecology, neurology, medical genetics, pediatric oncohematology, and other

pediatric areas, as well as biomedical research in various fields carried out by the Biomedical Research Unit (Figures 2 and 3).

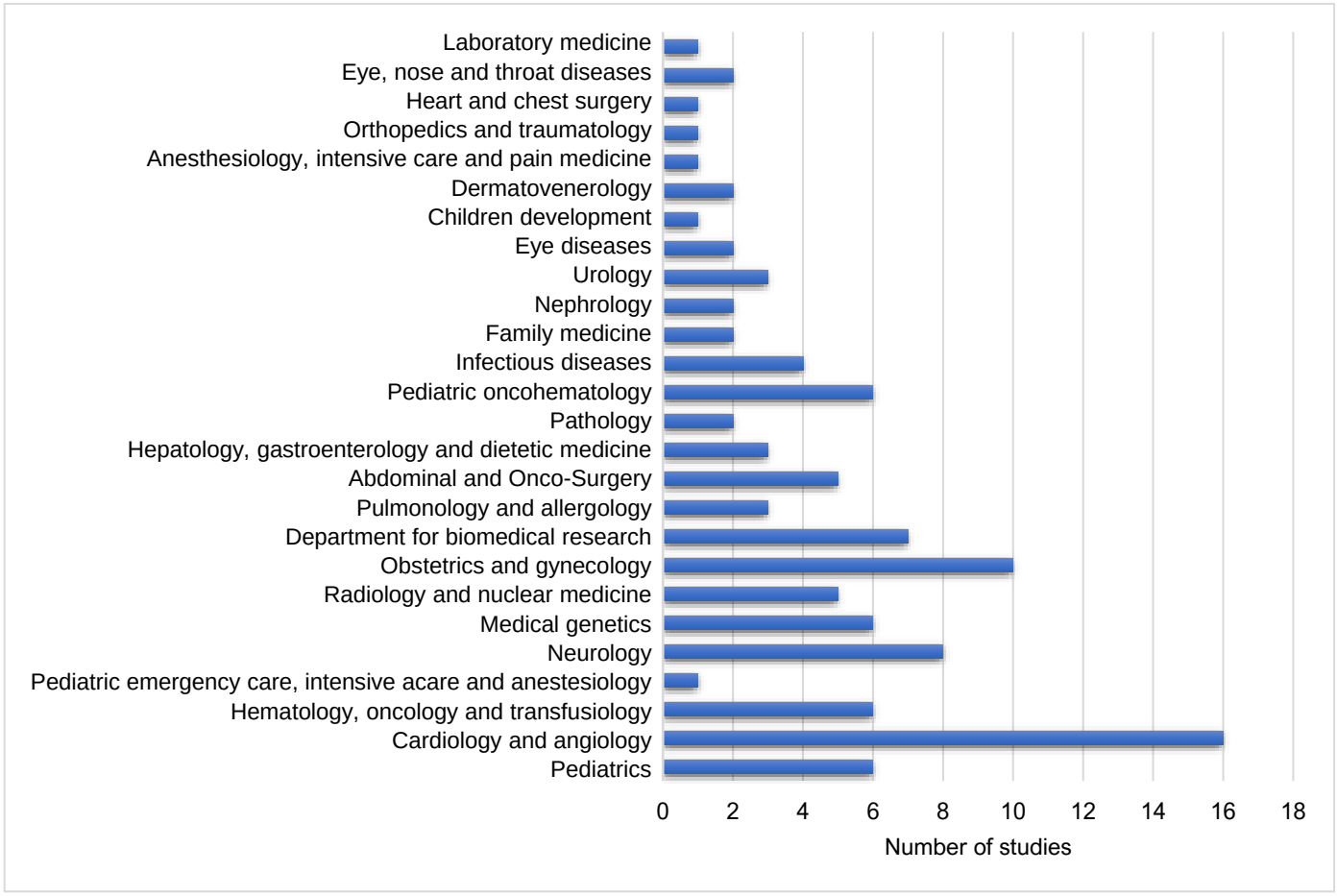

Figure 2: Main therapeutic areas of biomedical research at VUH SK in 2022.

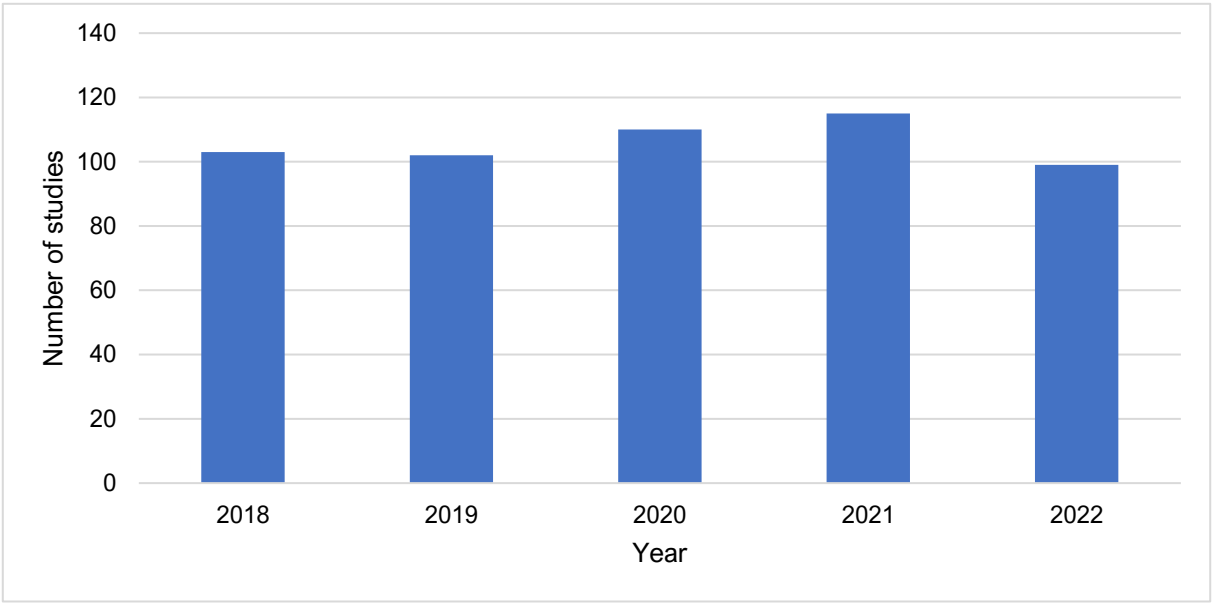

Figure 3. Newly initiated biomedical research at VUH SK (2018-2022).

The following medical device studies have been or are being carried out at VUH Santaros Klinikos, the only centre in the Baltics:

- APAMA 1 - a balloon for pulmonary vein isolation (treatment of atrial fibrillation);
- AFERA 2 - catheter and navigation system (for atrial fibrillation);
- Beat to beat - pacemakers that also lower arterial blood pressure;
- CCMs - pacemakers that improve myocardial contractility;
- Double-Check AF is a non-commercial study carried out in collaboration with Kaunas University of Technology - a wearable watch to detect atrial fibrillation and extrasystoles;
- HYDRA - transcatheter aortic valve implantation study (monitoring);
- Accu-CINCH is a left ventricular ring designed to restore left ventricular geometry and reduce mitral valve leakage;
- FAME III - percutaneous interventional drug-eluting stents;
- TRISTAR - a tricuspid valve ring for valve correction;
- PLA - Pulsed Field Ablation System study to treat paroxysmal atrial fibrillation;
- E-SAFE - study to measure oesophageal temperature and the continuous temperature of the distraction probe during atrial fibrillation ablation;
- KALPA™ - a study to assess the safety and efficacy of a medical device and the mapping, imaging and management capabilities in patients undergoing left atrial appendage closure;
- Leaflex Performer - a clinical trial to prove the safety and effectiveness of a medical device;
- NuVera ICE - catheter insertion during percutaneous procedures that use septal puncture to access the left atrium;
- CCM-HFpEF - a safety and performance study of an implantable device, the Sphere-9 catheter and Affera tagging, and a radiofrequency pulsed field ablation system for the treatment of atrial fibrillation;
- The CorFlow CoFI™ System - a medical device that combines the ability to measure the state of the microcirculation (diagnosis) with therapeutic approaches to treat microvascular obstruction after myocardial infarction;
- Myval™ - percatheter heart valve system;
- Bolt Lithotripsy RESTORE FIH (RESTORE FIH) - a lithotripsy system with angioplasty to help treat narrowing/clogging of the arteries in the heart or legs.

VUH SK biomedical research partners include Abbvie, Amgen, Merck, Servier, Sanofi, Novartis, Bayer, Biotex, Boehringer-Ingelheim, Takeda, Hoffmann-La Roche, Shire, Celgene, Odonate Therapeutics, Gilead, Biogen, Pfizer, Dr. Falk Pharma, Astex Pharmaceuticals, NOVO NORDISK, PAREXEL, Astrazeneca, Takeda Development, InDex Pharmaceuticals AB, Syneos Health, Alnylam Pharmaceuticals, Onorach, F. Hoffmann-La Roche, Alvotech Swiss AG, Pharm-Olam International, Actelion Pharmaceuticals, GlaxoSmithKline Biologicals SA, and other representatives of the innovative pharmaceutical industry. Medical device research partners include Micro Interventional Devices Inc, St Jude Medical Coordinating Centre, Medtronic, Millipede, PiCardia, NuVera Medical, K2 Medical Ltd, CorFlow Therapeutics AG, Meril Life Sciences, Abbott, CoreMedic, Biotest AG and others.

Research partners are Vilnius University (Lithuania), Research Council of Lithuania (Lithuania), National Cancer Institute (Lithuania), Centre for Innovative Medicine (Lithuania), Gediminas Technical University (Lithuania), Kaunas University of Technology (Lithuania), Institute of Biotechnology (Lithuania), New York University School of Medicine (USA), University of Cologne (Germany), University of Rostock (Germany), Stanford University (UK), University of Aalborg (Denmark), Erlangen University Hospital (Germany), Heidelberg University Hospital (Germany), Menzies Research Institute (Tasmania), INSERM Research Institute (France), International Specialist Societies, European Society of Cardiovascular and Interventional Radiology, Lithuanian Stroke Association, Dutch-Belgian Cooperative Haematology-Oncology Research Group HOVON, Medical University of Vienna (Austria), Hamilton Health Sciences Corporation (Canada), EuroSurg Collaboration, PSI CRO, Angion Biomedica Cor, BIO1, Karolinska University Hospital (Sweden), University of Leipzig (Germany), University of Leipzig (Germany), Heidelberg University (Germany),

University College Dublin (Ireland), National University of Ireland in Dublin, University of Cologne (Germany), and other research institutions.

In 2022, students of the Faculty of Medicine of Vilnius University contributed to clinical case reports and questionnaire-based studies in VUH SK. There were 32 voluntary work contracts with students, and dozens of bachelor and master students' theses were carried out under the supervision of specialists working at the hospital (Figure 4). VUH SK is one of the main practice bases for students of medicine, nursing and public health.

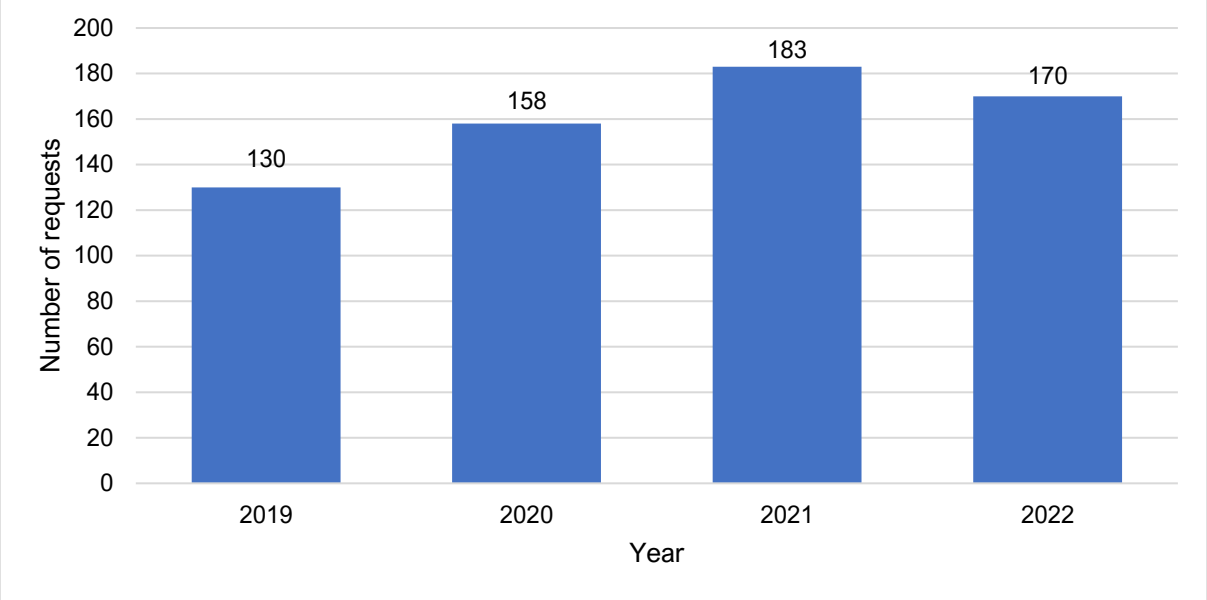

Figure 4. Student research projects at VUH SK.

VUH SK has been authorised by the State Medicines Control Agency to organise Good Clinical Practice (GCP) training. The Good Clinical Practice Fundamentals and Refresher Training can be taken remotely: investigators can attend the training course and take the final test at any time, at any place convenient to them. Those who successfully complete the course and pass the test will be awarded a certificate of Good Clinical Practice Fundamentals (8 academic hours) training or a certificate of Good Clinical Practice Refresher/Update (4 academic hours) training.

Annual evaluation of research activities – results of VUH SK in 2021

Based on the order of the Ministry of Education, Science and Sports of the Republic of Lithuania, the Research Council of Lithuania annually conducts an expert evaluation of research and experimental development (R&D) of universities and research institutes. From October 2022, the results of the evaluation of the institutions' activities in 2021 are published. The annual evaluation of the institutions' research and experimental development (R&D) conducted by the Research Council of Lithuania examines the units of research dissemination (i.e., research works) at each institution and the funds received from R&D projects and contracts.

When assessing articles in the natural (N), technological (T), medical and health (M), agricultural (A) and social (S) sciences, the experts exclude those not belonging to a predefined list of reputable journals. The lists are updated during each assessment and can serve as guidelines to help researchers choose the right journal. Once the evaluation of the dissemination units (works) in the scientific fields is completed, lists of internationally recognised publishers are also compiled according to the scientific fields or groups of scientific fields, such as N, T, M, A, S and Humanities (H). These lists are revised each year and can be used by institutions to select an appropriate publisher. Following the evaluation, the list of R&D projects under international programmes is updated, indicating which international projects are recognised as R&D and the proportion of their funding that can be credited.

According to the results published by the Research Council of Lithuania (RCL), 235 published scientific papers have been recognized at VUH SK for the reporting year 2021**. The number of credited papers has been increasing over time, and more and more VUH SK publications are among the top 10% most cited in the world (Figure 3).**

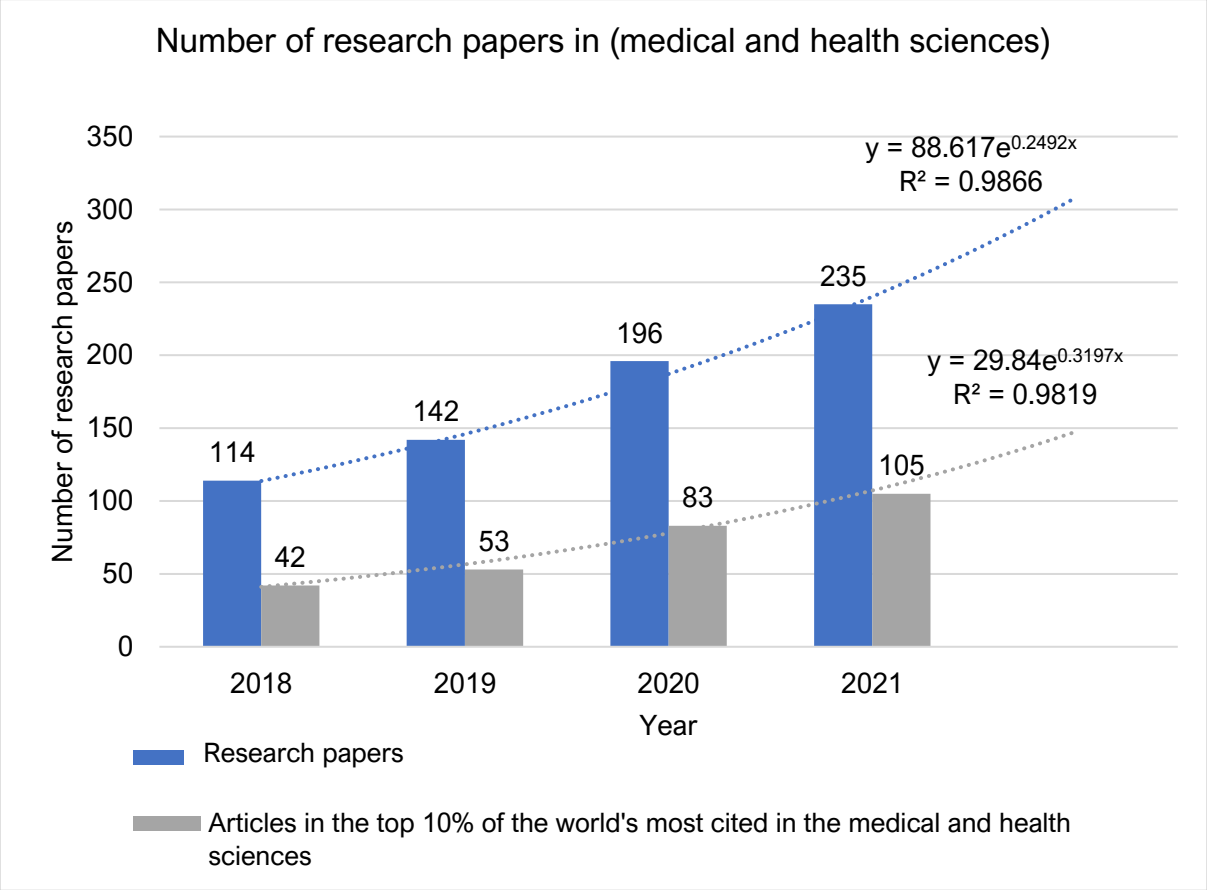

Figure 3. The number of VUH SK research papers recognized by the Research Council of Lithuania expert evaluation of research and experimental development (R&D) of universities and research institutes in 2018-2021 and the prediction of future publishing, assuming an exponential increase in the number of research production.

According to the assessment of the units of dissemination published by institutions in 2021, the **weighted sum of the formal assessment of the units** credited to VUH SK **is 344.94 points (Figure 4).** In terms of published results, this year VUH SK remained in the third position among 21 institutions (category of medical and health sciences).

According to the results of the evaluation of R&D projects and contracts published by the RCL, VUH SK is the second institution in the field of medical and health sciences in terms of the funds received from the execution of orders for research and experimental (social, cultural) development by economic entities – EUR 313.7 thousand (Figure 5). VUH SK also received EUR 879.2 thousand from participation in international research programme projects (IRP). According to the evaluation results, VUH SK is the institution with the largest amount of funding from IRP in the field of medicine and health sciences.

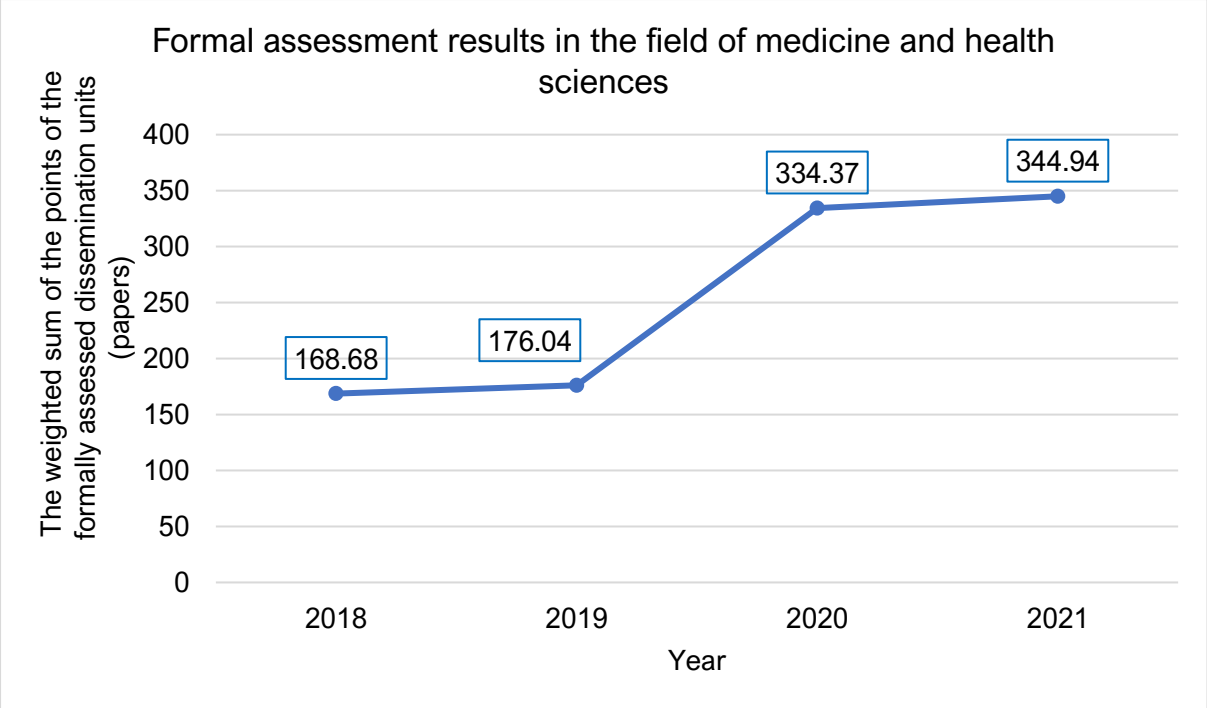

Figure 4. Results of the Research Council of Lithuania expert evaluation of research and experimental development (R&D) of universities and research institutes in 2018-2021.

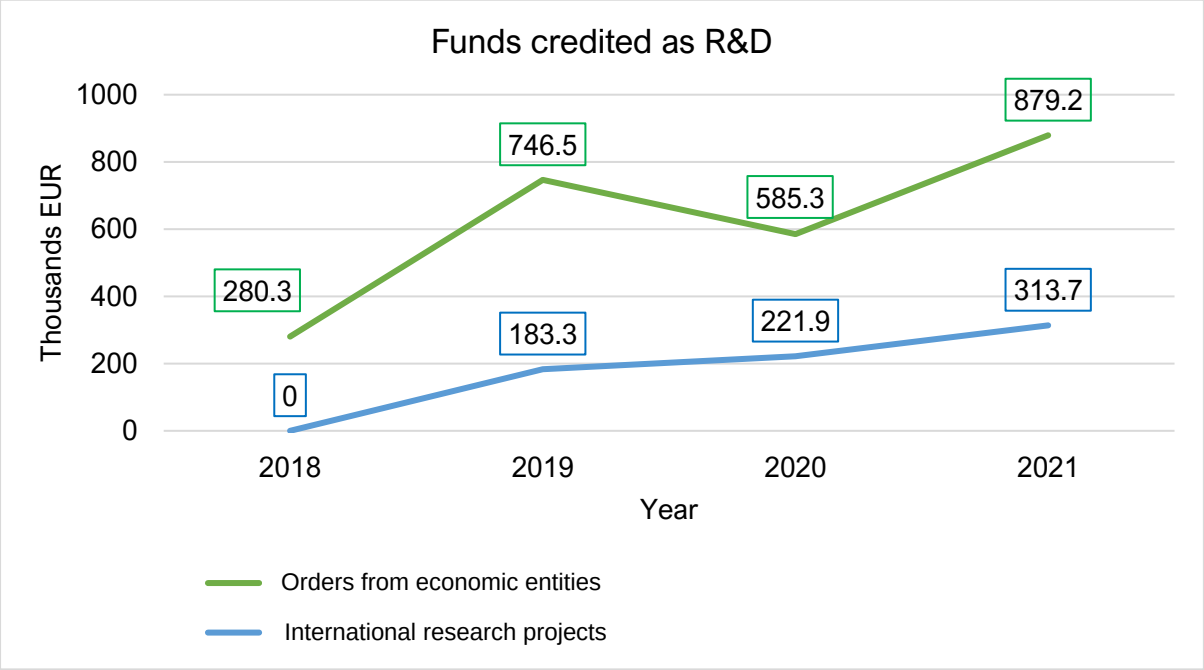

Figure 5. R&D funds credited to VUH SK during the Research Council of Lithuania expert evaluation of universities and research institutes.

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Centre for Eye Diseases

Multidisciplinary and international research in 2022

Phenotype-genotype associations and prognostic factors in collagen IV alpha-345 nephropathies

In 2022, representatives of the Centre for Eye Diseases at Vilnius University Hospital Santaros Klinikos (VUH SK) were involved in an international study in collaboration with the Centre for Nephrology and the University of Rostock (Germany). The **aim of the study was to assess the prevalence, genotype-phenotype correlations, biomarkers and new diagnostic tools for IV alpha-345 nephropathy in Lithuania and Europe**. The study involves patients with Alport syndrome undergoing molecular genetic and phenotypic testing. The most common ocular abnormalities observed in Alport syndrome patients are anterior lenticonus, punctate or macular retinopathy, and less commonly – posterior polymorphic corneal dystrophy, secondary hypercalcemic foci in the conjunctiva and sclera, corneal opacities, cataracts, etc. The research is ongoing and some of the results have already been presented in Frontiers in Medicine[1].

Congenital nasal lacrimal duct obstruction: clinical and histological findings.

A retrospective interventional clinical trial conducted at the VUH SK Centre for Eye Diseases and the National Center of Pathology between 2010 and 2021 was completed in 2022. The **study evaluated the histological and clinical findings of dacryocystorhinostomy surgery in patients with congenital nasal lacrimal duct obstruction**. Congenital nasal lacrimal duct obstruction is a common disease of the lacrimal duct, usually caused by nonspecific inflammation of the lacrimal sac and nasal lacrimal duct and the resulting fibrosis obstructing the duct (Figure 1). The main symptom of this disease is persistent tearing, which is adversely affected by the sun, wind or cold. Results of the 275 patients included in the study werw published January 2022[2].

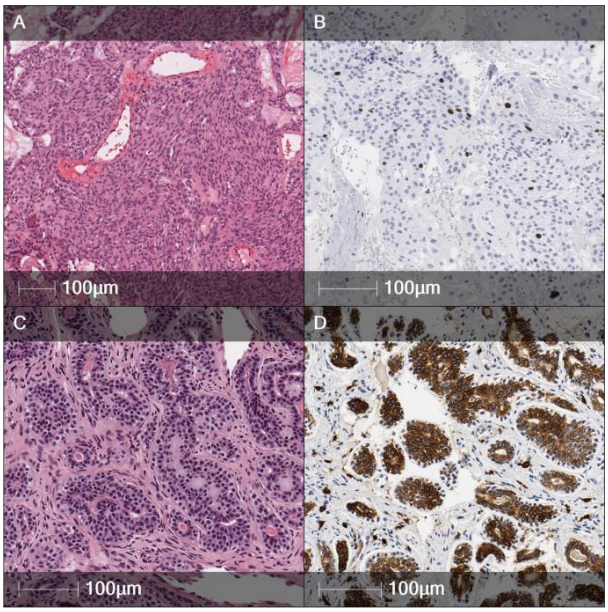

Figure 1. Histological data of the tumours. ***A.*** *Eccrine spiradenoma. Magnified image, haematoxylin/eosin (H/E) stained tissue.* ***B.*** *Epithelial Ki67 proliferation index of eccrine spiradenoma was 4%.* ***C.*** *Adenoid cystic carcinoma. Magnified view of H/E-stained tissue with secretion in the duct.* ***D.*** *Adenoid cystic carcinoma cells were CD117 positive.*

Participation in EuroNanoMed (European Innovative Research & Technological Development Projects in Nanomedicine)

More than 44,000 corneal transplants are performed worldwide every year for a variety of eye disorders, chemical injuries or infections, and the need for such operations is only increasing. The main factor limiting the number of corneal transplants is the shortage of donor tissue. This has led to the development of various artificial corneal analogues that could replace biological tissue. From 2018 to 2022, representatives of the VUH SK Centre for Eye Diseases participated in the international study EuroNanoMed (European Innovative Research & Technological Development Projects in Nanomedicine). The **aim of the study is to develop a liquid corneal filler (LiQD-Cornea) as an alternative to corneal transplantation for high-risk patients.** The project is coordinated by the Maisonneuve-Rosemont Research Centre in Montreal (Canada), and involves Vilnius University (Lithuania), Estonian University of Life Sciences (Estonia), and the biotech company Oz Biosciences SAS (France). The project was designed to evaluate the efficacy of a new formulation of liquid corneal filler. The old formulation was supplemented with an inflammation-inhibiting phosphorylcholine polymer network incorporating peptides with antiviral activity. An *in vivo* model of inflammatory corneal infection using Herpes simplex virus serotype 1 (HSV-1) was used. After obtaining permission from the Lithuanian Ethics Committee for the use of experimental animals, a rabbit model of corneal damage was used to mimic a severe HSV-1 infection (i.e., one in which uncontrolled inflammation can lead to corneal perforation). In this work**, it was shown that a novel formulation of LiQD-Cornea can induce corneal regeneration after perforation in the tested rabbit, as well as allow a more rapid inhibition of inflammation.**

Retinal capillary characteristics and their relation to cardiovascular parameters in metabolic syndrome

Systemic arterial hypertension is still one of the leading causes of morbidity and mortality worldwide. Early diagnosis, identification and correction of risk factors are important to reduce the risk of cardiovascular disease. Metabolic syndrome (MetS) is a group of interrelated risk factors of metabolic origin that directly contribute to cardiovascular disease. The blood vessels of the whole body, including the retinal vessels, are affected by hypertension, causing microvascular thinning. The **retina is the only place in the human body where the circulatory and vascular status can be directly monitored and studied *in vivo***. Optical coherence tomography angiography (OCTA), a rapid and non-invasive test, is increasingly being used to assess the structure of retinal capillaries. Evidence suggests that structural architectural changes in retinal capillaries may be the earliest markers of ischaemia and/or hypoxia, even before changes in the arteries and veins are present. On the other hand, the literature still lacks detailed data on microcirculatory alterations in MetS. As individual MetS risk factors are independently associated with retinal vascular changes, their early detection could provide an additional marker for screening MetS patients and assessing their risk of cardiovascular damage. A **prospective study has been initiated and is ongoing at the** VUH SK Centre for Eye Diseases from 2020 to 2021 **to assess the characteristics of the retinal capillary network in patients with metabolic syndrome** and its relation to changes in arterial stiffness, myocardial structure and function, and metabolism.

Structural and functional progression of glaucoma after trabeculectomy

Glaucoma is the most common cause of irreversible blindness worldwide, leading to a poor quality of life for patients and increasing financial burden for many countries. The global prevalence of glaucoma among people aged 40-80 years is estimated at 3.54% (95% confidence interval 2.09-5.82). The prevalence of this disease is increasing because of a growing and ageing population. The number of people suffering from glaucoma in this age group is expected to reach 111.8 million worldwide by 2040. Primary open-angle glaucoma is usually asymptomatic and is often detected only in its late stages. It is estimated that 10-39% of patients are diagnosed with glaucoma when lesions are already evident. As the population ages and life expectancy increases, the proportion of patients with advanced glaucoma is also likely to increase. As the disease progresses, deteriorating quality of life, social exclusion and financial strain become increasingly burdensome for the patients.

The study on factors associated with the progression of glaucoma was continued at the VUH SK Centre for Eye Diseases in the years 2021-2022 (investigators E. Jašinskienė, Dr. A. Kadziauskienė, **Assoc. Prof. Dr. R. Ašoklis**, Prof. Dr. L. Schmetterer). The aim of this study is to determine the dynamics of the structural and functional parameters of the posterior pole of the eye and the factors associated with glaucoma progression. This prospective study involves instrumental studies at the VUH SK Centre for Eye Diseases, such as spectral domain optical coherence tomography and optical coherence tomography angiography, which allow *in vivo* objectification, quantification and documentation of the morphological and blood flow parameters of the optic nerve disc and retina that characterise glaucomatous neuropathy. Depth-enhanced optical coherence tomography allows visualisation of the deep structures of the posterior pole of the eye, such as the porous plate and choroid, and assessment of their morphological characteristics.

The study on glaucoma progression after surgical intraocular pressure reduction is a continuation of a long-standing collaboration with researchers at the Singapore Eye Research Institute. Previous studies at the VUH SK Centre for Eye Diseases allowed to evaluate the progression of structural and functional glaucomatous damage after trabeculectomy surger. Structural and functional parameters of patients 3-7 years after trabeculectomy were analysed to elucidate the determinants of glaucoma progression. Currently, 38 patients are included in the study. The aim is to include 110 patients.

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Centre for Obstetrics and Gynaecology

Non-invasive detection of immunological markers in amniotic fluid during preterm labour

In 2022, the Center for Obstetrics and Gynecology of Vilnius University Hospital Santaros Klinikos (VUH SK) continued and completed a study titled "Non-invasive detection of immunological markers in the amniotic fluid during preterm birth", funded by the Research Council of Lithuania. Four of the six members of the research team are doctors at the Center for Obstetrics and Gynecology: **Prof. Dr. Diana Ramašauskaitė, Dr. Ingrida Pilypienė, Dr. Greta Balčiūnienė and dr. Violeta Gulbinienė.**

Building on previous work on preterm birth and intra-amniotic infection and/or inflammation, the Fetal Inflammatory Response Syndrome (FIRS) and neonatal outcomes were investigated by looking at markers in amniotic fluid.

Fetal inflammatory response syndrome (FIRS) is a systemic fetal inflammatory response in which cytokine levels are elevated because of amniotic infection and/or inflammation. FIRS leads to increased neonatal morbidity and mortality and increases the risk of short- and long-term sequelae such as respiratory distress syndrome, sepsis, bronchopulmonary dysplasia, intrascleral haemorrhage, periventricular leukomalacia, retinopathy of prematurity, sensorineural hearing loss and neurodevelopmental disorders including cerebral palsy.

In this study, we evaluated the role of immunological markers such as TNF-α, MMP-8, suPAR, EGF, IL-6, IL-10, IL-17, S100b protein, defensins, surfactant protein A, RANTES, Toll-like receptors 2 and 4, and TGFβ in predicting FIRS and neonatal outcome in cases of preterm amniotic fluid leakage up to 34 weeks of gestation. The aim of this study was to diagnose FIRS before birth by non-invasive vaginal collection of amniotic fluid. This procedure is easy to perform, does not require special skills and carries no additional risks.

Key findings:

1. MMP-8, TNF-α, IL-6, IL-10, IL-17, suPAR, S100B and defensins in non-invasively collected amniotic fluid are statistically significant diagnostic markers for FIRS. TNF-α and MMP-8 have the highest predictive value for FIRS (Figure 1).[1]

2. Non-invasively collected fetal water EGF concentrations are an indicator of functional lung maturity in preterm neonates, related to gestational age and reflecting the respiratory outcome of preterm neonates after birth (Figure 2). An EGF cutoff concentration of < 35 pg/ml significantly predicted the risk of severe neonatal respiratory outcomes: severe respiratory distress syndrome, the need for respiratory therapy for more than 4 days, the need for surfactant, the need for artificial pulmonary ventilation, and the risk of chronic lung disease[2].

3. TNF-α and EGF in non-invasively collected amniotic fluid are reliable prognostic markers of chronic lung disease in preterm infants.[2]

4. Analysis of non-invasively collected amniotic fluid can help to assess the risk of fetal inflammatory response syndrome and neonatal outcome in the event of premature rupture of membranes up to 34 weeks of gestation and can therefore be used as an alternative to invasive amniocentesis.[1,2]

More data from the study on the histological diagnosis of chorioamnionitis is available in the VUH SK issue of "Research and Innovation" of 2021.

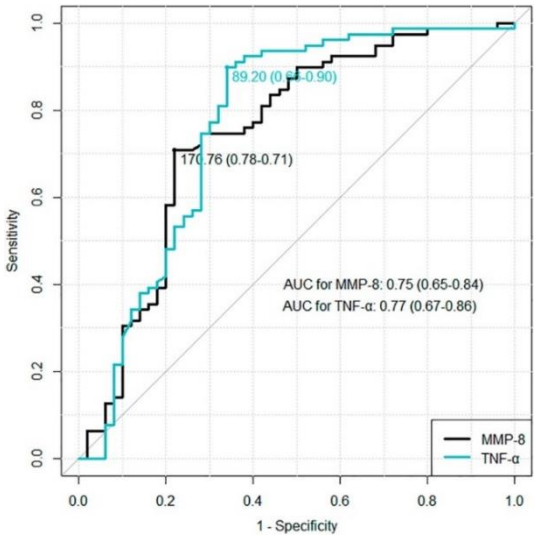

Figure 1. Diagnostic accuracy of fetal inflammatory response syndrome using biomarkers. MMP-8 - matrix metalloproteinase-8, TNF-α - tumour necrosis factor alpha.

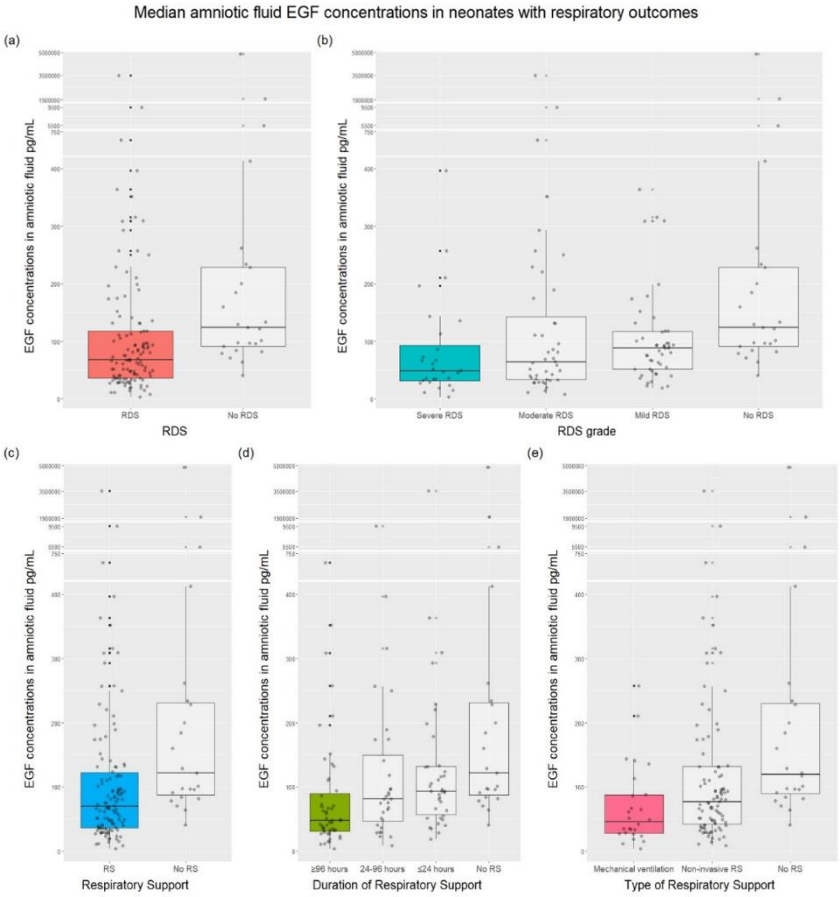

Figure 2. Fetal water EGF concentrations according to respiratory outcomes in preterm neonates. RDS - respiratory distress syndrome, RDS grade - respiratory distress syndrome severity, Respiratory support - respiratory therapy requirement, Duration of respiratory support - duration of respiratory therapy, Type of respiratory support - type of respiratory therapy, EGF - epidermal growth factor.

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Centre for Ear, Nose and Throat Diseases

Care for rare hearing impairment, research innovations and novel procedures

Centre of Excellence for Rare Hearing Impairment and Hearing Implantation

The Centre for Rare Hearing Impairments and Hearing Implantation at the Centre for Ear, Nose and Throat Diseases at Vilnius University Hospital Santaros Klinikos (VUH SK) was established in 2018. It offers consultations with otorhinolaryngologists (otolaryngologists, audiologists), radiologists, geneticists, anesthesiologists, developmental specialists, as well as cooperation with sign language educators and patient self-help communities. The multidisciplinary team of this Centre of Excellence has one goal in mind – to provide modern, timely and high-quality diagnosis and treatment of severe and rare hearing disorders in children and adults. **In 2022, the Centre of Excellence became a full member of the European Reference Network (ERN) CRANIO (ERN for rare and/or complex craniofacial anomalies and ear, nose and throat (ENT) disorders) (Figure 1).** In collaboration with the international medical community, we are building knowledge on rare hearing disorders, contribute to the development and implementation of algorithms for their diagnosis and treatment, and to the creation of an international registry of rare hearing disorders. CRANIO ERT also promotes communication between professionals and the sharing of best practices - in **2022, VUH SK representative Dr. D. Vaitkūnaitė-Zubriakovienė took part in the ERT exchange programme – she did an internship in Italy at the University Hospital of Padua.**

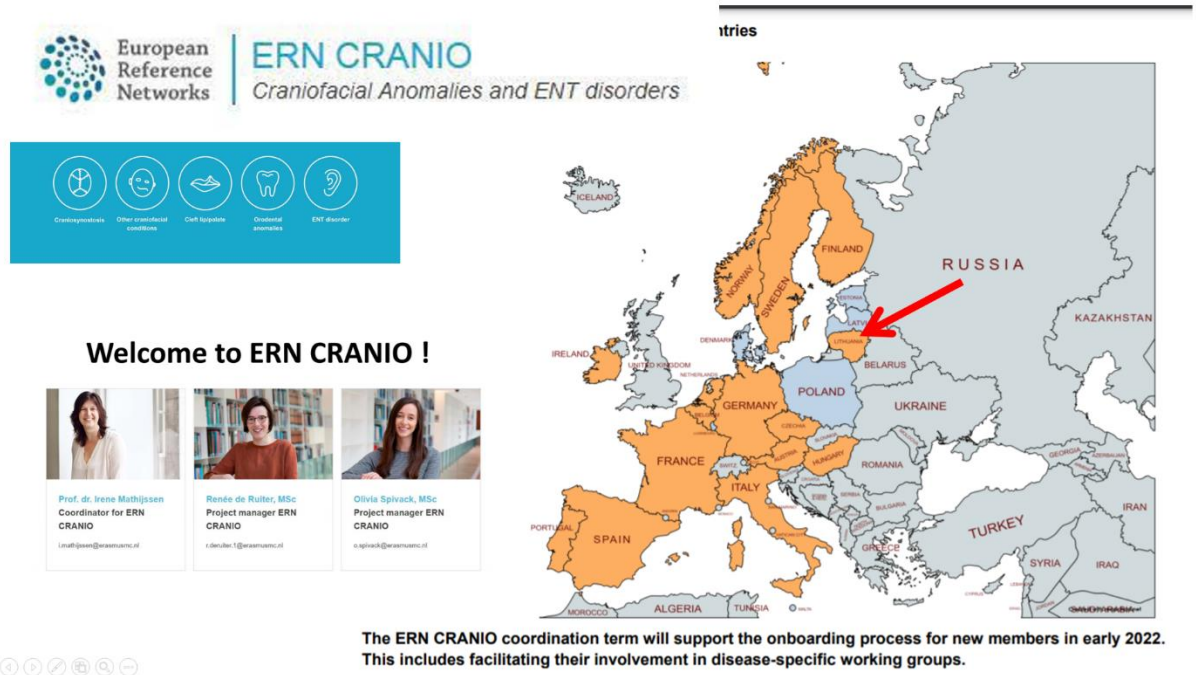

Figure 1. Map of the members of the European Reference Network for Craniofacial Anomalies and Diseases of the Ear, Nose and Throat.

The Centre of Excellence for Rare Hearing Disorders and Hearing Implantation has the most extensive experience in Lithuania and Eastern Europe in cochlear implantation (unilateral or bilateral), middle ear hearing system implantation, and other reconstructive ear surgery. Detailed post-operative audiological follow-up is carried out, with comprehensive hearing tests, assessment

of speech development and speech perception. Moreover, the assessment of sound source localisation and musical abilities started in 2022.

Localising sounds in our environment is one of the key sensory abilities for communicating and staying safe (Figure 2). Listening to music requires to distinguish tone, rhythm, timbre, dynamics and to feel emotions when listening to the sounds of a particular piece or instrument. It can be assumed that only by integrating all these different features of music into a whole can we fully enjoy and make sense of music.

New methodologies introduced at the Centre for Ear, Nose and Throat Diseases in 2022 aim to assess how people with impaired basic hearing can listen to music and perceive the information it conveys, as well as orient themselves in space based on the source of sound.

Figure 2. Sound localisation test equipment.

Otoneurological tests

The Vestibular Function Testing Room at the VUH SK Centre for Ear, Nose and Throat Diseases was established in 2015. Recently, it has expanded its range of activities, introducing improved programmes, new testing methodologies, and continued research. The optimally equipped otoneurological testing system is one of few in the Baltic region. It allows timely diagnosis of disorders causing vertigo and allows to perform balance testing by combining the results of high-resolution MRI, static posturography, videonystagmography, caloric, oculomotor, rotational and head impulse tests. Results of ongoing research based on findings of the dissertation “Importance of clinical tests and radiological findings on the peripheral vestibular function for the diagnosis of Meniere’s disease” (defended by Dr. A. Paškonienė at Vilnius University in 2019), are being presented at important global resarch events.

Innovations in endoscopic endonasal skull base surgery

Less invasive endoscopic skull base and brain surgery has become the standard for treating a wide range of conditions in the world's best ENT centres. This type of surgery was introduced at VUH SK in 2015, when the Centre for Neurosurgery was established. Since then, a team of neurosurgeons and rhinologists has successfully performed more than 200 endoscopic skull base operations. These operations are an example of the application of modern technologies in medicine. The natural nasal passages are used as a corridor to reveal deeper anatomical structures that are normally difficult to reach: the palatine fossa, the infratemporal fossa, the skull base, the eye socket, the eyeball and the sinus cavernosus. The latest medical technologies are used in these operations: high-definition video systems, endoscopes, lasers, shaver, neuronavigation (used in removal of anterior and posterior skull base tumours, congenital and acquired meningoencephaloceles and reconstruction of skull base defects), Figure 3. The specialists of the Centre for Ear, Nose and Throat Diseases not only continuously improve their knowledge in the most renowned endoscopic surgery centres all over the world, but also share their experience at

international conferences, train foreign colleagues in dissection courses, and co-author scientific articles and books.

Figure 3. Neuronavigation system in the operating theatre of VUH SK.

The Centre is constantly introducing innovations in surgical techniques and the most advanced global surgical technologies. The majority (98%) of pituitary tumours are operated on by endoscopic endonasal removal using a transsphenoidal approach. At the Centre for Ear, Nose and Throat Diseases, specialists were the first in Lithuania to introduce the four hands-two nostril technique, where a ENT specialist and a neurosurgeon work together to ensure maximum surgical success and uninterrupted interdisciplinary cooperation. In addition, the recent introduction of the latest endoscopic endonasal hydroscopy and hydrodissection technique has significantly improved the results of radical removal of pituitary tumours. Endoscopic hydroscopy is a technique whereby, after removal of a pituitary tumour, the invisible (microscopic) cells of the tumour to the eye are flushed out with saline water using an endoscope and a special instrument. For better post-operative results, an innovative technique of multi-layer duroplasty has recently been introduced, which helps to avoid serious complications. It uses a multi-layered closure of the cranial defect by applying a nasal septal flap with blood supply, fat, muscle fascia and cartilage tissue.

Minimally invasive endolaryngeal treatment and testing in laryngology

In 2022, a combined surgical and medical treatment for laryngeal stenosis was introduced at the VUH SK Centre for Ear, Nose and Throat Diseases. For the first time, the treatment combined surgical scar removal with CO_2 laser and mitomycin C, which significantly reduces the risk of restenosis and the need for additional medical interventions. Stenosis of the vocal cords is caused by scarring and fibrosis, a threatening clinical condition due to the possible narrowing or complete obstruction of the airway, where patients are forced to live permanently with a tracheostoma, with a severely compromised quality of life and social problems. Soon, it is planned to start performing these procedures under local anaesthesia, using next-generation laser technology.

The Centre's new technology for the diagnosis of laryngeal cancer is Narrow band imaging (NBI) endoscopy. This technique is based on the penetration of different wavelengths of light into the mucosa and the ability of haemoglobin to absorb blue (415 nm) and green (540 nm) light waves. Compared to conventional testing methods, this method is more sensitive and specific for the detection of laryngeal cancer. It is also used during surgery to see intraepithelial papillary capillary loops during the intervention itself and thus to predict more precisely the extent of surgery.

Centre for Dermatovenerology

Clinical research, innovations and events organised by the Centre for Dermatovenerology in 2022

Studies on innovative medicinal products

The Centre for Dermatovenerology of Vilnius University Hospital Santaros Klinikos (VUH SK) is actively **involved in multicentre, large-scale clinical trials**, which provide patients with severe chronic skin diseases that significantly reduce their quality of life with access to the most advanced treatments to date (Table 1). **In 2022, there are six clinical trials of biologic therapies**, three of which are for psoriasis patients, two for atopic dermatitis and one for suppurative hidradenitis. These innovative therapies allow patients to significantly improve their disease course and quality of life, while providing researchers and sponsors with valuable scientific knowledge on efficacy, safety, tolerability, pharmacokinetics and immunogenicity.

Disorders	Medicinal product	Partner
Suppurative hidradenitis	Secukinumab	Novartis
Atopic dermatitis	Nemolizumab	Galderma
Atopic dermatitis	Lebrikizumab	Dermira
Psoriasis	Adalimumab	Samsung Bioepis
Psoriasis	Ustekinumab	Samsung Bioepis
Psoriasis	Ustekinumab	Amgen

Table 1. List of clinical trials conducted at the Centre for Dermatovenerology in 2022

Guidelines to improve the diagnosis and treatment of skin melanoma

Skin melanoma is potentially the most dangerous of all skin tumours, accounting for around 90% of skin cancer deaths, so early diagnosis is essential to improve patient survival and reduce the burden of this disease.

To summarise the current knowledge about skin melanoma, dermatovenerologists of the Centre for Dermatovenerology of VUH SK, Assoc. Prof. Dr. J. Grigaitienė, I. Gylienė and L. Lukavičiūtė, have prepared and presented a **methodological document "Skin melanoma".** The aim of this document is to discuss, on the basis of the best medical evidence, **tactics for the prevention, diagnosis and treatment of skin melanoma**, with a view to earlier diagnosis and a better prognosis of the disease, as well as to ensure that everyone who is examined for suspected or confirmed melanoma receives well-organised, comprehensive, professional and timely care, irrespective of the institution to which the patient is referred to in Lithuania.

The guidance document **is intended for healthcare professionals** (in particular general practitioners, dermatovenerologists, radiologists, pathologists, chemotherapeutic oncologists,

radiotherapeutic oncologists, surgical oncologists of various specialties, nurses, and other healthcare professionals) who provide services, care and support for patients with suspected or diagnosed skin melanoma, as well as for the patients and their families, caregivers, social workers etc.

In collaboration with colleagues from plastic and abdominal surgery, oncologists, pathologists, radiologists and pediatric onco-chemotherapists, a **common protocol for the diagnosis and treatment of skin melanoma** was developed at **VUH SK.** This protocol helps to ensure the accurate and high-quality performance of diagnostic and therapeutic procedures for melanoma, as well as the principles of sequencing treatment. It also defines the safe, rational and efficient performance of all diagnostic and therapeutic procedures for cutaneous melanoma according to their indications, efficacy and the lowest risk of potential complications.

Diagnosis and treatment of hair diseases

In 2022, the Centre for Dermatovenerology at VUH SK **also focused on improving the diagnosis and treatment of various hair disorders**. Doctors at the centre use the **Fotofinder Trichoscan** digital dermatoscope to perform digital hair assessment. The Centre has started to organise dermatovenereologists' consultations to discuss complicated cases, including the differential diagnosis of alopecia, its examination and treatment tactics. Presentations on the latest diagnostic and therapeutic strategies are given at weekly meetings to help expand competences in the treatment of hair diseases.

For focal alopecia, where local and systemic treatments are ineffective or not tolerated, the Centre offers an innovative treatment with **topical immunotherapy with diphencyprone** (DCP). Local immunotherapy with DCP is one of the most effective treatments for focal alopecia. The triggered human immune system causes inflammation in the superficial layers of the skin, which can lead to hair regrowth. According to studies, more than 50% of patients treated with DCP achieve significant clinical improvement and hair regrowth.

Skin cancer prevention campaign

In June 2022, doctors and staff at the Centre for Dermatovenerology of VUH SK carried out a public screening of skin lesions for the public. The campaign, which took place on the premises of Vilnius City Hall, attracted great public interest. A total of **606 persons were screened**, among them **33 cases of basal cell carcinoma and 5 cases of squamous cell carcinoma** were suspected as non-melanoma skin cancers**. There were also 5 suspected cases of melanoma,** 11 precancerous lesions of actinic keratosis and 73 atypical moles, which were subsequently re-evaluated in the treatment facility. On average, 40.4 people were examined by one doctor, with an average examination time of 7.5 minutes. The initiative also provided participants with valuable knowledge on sun protection and information on self-examination.

Figure 1. Dermatovenerology Centre staff at the skin cancer prevention campaign on 16 June 2022.

Scientific-practical conferences

The Centre for Dermatovenerology, in collaboration with the Faculty of Medicine of Vilnius University, the Lithuanian Society of Dermatovenerology and other partners, has organised several **scientific-practical conferences** for dermatovenerologists, family and other physicians and medical staff. Some of the most important conferences include the 6th Republican Conference "Dermatovenerologists' Afternoon", organised from 14 to 27 February 2022, and the International Conference "Modern Dermatovenerology: looking forward to the future", held on 29 April 2022, where expert speakers from Lithuania, Latvia, Germany, Ukraine, Poland and Italy shared their knowledge.

Centre for Hematology, Oncology and Transfusiology

COVID-19 research axis

Immune plasma neutralisation testing

The onset of the COVID-19 SARS-CoV-2 omicron variant wave has reduced the list of therapeutic options for the infection. Many monoclonal antibodies targeting the S protein of the virus were not suitable for neutralising the omicron sub-variants BA.1 and BA.2. Given that the virus is continuously mutating and that plasma from recovered patients with high levels of antibodies to COVID-19 can be an effective treatment for the disease, there was a need to test whether the immune plasma collected in previous waves of COVID-19 was able to neutralise the BA.1 and BA.2 omicron sub-variants circulating in the first half of 2022.[1]

The study was conducted at the Centre for Hematology, Oncology and Transfusiology at Vilnius University Hospital Santaros Klinikos in 2022 and involved three groups:

1. Persons vaccinated against COVID-19 three times and not exposed to COVID-19.
2. Persons who have been vaccinated against COVID-19 with at least one dose and had the COVID-19 delta variant.
3. Persons who have been vaccinated against COVID-19 with at least one dose had the COVID-19 omicron variant.

The plasma samples used in the study were obtained from the VUH SK Biobank. The concentrations of binding antibodies as well as omicron variant neutralising antibodies were determined in all samples. The results showed that plasma from vaccinated individuals or those vaccinated and previously infected with the delta variant was able to neutralise the omicron variant of SARS-CoV-2, but that the neutralisation rate was statistically significantly higher in individuals who had previously been infected with the omicron variant (Figure 1).

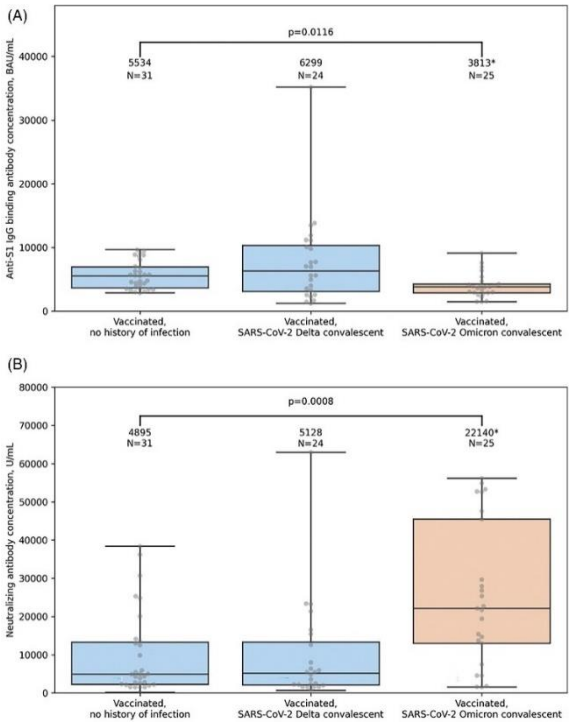

Figure 1. Concentrations of binding (A) and neutralising (B) antibodies produced in different groups of the subjects investigated.[1]

The study showed that plasma samples from individuals previously exposed to the omicron variant have the strongest neutralising potential, which may make such plasma more suitable for the treatment of COVID-19 caused by the omicron strain. These results are directly applicable to the treatment of COVID-19 patients at VUH SK. It is important to take the findings of the study into account in blood centre planning and in the evaluation of the collection of immune plasma during the next wave of COVID-19.

The EUCARE project

VUH SK, together with 17 partners from all over the world, has been granted the project "European cohorts of patients and schools to advance response to epidemics (EUCARE)". The **project coordinator and representative at VUH SK is Daniel Naumov**. In this project, researchers from different disciplines are working together to provide sound research-based evidence to address coronavirus strains and the COVID-19 pandemic, with a focus on hospitalised patients, vaccinated healthcare workers and educational institutions.

The project requires biological samples and health information to achieve its objectives. VUH SK is a key partner in the project as it is involved in the collection of the three project cohorts[2] : 1) hospitalised COVID-19 patients, 2) healthcare professionals, 3) "long COVID-19" patients.

Owing to the presence of a Biobank, VUH SK made a significant contribution to the retrospective inclusion of the data of subjects who visited the hospital and agreed to participate in the VUH SK Biobank (Figure 2).

Figure 2. Retrospective transmission of health information from the VUH SK Biobank to the EUCARE project.

Initial analyses of the collected data are currently underway, and VUH SK is continuing other activities in the project by enrolling subjects prospectively.

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Research projects with samples and health information from the Biobank

What is a Biobank?

A biobank is a collection of biological material and related health information that is dynamic, continuously updated and used in biomedical research. The Biobank is a bridge between science and clinical practice: on the one hand it directly addresses the challenges of clinical work, on the other hand – it attracts researchers who can use their knowledge and expertise in a healthcare setting. Such biomedical research often requires high quality, well-described biological samples and health information, which is exactly what the Biobank of Vilnius University Hospital Santaros Klinikos (VUH SK) can offer.

The aim of the Biobank is to provide Lithuanian and foreign research and industry community with access to a large number of standardised and systematically registered samples of human biological material to help in the search for fundamental knowledge about various diseases, ways to optimise and improve the diagnosis or treatment of diseases.

The Biobank collects a wide range of samples from patients with hematological, oncological, infectious, genetic, rare and chronic non-infectious diseases: lymph nodes, serum, plasma, bone marrow, nasopharyngeal swabs, saliva, purified ribonucleic acids (RNA), deoxyribonucleic acids (DNA), viable cells or other residual samples left over after diagnostics (Figure 1). Samples may also be accompanied by health information, which is stored separately in the VUH SK Electronic Medical Record.

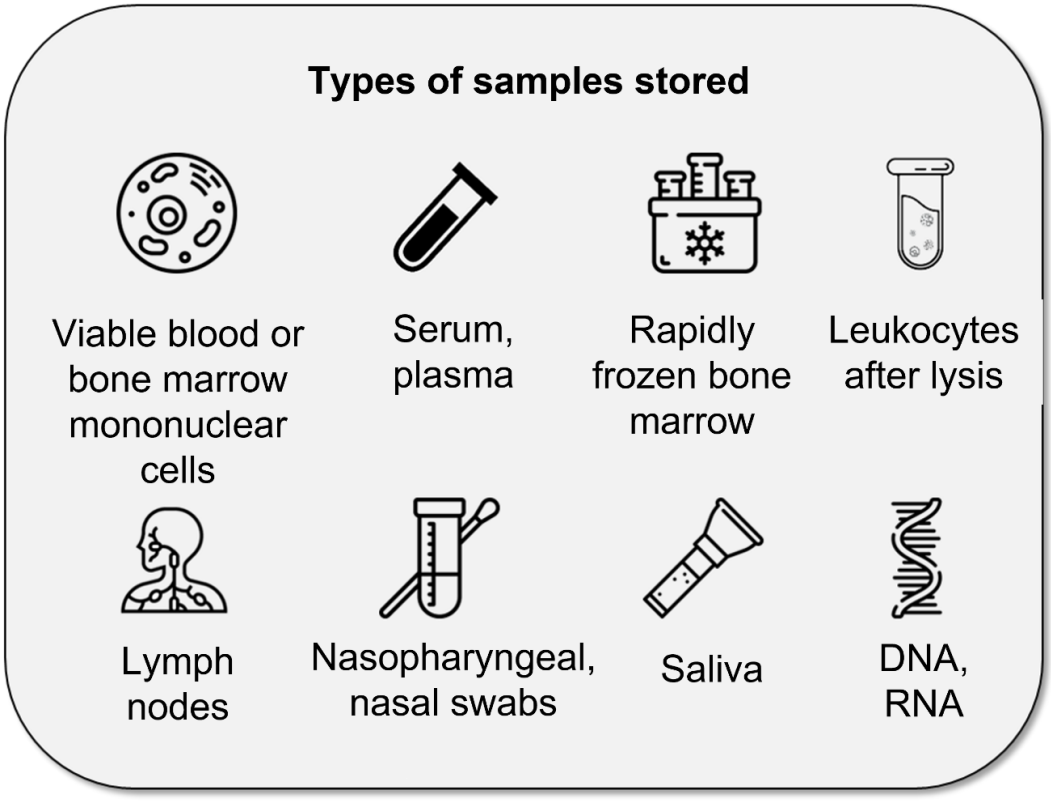

Figure 1. Types of samples stored in the VUH SK Biobank.

What's new in 2022?

It is encouraging to note that in 2022, more and more patients have become involved in Biobanking – as many as 2086 patients have signed the Biobanking Consent Form, and in total 8941 people are already involved in Biobanking activities.

The VUH SK Biobank is now even more visible in the international scientific community. The **Biobank's collections (Figure 2) can also be found on the BBMRI-ERIC Directory website, which provides information on the major European biobanks.**[1]

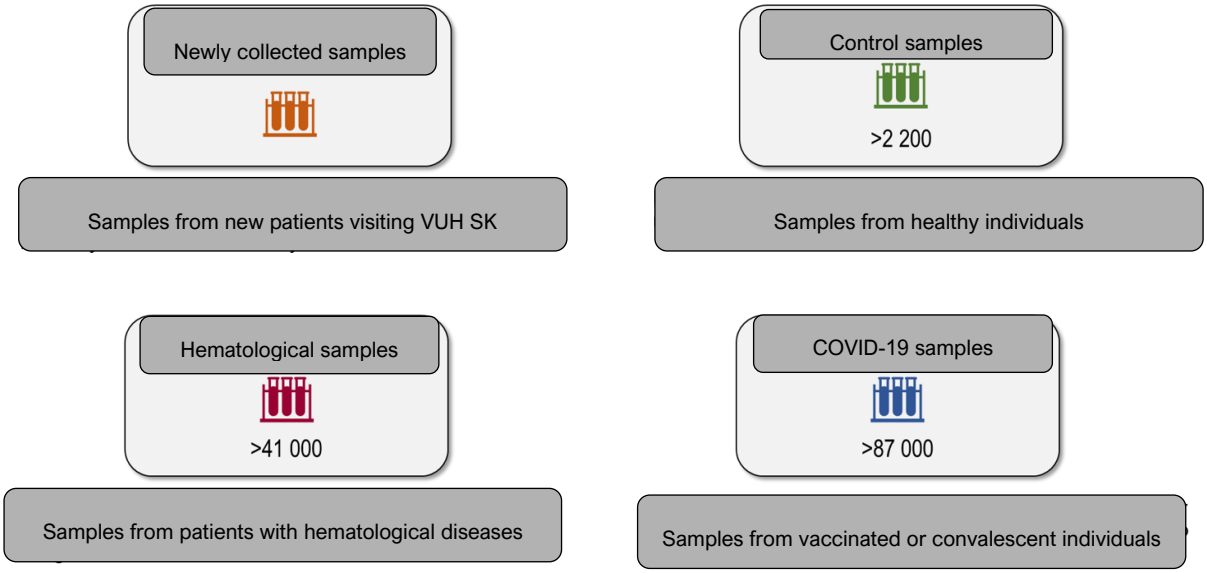

Figure 2. Biobank collections.

In 2022, the Biobank not only continued its cooperation with long-standing partners, but also gained new ones (Table 1).

Partners	Research
Droplet Genomics UAB	Bone marrow analysis of AML patients receiving Venetoclax-based therapy using single-cell RNA sequencing
VUH SK	Investigating the immunogenicity, safety and efficacy of SARS-CoV-2 vaccines in the immunosuppressed population
VUH SK	A retrospective study of COVID-19 outcomes in oncohematology patients treated with SARS-CoV-2 convalescent plasma
VUH SK	Synergies between Venetoclax, Cytarabine and Actinomycin D found *ex vivo* in acute myeloleukaemia samples *in vivo*
UAB “Imunodiagnostika”	Development of innovative tests for SARS-CoV-2 infection
UAB “Cureline Baltic”	Collection of Human Biospecimens for Genomics, Proteomics and Biomarker Research

UAB “Cureline Baltic”	Collection of biological samples from patients with acute myelo-leukaemia, optimised for proteomic tumour analysis, for submission to the Clinical Proteomic Tumour Analysis Consortium (CPTAC)
EuResist	Cohort study of healthcare workers in the EuCARE project
EuResist	Cohort study of hospitalised COVID-19 patients within the EuCARE project
EuResist	Multicentre study on residual effects after COVID-19

Table 1. Studies using biological samples and health information from the VUH SK Biobank in 2022.

Most of the research that required the biological samples and health information collected by Biobank in 2022 was related to the management of the COVID-19 pandemic: analysing the disease course of COVID-19 patients, selecting the best treatment strategies, and designing and applying vaccination strategies. The results of these studies have also been directly translated into daily clinical practice.

Biological samples and health information from the Biobank are also used in cancer research, such as analysing the effects of drugs on cancer cells, and studies on immunosuppressed individuals.

For more information on the activities of VUH SK Biobank, please visit www.hotc.lt/biobankas/.

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Clinical trials of acute leukaemias

RNA sequencing of single acute myelogenous leukemia cells

In cooperation with the biotechnology company "Droplet Genomics", in 2022, at the Centre for Hematology, Oncology and Transfusiology Center of Vilnius University Hospital Santaros Klinikos (VUH SK HOTC), a study title "Analysis of single-cell RNA sequencing of bone marrow samples of patients with refractory or relapsed acute myeloid leukemia treated with Venetoclax" was carried out. The aim of the study is to identify, at the single cell level, new, specific mechanisms of resistance to target therapies in acute myeloleukemia, which will allow the selection of the most optimal lifesaving therapy for patients in the future.

Pre-clinical studies on drug synergy in acute myeloid leukemia

Translational research on synergies between chemotherapy and drugs for various targets is continued at VUH SK HOTC and uses acute myeloblastic leukemia (AML) cell lines and *ex vivo* cells from relapsed/refractory AML patients. The aim of the study is to identify the most effective combinations of drugs that can be used to plan further clinical trials and to tailor the most effective treatment for the patients. The project "Development of innovative therapies and prognostic tools for the treatment of chemotherapy-resistant acute myelogenous leukemia", in collaboration with the Institute of Biochemistry of the Life Sciences Centre of Vilnius University, was completed in 2022 and two papers overviewing the results were published.[1-2]

Monitoring patients with relapsed/refractory acute myeloid leukemia

Specialists at VUH SK HOTC are conducting a follow-up study "Study of the clinical course and medical care of patients with treatment-resistant oncological and blood disease", which monitors patients with relapsed/refractory AML, evaluates the efficacy and safety of combination therapies based on novel target therapies, as well as the prognostic factors influencing the survival rate, response to treatment and remission time. Two papers summarising the results of the study were published in 2022[3-4], and the results were presented at the largest annual congress of the European Hematology Association (EHA 2022).[5] Also, for the second consecutive year, the HOTC study results were presented at the American Society of Hematology's Annual Congress (ASH 2022), the world's most important haematology event, and the results were published in Blood, a hematology journal having the highest citation index.[6]

Collaboration with the HOVON and EORTC study groups in the treatment of acute myeloblastic leukemia

VUH SK HOTC, in collaboration with the HOVON Research Centre in the Netherlands, participates in multi-centre, large-scale clinical trials to provide patients with acute myeloid leukemia with state-of-the-art treatment. HOTC is currently running two clinical trials investigating the safety and efficacy of combination treatment with targeted therapies (Ivosidenib / Enasidenib / Gilteritinib / Midostaurin) and standard chemotherapy. The final results of the EORTC 1301 phase III clinical trial were also presented in 2022.[7]

Collaboration with MD Anderson Cancer Center, USA

In 2022, the extraordinary story of the recovery of a patient with treatment-resistant acute myeloid leukemia from our centre was published, in collaboration with the world's leading cancer centre, where a clinical trial of Revumenib, a new targeted therapy, is underway. The results of the clinical trial were presented at the American Society of Hematology 2022 Congress[8], and the Phase II clinical trial of this drug will be extended at VUH SK HOTC from 2023.

Collaboration with the NOPHO Study Group in the treatment of acute lymphoblastic leukemia

VUH SK HOTC's long-standing collaboration with the Nordic Society of Paediatric Haematology & Oncology (NOPHO) study group has led to the introduction of a modern acute lymphoblastic leukaemia treatment protocol, ALLTogether, in 2022.

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Clinical trials on chimeric antigen receptor T lymphocytes (CAR-T)

CAR-T training at Vilnius University Hospital Santaros Klinikos

In 2022, specialists from the Centre for Hematology, Oncology and Transfusiology at Vilnius University Hospital Santaros Klinikos (VUH SK HOTC), in accordance with the principles of good manufacturing practice and the hospital exception rule, have introduced a technology for the preparation of the chimeric antigen receptor T-cell (CAR-T) CD19 advanced therapy. CAR-T CD19 has been made available to lymphoma and leukaemia patients treated at VUH SK. Nine patients have already been treated with this technology in 2022, and the collection of CAR-T samples and health information in the Biobank has been launched, with subsequent biomedical research planned.

CAR-T CD20/CD19 clinical trial

For the second year, VUH SK HOTC is also participating in a Phase II randomised multicentre clinical trial comparing CAR-T dual CD20 and CD19 targets with standard chemotherapy in resistant aggressive B-cell lymphoma.

Genomics and data science research

Searching for *de novo* mutations in next-generation sequencing data

The Centre for Hematology, Oncology and Transfusiology at Vilnius University Hospital Santaros Klinikos (VUH SK HOTC) is developing the application of deep learning neural networks to next-generation sequencing (NGS) data. An article on the application of neural networks for the detection of *de novo* mutations in NGS data, DeNovoCNN, was published in 2022.[12] A new version of the tool is currently under development at the HOTC. Other existing tools such as DeepVariant or SpliceAI are also applicable.

Search for new genetic factors for oncohematological disease risk

HOTC applies NGS data aggregation methods to discover new oncohematological risk genes. One of the methods is gene set enrichment analysis (GSE), which allows the identification of classes of genes or proteins that show a higher frequency of observed changes in oncohematological diseases compared to controls.

Implementation of the OMOP data standard

The Observational Medical Outcomes Partnership (OMOP) data standard was launched at HOTC in 2022. The OMOP standard is designed to describe and compare clinical data (interventions, drugs, diagnoses, etc.) between different facilities. This allows the pooling of multiple cohorts of patients and a more detailed analysis in the search for new prognostic factors.

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Centre for Infectious Diseases

Vilnius University Hospital Santaros Klinikos continues its participation in the European Union Vaccine Research Network VACCELERATE

VACCELERATE (https://vaccelerate.eu/) is a clinical research network for the coordination and conduct of COVID-19 vaccine trials. The network is comprised of academic institutions from all over Europe: The consortium is led by the University of Cologne, Germany, and currently includes 29 national partners in 18 EU-member states and 5 countries associated to the EU Horizon 2020 research programme, Figure 1.[1-3]

VACCELERATE is funded by the European Commission's activities for future pandemic preparedness, the HERA Incubator, an instrument that was created in analogy to the United States' BARDA. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101037867. **The project coordinator in Lithuania is Prof. Dr. Ligita Jančorienė, Head of the Centre for Infectious Diseases at Vilnius University Hospital Santaros Klinikos (VUH SK). The project implementators at VUH SK are Assoc. Prof. Dr. Birutė Zablockienė, Assoc. Prof. Dr. Inga Ivaškevičienė and others.**

VACCELERATE offers expertise, services, resources and solutions to speed up existing and upcoming development programmes as well as market authorizations for new vaccines and vaccination strategies. The network serves as a single entry-point for all stakeholders in COVID-19 vaccine development (pharma, academia, European Commission, EMA, ECDC, national health authorities and others) for phase 2 and 3 trials in Europe. The network will address any research question of interest, such as vaccine efficacy in virus variants, trials in children, pregnant women, immuno-compromised patients, trials on combination of different vaccines etc. The establishment of a European Volunteer Registry (https://vaccelerate.eu/volunteers/) for vaccine trials provides fast and efficient recruitment of trial participants (Figure 2). As of May 2022, the Volunteer Register form is available in 12 countries and translated into 14 languages. More than 100,000 volunteers have registered so far, mostly from Germany. In the first year since the launch of the VACCELERATE consortium and the creation of the volunteer registry, more than 15,000 volunteers have been enrolled in clinical trials through the registry. The VACCELERATE Volunteer Registry is an active way for Europeans to join the COVID-19 clinical trials in 12 countries (i.e. Austria, Cyprus, Germany, Greece, Ireland, Ireland, Lithuania, Norway, Portugal, Spain, Sweden, Turkey and Turkey). The Register is currently being implemented in 5 more countries (i.e. Belgium, Czech Republic, Hungary, Israel and the Netherlands).

VACCELERATE conducts capacity mapping of new clinical trial sites and laboratories with standardized methods and protocols, and provides standardized educational measures, training and quality management for harmonized vaccine trials. As of November 2021, 470 centers from 40 European countries have registered in VACCELERATE EUVAP (European vaccine trial accelerator platform) (www.euvap.eu). Of these, 162 centers (34.5%) are interested in participating in Phase I trials, 283 (60.2%) in Phase II trials, 368 (78.3%) in Phase III trials and 207 (44.0%) in Phase IV trials. Infectious diseases were identified as the main area of expertise in 103 centers (21.9%), while 42 (8.9%) centers specialized in immunosuppressed patients. Two hundred and thirty centers (48.9%) are able to enroll children and 380 (80.9%) adults. In less than one year, EUVAP has become the main platform for coordinating clinical trials in Europe (https://vaccelerate.eu/experts/), involving 10 clinical trial sponsors. EUVAP has mapped the

European Competent Clinical Trial Centers with the capacity to conduct COVID-19 vaccine trials. Sponsors can use EUVAP as a single platform covering many clinical trial centers in Europe.

Figure 1. 488 clinical trial centres have joined the VACCELERATE clinical trial platform EUVAP by the end of 2022. A further 33 trial centres have expressed interest. EUVAP map (above). VACCELERATE consortium partners (bottom)

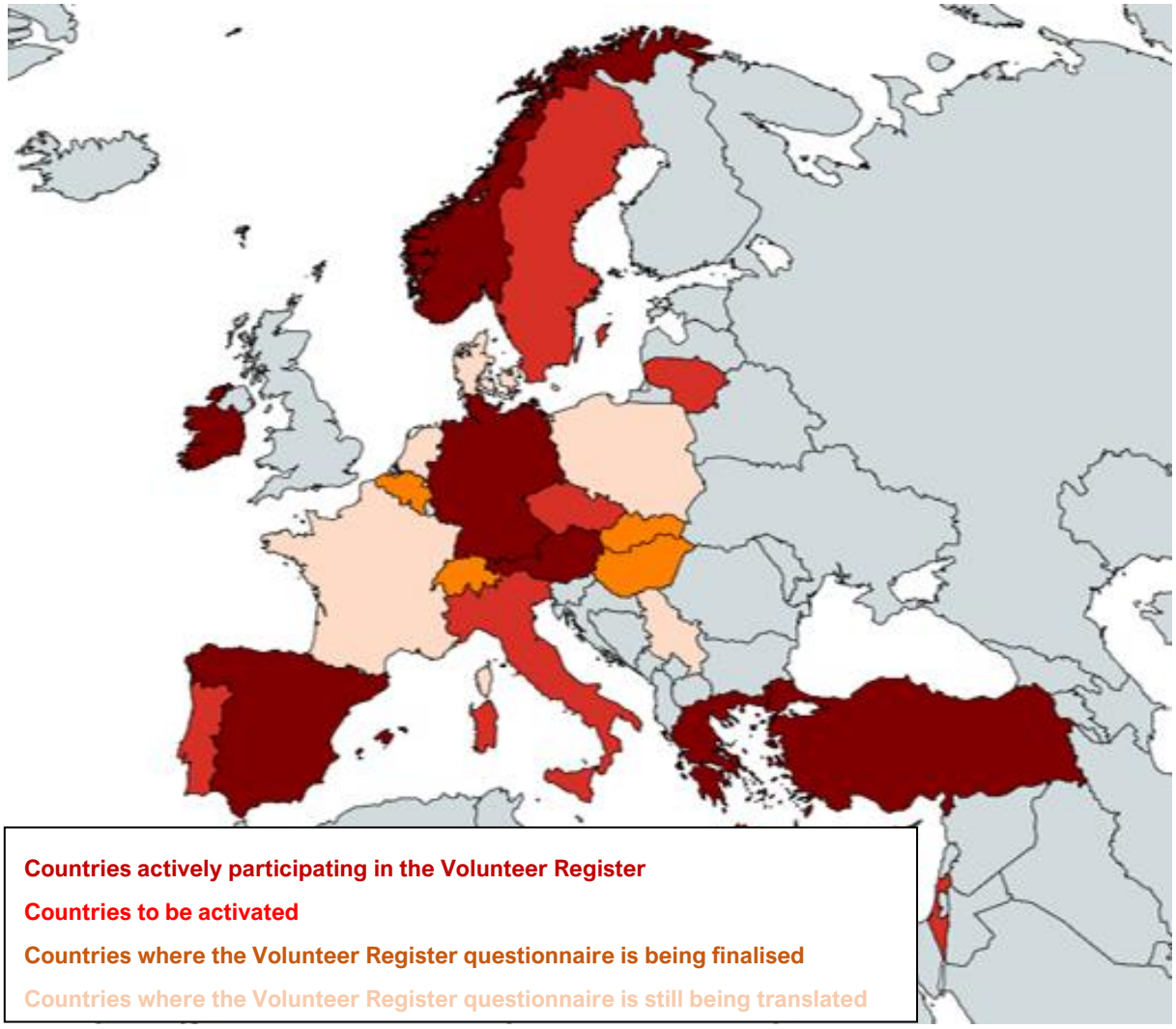

Figure 2. Countries participating in the Volunteer Register. The Volunteer Register is available in different countries and in several local languages. More and more countries are joining it. More than 100 000 volunteers have already registered.

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VEBIS - European Hospital COVID-19 and Influenza Surveillance, Risk Factors, Vaccine Efficacy, Burden and Impact Study

I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe), the Influenza Vaccine Effectiveness Monitoring Network (I-MOVE), established in 2007, was the first network to monitor the effectiveness of influenza vaccines in the European Union (EU) and the European Economic Area (EEA).

In February 2020, the I-MOVE partners formed the I-MOVE-COVID-19 consortium to establish epidemiological, clinical and virological data on SARS-CoV-2 infection and the efficacy of COVID-19 vaccines.

I-MOVE-COVID-19 consortium has joined the European Centre for Disease and Control (ECDC) as part of the ongoing research on SARS-CoV-2 infection, influenza and other respiratory infections and has been renamed the VEBIS (Vaccine Effectiveness, Burden and Impact Studies of COVID-19 and Influenza) consortium. The data collected in Vilnius University Hospital Santaros Klinikos (VUH SK) as well as data collected in the Lithuanian University of Health Sciences will be shared with the VEBIS consortium (formerly known as I-MOVE-COVID-19), the coordinators of which will carry out a joint analysis of the depersonalized data from all countries.[1-8] **The principal investigator is Prof. Dr. Ligita Jančorienė, Head of the Centre for Infectious Diseases, VUH SK, and the investigators are Assoc. Prof. Dr. Birutė Zablockienė, Ieva Kubiliūtė, PhD student, dr. Jurgita Urbonienė, researcher Akvilė Rudėnaitė, Fausta Majauskaitė and others.**

In accordance with European Commission (EC) requirements, depersonalized data are shared with the COVID-19 Data Portal (https://www.covid19dataportal.org/) and the European Centre for Infectious Diseases Control (ECDC), thus providing epidemiological, clinical and virological information on SARS-CoV-2 and influenza infections and the efficacy of their vaccines. The aim of this international multicenter study is to monitor the prevalence and dynamics of SARS-CoV-2 and influenza infections, to determine the risk factors for COVID-19, and to determine the effectiveness of vaccination in a cohort of hospitalized persons. Main objectives:

- To systematically assess the clinical, epidemiological and virological characteristics of patients hospitalized for severe acute respiratory tract infection (SARS-CoV-2) (surveillance study);
- To identify factors that confer risk of SARS-CoV-2 infection and protect against the development of severe COVID-19 disease and the long-term psychological and functional consequences of COVID-19 disease (risk factor study);
- To determine the efficacy of COVID-19 and influenza vaccination against laboratory-confirmed SARS-CoV-2 and influenza, and other severe outcomes.

There is a need to methodologically monitor the dynamics and trends in the incidence of patients hospitalized for severe acute respiratory infections (SARI), to identify factors that determine the risk of developing COVID-19 disease and the development of severe disease and its long-term consequences. With the introduction of COVID-19 vaccines, there is a need to better understand the real-life, actual effectiveness of vaccination in protecting against SARS-CoV-2 infection and the different disease outcomes. The study follows detailed procedures, thus ensuring a uniform, rigorously defined patient inclusion process. Most of the investigators involved in the study have experience with similar methodologies, having been involved in international influenza vaccine efficacy trials with the I-MOVE consortium since 2012. The vaccine efficacy study shall run from 1 April 2021 to 31 December 2023. The consortium coordinators will carry out a pooled analysis of the depersonalized data from all countries. In line with EC requirements, the depersonalized data will also be shared with the COVID-19 Data Portal (https://www.covid19dataportal.org/) and the

VEBIS (formerly I-MOVE-COVID-19) consortium (https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-against-severe-acute-respiratory).

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World Health Organization SOLIDARITY and SOLIDARITY PLUS trials - An International Randomized Trial of Additional Treatments for COVID-19 in Hospitalized Patients Who Are All Receiving the Local Standard of Care

The World Health Organisation (WHO) helped evaluate drugs by randomizing their effects on important outcomes. In WHO Solidarity trial between March 22, 2020, and Jan 29, 2021, 14 304 potentially eligible patients were recruited from 454 hospitals in 35 countries in all six WHO regions. There were evaluated four repurposed drugs, and now guided by an independent Expert Group, is evaluating addition to the local Standard of Care of other potential drugs in Solidarity plus trial. (Figure 1).

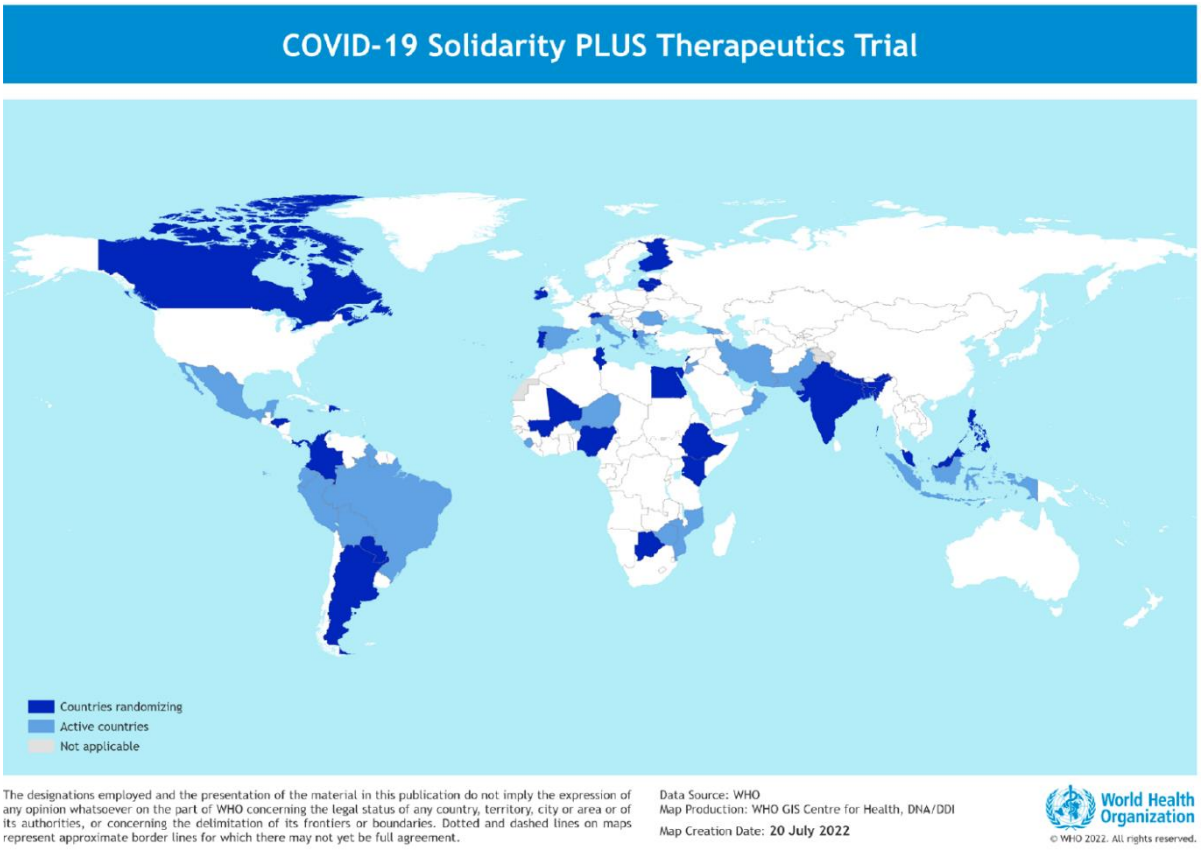

Figure 1. Participants in the Solidarity PLUS trial.

In 2021 the Solidarity trial reported among COVID-19 inpatients interim mortality analyses for four repurposed antiviral drugs. Lopinavir, hydroxychloroquine, and interferon (IFN)-β1a were discontinued for futility but randomisation to remdesivir continued. In 2022 the final results of Solidarity and meta-analyses of mortality in all relevant trials to date were reported. The Solidarity trial enrolled consenting adults aged ≥18 years, recently hospitalised with, in the view of their doctor, definite COVID-19 and no contraindication to any of the study drugs, regardless of any other patient characteristics. Participants were randomly allocated, in equal proportions between the locally available options, to receive whichever of the four study drugs (lopinavir,

hydroxychloroquine, IFN-β1a, or remdesivir) were locally available at that time or no study drug (controls). All patients also received the local standard of care. No placebos were given. The protocol-specified primary endpoint was in-hospital mortality, subdivided by disease severity. Secondary endpoints were progression to ventilation if not already ventilated, and time-to-discharge from hospital. Final log-rank and Kaplan-Meier analyses were presented for remdesivir, and are appended for all four study drugs. Meta-analyses give weighted averages of the mortality findings in this and all other randomised trials of these drugs among hospital inpatients. The main interpretation of the Solidarity trial result is that remdesivir has no significant effect on patients with COVID-19 who are already being ventilated. Among other hospitalised patients, it has a small effect against death or progression to ventilation (or both).

Solidarity trial International Steering Committee member and principal investigator at VUH SK is Prof. Dr. Ligita Jančorienė, Head of the Centre for Infectious Diseases. Investigators at VUH SK are Assoc. Prof. Dr. Birutė Zablockienė, Mindaugas Paulauskas, Ugnė Sakalauskienė and others.

In 2022, the Solidarity trial protocol was updated and the Solidarity plus trial was started. The primary outcome in the Solidarity plus trial is in-hospital mortality from any cause, and the primary analyses are of mortality in all randomised patients. The major secondary outcomes were initiation of ventilation, and duration of hospital stay. It is not expected that any of the treatments currently being tested will have a large effect on the risk of death, but if any had just a moderate effect and was widely practicable then this could avoid large numbers of deaths. Conversely, demonstration that certain agents have no material effect on major outcomes would be of value. Moderate effects can, however, be reliably demonstrated or refuted only by large-scale randomized evidence. Study products: Artesunate (this is the standard treatment recommended for the treatment of severe malaria); Infliximab (this is the standard treatment that is given repeatedly for the treatment of psoriasis); Imatinib (this is the standard maintenance treatment which is at the lower end of that used for several years in the treatment of hematological malignancies). The trial is ongoing.

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Centre for Cardiology and Angiology

Three-dimensional imaging of the tricuspid valve

As the incidence of heart valve diseases is increasing, the Centre for Cardiology and Angiology of Vilnius University Hospital Santaros Klinikos is also seeing increasingly more cases of tricuspid valve regurgitation. The incidence of this disease increases with age, with a prevalence of around 4% among those aged over 75. High-grade tricuspid regurgitation is known to be associated with a higher mortality rate, and the outcome is particularly poor in the presence of right ventricular insufficiency. On the other hand, timely detection and treatment of significant tricuspid regurgitation leads to a better prognosis.

Echocardiography is the main way to study heart valve pathology. The tricuspid valve is a spatial structure, therefore, it is not optimal to assess it using only two-dimensional echocardiography. Three-dimensional imaging of the tricuspid valve allows a more detailed assessment of the valve geometry, anatomy, the degree of leakage and its mechanical properties, the position of the wires of the devices located in the right cavity (e.g. pacemaker, cardioverter defibrillator), and the influence of these wires on the development of the regurgitation.

In addition to surgical techniques for the treatment of tricuspid regurgitation, percutaneous therapies are rapidly developing worldwide. Three-dimensional echocardiography is particularly useful in the investigation and selection of patients for these procedures, as well as in monitoring the operator's actions during the procedure, assessing the outcome of the procedure and subsequently monitoring the course of the patient's disease.

The STTAR clinical trial was conducted at the VUH SK Centre for Cardiology and Angiology in 2022 to evaluate the efficacy and safety of percatheter tricuspid valve annulus narrowing using the *Micro Interventional Device*. To date, 11 such procedures have been performed. In all patients, the tricuspid valve annulus was narrowed and in five patients the regurgitation of the tricuspid valve was reduced by at least one degree (Table 1, Figure 1). In all patients, 3D tricuspid valve images were analysed in two ways: 3D MPR (multiplanar reconstruction) and 4D Auto TVQ (Tricuspid Valve Quantification) (EchoPAC; GE *Healthcare*), Figure 2.

	3D MPR (multiplanar reconstruction)	**4D Auto TVQ model**	**p value**
TV ring circumference, cm	14.3 (13.75, 14.93)	13.75 (13.53, 14.4)	0.393
TV ring area, cm^2	15.75 (14.93, 16.93)	14.3 (13.35, 15.75)	0.315
TV ring size, cm	4.5 (4.2, 5,1)	4.3 (4.0, 4.5)	0.315
TV ring minimum dimension, cm	4.2 (4.0, 4.5)	4.2 (3.7, 4.7)	0.684

Table 1. Tricuspid valve (TV) annulus dimensions were measured using two different methods: 3D MPR (multiplanar reconstruction) and 4D Auto TVQ (Tricuspid Valve Quantification) software.

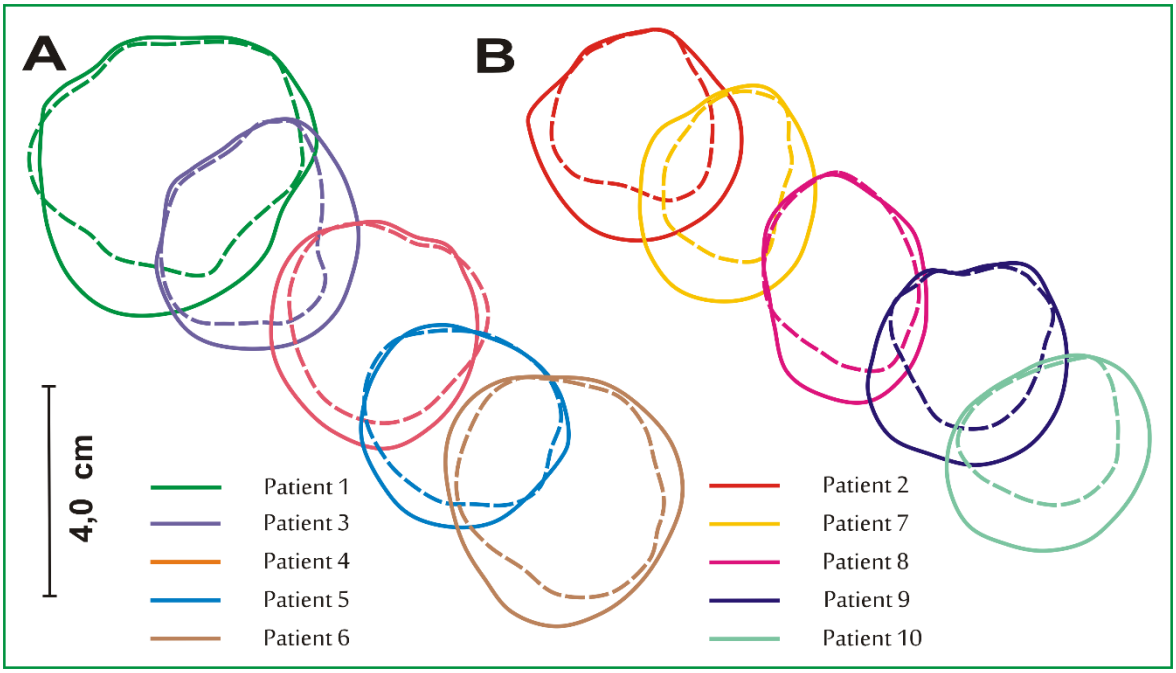

Figure 1. Change in tricuspid valve annulus in the unsuccessful (A) and successful (B) percatheter groups.

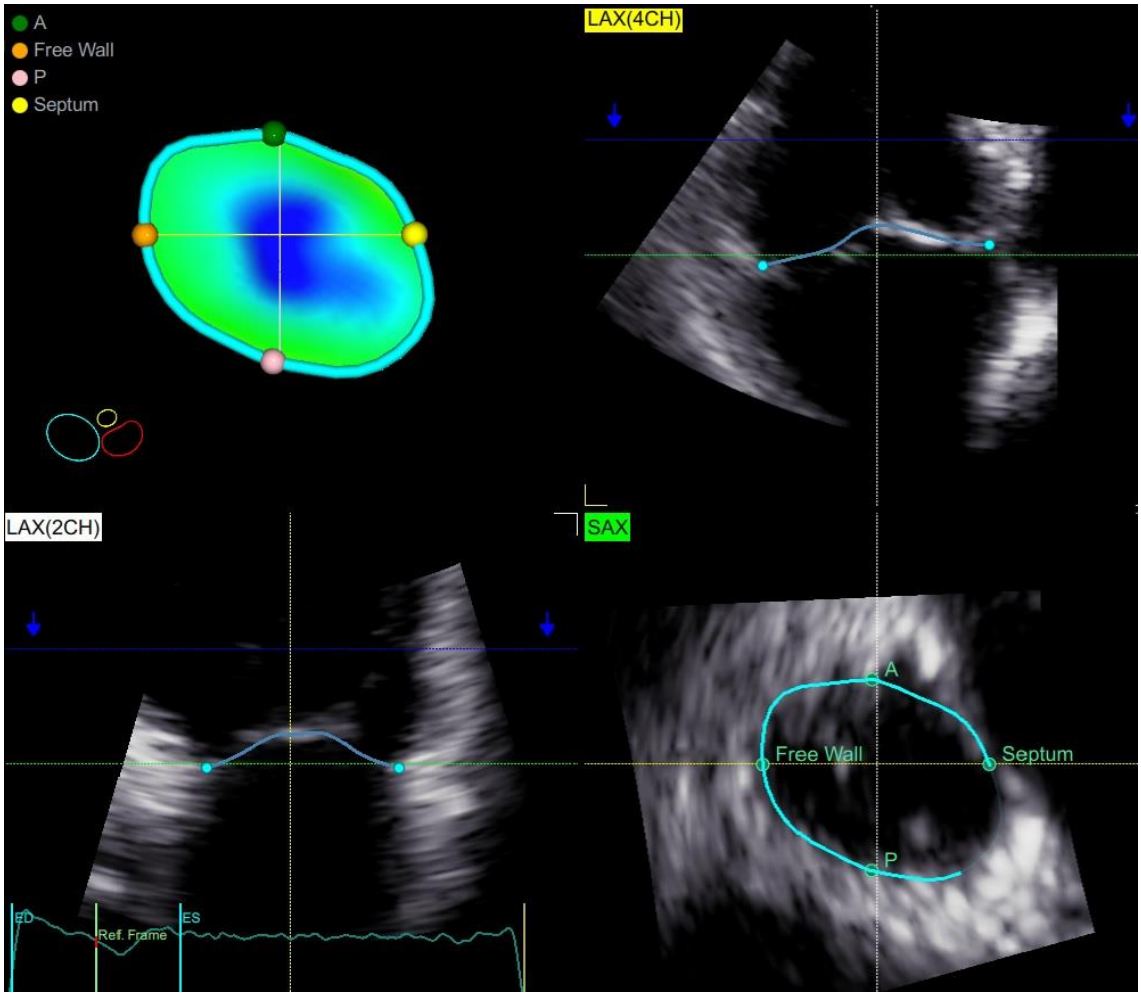

Figure 2. Model of a tricuspid valve created using 4D TVQ software.

Three-dimensional representation of the tricuspid valve has wider applications. In the research work of PhD student G. Bieliauskienė (supervisor Prof. Dr. D. Zakarkaitė), three-dimensional images of 155 patients with different degrees of tricuspid valve regurgitation were analysed. Statistical analysis revealed threshold values of tricuspid valve annulus area for different degrees of regurgitation (Figure 3). The combined effect of tricuspid annulus dilatation and cusp restriction on tricuspid regurgitation rate was also investigated.

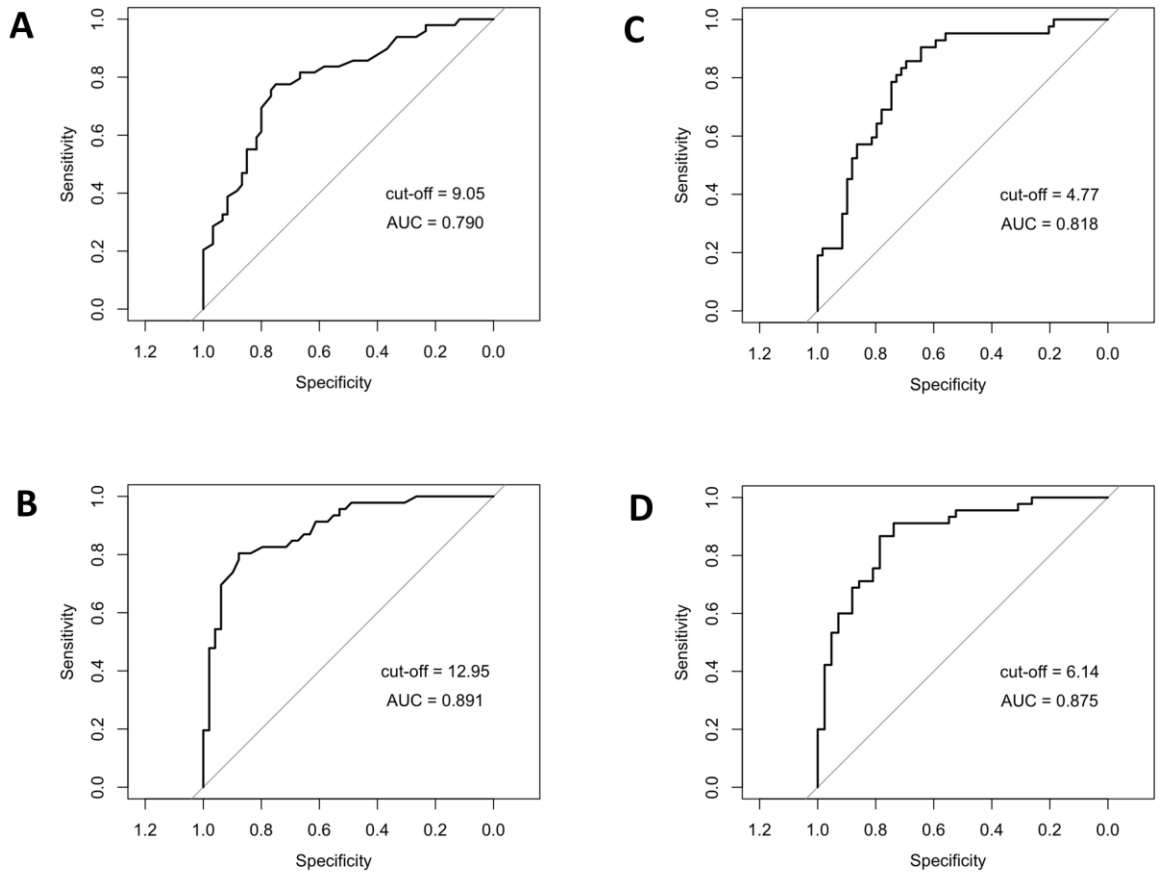

Figure 3. Receiver Operating Characteristics (ROC) curves showing the threshold values for the tricuspid valve area (A, B) and tricuspid valve area per indexed body surface area (C, D) for low and moderate tricuspid valve regurgitation (A, C) and for moderate and high tricuspid valve regurgitation (B, D).

Another clinical trial, *Vdyne Vista*, is being conducted at the Centre for Cardiology and Angiology at VUH SK to evaluate the efficacy and safety of a new percutaneously implanted artificial tricuspid valve prosthesis. Patient recruitment is ongoing.

The three-dimensional representation of the tricuspid valve allows a more detailed assessment of the dimensions and geometry of the tricuspid valve, providing additional information on the degree of leakage of this valve and the leakage mechanism. Timely and detailed assessment of the tricuspid valve status helps to select patients for percatheter procedures or to refer them in time for surgical treatment of the valve.

Clinical Radiation Surveillance Division

Nuclear medicine research through the eyes of a medical physicist

The Clinical Radiation Surveillance Division of Vilnius University Hospital Santaros Klinikos (**headed by Assoc. Prof. Dr. Birutė Gricienė**) conducts research on medical and occupational exposure to ionising radiation and its optimisation. In 2022, the focus is on research on nuclear medicine patients and staff and cooperation with the International Atomic Energy Agency (IAEA).

Nuclear medicine research

Nuclear medicine is a field of medicine in which different radiopharmaceuticals are used to diagnose, treat, or monitor disease response. The accuracy of the activity of radiopharmaceuticals administered to patients depends on quality control measurements and calibrations of the radiopharmaceutical activity meters, ensuring traceability with the secondary standards. Since 2016, intercomparison measurements were carried out[1], which allowed to evaluate the uncertainty of the equipment used depending on the radionuclide, source geometry and the metrological traceability. The readings of radiopharmaceutical activity meters used in nuclear medicine are important for evaluating the physical parameters of diagnostic equipment: spatial resolution, gamma camera non-uniformity, positron emission tomography equipment standardized accumulation value, as well as performing patient dose calculations and ensuring quality control and radiation safety. Expert medical physicist **Kirill Skovorodko** participated in the preparation of European Federation of Medical Physics Organization guidelines on the performance of quality control of PET/CT and PET/MRI scanning equipment[2].

In collaboration with personal health care institutions (nuclear medicine departments) and the Radiation Protection Centre, data on the activity levels of drugs (^{99m}Tc,^{18}F) administered to nuclear medicine patients in different procedures were collected during 2017-2022. The results of the surveys were used to update the Lithuanian national diagnostic reference levels.[3] The analysis of the data on activities administered to patients showed (Figure 1) that newer patient scanning equipment with CZT (cadmium-zinc telluride) digital detectors allows a reduction in the administered radiopharmaceutical activities by about 15%.

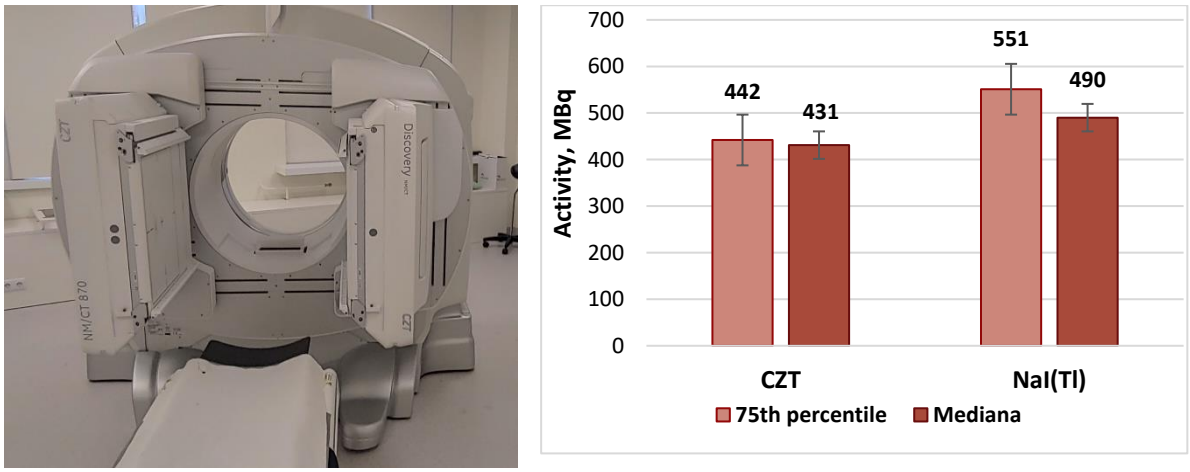

Figure 1. Comparison of the activity used for bone scintigraphy studies comparing the older generation SPECT equipment NaI(Tl) (2017-2019) with the innovative SPECT CZT equipment (left) for 2020-2021.

Investigations of workers' hand exposure

Activities with radiopharmaceuticals in nuclear medicine result not only in whole-body irradiation, but also in a higher hand-equivalent dose. Currently, hand dose measurements for workers are carried out by wearing a ring dosimeter on the finger, but due to the uneven distribution of doses in the hands, the actual dose value at the fingertips may be much higher than dose recorded by the dosimeter. In order to investigate and optimize doses and exposure risks in more detail, studies on the exposure of the hands of nuclear medicine workers were conducted in 2020-2022[4] (Figure 2). The results were presented at the international IAEA conference in Geneva[5]. The results obtained during the research will help to assess the actual exposure doses of workers, but also identify the work specifications and skills required during different procedures (e.g. preparing, injecting radiopharmaceutical preparations).

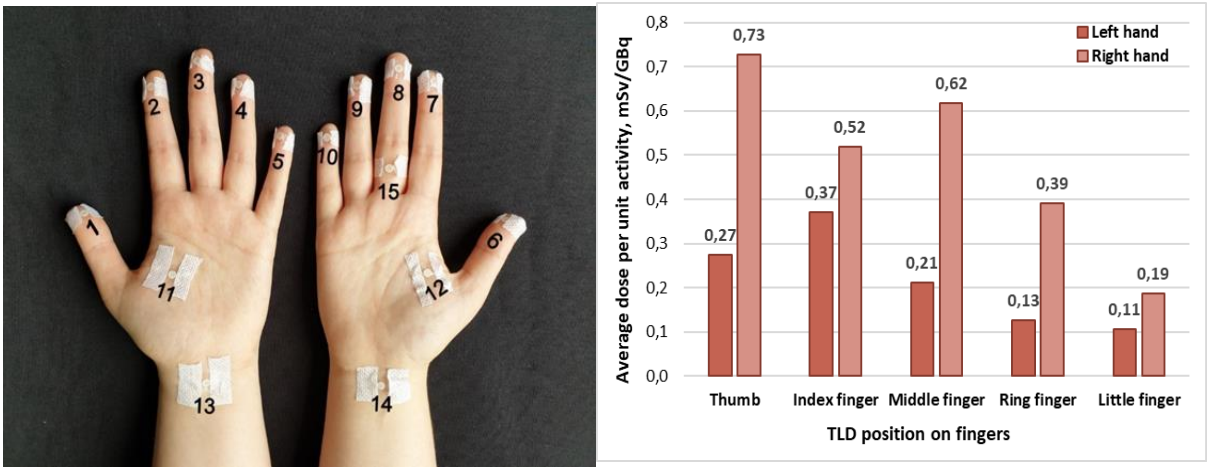

Figure 2. Positions of dosimeters on the hands (left) and measured average finger doses while working in a hot lab with ^{99m}Tc (right).

Doctoral and postdoctoral studies

Dr. Kristina Kristinaitytė, a medical physicist at the Clinical Radiation Surveillance Division, completed her postdoctoral studies at the Institute of Physical Chemistry (IPC) in Warsaw in 2022. The aim of her project was to develop a methodology for real-time monitoring of photochemical reactions by combining nuclear magnetic resonance spectroscopy and UV illumination. Light-based fabrication techniques allow us to remotely control when, where and which photoreaction is active. This property has wide applications in medicine, including tissue engineering, photodynamic therapy, detection of singlet oxygen in biological systems, development of biosensors, pH-meters or molecular containers for drug delivery.

Expert medical physicist **Kirill Skovorodko** participated in a doctoral internship at the Center for Energy, Environmental and Technological Research (CIEMAT) in Madrid, during which he acquired practical skills that enable accurate measurements of radionuclide activity in the range from Bq to MBq. This range is important for nuclear medicine diagnostics and treatment, verification and calibration of dosimeters and activity meters, as well as for environmental monitoring and testing of low-concentration samples.

Participation in activities of the International Atomic Energy Agency (IAEA)

The IAEA organises research, provides advice and expert assistance to various countries on the safe use of sources of ionising radiation. In the context of the growing threat of terrorism due to the illegsl use of these sources, the IAEA develops international guidance on the use of high-activity sources. **Assoc. Prof. Dr. Birutė Gricienė** a member of the IAEA expert working group, was involved in different activities of the IAEA during 2022 including the preparation of the IAEA's international recommendations on preparedness for the protection of sources and response in the event of an unwanted event. In addition, she as an international expert participated in IAEA ORPAS

missions to Slovakia and the Philippines in order to assess their readiness and compliance with international standards in the field of radiation protection of radiation workers. She also chaired the radiation safety culture session at the International Conference “Safety and Security of Radioactive Sources – Accomplishments and Future Endeavours” that was held between 20-24 June 2022 in Vienna.

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Centre for Laboratory Medicine

Research projects in 2022

In 2022, the staff of the Centre for Laboratory Medicine of Vilnius University Hospital Santaros Klinikos (VUH SK LMC) participated in the project "Detection of SARS-CoV-2 virus in throat lavage with saline fluid" between VUH SK and the Centre for Infectious Diseases (headed by Assoc. Prof. Dr. D. Vitkus, representatives of LMC D. Karčiauskaitė, D. Karosienė), and also joined various studies carried out by VUH SK:

- "A platform for non-invasive methods for early diagnosis and prognosis of severe acute pancreatitis" (D. Vitkus).
- AML-CHIP-2022 (NOPHO-DB-SHIP Consortium, R. Matuzevičienė).
- Acute lymphoblastic leukaemia study "Altogether - A Treatment Study Protocol of the ALLTogether Consortium for Children and Young Adults (1-45 years of age) with Newly Diagnosed Acute Lymphoblastic Leukaemia" (R. Matuzevičienė).
- Individualised testing of the upper respiratory tract microbiome - a new diagnostic and healthcare tool - "YourAirwayMicrobiome" (R. Malickaitė, L. Jurgauskienė, S. Kiverytė).
- Virulence potential of meningococcal isolates: prerequisites for effective molecular diagnosis of invasive meningococcal infection.
- Joint research project of the VU Life Sciences Centre and VUH SK "Investigation of genetic determinants of antibiotic resistance in opportunistic pathogens Acinetobacter baumannii and *Stenotrophomonas maltophilia*" (S. Kiverytė).

In 2022, the LMC also co-authored articles published in Clarivate Web of Science indexed publications.[1-17]

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Centre for Medical Genetics

Preimplantation genetic testing

Preimplantation genetic testing (PGT) is a genetic testing procedure that is performed before the implantation of embryos for the identification of genetic abnormalities. PGT is commonly performed when one or both parents are carriers of genetic changes that lead to serious, life-threatening or severely disabling diseases and have a high risk of passing them on to their children. The test is performed on the third or fifth day after the in vitro fertilization (IVF) procedure, examining one or more cells of the IVF-created embryo. Depending on the cause of the genetic disease, the PGT is applied individually to each family, specifically examining particular familial mutations or chromosomal changes that cause the disease.

PGT has been implemented at Vilnius University Hospital Santaros Klinikos since the enforcement of the legal act of in vitro fertilization in Lithuania on 01/01/2017. The first PGT was performed in September 2017 at the Centre for Medical Genetics.

44 PGT cycles have been performed between 2017 and 2022, resulting in 8 PGT babies being born (Figure 1).

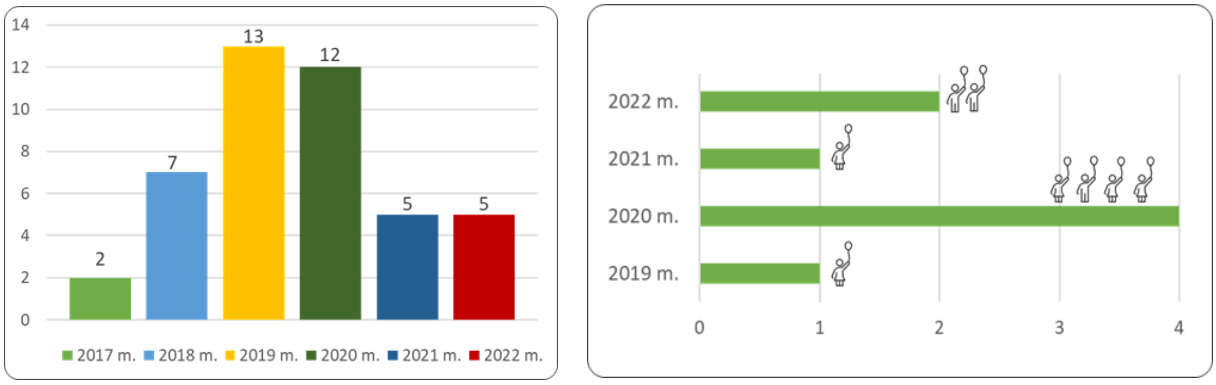

Figure 1. Number of preimplantation genetic tests (PGT) performed at the VUH SK Centre for Medical Genetics in 2017-2022 (left), number of children born after PGT in 2019-2022 (right).

The most common indications for PGT were structural chromosomal rearrangements such as Robertsonian translocations, reciprocal translocations and chromosome inversion. Six PGT procedures were performed for monogenic diseases: spinal muscular atrophy, cystic fibrosis, Lesch-Nyhan syndrome, Dent's disease and muscular dystrophy-dystroglycanopathy. Four PGT procedures were performed for sex chromosome abnormalities (Figure 2). The first results of PGT were summarised in scientific publications.[1,2]

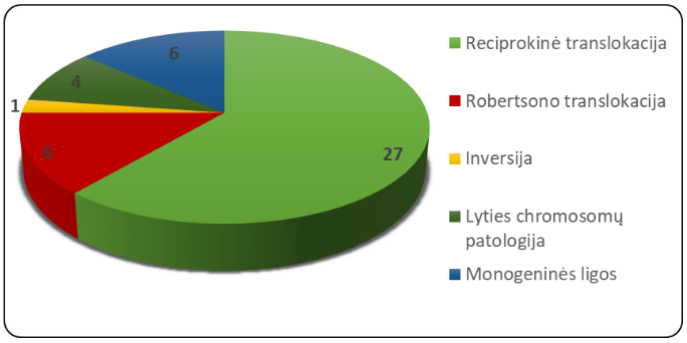

Figure 2. Indications for PGT.

Molecular genetic testing for spinal muscular atrophy

The spinal muscular atrophies are a clinically and genetically heterogeneous group of neuromuscular disorders. Proximal spinal muscular atrophy (SMA) is an autosomal recessive hereditary disease characterized by the degeneration of survival α-motor neurons in the spinal cord. With an estimated birth prevalence of ~1/10,000 and a worldwide carrier frequency of 1/51 SMA is among the most frequent autosomal recessive hereditary disorders (Figure 3) and is historically the leading genetic cause of infant mortality.

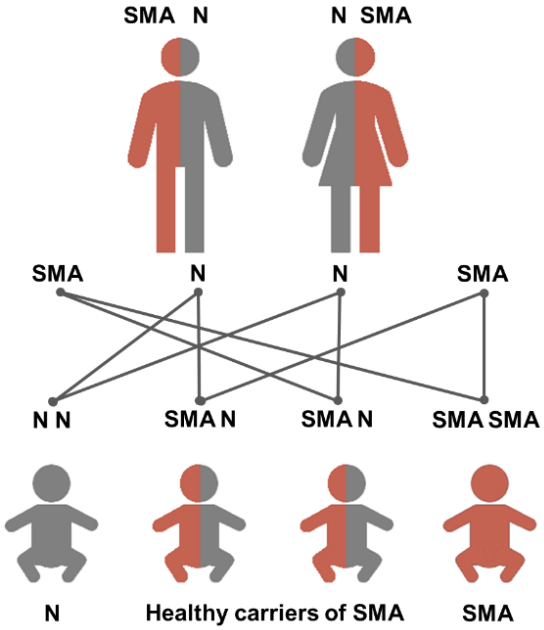

Figure 3. The inheritance of spinal muscular atrophy.

SMA is clinically classified into four types: acute, intermediate, mild, and adult. No restricting clinical criteria are warranted before undertaking DNA analysis (this is certainly so in neonatal cases in which a rapid molecular genetic analysis and diagnosis might be extremely helpful). Almost thirty years ago (1995), the genetic cause for SMA was identified. Approximately 95-98% of SMA patients, independent of the phenotype type, carry homozygous loss of function mutation (mostly a deletion of exon 7) of the survival motor neuron 1 (*SMN1*), and the copy number of the nearly identical copy gene *SMN2* inversely correlates with disease severity. *SMN2* is considered a sensitive and accurate prognostic biomarker for SMA.

The absence of *SMN1* exon 7 in SMA patients as a diagnostic test for SMA was used in the Center for Medical Genetics **since 1998** (Fig.2). Confirmation of the clinical diagnosis or suspicion of SMA by the detection of homozygous *SMN1* exon 7 deletion is still used in daily practice as it is a fast, inexpensive, and reliable method. However, the absence of a homozygous *SMN1* deletion does not rule out a diagnosis of SMA since 2-5% of cases are known not to have a homozygous *SMN1* deletion, a proportion of those SMA patients harbors conversion or hemizygous deletion together with a point mutation in one or extremely rarely in both *SMN1* alleles. So, **since 2012** quantitative assays based on a determination of *SMN1* and *SMN2* exons 7 copy number is being performed.

This method allows the identification of SMA patients with a homozygous *SMN1* deletion; SMA patients with one *SMN1* copy, who might be compound heterozygous for a second, subtle *SMN1* variant; the exact number of *SMN2* copies; and healthy heterozygous carriers.

However, the existence of two *SMN* genes in the human genome hinders (burdens) the search for point variants in *SMN1*. Identification of point *SMN1* mutation(s) is possible via Sanger or next generation sequencing **since 2015**. NGS approaches include a multigene panel that includes *SMN1*, *SMN2*, and other genes that cause neuromuscular diseases. **Since 2017** preimplantation genetic testing (PGT) through in-vitro fertilization has been introduced as an alternative to prenatal diagnosis to increase the options available for couples who are at risk for SMA to reduce their chance of initiating an affected pregnancy. PGT was efficiently applied for two couples with a history of SMA.

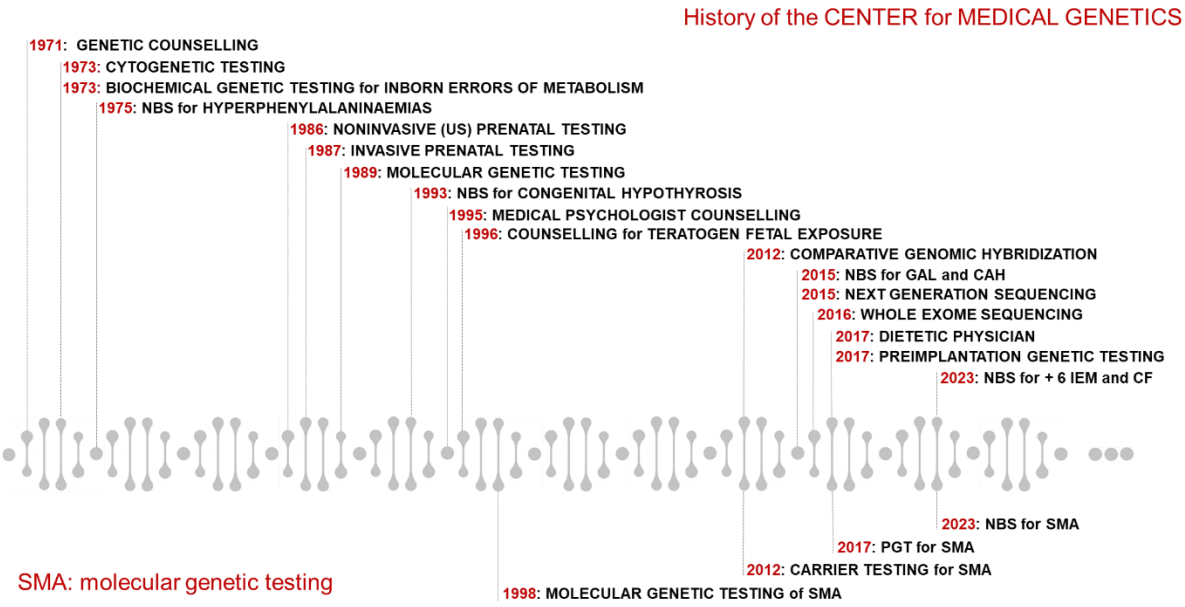

Figure 2. The timeline of approaches applied in the Center for Medical Genetics

Over 600 tests were performed to confirm or to contradict the clinical diagnosis of SMA or to determine carrier status in the Center for Medical Genetics **since 1998**. SMA diagnosis was confirmed for 109 patients.

The recently introduced disease-modifying treatment (approved for treatment, pre-clinical or early clinical development) improves the outcome of this disease, in particular when applied at an early stage of progression or of the pre-symptomatic period. So SMA has been targeted as part of newborn screening (NBS) programs in different countries over the last decade. Following long lasting effort to convince the government of the significance of SMA NBS screening in Lithuania, NBS for SMA will be performed at the Center for Medical Genetics **from 2023**. The molecular genetic testing approach will be used for the first time for NBS in Lithuania.

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Centre for Nephrology

Kidney transplantation

Kidney transplantation is associated with lower mortality and better quality of life compared to dialysis treatment for kidney disease. The care of kidney transplant recipients and the improvement of their survival rates is one of the main priorities of the Centre for Nephrology of Vilnius University Hospital Santaros Klinikos (VUH SK).

Investigating biomarkers of kidney graft rejection

Adter kidney transplantation, patients at the Centre for Nephrology of VUH SK undergo kidney graft biopsies to diagnose graft rejection and other pathologies. This is an invasive method of investigation, and therefore a study on biomarkers of graft rejection has been initiated at the Nephrology Centre of VUH SK (**Ernesta Mačionienė,** MD, PhD student, Faculty of Medicine, Vilnius University, supervisor **Prof. Dr. Marius Miglinas**), in which chemokines 9 and 10 are detected in a patient's urine sample for non-invasive and early suspicion of graft rejection. The study is carried out in collaboration with the Life Sciences Centre of Vilnius University. As these markers have a high negative predictive value, they can be used to monitor the patient: low values exclude graft pathology and indicate a good prognosis, while an increase in marker levels is an early indicator of possible graft rejection or viral infection, which can lead to a timely referral for more detailed investigations.

Urinary biomarkers will reduce the need for invasive testing methods and allow early detection of pathological conditions in the kidney graft, which, if addressed in time, can improve graft survival.

Molecular microscopy diagnostic system

Recent studies have shown that **molecular microscopy is more accurate** in detecting graft rejection reactions **than conventional methods** (such as biopsy of the transplanted kidney) which often lead to disagreements between doctors when assessing biopsy results. As the evaluation of histological examination relies on visual recognition based on experience, it is not particularly accurate as pathologists may have different opinions. The Molecular Microscopy Diagnostic System (MMDS) uses gene chips (similar to computer chips) to read molecules from kidney graft biopsies. The Molecular Microscopy System developed by the **Alberta Transplant Applied Genomics Centre (ATAGC, Canada)** and researchers in North America, Europe and Australia, uses **software to automatically convert microchip readings into diagnoses**. The MMDS isolates informational RNA from kidney tissue and measures genome-wide gene expression using microarrays with 50 000 sample sets that are 99% reproducible. Machine learning algorithms translate the expression measurements into diagnostic probabilities in a report that expresses the three-dimensional ratio of each new biopsy to a reference set with 99% accuracy. The molecular microscope is thus changing the “rules of the game” in transplantation medicine, providing doctors with new insights to help manage the rejection and treatment of kidney transplants. Researchers of the Centre for Nephrology **M. Miglinas, E. Ašakienė, A. Vickienė and E. Mačionienė, in collaboration with ATAGC** (led by **Prof. Dr. Philip Halloran**), are applying the MMDS approach to renal transplant patients.

Donor-derived cell-free **DNA** (dd-cfDNA) is another non-invasive biomarker that can also be used to detect rejection reactions in transplanted kidneys. Nephrology Centre investigators are participating in the international **TRIFECTA** study (Figure 1), whose analysis showed that **plasma dc-cfDNA from kidney transplant patients correlates with active molecular and histological rejection reactions in transplanted kidney biopsies, potentially decreasing the need for the invasive technique of kidney graft biopsies.**[1-3] .

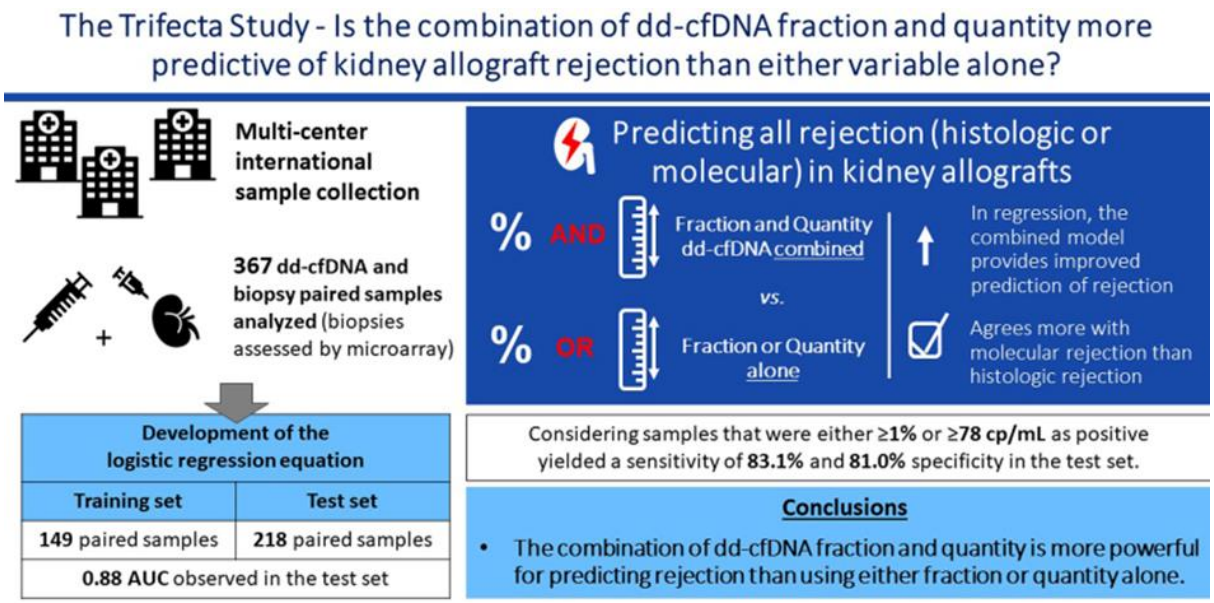

Figure 1. TRIFECTA study methodology and main results.

Personalised immunosuppressive therapy after kidney transplantation

Kidney transplantation is the optimal method of renal replacement therapy for patients with end-stage chronic kidney disease. Immunosuppressive therapy is standardised worldwide and patients are treated with calcineurin inhibitors, mycophenolic acid and glucocorticosteroids. However, this standardised treatment is not based on the individual characteristics of each patient, the optimal dosage for each patient, or the susceptibility of the patient's body to adverse reactions. Therefore, the Centre for Nephrology of VUH SK has started to test patients on the basis of the genetic expression of cytochrome P450 3A5 (CYP3A5) and its isoenzymes involved in the metabolism of the calcineurin inhibitor tacrolimus. These patients require up to 50% higher doses of drugs and testing helps to reduce the risk of graft rejection and to decide on the prescription of extended-release tacrolimus in order to improve patient and graft survival. For kidney transplant recipients, we use a tailored tacrolimus dosing algorithm, the iBOX prognostic system, and tailor the treatment to the immunological risk of the recipient.

Treatment of cytomegalovirus infection

Immunosuppression after kidney transplantation is a major risk for various infections. One of them is cytomegalovirus (CMV) infection, which is diagnosed and treated at the Centre for Nephrology of VUH SK. However, there are cases when routine treatment with ganciclovir, valganciclovir or foscarnet is not sufficient. To genetically identify treatment-resistant forms, we collaborate with the Charité Hospital laboratory in Berlin, Germany, and then are able to prescribe the right treatment for CMV infection. In the case of resistant CMV, we have successfully used innovative treatments such as CMV hyperimmune globulin and maribavir.

Pancreatic islet transplantation

There are many patients with diabetes mellitus who are undergoing kidney-only transplantation and who should be given the opportunity to alleviate their diabetes and prolong the survival of the transplanted kidney. We hope that pancreatic islet transplantation after kidney transplantation can soon be offered as a standard treatment option. In 2021, the first pancreatic islet transplantation procedure in Lithuania and the Baltic States was performed in a patient of the Centre for Nephrology Centre after a kidney transplant at VUH SK. The procedure was successful and reduced the patient's need for insulin and dangerous hypoglycaemia. On 1st of July, 2022, the Committee for the Evaluation of Personal Health Care Services of the Ministry of Health of the Republic of Lithuania included pancreatic islet transplantation for kidney transplant patients in the procedures covered by the Compulsory Health Insurance budget.

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Assessing and improving the nutritional status of patients with chronic kidney disease

Since 2015, the Centre for Nephrology of Vilnius University Hospital Santaros Klinikos has been focusing not only on the treatment of kidney disease, but also on assessing patients' diet and nutritional status.[1] Adequate nutrition is very important for patients from the early to the end stage of kidney disease, as well as for those on dialysis or living after a kidney transplant.

Protein energy wastage and fragility are associated with poorer kidney transplant outcomes. On the other hand, new-onset diabetes, obesity and accelerated atherosclerosis after transplantation also have a significant impact on the overall prognosis of the patient. Currently, a study is being conducted at the Centre for Nephrology (**Diana Sukackienė, MD, PhD student at the University of Vilnius University, supervisor Prof. Dr. Marius Miglinas**) that is evaluating the nutritional status, body composition, and biochemical nutritional markers of the recipients before and one year after kidney transplantation.

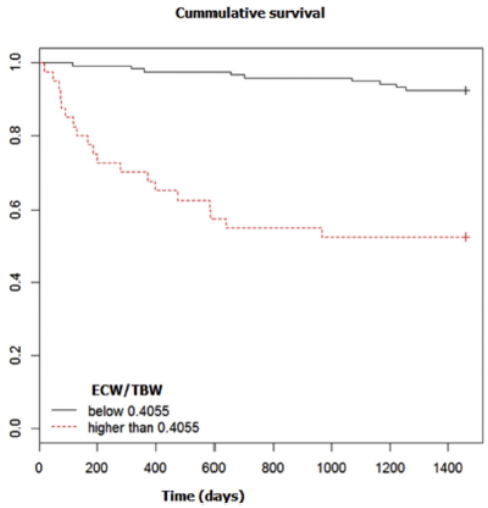

Fig. 4. Kaplan-Meier analysis for event-free survival. P < 0.001.

Figure 1. The impact of the Edema Index (ECW/TBW) on patient survival.

In addition to world-standardised dietary assessment questionnaires, we use a bioelectrical impedance analyser to assess nutritional status, which measures body composition (total, intra- and extracellular water, fatty and non-fatty body mass, and edema index). The **aim of the study is to assess the positive and, in particular, the negative changes in nutritional status and the factors associated with them, and to prescribe timely preventive and therapeutic measures.**

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Rare Kidney and Metabolic Diseases Diagnostic and Treatment Unit (RKMdTU) – new support for patients with rare kidney and metabolic diseases

In the European Union, a rare disease is defined as a disease affecting no more than 5 out of 10,000 people (1 in 2,000). Despite the rarity of these diseases, the total number of people with rare diseases is increasing every year. As new diagnostic and therapeutic approaches have become available worldwide, there is also a growing need in Lithuania to go beyond the theoretical foundations of rare kidney and metabolic diseases, to build up our experience and to provide optimal integrated specialist care for a particular disease.

In accordance with the Annex to the Description of the Procedure for the Provision of Day Hospital Services and Payment of their Costs (Order No V-2231 of the Ministry of Health of the Republic of Lithuania, 202/10/09) and in order to optimise the provision of personal health care services for metabolic diseases (Fabry's disease, alpha-mannosidosis, mucopolysaccharidosis, etc.) and for rare kidney diseases (hereditary tubulopathies, Alport's syndrome, thrombotic microangiopathies, tuberous sclerosis, polycystic kidney disease, etc.) the **Centre for Nephrology of Vilnius University Hospital Santaros Klinikos established the first Rare Kidney and Metabolic Diseases Diagnostic and Treatment Unit (RKMdTU) in the Baltic States on 2021/08/01, which will provide comprehensive services to patients with rare kidney and metabolic diseases.**

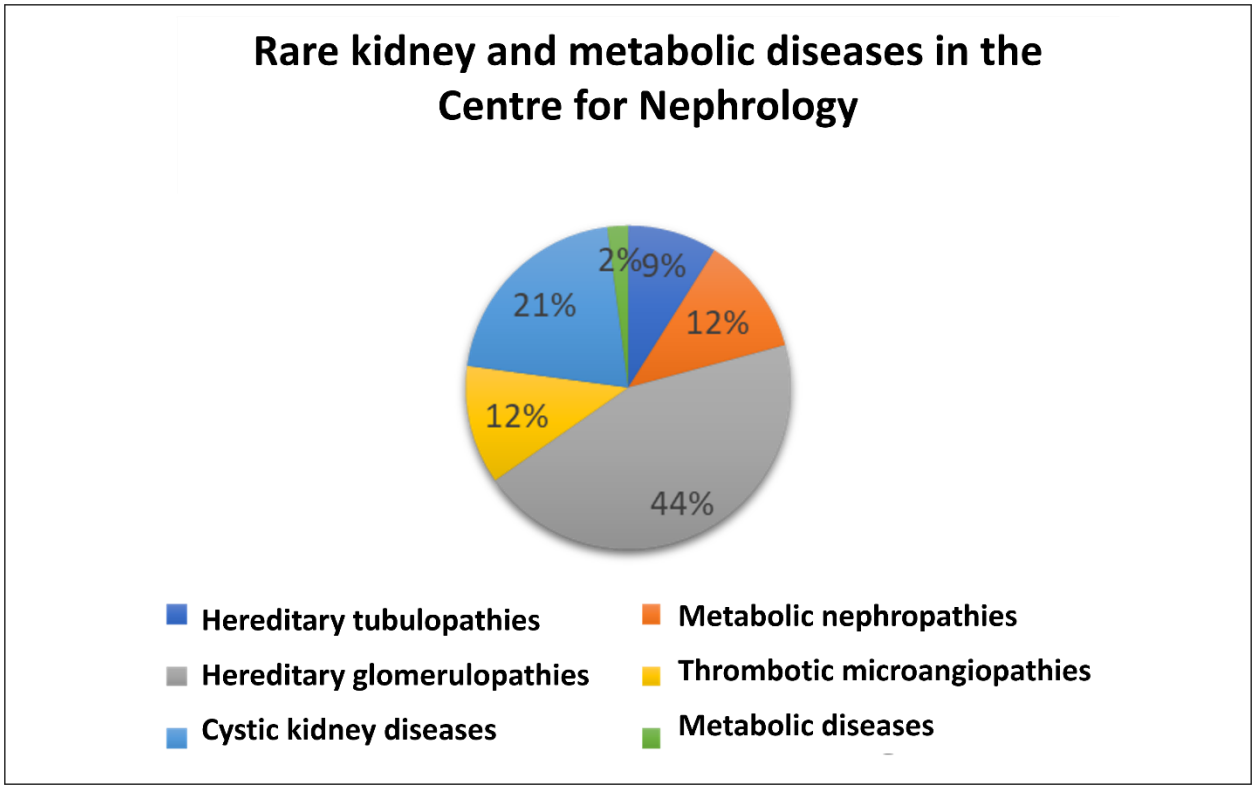

Figure 1. The distribution of patients with renal and metabolic diseases in the Rare Kidney and Metabolic Diseases Unit of the VUH SK Nephrology Centre.

The main features of the new RKMdTU are:

1. **Providing day hospital services for patients with renal and metabolic diseases,** prescribing up-to-date drug therapy and infusions of orphan drugs (e.g., enzyme replacement therapy, biologic therapy), and providing multidisciplinary consultations for patients with rare diseases.
2. Counselling, diagnosis, care, long-term monitoring, evaluation and treatment of patients with renal, rare renal and metabolic diseases, as well as the evaluation of the efficacy of specific drugs.
3. Preparing and submitting documents for orphan drugs to the Commission for Reimbursement of Very Rare Diseases of the State Patients' Fund.
4. Conduct clinical and biomedical research related to rare renal and metabolic diseases (TusCom, BioAlport, ALPART, Fabry registry, alpha-Manosidosis registry, thrombotic microangiopathy search algorithm, etc.; principal investigators and researchers – **Prof. Dr. Marius Miglinas, Dr. Agnė Kerpauskienė, Prof. Dr. Rimantė Čerkauskienė**), to publish the results obtained.[1-3]
5. Collaborate with other VUH SK Centres of Excellence, the Centre for Medical Genetics, the Centre for Pediatrics and other Lithuanian healthcare institutions as well as genetics laboratories in other countries (e.g., Centogene, Archimed, Blueprint Genetics) and with international scientific organisations (e.g., ERKNet).

Figure 2. Care for patients with rare kidney and metabolic diseases is provided at the specialised Day Hospital for Rare Kidney Diseases of the VUH SK Centre for Nephrology Centre. In the photo: Head of the Nephrology Centre Prof. Dr. M. Miglinas, Agnė Kerpauskienė, nurse-manager Roberta Vaičiūnaitė.

The Rare Kidney and Metabolic Diseases Unit is a new and the only specialised adult centre in the Baltics and Eastern Europe that provides patients with rare kidney and metabolic diseases with a full range of care, from diagnosis and treatment on an outpatient or day hospital basis to long-term follow-up and case management.

The staff of the department provides training on rare diseases to Lithuanian and foreign doctors and medical specialists, cooperates with patients and their families, helps to create patient organisations, actively cooperates with the Pediatric Centre of the VUH SK in the transfer of patients with rare renal and metabolic diseases to adulthood and tries to introduce all the latest diagnostic and therapeutic options to patients with rare renal and metabolic diseases.

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Phenotype-genotype associations and prognostic factors in collagen IV alpha 345 nephropathy (Alport syndrome)

Hematuria is one of the most common urine findings in clinical practice and can mask the diagnosis of Alport syndrome. Alport syndrome (AS), or collagen IV alpha 345 nephropathy, is a rare disease of genetic origin leading to progressive impairment of kidney function, vision, and hearing. At least 10 per cent of young adults who require long-term renal replacement therapy have inherited kidney disease.

More than 3000 variants in the *COL4A3, COL4A4, COL4A5* genes have now been identified in AS, leading to a range of disease manifestations from isolated haematuria to end-stage chronic kidney disease. There is a rapidly growing global need to find new diagnostic options for Alport syndrome and to implement programmes to prevent disease progression. Early diagnosis of AS helps to halt the progression of the disease, resulting in a delay in the need for renal replacement therapy, increased life expectancy and improved quality of life.

Patient search programmes, identification of genetic variants of *COL4A3-A5* and AS inheritance, and genotype-phenotype correlations help to better understand the course of the disease, its pathogenesis, and the risk of progression, and therefore, since 2014, the doctors of the Centre for Nephrology of Vilnius University Hospital Santaros Klinikos, and the researchers of Vilnius University (**PhD student Agnė Kerpauskienė, Prof. Dr. Marius Miglinas, Prof. Dr. Rimantė Čerkauskienė, thesis supervisor Prof. Dr. Arvydas Laurinavičius**), together with the Faculty of Medicine of Vilnius University and international Alport syndrome scientific societies from Australia (**Prof. Dr. Judtih Savige**), the United Kingdom (Alport syndrome expert workshops) and Germany (Centogene laboratory, **Prof. Dr. Arndt Rolfs**), have started to run an Alport syndrome research programme in Lithuania at the VUH SK Centre for Nephrology (Figure 1).

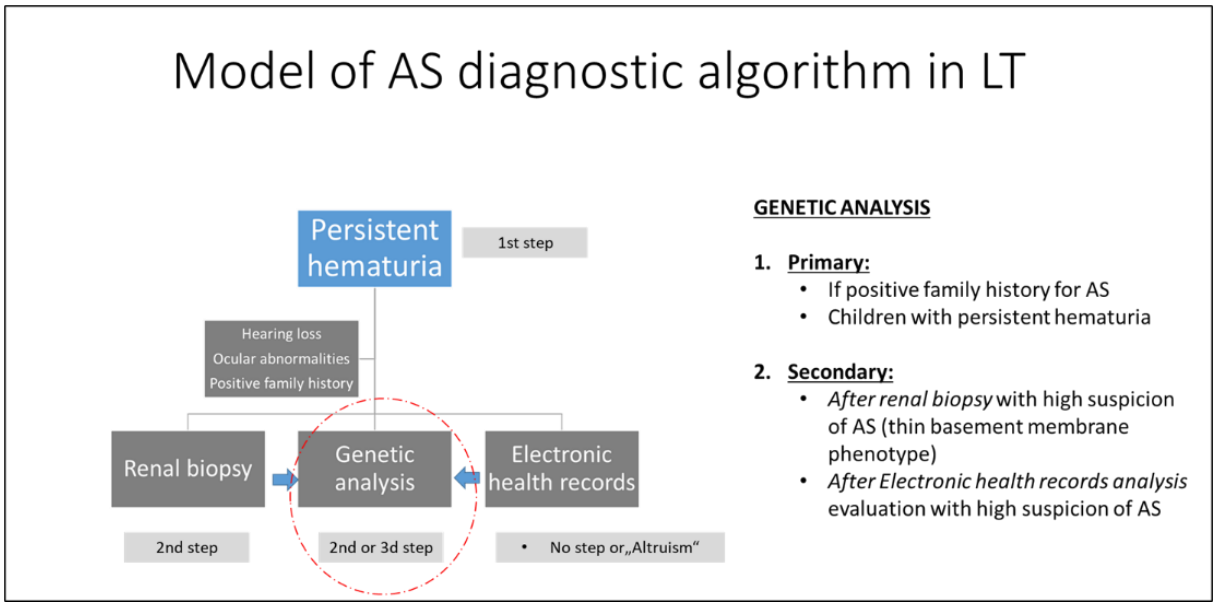

Figure 1. Alport syndrome diagnostic algorithm model.

Molecular genetic analysis using next-generation sequencing was performed on 171 individuals with suspected AS. Alport syndrome was genetically diagnosed in 99 patients and 44 mutations were identified, of which 27 were variants in the *COL4A3, COL4A4, COL4A5* genes, never reported

in the literature.[1] New genetic variants have been added to global genetic databases (e.g., LVOD). Three individuals were diagnosed with the extremely rare digenic Alport syndrome, where alterations were found in two of the three collagen IV-encoding genes, *COL4A3* and *COL4A4*, and *COL4A4* and *COL4A5*.[2]

All probands had hematuria and four (7.8%) had end-stage chronic kidney disease. The newly identified variants accounted for more than half of the total number of variants found in the 171 individuals from 109 unrelated families who underwent genetic testing. We identified pathogenic or potentially pathogenic variants in all individuals with end-stage chronic kidney disease or with ocular lesions associated with more severe Alport syndrome. The frequency of detection of pathogenic variants was lower in those with isolated persistent haematuria (those with potentially pathogenic or unknown pathogenic variants). **These results increase the number of known *COL4A3, COL4A4* and *COL4A5* variants and our understanding of the genotype-phenotype relationships in AS. Genetic variants in *COL4A3-5* have a significant impact on the diagnosis, treatment and prognosis of individuals with AS.**[3,4]

Therefore, the main aim of this study was to evaluate the clinical significance of collagen IV α345 gene mutations and to determine the genotype-phenotype association between Alport syndrome and other collagen IV α345 nephropathies in Lithuanian families, to develop an effective algorithm for AS detection and to improve the diagnosis of this disease in the Lithuanian Hospitals.

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Peritoneal dialysis and hemodialysis services in 2022

Peritoneal Dialysis Reference Centre in Lithuania

Since 2011, Vilnius University Hospital Santaros Klinikos (VUH SK) Dialysis Unit of the Centre for Nephrology has been operating a peritoneal dialysis unit, which became particularly active during the quarantine period of the COVID-19 pandemic, when patients opted for home dialysis. It is now the largest and most advanced home dialysis centre in Lithuania: 70% of patients are treated with automated dialysis, and remote monitoring of the procedure via internet connection has been introduced.

Home dialysis not only avoids the need to travel to a dialysis centre and undergo the procedure there. It has been shown to preserve residual kidney function for longer, with less nutritional restriction and better monitoring of parameters after kidney transplantation. In addition, patients can travel freely and remain socially active.

Following the COVID-19 pandemic restrictions in Lithuania, peritoneal dialysis patients started to receive **telemedicine**, often with reimbursable medicines being prescribed remotely. Unlike haemodialysis, peritoneal dialysis patients have fewer visits to the treatment facility, in some cases with live home visits or home teaching, and 24-hour nurse/physician consultation.

In 2022, 24 new patients were started on peritoneal dialysis and 9 underwent kidney transplants, one of the highest rates of recipient preparation in the country. **The ShareSource platform was launched to monitor patients' adherence to therapy and to record machine alarms.** Training is provided to other centres planning to implement peritoneal dialysis services, and more complex cases and complications are consulted and treated in other hospitals. Several times a year, the Nordic Peritoneal Dialysis Council events are attended – in 2022 the council meeting took place in Vilnius.

Modern hemodialysis – the mainstay of nephrology services

The Dialysis Unit of the VUH SK Centre for Nephrology provides intermittent hemodialysis services[1] for patients in all departments of the hospital. In 2022, an increase in services was observed after the pandemic, during which outpatients were transferred to other centres and services were intensively provided to the COVID-19 units.[2] **During the pandemic, COVID-19 patients were included in the European Clinical Course and Outcome Database "ERACODA" for patients with infection.**[3,4]

Scheduled haemodialysis is carried out in three shifts, while emergency haemodialysis is carried out around the clock. By December 2022, 5778 haemodialysis treatments have been performed, 70% of which were for inpatients requiring intensive care. In addition, 20 patients receiving haemodialysis from home are continuously monitored and 30% of chronic haemodialysis patients are treated with a modern procedure – hemodiafiltration with continuous production of replacement solution – in the hope of improved survival and fewer complications. Finally, an innovative ultra-high permeability dialysis membrane for the removal of intermediate-mass uremic toxins has been introduced at the VUH SK Centre for Nephrology.

The Dialysis Unit of the VUH SK Centre for Nephrology is also participating in a **study,** together with other European centres, on a **first-in-human reproducible synthetic hemodialysis graft**, which is expected to provide an effective alternative to the arteriovenous fistula.

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Relationship of sodium excretion, arterial blood pressure and renal damage in a study of sodium intake in the Lithuanian population

With rates of cardiovascular disease increasing worldwide, reducing salt intake is one of the most cost-effective strategies to tackle the epidemic of high blood pressure, which is associated with higher incidence of cardiovascular and kidney disease, and to improve population health and life expectancy. The World Health Organisation (WHO) recommends a daily intake of less than five grams of salt. To date, there have been no reliable studies assessing sodium (and salt) intake in the population. Therefore, in 2019-2020, specialists of the Centre for Nephrology of Vilnius University Hospital Santaros Klinikos (principal investigator **Prof. Dr. M. Miglinas, Urtė Žakauskienė, Ernesta Mačionienė, Diana Sukackienė, Lina Zabulienė**) conducted a study in collaboration with the WHO and the State Public Health Promotion Fund under the Ministry of Health to assess salt intake in the Lithuanian population.[1-3]

The study showed that most participants (87.5%) consumed >5 g of salt per day, and only 12.5% of subjects had salt intakes that met the WHO recommendations (Figure 1). The national average salt intake is estimated to be 10 grams/day, which is twice the WHO recommendation.

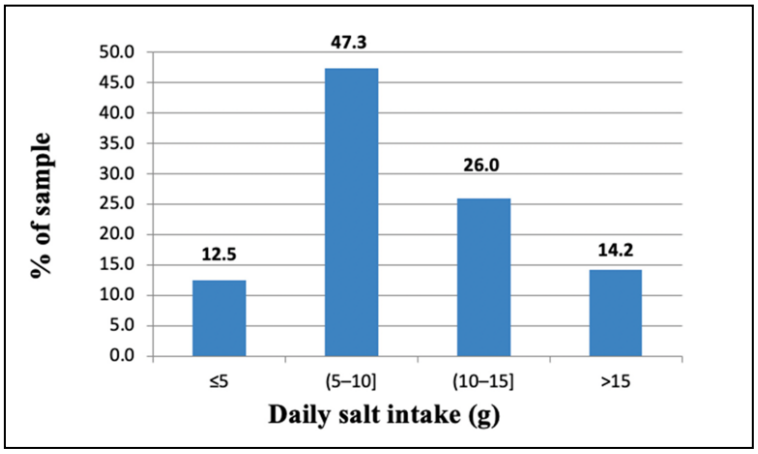

Figure 1. Subgroups of subjects according to salt intake.

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Personalisation of renal replacement therapy based on collagen marker imaging using polarimetric nonlinear microscopy and artificial intelligence optimisation algorithms

According to the International Society of Nephrology (ISN), more than three million people worldwide are currently receiving renal replacement therapy for chronic kidney disease, with dialysis being the predominant type of therapy. With an average of the same number of deaths each year because of inadequate treatment, chronic kidney disease poses an increasing challenge to the daily practice of the nephrologist as the population of patients grows.

The formation of arteriovenous fistulas (AVFs) to ensure access to haemodialysis remains the gold standard in chronic kidney disease treatment guidelines. One of the complications of AVF formation is hyperplasia of the neointimal layer of the vein, which leads to a failure of the fistula to function successfully. On the other hand, the histopathological parameters of the veins involved in AVF formation have not been extensively investigated. In the largest multicentre study to date, the Hemodialysis Fistula Maturation (HFM) Study, an international group examined the veins of AVFs itoelucidate the histopathological characteristics that lead to hyperplasia of the AVF neointima layer.

Examination of 554 venous samples showed that neointimal hyperplasia is characteristic of most AVFs, with a concentric or eccentric distribution, and accumulations of proteoglycans and collagen in the venous matrix. The influence of collagen fibre distribution in the tissue is poorly understood and opens a wide range of possibilities for further research. One of these is structural tissue imaging based on polarimetric nonlinear microscopy. This is an innovative approach that has not been applied in nephrology so far. Collagen fibres have a non-centrosymmetric structure and can therefore be efficiently visualised by second harmonic generation microscopy. One of the major advantages of this method is that the specimen to be visualised does not need to be further processed by staining with conventional light microscopy techniques, and the resulting three-dimensional (3D) images provide a much more detailed view of the specimen.

In this project, nephrologists Prof. Dr. M. Miglinas, Dr. L. Rimševičius, vascular surgeons Dr. B. Vaišnytė, Dr. S. Norvydas of Vilnius University Hospital Santaros Klinikos (VUH SK), pathologists Dr. E. Žurauskas, Dr. J. Besusparis of the National Center of Pathology, and PhD student V. Samsonė, in collaboration with the University of Toronto (Canada, Prof. Dr. V. Barzda and his team) and the Laser Research Centre of Vilnius University, launched an innovative Second-Harmonic Generation (SHG) microscopy method in October 2022 (Figure 1) to determine the influence of collagen fibre distribution in tissues on the efficiency of dialysis connections and to introduce an artificial intelligence (AI)-based early diagnosis methodology based on the detection of novel predictive collagen markers.

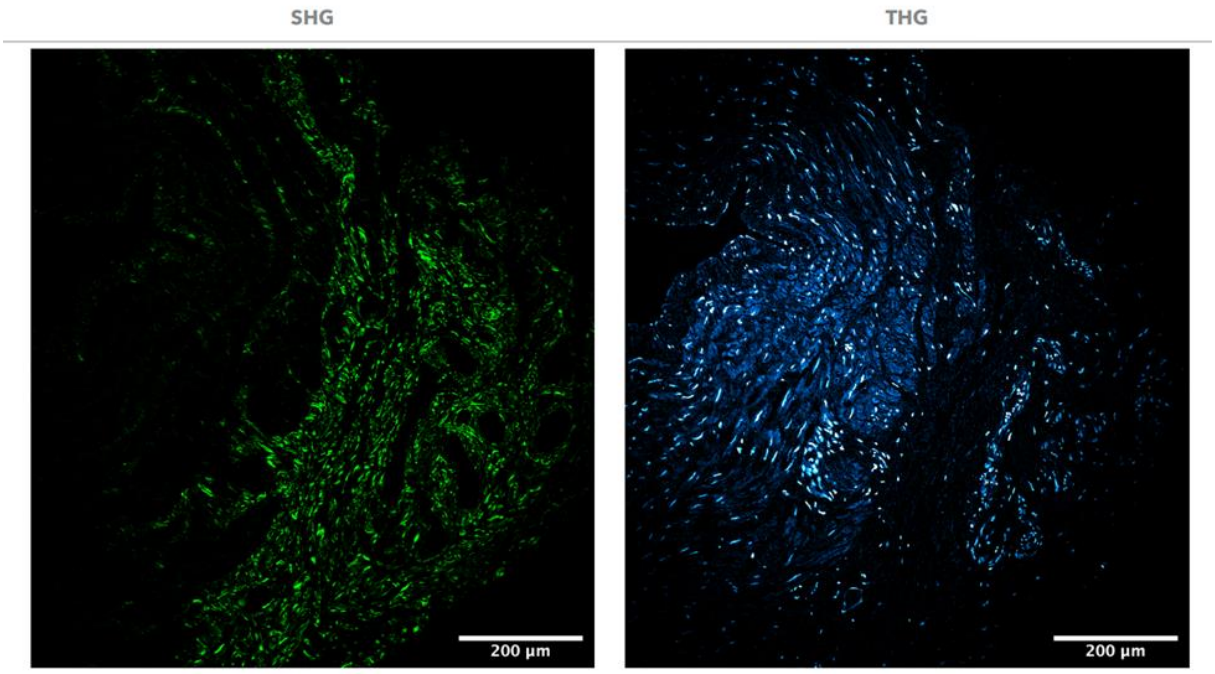

Figure 1. Vena cephalica image from the removed arteriovenous fistula obtained by nonlinear microscopy (SHG and THG).

Risk factors for chronic kidney disease after partial nephrectomy

In 2022, a prospective study on the assessment of kidney function after cancer surgery continued at the Centre for Nephrology and the Centre for Urology of Vilnius University Hospital Santaros Klinikos (VUH SK).[1-2] Lithuania is the second European country in terms of the incidence and prevalence of kidney cancer, which has led to an increase in the number of laparoscopic and open kidney resections (partial removal of a kidney with a mass) and radical nephrectomies (complete removal of a kidney). The main aim of these operations is to cure patients of their kidney cancer, but some patients develop renal impairment, post-operative acute kidney injury (AKI) and chronic kidney disease (CKD). **Under the supervision of Prof. Dr. Marius Miglinas and Prof. Dr. Feliksas Jankevičius, urologist and PhD student Jurijus Makevičius,** evaluated the data after renal resection (IR) with ischaemia in 91 patients enrolled between January 2016 and December 2019 (patients had to have a preoperative glomerular filtration rate (GFR) ≥60 mL/min/1,72 m^2, and to be free of pathological albuminuria), Figure 1.

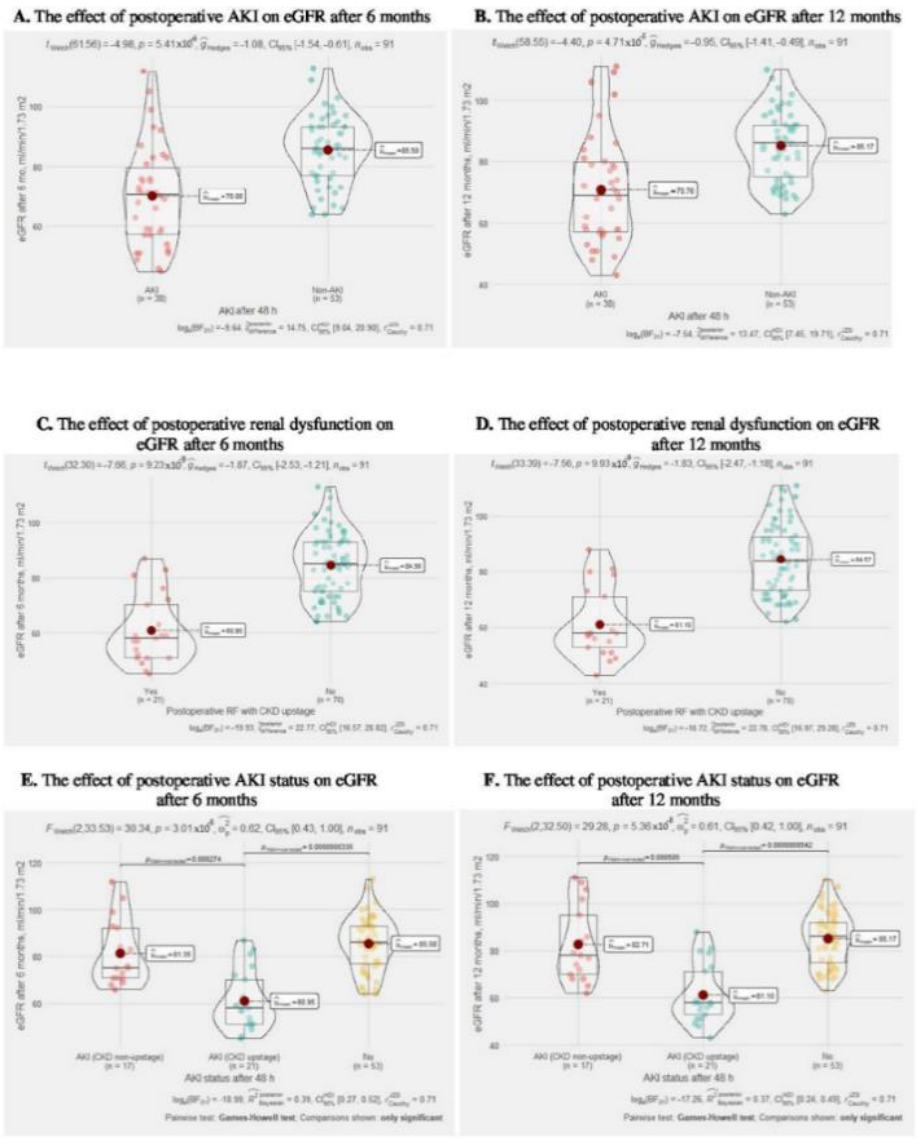

Figure 1. Risk factors for chronic kidney disease after partial nephrectomy.

Thirty-eight (41.8%) patients had postoperative AKI due to intraoperative hypotension (IOH, odds ratio (OR) 1.07, 95% confidence interval (CI) 1.03-1.10, $p < 0.001$) and neutrophil lymphocyte ratio (NLR, OR=1.50, 95% CI 1.19-1.88, $p < 0.001$). Only clinically significant postoperative AKI contributed to the decrease in GFR at 6 and 12 months, $p < 0.0001$ (Figure 1), with IOH as a risk factor (OR=1.06, $p < 0.001$). The most important prognostic factor for postoperative AKI is an NLR greater than 3.5. Postoperative CKD occurred in 14 (15.4%) patients after 6 months of follow-up. After 12 months of follow-up, CKD was diagnosed in 15 (16.5%) patients. Estimated blood loss >500 ml (OR=11.13, 95% CI 1.88-65.92, p=0.008) at the time of renal resection and larger resection volume (OR=1.05, 95% CI 1.05-1.10, p=0.033) and IOH time (OR=1.11, 95% CI 1.03-1.19, p=0.005) were the main risk factors for CKD.

These results have provided more information on AKI and CKD after kidney resection and allow us to predict post-operative renal function and plan the surgical volume accordingly.

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Centre for Neurology

Continuous focus on epilepsy care and insights into sleep quality during the COVID-19 pandemic

Epilepsy and mental health – validated assessment tools for the Lithuanian population

In 2022, the Centre for Neurology of Vilnius University Hospital Santaros Klinikos (VUH SK) continued the validation of psychometric scales among people with epilepsy (PWE) living in Lithuania – the psychometric properties of the **Patient-weighted 31-item Quality of Life in Epilepsy Inventory (QOLIE-31) and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)** have been published (principal investigator **Prof. Dr. Rūta Mameniškienė**).[1-2] Both **questionnaires** were found to **have good reliability and validity and can be used among Lithuanian speaking PWE** to assess their quality of life (QOLIE-31) and suicidal ideation (NDDI-E). It was also revealed that both scales correlate with each other ($r=0.663$, $p<0.001$, $n=303$) and can be effectively used together. The instruments measuring quality of life and suicidal ideation in epilepsy allow professionals to assess aspects of the patient's life and psychological state that may be overlooked during routine consultations. For instance, an assessment of data from the National Compulsory Health Insurance Fund (January 2014 to May 2020) found that the prevalence of mood disorders among PWE in Lithuania is only around 8%, while the true prevalence of these disorders is likely to be between 20% and 30%, according to data from other countries.[3] The latter study also revealed that a diagnosis of a mental disorder is not associated with a higher mortality rate among PWE when the influence of somatic disorders on the likelihood of mortality is included in the analysis. As mood and anxiety disorders are rarely diagnosed, the results should be validated using epilepsy-specific questionnaires to identify these mental conditions.

Epilepsy Actualities – Conference “The epilepsy saga of Ieva’s family”

On 14 October 2022, Lithuanian epilepsy specialists had the opportunity to discuss current issues related to epilepsy diagnosis and treatment options, adverse drug reactions, comorbidities, and social issues in a conference titled “The epilepsy saga of Ieva’s family”. The conference programme consisted of a comprehensive presentation of the life and care of one hypothetical epilepsy patient, Ieva. This conference format allowed to actively involve the audience and hear more views on the best ways to address major problems that arise in the investigation, treatment and management of epilepsy. In addition to the doctors from VUH SK and the Lithuanian University of Health Sciences, the conference program included lectures by invited guests Dr. R. Aranauskas (Norway, presentation topics – diagnosis and treatment of depression and psychosis comorbid to epilepsy), Assoc. Prof. Dr. R. Badaras (Lithuania, presentation topics – alcohol provoked seizures, cannabis and epilepsy) and Assoc. Prof. Dr. M. Nikanorova (Denmark, presentation topic – childhood epilepsy syndromes in adulthood).

The COVID-19 pandemic – an opportunity to search for the determinants of quality of sleep

In 2022, two cross-sectional questionnaire surveys were carried out at the VUH SK Centre for Neurology, providing information on the impact of COVID-19 pandemic management measures on sleep quality in the general population (principal investigator **Prof. Dr. Rūta Mameniškienė**). The evaluation of the responses of students from several gymnasiums in Vilnius showed that **after returning to school after the COVID-19 pandemic, the highschooler rating of the quality of their lessons and their physical health improved while the quality of their sleep and mental health appeared to worsen.**[4] This was confirmed by standardised scales, which revealed high levels of anxiety symptoms and poor sleep quality for many students. These results suggest that new changes in students' regimes (e.g., starting school later, integrating distance learning into the

classroom grid) could have benefits for their mental health and sleep quality (especially when the two are known to be correlated, Figure 1).

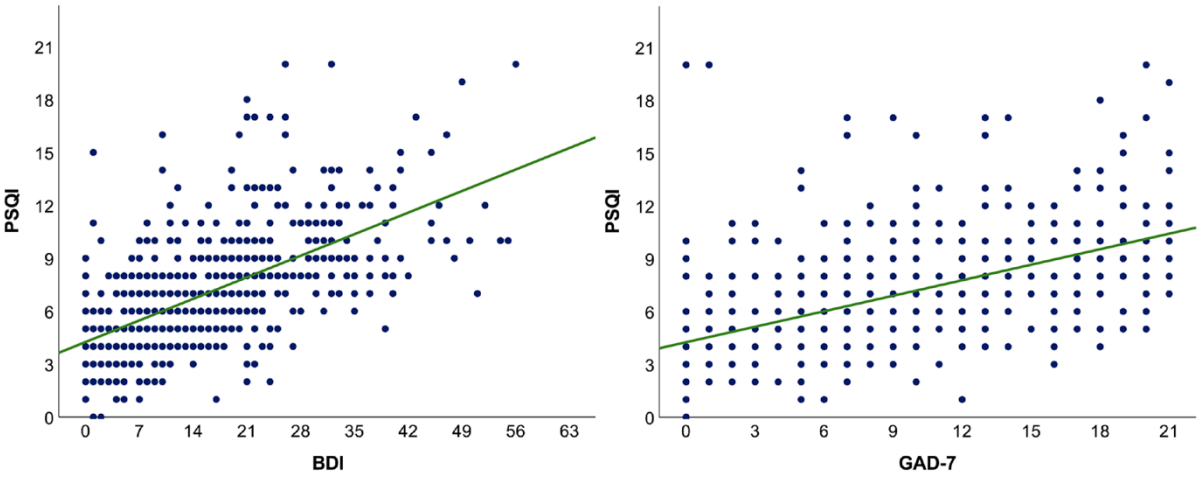

Figure 1. The relationship between sleep quality and symptoms of depression and anxiety among high school students. The green line represents the linear regression equation. BDI – Beck Depression Inventory, GAD-7 – Generalized Anxiety Disorder Scale-7, PSQI – Pittsburgh Sleep Quality Index.[3]

Determinants of sleep quality during the COVID-19 pandemic were assessed in a population of slightly older working-age individuals.[5] Poor sleep hygiene habits, high levels of anxiety and altered eating habits were found to be associated with poorer sleep. On the other hand, sleep quality was not associated with absenteeism (hours lost due to illness), which was positively influenced only by moderate physical activity (Figure 2). In conclusion, **young adults were able to remain fit for work during the COVID-19 pandemic despite changes in sleep**. Sleep hygiene is one of the modifiable factors of sleep quality, which may be positively influenced by patient and public education.

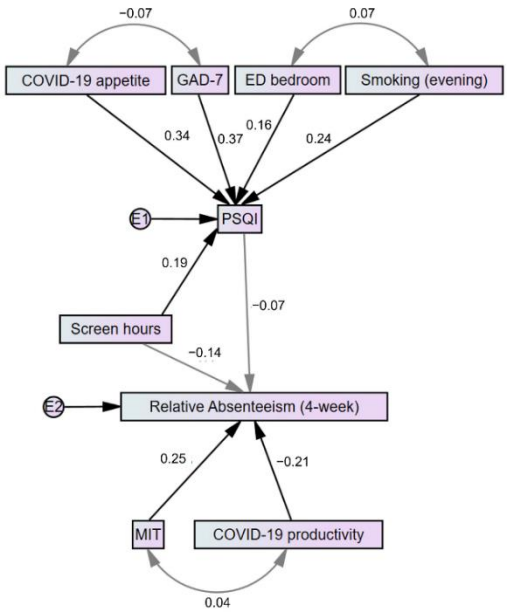

Figure 2. Path analysis showing the relationship between sleep quality and absenteeism. The grey lines show relationships that are not statistically significant. Numbers denote either the beta coefficients or the correlation coefficients of the respective regression model (single and double arrows, respectively). E – error, ED bedroom – use of electronic devices in the bedroom, GAD-7 – Generalized Anxiety Disorder Scale-7, MIT – moderate-intensity physical activity, PSQI – Pitsburg Sleep Quality Index.[4]

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Centre for Organ Transplantation Coordination

Breakthroughs in cornea, pancreatic islet and liver transplantation

LiQD-Cornea Liquid Corneal Filler

In 2022, the Centre for Organ Transplantation Coordination of Vilnius University Hospital Santaros (VUH SK OTCC) joined the VUH SK Centre for Eye Disease in the project "LIQD-CORNEA". Using a rabbit model of corneal damage mimicking a severe Herpex simplex virus (HSV-1) infection, the project evaluated the efficacy of a liquid corneal filler developed by the project partners, supplemented with silica nanoparticles with GF19 peptide and a special ointment, and the efficacy of a liquid corneal filler alone. The study was carried out under the supervision of the Maisonneuve-Rosemont Research Centre of Montreal (Canada), with the participation of Vilnius University (Lithuania), Estonian University of Life Sciences (Estonia) and the biotechnology company Oz Biosciences SAS (France). During the project, 3 rabbits (12.5%) died due to a generalised viral infection and the rest (87.5%) survived. No eyes were lost due to the inflammatory reaction. In all experimental groups, the eyes of the animals using the liquid corneal filler showed a weaker inflammatory reaction compared to the control cyanoacrylate filler. Thus, the project successfully tested the developed experimental surgical model and liquid cornea could become a new corneal perforation sealant in the future. You may also read about this project on page 13 of this issue.

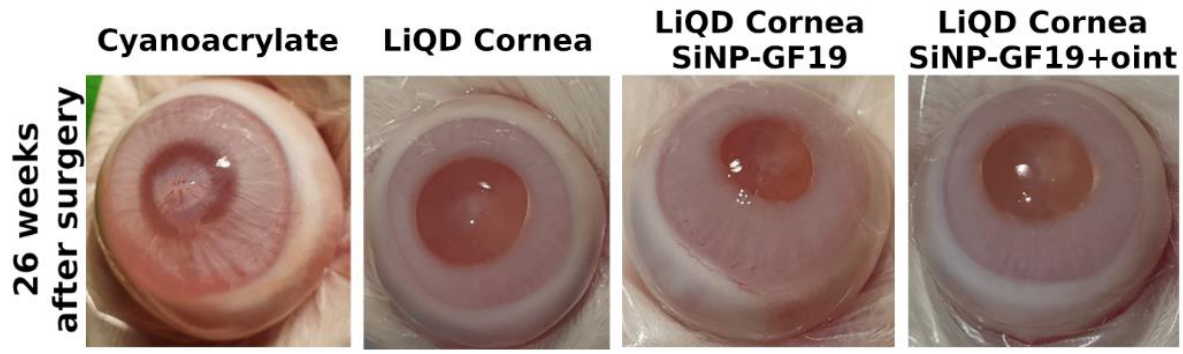

Figure 1. Corneal tissue 26 weeks after surgery and liquid cornea application

Pancreatic islet transplantation

In 2021, the first pancreatic islet transplantation procedure was performed in a patient after a kidney transplant at VUH SK. This procedure was successful and reduced the patient's need for insulin and events of dangerous hypoglycaemia. Once this procedure has been confirmed as safe and necessary, the aim was to make pancreatic islet transplantation available to other patients. Transplantation using a pancreas from a deceased donor is planned not only for patients with type 1 diabetes after kidney transplantation, but also for patients with labile type 1 diabetes. Also, patients who are scheduled for pancreatectomy would be subjected to pancreatic islet autotransplantation. Pancreatic islet transplantation for these patients is included in the procedures covered by the National Compulsory Health Insurance Fund by decision of the Committee for the Evaluation of Personal Health Care Services on 1 July 2022. You can also read about the changes in the reimbursement of pancreatic islet transplantation on page 51 of this publication.

Innovative abdominal surgery

In 2022, specialists of VUH SK OTCC also participated in some of the first breakthrough liver transplantation surgeries in Lithuania and the Baltic States – in one of them, hypothermic

oxygenated artificial liver perfusion was used to maintain the donor's liver, and in the other – for the first time – a liver from a non–heart-beating donor was used (see more on pages 76-77). These operations demonstrate the comprehensive experience of VUH SK to maximise the number of liver transplants and thus save the patients that are most in need.

R&D projects

In 2022, specialists of VUH SK OTCC participated in various Lithuanian and international projects:

- Research Council of Lithuania (RCL), measure 01.2.2-LMT-K-718 “Targeted research in the field of smart specialisation” activity “Research carried out by high-level research groups to develop results that are relevant to the economic sectors and that could be commercialised” (SMART): “Single cell genomics research – mapping of hepatic cells”;
- Agency for Science, Innovation and Technology (MITA), Instrument No 01.2.2-MITA-K-702 “Promotion of commercialisation and internationalisation of R&D results” (EUREKA): “Next-generation artificial micro-circuit model simulating liver functionality” (No 01.2.2-MITA-K-702-10-0006);
- EU Twinning project: 'Support in strengthening of the capacities of relevant institutions within the substances of human origins (SoHO) system' ('Lithuania-Serbia Transplantation and Organ Donation systems');
- Coordination of the Lithuanian representation of the international consortium “European Initiative to UNderstand CANcer (UNCAN.eu), application for a coordination and support action to generate a blueprint for UNCAN.eu”.

Pediatric Centre

International collaboration helps raise awareness of arterial hypertension in children and young adults

In 2022 Vilnius university hospital Santaros klinikos (VUH SK) and the VUH SK Pediatric Center were part of the **COST**[1] action **HyperChildNet**[2] (reference number CA 19115) establishing a European sustainable and multidisciplinary network of internationally renowned researchers, clinicians, health economists, and other specialists **focusing on acquiring a holistic understanding of the factors affecting high blood pressure (BP) in children** in order to propose and implement **corrective and preventive actions** both globally and locally.

VUH SK is among 37 hospitals and research facilities from 22 countries participating in **HyperChildNet**[2]. The head of Pediatric Center **Prof. Dr. Augustina Jankauskienė** and **Dr. Karolis Ažukaitis** are part of the project's management committee, but two young people from VUH SK joined the group as well enabling to extend research and networking. **Prof. Dr. Augustina Jankauskienė** is also the vice-leader of a working group investigating the impact of pediatric arterial hypertension.

Pediatric arterial hypertension training school in Vilnius

On June 13-15, 2022 pediatric arterial hypertension training school **„Advances and controversies in pediatric primary hypertension"** was held in Vilnius (Figure 1). The three-day training was organized by the Lithuanian pediatric nephrology society in collaboration with VUH SK as part of the **HyperChildNet**[2] project. Experts from Lithuania, Spain, Germany, Poland, Greece, and United Kingdom shared their knowledge. One of the aims was to improve the education of young clinicians and specialists and to inspire young researches as well as support innovation.

Figure 1. Training school in Vilnius "Advances and controversies in pediatric primary hypertension".

The impact of pediatric primary arterial hypertension

Together with experts taking part in **HyperChildNet**[2] from around Europe specialists from VUH SK carried out a series of investigations to analyse the impact of primary arterial hypertension (PH) in children and young adults.

In a **systematic review** of studies reporting the determinants of impaired structure and function, significant disparities were identified among children and young people (CYP) (up to 25 years) with PH[3]. Overall, 90% and 86% of the **studies reported higher carotid-femoral pulse wave velocity (cfPWV) and carotid intima-media thickness (cIMT) in CYP with elevated BP, respectively, as compared to normotensive controls.** Carotid IMT was associated with BP indices in 50% and with BMI in 25% of the studies included in the systematic review. In contrast to cIMT, the increase of cfPWV was almost exclusively determined by BP.

Within HyperChildNet, a **systematic review** was carried out **to evaluate publications on cognitive functioning among CYP with PH** (13 studies; <18 y. o. subjects)[4]. Most of the studies reported **worse results of cognitive function tests among CYP with PH**. Some studies suggested that cognitive functioning may improve after starting antihypertensive treatment. Ambulatory blood pressure monitoring was shown to be more strongly related to cognitive testing results than office measures of blood pressure. **Significant confounders, namely obesity and sleep apnea, were identified throughout the studies**. The systematic review indicated that evidence relating PH with poor cognitive functioning among youth is usually based on indirect measures of executive functions (e.g., questionnaires) rather than objective neuropsychological tests.

Through international collaboration VUH SK specialists alongside other experts executed **meta-analysis and meta-regression** (51 studies; 5622 subjects younger than 21 y. o.) **to assess the prevalence of left ventricular hypertrophy (LVH) and its determinants in CYP with PH5**. The overall prevalence of LVH in children and young adults with primary arterial hypertension was 30.5% (95% CI 27.2-33.9), eccentric LVH was the predominant hypertrophy phenotype. In the meta-regression, only **body mass index (BMI) z-score was significantly associated with LVH prevalence** (Figure 2; estimate 0.23, 95% CI 0.08-0.39, p = 0.004).

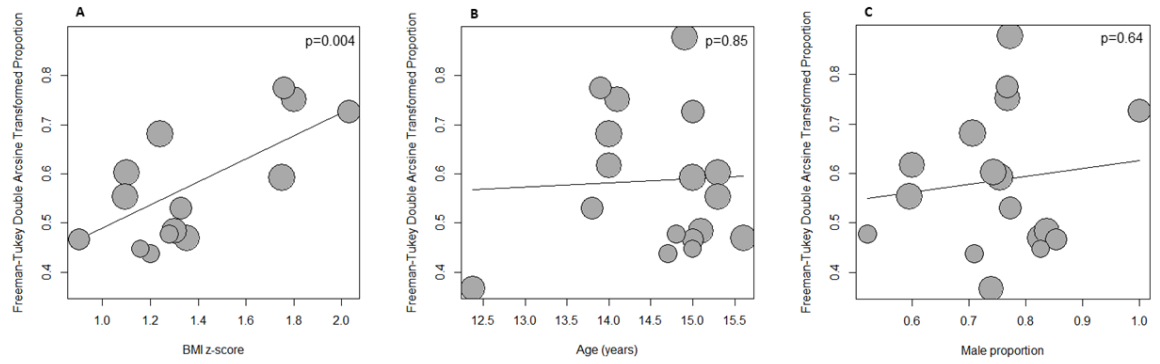

Figure 2. Bubble plot showing the relationship between LVH prevalence and BMI z-score (A), age (B), and male proportion (C) in the subset of studies.[5]

A systematic review and meta-analysis (22 studies; 3460 subjects ages 5-21 y. o.) **of left ventricular systolic and diastolic function in children and adolescents with PH** was performed[6]. When compared with normotensive subjects, **children and young adults with PH had an increased heart rate** (mean difference (MD) 5.59; 95% CI 3.28-7.89) and **increased fractional shortening** (MD 1.04; 95% CI 0.48-1.60), but did not differ in ejection fraction. Hypertensive children and young adults had also **lower E/A values** (MD 0.21; 0.33-0.09), **greater values of E/e'** (MD 0.59; 0.36-0.82) and **greater global longitudinal stress** (MD 2.50; 2.03-2.96) when compared to those with normotension.

Tools to evaluate arterial blood pressure in children

HyperChildNet[2] experts created **calculators to assess office**[7] **and 24-h ambulatory**[8] **blood pressure** in children and young people based on 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. These tools are free of charge to the public and will enable accurate and timely evaluation of abnormal blood pressure in children and young people in Lithuania and other countries.

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Medical treatment of arterial hypertension in children and adolescents in Lithuania

The global prevalence of arterial hypertension (AH) in the pediatric population is increasing, but therapeutic approaches and the choice of the most suitable antihypertensive medications remain challenging. Specialists form Vilnius University Hospital Santaros Klinikos and the Faculty of Medicine of Vilnius University conducted the first study in Lithuania analyzing the real-world pharmacological treatment of pediatric AH [1].

The approach to pharmacological therapy of AH is important because once the treatment is started it will continue for a long part of the child's life. To answer the question **"How is pediatric hypertension treated in Lithuania?"** a team of pediatric nephrologists performed a cross-sectional analysis using nationwide coded data for the year 2019. The results were presented at the "54th European Society for Pediatric Nephrology Annual Meeting".

The incidence of pediatric AH in 2019 was 0.29 %. Medications were prescribed to 633 children in total and the treatment rates were **39.8% for primary hypertension** and **66.3% for secondary hypertension**. Angiotensin-converting enzyme inhibitors (ACEi) were the most frequently prescribed class of medications irrespective of AH etiology followed by beta-blockers (BBs). Calcium channel blockers and angiotensin receptor blockers (ARBs) were the third and fourth most frequent choices. Other medication classes (diuretics, imidazoline receptor agonists, alpha-blockers, combined ACEi with diuretics) were only used in the treatment of secondary AH (Figure 1).

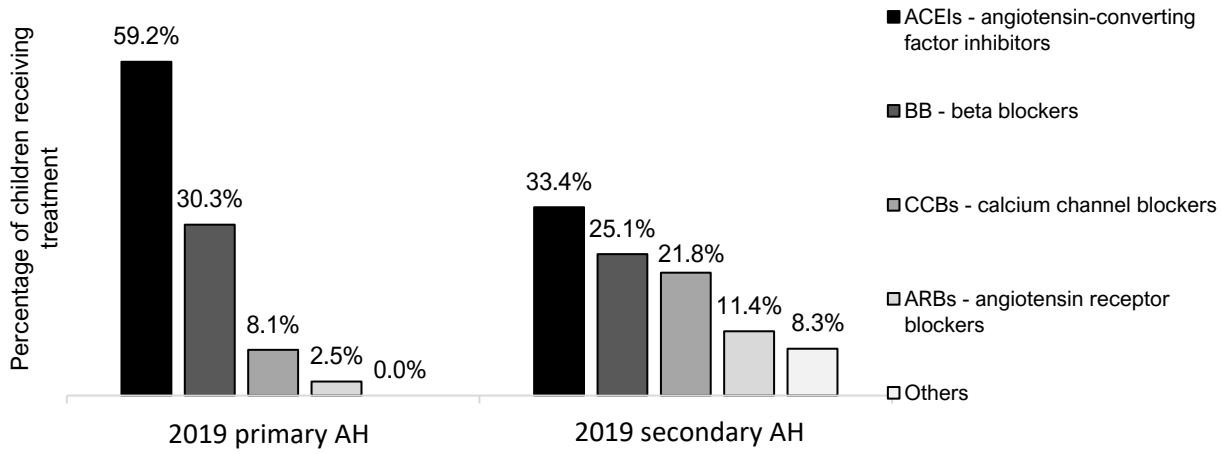

Figure 1. Distribution of drug classes used for the treatment by etiology of AH. Abbreviations: ACEi—angiotensin converting enzyme inhibitor, BB—beta blocker, CCB—calcium channel blocker, ARB—angiotensin receptor blocker.

In terms of drug groups, the most prescribed drugs were: **enalapril for ACEIs**, **metroprolol for BBs** and **losartan for ARBs**. It is interesting to note that, in Lithuania, children were prescribed drugs that are not recommended by the international guidelines for the treatment of AH, such as lacidipine and moxonidine. The use of these drugs may be influenced by trends in the treatment of adult AH.

In summary, the data presented here show that the **diagnosis of AH in children in** Lithuania **is inadequate. BBs are prescribed too often**, while **diuretics and ARBs are prescribed too rarely**. Although current guidelines suggest prescribing antihypertensive treatment to all children with secondary AH, the proportion of children with this form of hypertension treated in Lithuania remains too low.

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Centre for Abdominal and Onco-Surgery

Innovative surgery and active research in 2022

The Centre for Abdominal and Onco-Surgery (**head – academic Prof. Dr. Kęstutis Strupas**) of Vilnius University Hospital Santaros Klinikos (VUH SK) has hepatopancreatobiliary and transplantation (HPB+Tx), gastrointestinal (GI)-metabolic-endocrine, and colorectal surgical working groups, which have been actively continuing their clinical and research activity in 2022.

Hepatopancreatobiliary (HPB) surgery and transplantology

30 May 2022 was a historic day for VUH SK – for the first time in the Baltic States, the liver transplant team performed a donor liver transplantation using hypothermic oxygenated artificial liver perfusion. The team has been consistently preparing for this important step. Its members – surgeons and perfusionist Eglė Vičkačkaitė – have been training and participating in perfusion training at a simulation centre in the Netherlands. They also received training in German transplant centres and courses in Poland.

Ischaemia-reperfusion injury has a significant impact on both early and late liver transplant outcomes. Static ice-cold liver preservation is the gold standard in clinical practice but is optimal only in donations where standard donor selection criteria are applied. The use of donor organs with extended selection criteria can significantly increase the number of transplants performed and reduce the waiting list for transplantation. However, such selection is associated with significantly poorer transplantation outcomes, as donor organs are more susceptible to static cold preservation in such cases. Hypothermic oxygenated artificial perfusion restores the energetic resources of the liver, and the results of transplantation of advanced criteria donor livers with hypothermic oxygenated artificial perfusion may be comparable to those expected after static cold preservation of standard criteria donor livers.

Figure 1. Hypothermic oxygenated artificial hepatic perfusion procedure. From left to right: partner company representative Povilas, gastroenterologist Gabrielė Milaknytė, abdominal surgeon Mindaugas Kvietkauskas, perfusionist Eglė Vičkačkaitė, perfusion expert from the Netherlands Ton Muneij, abdominal surgeon Rokas Račkauskas, and operating theatre nurse Ramunė Pleikienė.

In 2022, for the first time in Lithuania and the Baltic States, a liver transplantation from a non-failing heart donor was performed at the VUH SK - more than 30 different specialists were involved in the process, including anaesthesiologists-resuscitationists, surgeons and perfusionists. After cardiac arrest, regional organ perfusion was used to preserve the abdominal organs, followed by explantation. Subsequently, hypothermic oxygenated artificial perfusion was used to preserve the donor liver. This is another important step to increase the number of liver transplants performed and reduce the waiting list.

Coloproctology

In 2022, Dr. M. Kryžauskas, a physician at the Centre for Abdominal and Onco-Surgery defended his PhD thesis "The problem of preventive ileostomy in colorectal surgery" at Vilnius University. He and his co-authors have published seven articles on the topic of his thesis, which are indexed in the Web of Science database and are in the first to third quartiles.[1]

The Centre for Abdominal and Onco-Surgery at VUH SK has also introduced an innovation in the treatment of rectal tumours – Total Neoadjuvant Therapy (TNT), which involves both systemic chemotherapy and neoadjuvant chemoradiotherapy before surgery. This tactic is particularly useful in the treatment of lower third rectal cancers. Another innovation introduced at the Centre is a follow-up MRI scan after neoadjuvant treatment, which will help to decide whether there is an indication for surgery and, if so, what is the optimal surgical tactic. In the field of rectal cancer therapy, there remains a serious debate among specialists about the most appropriate surgical treatment, the results of neoadjuvant and isolated surgery are compared. Finally, in 2022, the Centre introduced three-dimensional transrectal sonoscopy, an important diagnostic method for pelvoperineal (pelvic organs and diaphragm) diseases, while laser haemorrhoidectomy is already becoming an innovative standard, and is reportedly starting to be used in other Lithuanian medical institutions. Multidisciplinary research in collaboration with other units of VUH SK is also continued.[2]

Gastrointestinal and metabolic surgery

Around 80% of patients with gastric cancer at the Centre for Abdominal and Onco-Surgery will have undergone laparoscopic surgery by 2022. This is a good result and part of an ongoing project with the National Cancer Institute (NCI) – the Vilnius Gastric Cancer Research Centre.[3] A multicentre biomedical study "Prospects for the use of PIPAC in a combination treatment scheme for advanced gastric cancer" has also been initiated with the NCI. This is expected to be another opportunity to optimise the treatment of gastric cancer.

In 2022, the first modern minimally invasive combined laparoscopic-endoscopic surgery for bile duct stones was performed at VUH SK in collaboration with the staff of the Endoscopy Unit of the Centre for Abdominal and Onco-Surgery and the Centre for Hepatology, Gastroenterology and Dietetics. Patients operated on have previously had Roux-en-Y gastric bypass operations for obesity. One of the drawbacks of the Roux-en-Y gastric bypass is the surgically modified gastric anatomy, which does not allow transoral flexible videoduodenoscopy and cannulation of the common bile duct and removal of the bile duct stones. Thus, the innovative surgical technique allowed these patients, who presented after previous operations for obesity, to avoid the need for an extended biliary surgical revision.

Endocrine surgery

Multidisciplinary decision-making by physicians, with each case being discussed in a consensus of surgeons, endocrinologists and interventional radiologists, has become the standard of good practice in endocrine surgery. The VUH SK Centre for Abdominal and Onco-Surgery provides state-of-the-art thyroid surgery with a focus on patient safety, using "hidden" incision techniques to avoid scarring of the neck. This year, a state-of-the-art neuromonitoring system has already become a routine part of the surgical process, allowing for maximum safety of the nerves innervating the vocal apparatus during thyroid and parathyroid surgery. The Centre performs traditional (open), laparoscopic and retroperitoneoscopic adrenal surgery. The use of modern electrosurgical devices shortens the operation and anaesthesia times. In some cases, state-of-the-art thermal ablation technologies (e.g., microwave ablation, radiofrequency ablation, laser ablation)

are also used where available and indicated. Finally, on 6-7 December 2022, for the first time in the Baltics, the “Modern Endocrine Surgery Training” was organised at VUH SK. This is a result of a great recognition of the staff working in this field.

Key publications and projects for 2022

In 2022, the VUH SK Centre for Abdominal and Onco-Surgery continued national and international projects “Parallel Laboratories” (research funded by the Research Council of Lithuania (RCL) High Level Research and Experimental Development (SMART), in collaboration with the Life Sciences Centre of Vilnius University (VU GMC)), “Healthy Ageing” (research funded by the RCL; collaboration with VU GMC), “Eureka” (MITA-funded instrument, collaboration with the University of Graz (Austria) and UAB Femtika), as well as the continuation and initiation of 15 and 4 biomedical studies, respectively, with results published in 21 publications (journals indexed in the Web of Science).[4-11]

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Centre for Pulmonology and Allergology

Age as a risk factor for complications during or after bronchoscopic lung biopsy

Bronchoscopic lung biopsy (BLB) is a widely used procedure. As the world's population ages, more BLBs are being performed in older people with comorbidities. The aim of this study was to investigate whether older age is a risk factor for BPB-related complications.

The results of a prospective study conducted at the Centre for Pulmonology and Allergology at Vilnius University Hospital Santaros Klinikos (VUH SK) were published in 2022.[1] 786 patients (60.6% male) with a mean age of 57 ± 16 years who underwent BPB were included. Complications due to BPB were evaluated. Bleeding and pneumothorax were graded as grade I° or II° according to their severity. Factors that may increase the risk of complications were analysed, with emphasis on age.

The analysis of the study data (Figure 1) identified 57 (7.2%) cases of BPB-related complications. Twenty-seven (3.4%) cases of pneumothorax were observed, of which 19 (70%) required chest drainage. There were also 30 (3.8%) bleeding complications, of which 4 (16%) were severe. The incidence of bleeding was higher in the age group ≥ 65 years, p = 0.001. The risk of bleeding was 3.2 times higher in older patients (95% confidence interval 1.51-6.87).

Thus, older age has been observed to be associated with a higher incidence of mild bleeding during BPB. However, despite age, the risk of life-threatening complications of BPB is low and older age should not be considered as a contraindication to the procedure if it is needed.

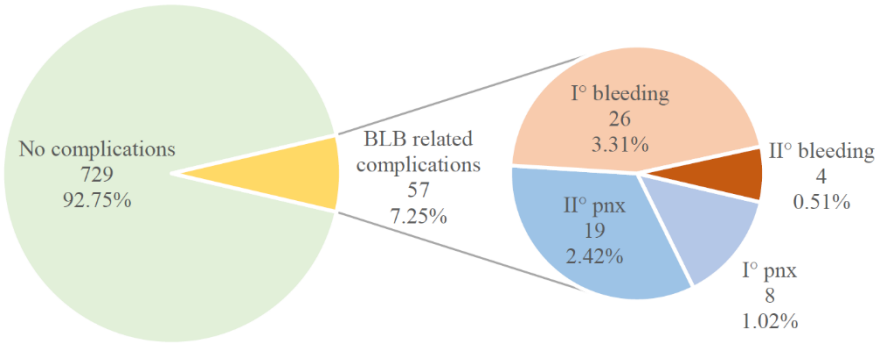

Figure 1: Complication rates of bronchoscopic lung biopsy procedure.[1] Pnx - pneumothorax.

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A prospective observational study of treatment failure in non-invasive respiratory failure in COVID-19 patients

The best respiratory support tactic for COVID-19 in acute hypoxaemic respiratory failure (AHRF) is not yet known. Patients with AHRF may benefit from the use of a high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV). The aim of a prospective observational study conducted in 2022 at the Centre for Pulmonology and Allergology of Vilnius University Hospital Santaros Klinikos, was to investigate predictive factors for failure of HFNC and NIV in individuals with COVID-19 who have AHRF.

124 patients participated in the study. A stepwise treatment approach was used. HFNC and NIV were administered to 124 (100%) and 64 (51.6%) patients, respectively. Thirty (24.2%) of the 124 patients were intubated and received invasive mechanical lung ventilation.

85 (68.5%) of all patients in the study were successfully cured. Patients who required NIV were more likely to fail treatment (70.3% vs. 51.6%, p = 0.019), and a higher mortality rate (59.4% vs. 31.5%, p = 0.001) was observed in comparison to patients who received HFNC. Logistic regression showed that respiratory rate oxygenation (ROX) index at 24 h (odds ratio (OR) = 0.74, p = 0.018) and Charlson comorbidity index (CCI) (OR = 1.60, p = 0.003) were predictive factors for the efficacy of treatment with HFNC. For the ROX index at 24 hours and the CCI, the optimal cutoff values for the outcome of HFNC treatment were 6.1 (area under the curve (AUC) = 0.73) and 2.5 (AUC = 0.68), respectively. Serum ferritin level (OR = 0.23, p = 0.041) and lymphocyte count (OR = 1.03, p = 0.01) were validated as predictive factors for NIV ineffectiveness. Serum ferritin level with a cutoff value of 456.2 ng/mL (AUC = 0.67) (sensitivity 70.5%, specificity 68.7%) and lymphocyte count less than 0.70/mm3 (AUC = 0.70) (sensitivity 84.0%, specificity 56.2%) were associated with a lack of NIV effect.

Thus, the ROX index at 24 h, CCI, as well as serum ferritin level, and lymphocyte count can be used as markers for HFNC and NIV failure, respectively, in SARS-CoV-2-induced AHRF patients. (Figure 1).[1]

Treatment Group	Characteristics	Sensitivity (%)	Specificity (%)	Cut-Off Value	AUC (95% CI)	*p*-Value
HFNC (N = 124)	CCI	64.1	75.0	2.5	0.73 (0.64–0.82)	**<0.001**
	ROX index at 24 h	81.2	51.7	7.1	0.68 (0.59–0.78)	**<0.001**
NIV (N = 64)	Lymphocyte count, per mm^3	84.1	56.2	1.0	0.70 (0.55–0.85)	**0.009**
	Ferritin, ng/mL	70.5	68.7	456.2	0.67 (0.51–0.84)	**0.037**

Significant values are shown in bold. HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; CCI: Charlson comorbidity index; ROX: the respiratory rate oxygenation; AUC: area under the ROC curve; CI: confidence interval.

Figure 1. ROC curve data for predictive models of undertreatment in HFNC and NIV failure.[1]

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Epidemiology of chronic obstructive pulmonary disease (COPD) co-morbidities in the Lithuanian national database: a cluster analysis

People with chronic obstructive pulmonary disease (COPD) often suffer from a wide range of comorbidities and multimorbidity, which overload healthcare systems and lead to increased mortality. In 2022, a study was carried out at the Centre for Pulmonology and Allergology at Vilnius University Hospital Santaros Klinikos to assess the impact of COPD on the likelihood of comorbidities and their clustering.[1]

A cross-sectional analysis of a countrywide database was done based on records of chronic diseases. COPD was defined by the code J44.8 and 6 months of bronchodilator use. Descriptive statistics and odds ratios (ORs) were determined for associations and agglomerative hierarchical clustering.

The study included 321 297 patients aged 40-79 years: 4834 of them had COPD. A significantly higher prevalence of cardiovascular disease (CVD), lung cancer, kidney disease, and COPD was found to be associated with a sixfold higher risk of lung cancer (OR=6.66, $p<0.0001$), a twofold higher risk of heart failure (OR=2.61, $p<0.0001$), and a twofold higher risk of CVD (OR=1.83, $p<0.0001$). Six groups of men and five groups of women with COPD were identified, as well as five and four groups for patients without COPD, respectively. The most prevalent cardiovascular cluster did not show a significant difference based on sex or the presence of COPD, but a differential association with dyslipidaemia was found.

The results of the study highlighted that the management and screening tools for many diseases should be adjusted, which would likely lead to better patient outcomes.

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Country-specific lockdown measures in response to the COVID-19 pandemic and its impact on tuberculosis control: a global study

Representatives from the Centre for Pulmonology and Allergology at Vilnius University Hospital Santaros Klinikos took part in an international study in 2022 to describe country-specific quarantine measures and tuberculosis (TB) indicators during the first year of the COVID-19 pandemic. Data on the closure of public spaces, social restrictions (e.g., compulsory face masks and hand hygiene, international and local travel restrictions, family visitation restrictions and school closures) were collected from 24 countries on five continents.[1] Quarantines – partial or total – have been imposed several times in most countries. The overall incidence of active TB, drug-resistant TB and latent TB was found to decrease during the pandemic. National quarantines were thus effective in stopping COVID-19 cases, but also had an indirect impact on the epidemiology of another infectious disease, tuberculosis.

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Management of obstructive sleep apnea in Europe – a 10-year follow-up

Back in 2010, a questionnaire survey on the management of obstructive sleep apnoea (OSA) in Europe identified differences between countries in terms of reimbursement, the qualifications of the sleep specialist and titration procedures. 10 years later, the ESADA (European Sleep Apnea Database) network carried out a follow-up study to investigate the evolution of OMA management over time – the questionnaire on sleep diagnosis, reimbursement, treatment and certification was updated with questions on telemedicine and distributed to European sleep centres to reflect European OMA management practices.

The study involved 26 countries (36 sleep centres), representing 20 ESADA and 6 non-ESADA countries, including Lithuania and the Centre for Pulmonology and Allergology of Vilnius University Hospital Santaros Klinikos. All 21 countries from the 2010 study participated as well. It was observed that, in 2010, OSA diagnostic procedures were performed mainly by specialized physicians (86%), whereas now mainly by certified sleep specialists and specialized physicians (69%). Treatment and titration procedures are currently quite homogenous, with a strong trend towards more Autotitrating Positive Airway Pressure treatment (in hospital 73%, at home 62%). From 2010 to 2020, home sleep apnea testing use increased (76%-89%) and polysomnography as sole diagnostic procedure decreased (24%-12%), Figure 1.[1] On the other hand, the availability of specialists has increased (from 52% to 65%), as well as the number of certified polysomnography assessors (certified physicians from 36% to 79%, certified technicians from 20% to 62%). Telemedicine in 2020 is frequently cited as a tool used for diagnosis (8%), treatment (50%) and monitoring (73%) of OMA.

Thus, over the last decade, the formal qualifications of sleep centre staff have increased, OSA diagnosis and treatment procedures have become more automated, and telemedicine has become relevant.

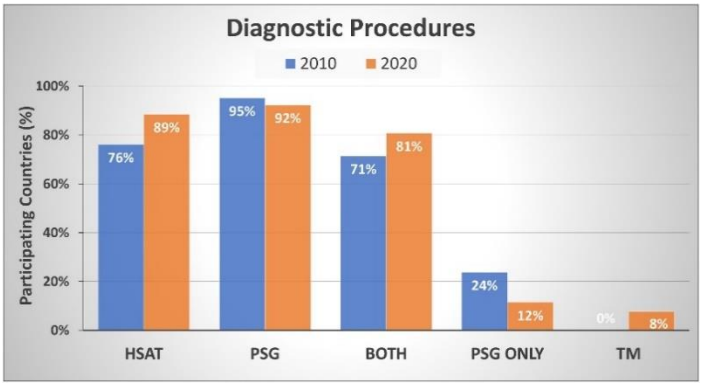

Figure 1. Diagnostic procedures for obstructive sleep apnoea: comparison of responses in 2010 and 2020 (percentage of participating countries, 2010: n=21, 2020: n=26)[1] . HSAT – home sleep apnoea testing, PSG – polysomnography, TM – telemedicine. Chi-square tests were performed to compare the groups, significance level set at 0.05. Only statistically significant results are shown.

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COVID-19 vaccination: is it safe to vaccinate after vaccine-related adverse systemic reactions?

Although allergic reactions to messenger RNA (mRNA) vaccines are known and reported, there is still a lack of detailed information on how to proceed with vaccination in the event of such a reaction. The aim of a study published in 2022 at the Centre for Pulmonology and Allergology of Vilnius University Hospital Santaros Klinikos (VUH SK), was to describe the symptoms of possible allergic reactions to mRNA vaccines and the results of repeated vaccination. A descriptive analysis of data from adult patients (over 18 years of age) vaccinated at the outpatient centre for Diagnostic and Treatment of Allergic and Immune Diseases at VUH SK was performed. All patients were vaccinated with the Pfizer-BioNTech Comirnaty® vaccine.

Between January 2021 and July 2021, 22 patients were vaccinated in the Centre.[1] Six patients experienced reactions after the first dose of Comirnaty® vaccine at another vaccination centre. In most of these patients, various types of rashes were observed. In one patient, an anaphylactic reaction was suspected. This patient underwent a skin prick test with the vaccine prior to vaccination with the second dose of Comirnaty® vaccine, and it was negative. The remaining 16 patients were vaccinated from the first dose onwards in the outpatient centre for Diagnostic and Treatment of Allergic and Immune Diseases because of pre-existing allergic reactions to other vaccines, medications or existing mast cell pathology. None of these patients developed rapid-type allergic reactions.

Thus, none of the patients vaccinated at our centre developed skin reactions after re-vaccination. Patients with a previous diagnosis of mast cell pathology or anaphylaxis were also successfully vaccinated.

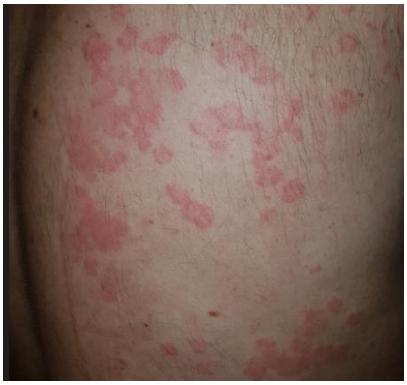

Figure 1: Acute urticaria in a 68-year-old patient 24 hours after the first vaccination, accompanied by fever. It resolved with antihistamines within 8 days. A second vaccination with the same vaccine did not cause complications.

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Centre for Radiology and Nuclear Medicine

New solutions for imaging

The Centre for Radiology and Nuclear Medicine of Vilnius University Hospital Santaros Klinikos (VUH SK RNMC) (**head – Assoc. Prof. Dr. Artūras Samuilis**) is constantly innovating in collaboration with other VUH SK centres as well as Lithuanian and foreign institutions. In 2022, the main areas of innovation were diagnostics of cardiovascular diseases, pelvic floor examinations, diagnostics and minimally invasive treatment of oncological diseases, diagnostics of diffuse liver diseases.

Computed tomography myocardial perfusion – a new diagnostic method for patients with coronary artery disease

Coronary artery disease (CAD) of atherosclerotic origin is one of the leading causes of death in Lithuania and worldwide. Prevention, early diagnosis and timely treatment of this disease are among the most important goals, and their achievement is associated with lower morbidity and mortality. Non-invasive cardiac imaging is currently one of the most accurate methods to diagnose or exclude CAD in a timely manner. In the diagnosis of CAD using non-invasive cardiac imaging, not only the detection of the disease is important, but also the assessment of its functional significance.

In cooperation with the Centre for Cardiology and Angiology (**represented by cardiologist Ernestas Dvinelis**), the VUH SK Centre for Radiology and Nuclear Medicine (**principal investigator – Prof. Dr. Algirdas Edvardas Tamošiūnas**), **for the first time in Lithuania**, cardiac computed tomography (CT) myocardial perfusion imaging has been introduced in CAD patients who require additional testing in the presence of marginal coronary artery lesions (Figure 1).

Cardiac CT myocardial perfusion provides an assessment of functional myocardial blood flow at rest and during hyperaemia (increased blood flow). Dynamic myocardial perfusion assesses the distribution of contrast material in the myocardium at different time points and allows the identification of the damaged myocardium. Cardiac CT myocardial perfusion is performed during CT angiography when a coronary lesion is detected to clarify the significance of the lesion. This comprehensive functional and anatomical assessment of CAD is more sensitive in detecting obstructive CAD than other myocardial perfusion studies (cardiac single-photon emission computed tomography or magnetic resonance imaging myocardial perfusion studies), thus saving the time for additional investigations and allowing for the selection of appropriate investigative and therapeutic tactics. However, the radiation exposure to the patient during the examination is also increased, so appropriate patient selection is appropriate for this procedure.

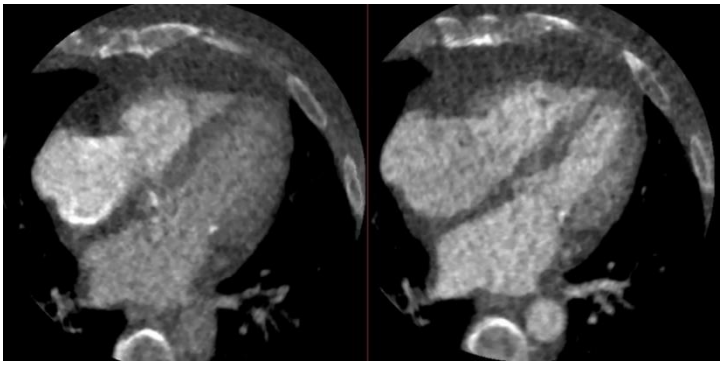


Figure 1. CT perfusion images of the cardiac myocardium. Evaluated in a 70-year-old man with atypical symptoms of angina pectoris. Coronary CT angiography showed no significant coronary artery lesions and no perfusion defects.

Dynamic pelvic magnetic resonance imaging - new opportunity in diagnostics of pelvic floor diseases

From the beginning of 2022, the Centre for Radiology and Nuclear Medicine at VUH SK, under **the leadership of Assoc. Prof. Dr. Dileta Valančienė, together with radiologists Jolanta Stankevičienė and Gintaras Vaivadaitė, for the first time in Lithuania** routinely applies magnetic resonance defectography. This examination detects signs, causes and degree of obstructive defecation, urinary or fecal incontinence, pelvic floor descent, pelvic organ prolapses and various types of intussusceptions. The mentioned disorders are quite common, especially in the elderly population, and significantly impair their quality of life.

Magnetic resonance (MR) defecography imaging (Figure 2), is performed according to the latest recommendations of the Pelvic Floor Working Group of the European Society of Urogenital Radiology (ESUR) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR). Rectal cleansing is needed ~2 hours before the examination. During the examination, the patient lies supine, with legs slightly bent and raised, the rectum is filled with ultrasound gel. Static high-resolution MRI T2W sequences are performed at rest in all three planes to assess the precise anatomy of the pelvic musculature and organs, as well as their possible structural abnormalities. Dynamic T2W sequences are performed in the sagittal plane, during which the patient actively executes commands (squeezing, straining and evacuation). Dynamic imaging helps to assess the severity of functional changes of the pelvis (pelvic floor muscle function, tone, displacement of the pelvic organs and helps to evaluate the function of pelvic musculature and organs). As the patient must actively follow commands and obey given instructions during the examination, it is important to select patients appropriately and to inform them of the planned examination.

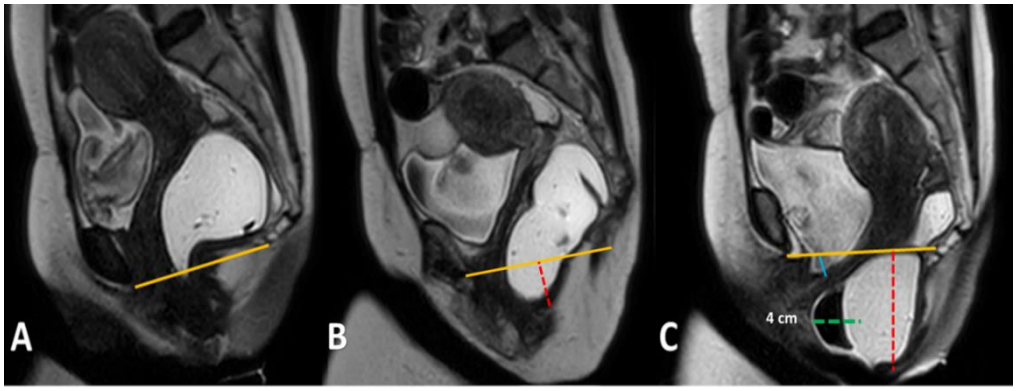


Figure 2. Dynamic T2W MRI images performed in a 47-year-old female patient during pelvic floor muscle contraction (A), flexion (B) and rectal emptying (C). Grade II° descent of the anorectal junction and pelvic floor grade (red dashed line), grade II° anterior rectocele (green dashed line), grade I° cystocele (blue line) are observed. Pubococcygeal line (solid yellow line).

The first experience of the VUH SK RNMC confirms reports from the scientific literature – pelvic floor and organ pathology is very complex and involves multiple compartments. Accurate assessment of findings might influence the choice of the prospective treatment and surgical technique. Correct diagnosis is the first step to help these patients before planning further therapeutic or surgical treatment.

The main benefits of magnetic resonance defecography include lack of ionizing radiation, exceptional soft tissue resolution, visualization of pelvic organ anatomy and its structural changes which are not possible to evaluate with conventional X-ray defecography. MRI defecography is not suitable for patients who have claustrophobia likewise it is not suitable for patients who cannot understand or follow given commands during examination because cooperation significantly affects the quality of the study.

The first results of the newly launched MRI defecography study were presented at the 8th Baltic Congress of Radiology.[1]

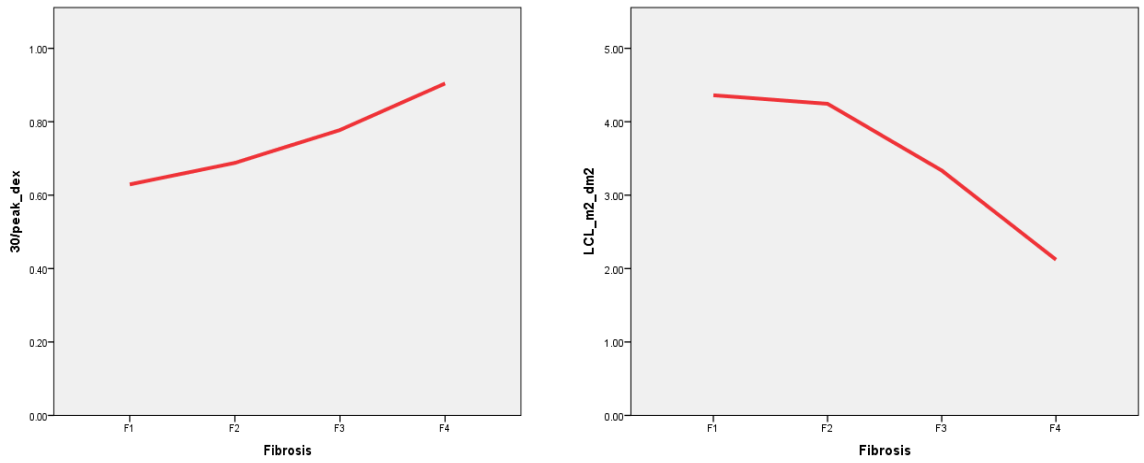
A new quantitative diagnostic method for the diagnosis of liver fibrosis

In 2022, a prospective study was completed at VUH SK, in which patients with chronic viral hepatitis received a new non-invasive quantitative diagnostic method – liver scintigraphy (a nuclear medicine exam) with ^{99m}Tc-mebrofenin (Bis(2-[[2-(3-bromo-2,4,6-trimethylanilin)-2-oxoethyl] -(carboxymethyl) amino] acetic acid (99mTc). The study was accomplished in cooperation of the Centre for Radiology and Nuclear Medicine (**representative Donatas Jocius and chief Prof. Dr. Algirdas Edvardas Tamošiūnas**), the Centre for Abdominal and Onco-Surgery, the Centre for Hepatology, Gastroenterology and Dietetics and the National Center of Pathology.

The prospective study was conducted in 72 patients with chronic viral hepatitis B and C, with a primary assessment of liver fibrosis prior to the initiation of viral hepatitis treatment. The results of liver scintigraphy were compared with the "gold standard" – liver biopsy.

The liver scintigraphy indices calculated during the study were statistically significant in distinguishing different stages of liver fibrosis (time to peak (min), 30/peak ratio, slope index, hepatic clearance ((%/min/m /dm^{22})), Figure 3.[2]

The highest value for area under the curve (AUROC) was observed for 30/peak ratio and hepatic clearance. These parameters allowed statistically significant distinction between the stages of liver fibrosis (F1-F4, according to the METAVIR classification).



(**A**) (**B**)

Figure 3. Correlation between the stage of liver fibrosis and parameters of liver scintigraphy. A – positive direct connection between liver fibrosis and 30/peak ratio – the higher stage of liver fibrosis, the bigger the retention of the radioindicator (99mTc-mebrofenin) is seen; B – negative direct connection between liver fibrosis and hepatic clearance – the higher the liver fibrosis is, the lower the hepatic clearance is.[2]

This study shows that liver scintigraphy with^{99m} Tc-mebrofenin is another non-invasive quantitative method to stage liver fibrosis. Moreover, it has several advantages over other non-invasive methods (ultrasound elastography or magnetic resonance elastography of the liver): liver scintigraphy not only assesses the degree of liver fibrosis, but also the function of the liver cells, and, in contrast to ultrasound elastography, it assesses changes in the entire liver parenchyma (both lobes of the liver).

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Radioembolization treatment with a radioactive holmium isotope of an advanced primary liver tumor – an innovation not only in Lithuania

Radioembolisation or Selective Internal Radiation Therapy (SIRT) is a minimally invasive procedure in which radioactive particles are selectively injected through a special catheter into the arteries that are supplying a malignant tumor. Thus, the tumor cells are affected by radiation from within. This procedure is applicable to patients with non-operable primary and secondary liver tumors.

In 2022, for the **first time in Northern Europe, radiologist Renata Komiagienė and interventional radiologist Dr. Marius Kurminas** planned and performed the **first** hepatic radioembolization procedure with radioactive holmium isotope (166Ho) on a patient with advanced hepatocellular carcinoma (primary malignant tumour of the liver) at the Centre for Radiology and Nuclear Medicine (VUH SK RNMC) of Vilnius University Hospital Santaros Klinikos.

Radioactive holmium isotope (166Ho) is a beta ray chemical element with a high excess energy, also featuring emission of gamma photons. The latter feature helps to see the isotope in the single-photon emission computerized tomography (SPECT) during imaging. This unique feature of holmium is quite useful even in the early stages of planning the treatment, when a portion of the radioactive scout dose is injected to the liver, on which basis individual therapeutical dose is calculated to the current patient when the SPECT is performed. Furthermore, it is evaluated whether there is additional attenuation of the radioactive chemical outside the liver. This imaging technique is also used after the treatment to verify the correct dose. Moreover, holmium isotope has its paramagnetic features, which enables visualization in the magnetic resonance imaging exam of how the radioactive isotope is distributed in the liver parenchyma while planning the treatment, and post-embolization.

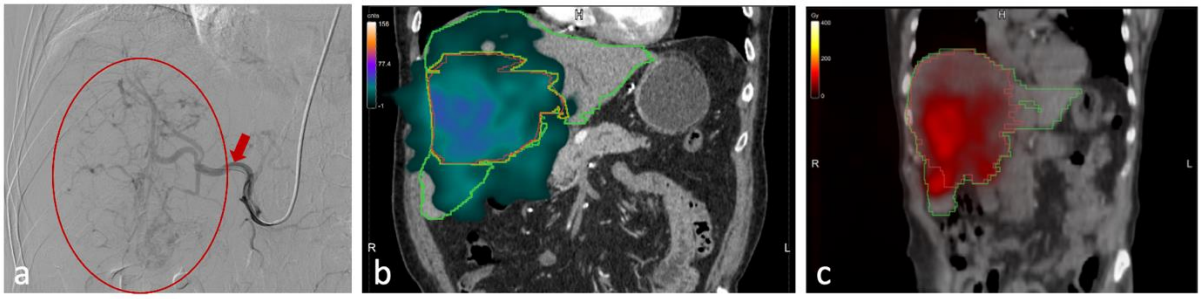

Figure 1. (a) Selective digital subtraction angiography of a liver artery - well vascularized lesion (red circle), which is fed by the branches of the right hepatic artery (red arrow); (b) SPECT scout and treatment (c) ^{166}Ho dose distribution in the hepatocellular carcinoma lesion (tumor) and liver parenchyma.

A multidisciplinary team of interventional radiologists, radiologists and nuclear medicine staff, radiation protection specialists, medical physicists, abdominal surgeons, gastroenterologists, oncologists and chemotherapy oncologists are involved in the assessment of patient suitability for the procedure, as well as in the preparation, the course of the procedure, the logistics of the radio-isotope itself, and the patient's follow-up post-procedure.

Radioembolization of surgically inaccessible and systemic chemotherapy-resistant malignant liver tumours with ^{166}Ho offers a modern alternative to the clinical standard – radioembolization with yttrium (^{90}Y) microspheres, because of its unique imaging properties. The fully predictable distribution of the agent in the liver parenchyma opens the door to individualised treatment planning and better patient selection in the fight against this threatening pathology.

Centre for Rehabilitation, Physical and Sports Medicine and Centre for Children's Physical Medicine and Rehabilitation

Biological Feedback Measurement and Analysis Technology Center for Strengthening Personal and Public Health (Bio-MAC)

In 2022, the Centre for Rehabilitation, Physical and Sports Medicine and the Centre for Children's Physical Medicine and Rehabilitation of Vilnius University Hospital Santaros Klinikos (VUH SK) continued the project led by specialists of Vilnius Gediminas Technical University (head – Prof. Dr. Julius Griškevičius) and partners from VUH SK and Kaunas University of Technology – the project "Bio-MAC - Biological Feedback Measurement and Analysis Technology Center for Strengthening Personal and Public Health", which aims to develop the existing concept of innovative solutions for the measurement and analysis of biofeedback, in order to offer solutions ready for commercialisation defined by the following unique features:

- real-time operation;
- application of non-invasive measurement methods;
- integrated ways of reducing measurement uncertainties based on intelligent methods;
- reduced the number of measuring instruments and the time of preparation for research;
- to specialize in independent monitoring of the state of health and proper and effective application of measures;
- possibility to adapt systems according to individual needs and change measurement conditions;
- specialize in continuous remote monitoring and quantification of health status/condition.

The project aims to develop three biofeedback measurement and evaluation products:

1. Stationary biofeedback measurement and evaluation platform with an expert system adapted to the medical profile user, with clinical effectiveness (e.g. applied treatment or rehabilitation program) quantification and decision-making capabilities, procedure performance guides and other similar tools.
2. The mobile biofeedback measurement and evaluation system is adapted to the individual needs of users and is able to recognize, evaluate and inform the user about dangerous registered values of biological parameters, critical indicators pointing to dangerous body reactions in order to avoid negative effects on the body.
3. The remote, real-time biofeedback measurement and evaluation system is intended for individuals in the risk group or those who require long-term condition monitoring in order to assess the body's compensatory and adaptive reactions over a longer period of time.

The project uses tools such as sensors, measurement systems based on image analysis, solutions based on artificial intelligence, virtual and augmented reality tools for interactive visualization.

Existing stationary systems on the market allow recording human movement, forces acting on the force plane during movement, perform accurate movement registration with a complex system calibration procedure, but there is no specialized parameterization of health progress and efficiency. The stationary system developed by the project is designed to increase the measurement efficiency by optimizing the preparation for the measurement (in terms of time, and in terms of the flexibility of individual adaptability to the user), the measurement time, the accuracy

of the measured and calculated parameters and the decision-making time - in order to provide real-time feedback. Most mobile systems with biofeedback are adapted for general monitoring of the user's physical activity and general physiological indicators, but are not adapted for serious, accurate and individual assessment and monitoring of a person's health status and do not allow the user to objectively and properly respond to the critical processes of the biological system in real time, therefore, the user subjectively assesses his health condition according to his competence. Most of these systems do not have a direct connection with competent medical personnel in the relevant field or an installed health status assessment system, do not have real-time data transmission, storage and long-term monitoring analysis.

The aim is to create specifications for Biofeedback measurement and evaluation platforms with an expert system adapted to rehabilitation specialists working with neurological, traumatological-orthopedic and cardiological patients, which would increase clinical efficiency in the individual selection and application of rehabilitation measures and methods, expanded quantitative assessment of physical parameters and decision-making possibilities, procedures performance guides, would make it possible to monitor the values of changing biological parameters, critical indicators pointing to dangerous body reactions in order to avoid negative effects, to follow the compensatory and adaptive reactions of the body over a longer period of time.

The team of VUH SK representatives (Prof. Dr. Juozas Raistenskis, Assoc. Prof. Dr. Aušra Adomavičienė, Dr. Ieva Eglė Jamontaitė, Jūratė Kesienė, Donatas Svirskis, Vaida Belickienė) is responsible for Verification of biological feedback measurement systems – the investigation and evaluation of the results of the biofeedback measurement and quantification systems being developed, provision of recommendations for the improvement of the systems. This will involve analysing the parameters of quantitative indicators of biofeedback of patients with a neurological, cardiological and traumatological-orthopedic profile, related to general physiological indicators, as well as direct observation of indicators of physical activity and motor functions (movements and mobility, changes of upper and lower limbs motor functions, balance and gait, coordination).

When applying biological feedback during the process of complex rehabilitation, it is very important to choose the means, methods and load for the restoration of motor functions as optimally as possible, based on the individual parameters of changes in the physical and functional condition of each patient. Monitoring of physiological parameters in real time would allow to adjust the rehabilitation program during the day taking into account the changes in the health indicators of the patient with different pathologies (ability to tolerate physical exertion, recovery indicators, changes during rest and exercise, indicators of physical capacity, etc.) and would provide an opportunity for real-time management by the patient himself , adjust and learn to control your body position, functional movements, correct posture and will ensure safe and correct mobility, which would be one of the essential goals of rehabilitation.

Centre for Family medicine

The achievements of specialists of the Centre for Family Medicine in research project activities

In 2022, specialists of the Centre for Family Medicine of Vilnius University Hospital Santaros Klinikos (VUH SK) **(head – Assoc. Prof. Dr. Lina Vencevičienė)** participated in various projects and clinical trials.

Healthcare specialists of the Centre for Family Medicine of VUH SK, together with partners from Aukštadvaris, Druskininkai and Pakruojis Primary Health Care Centers are implementing the project "Implementation of the Integrated Health Care Model in the Primary Care of Multimorbid Patients" (**Project manager – Head of the Centre for Family Medicine and Family Medicine Doctor Assoc. Prof. Dr. Lina Vencevičienė**).The project aims to improve the quality and accessibility of Lithuanian primary health care services for patients with two or more chronic diseases. Patients involved in the project undergo a holistic assessment of key aspects of their health status (disease symptoms and history, functional ability, quality of life and psychosocial factors). The primary health care teams are coordinated by a case manager who ensures that the patient's health is cared for in a continuous and coordinated manner. The case manager is responsible for the implementation and coordination of the individual health care plan which is based on the holistic assessment of key aspects of patient health status and his preferences (i.e., desired patient outcomes). Options for patients to improve their self-management were personalized and consistent with their individualized care plans. Multimorbid patients cases are discussed between general practitioners or multidisciplinary teams in more complicated cases. The development of an innovative and representative model to improve the quality of health care and establish better access to the services for the target population will be provided for public authorities with suggestions and recommendations for the monitoring and care of multimorbid patients.

Assoc. Prof. Dr. Lina Venceviciene, Head of the Centre for Family Medicine and Family Medicine Doctor participated in the study "Analysis of Biomarkers for Suicidal Tendencies and Depression, and Validation of the Prognostic Model in Lithuania". We investigate various objective biological factors associated with mental illnesses. Our goal is to link subjective experience of the patients to specific quantifiable biological, genetic and biochemical alterations, that can be then interfered on, and clinical outcomes and quality of life of those suffering from these diseases would be improved. Primarily we study influence of genetics, enzyme polymorphisms, biochemical factors on clinical outcome of mental health disorders, including depression, suicidal behaviours, addictions, and other stress related pathologies. Main research group activities – pharmacogenomics, biomarkers in suicidal behaviour and depression, biological therapy in somatic health and it's outcomes on perceived mental distress, epigenetic influences on disease severity. Our team combines experience and professionalism with youthful energy and drive, we have both established researchers and team of young prospective scientists, that are all active in various research projects all around the Europe. Our team have experts from various fields: psychiatry, medical genetics, toxicology, mental health policy, laboratory medicine and other. Lead researcher Algirdas Utkus, MD, PhD. Research Group: Laima Ambrozaitytė, PhD, Edgaras Dlugauskas, MD, PhD, Robertas Badaras, MD, PhD, Martynas Marcinkevičius, MD, Eimantas Matiekus, MD, Lina Vencevičienė, MD, PhD, Jurgita Songailienė, MD, PhD, Tomas Petrėnas, PhD, Andrius Kaminskas, PhD, Adelė Butėnaitė, MD, Aistė Lengvenytė, MD, PhD student, Robertas Strumila, MD, PhD student.

Assist. Prof. Dr. Kazys Simanauskas participated in a study and prepared a publication on the topic „Sodium, Potassium and Iodine Intake in an Adult Population of Lithuania".[1] Hypertension is a leading risk factor for cardiovascular events and death. A reduction in salt intake is among the most cost-effective strategies to reduce blood pressure and the risk of cardiovascular diseases. Increasing potassium lowers blood pressure and is associated with lower cardiovascular risk. Adequate iodine intake is important to prevent iodine deficiency disorders. Salt iodization is a key strategy to prevent such deficiency. In Lithuania, no surveys have been performed to directly assess sodium, potassium and iodine consumption. The aim of the present study was to measure sodium, potassium and iodine intake in a randomly selected sample of the adult Lithuanian population using 24 h urine collections, and to assess knowledge, attitudes and behavior towards salt consumption. Salt and potassium intakes were estimated in 888 randomly selected participants by 24 h urine sodium and potassium excretion and 679 individuals provided suitable 24 h urine samples for the analysis of iodine excretion. Average salt intake was 10.0 (SD 5.3) g/24 h and average potassium intake was 3.3 (SD 1.3) g/24 h. Only 12.5% of participants consumed less than 5 g/24 h of salt. The median value of urinary iodine concentration (UIC) was 95.5 μg/L. Our study showed that average salt intake is twice as high as the maximum level recommended by the World Health Organization while potassium and iodine intakes in Lithuania are below the recommended levels.

Assoc. Prof. Dr. Neringa Burokienė participated in a study and prepared a publication on the topic "Computational pharmacology: new avenues for COVID-19 therapeutics search and better preparedness for future pandemic crises".[2] The COVID-19 pandemic created an unprecedented global healthcare emergency prompting the exploration of new therapeutic avenues, including drug repurposing. Many ongoing studies revealed pervasive issues in clinical research, such as the lack of accessible and organised data. Moreover, current shortcomings in clinical studies highlighted the need for a multi-faceted approach to tackle this health crisis. Thus, we set out to explore and develop new strategies for drug repositioning by employing computational pharmacology, data mining, systems biology, and computational chemistry to advance shared efforts in identifying key targets, affected networks, and potential pharmaceutical intervention options. Our study revealed that formulating pharmacological strategies should rely on both therapeutic targets and their networks. We showed how data mining can reveal regulatory patterns, capture novel targets, alert about side-effects, and help identify new therapeutic avenues. We also highlighted the importance of the miRNA regulatory layer and how this information could be used to monitor disease progression or devise treatment strategies. Importantly, our work bridged the interactome with the chemical compound space to better understand the complex landscape of COVID-19 drugs. Machine and deep learning allowed us to showcase limitations in current chemical libraries for COVID-19 suggesting that both in silico and experimental analyses should be combined to retrieve therapeutically valuable compounds. Based on the gathered data, we strongly advocate for taking this opportunity to establish robust practices for treating today's and future infectious diseases by preparing solid analytical frameworks.

Assoc. Prof. Dr. Neringa Burokienė and **doctor Martynas Narkevičius** participated in a study and prepared a publication on the topic "Higher levels of stress-related hair steroid hormones are associated with the increased $SORE_2$ risk prediction algorithm in apparently healthy women".[3] Cardiovascular diseases (CVDs) are the major cause of death worldwide. Although the importance of conventional CVD risk factors, including older age, male gender, hypertension, obesity, dyslipidemia and hyperglycemia, is well-studied, psychosocial stress, which is considered an independent CVD risk factor, requires further investigation. Thus, we aimed to investigate the association between long-term secretion of stress-related steroid hormones, including cortisol, cortisone and dehydroepiandrosterone, and the 10-year fatal and non-fatal CVD risk estimated by the $SCORE_2$ risk prediction algorithm, as well as traditional CVD risk factors in a group of apparently healthy women. A total of 145 women (aged 50-64 years) participating in the national CVD prevention program were enrolled in the study. Sociodemographic, lifestyle, health-related characteristics, stress, anxiety and sleep quality indicators were evaluated using specific questionnaires. Anthropometric and arterial blood pressure measures were assessed by trained personnel, lipid and glucose metabolism biomarkers were measured using routine methods, and

hair steroid hormone levels were determined by ultra-high-performance liquid chromatography-tandem mass spectrometry. The results showed that higher levels of hair cortisol and cortisone are associated with increased $SCORE_2$ values. Moreover, significant associations between hair glucocorticoids and individual cardiovascular risk factors, including obesity, hypertension, dyslipidemia and hyperglycemia, were found. These findings indicate that stress-related hair steroid hormones might be valuable biomarkers for CVD prediction and prevention.

Assoc. Prof. Dr. Lina Venceviciene, Head of the Centre for Family Medicine and Family Medicine Doctor participated in a study and prepared a publication on the topic "Analysis of epigenetic changes in vitamin D pathway genes in rheumatoid arthritis patients".[4] Rheumatoid arthritis (RA) is an autoimmune inflammatory disease with complex etiopathogenesis launched by multiple risk factors, including epigenetic alterations. RA is possibly linked to vitamin D that is epigenetically active and may alter DNA methylation of certain genes. Therefore, the study aimed to evaluate the relationship between DNA methylation status of vitamin D signaling pathway genes (VDR, CYP24A1, CYP2R1), vitamin D level and associations with RA. Materials and Methods: Totally 76 participants (35 RA patients and 41 healthy controls) were enrolled from a case-control vitamin D and VDR gene polymorphisms study regarding age and vitamin D concentration. CpG islands in promoter regions of the VDR, CYP24A1, CYP2R1 genes were chosen for DNA methylation analysis by means of pyrosequencing. Chemiluminescent microplate immunoassay was used to assess 25(OH)D serum levels. RA clinical data, i.e. the disease activity score C-reactive protein 28 (DAS28 – CRP) as well as patient-reported outcome questionnaires were recorded. The study showed similar methylation pattern in the promoter regions of vitamin D pathway genes in RA and control group with $p>0.05$ (VDR gene 2.39% vs. 2.48%, CYP24A1 gene 16.02% vs. 15.17% and CYP2R1 2.53% vs. 2.41%). CYP24A1 methylation intensity was significantly higher in compare to methylation intensity of VDR and CYP2R1 genes in both groups (p0.05). A significantly higher CYP24A1 methylation intensity ($p=0.0104$) was detected in blood cells of vitamin D deficient (<50 nmol/l) RA patients vs. vitamin D deficient controls. Conclusions: Our data suggests some indirect associations between DNA methylation status of vitamin D pathway genes and vitamin D level in RA.

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Centre for Urology

Prostate cancer, clear cell renal cell carcinoma and urinary tract stones in 2022

In 2022, the Centre for Urology of Vilnius University Hospital Santaros Klinikos (VUH SK) continued several studies on oncological urinary tract diseases, kidney function, kidney stone disease and urinary tract strictures.[1-7] Specialists from the Centre also worked closely with researchers from the Life Sciences Centre of Vilnius University, the Faculty of Physics of Vilnius University and the National Cancer Institute. The focus of oncological research has been diagnostic tools for prostate and bladder cancer.

Multiparametric magnetic resonance imaging (MRI) Fusion-Guided Prostate Biopsy has been investigated for the detection of clinically significant prostate cancer. A total of 283 patients were included in the study. This study demonstrated that targeted prostate biopsy is sufficient for safe and sensitive identification of clinically significant PCa in primary biopsy-naive cases without the need to perform adapted systematic biopsy (Figure 1).[1]

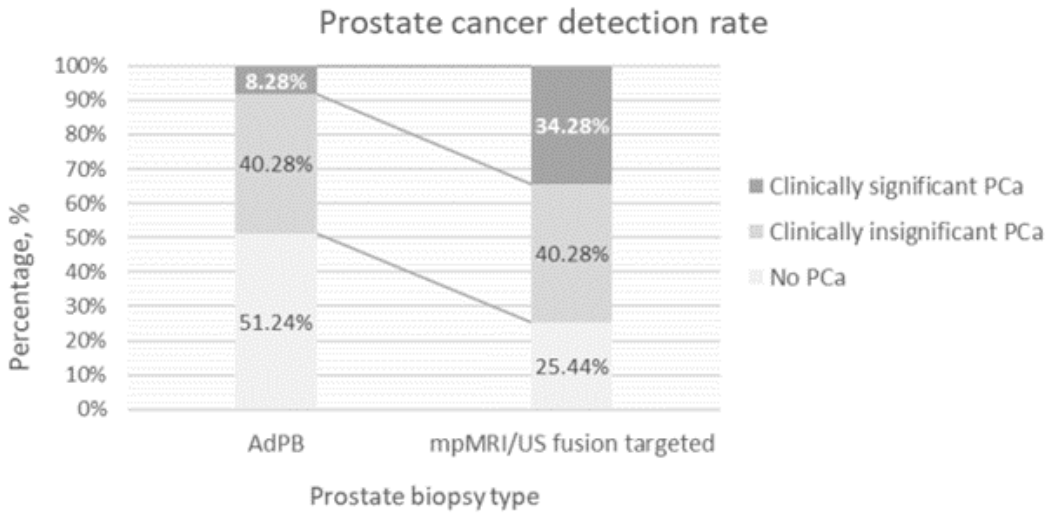

Figure 1. The comparison of diagnostic value of targeted and systematic prostate biopsy (n = 283). AdPB—12-core systematic biopsy ignoring index lesions, mpMRI/US fusion targeted prostate biopsy.[1]

Prostate cancer (PCa) is the second most common cancer in men. Radical treatment leads to good oncological results, although definitive treatment is associated with a significant number of serious side-effects. Modern medicine offers tissue-sparing techniques such as focal High Intensity Focused Ultrasound Ablation (HIFU) to PCa patients to provide cancer control equivalent to standard of care procedures, while reducing morbidity and complications. In 2022, the staff of the VUH SK Centre for Urology contributed to a review highlighting that focal HIFU therapy is a safe procedure, and the short-term cancer control rate is encouraging.[2] However, many patients require a second treatment or active surveillance.

Clear cell renal cell carcinoma (ccRCC) is the most common type of renal tumour and has the highest mortality rate among urogenital cancers, and new diagnostic and/or prognostic biomarkers are urgently needed. Based on whole-genome DNA methylation profiling of 11 pairs of ccRCC and non-cancerous renal tissues at VUH SK, methylation in the regulatory regions of ZNF677, FBN2, PCDH8, TFAP2B, TAC1, and FLRT2 was examined in 168 renal tissues and 307 urine samples. Samples were analysed using qualitative and quantitative methylation-specific PCR (MSP). This study revealed novel, potentially promising ccRCC DNA methylation biomarkers that can be applied for non-invasive urine-based ccRCC detection and monitoring.[3]

Despite the introduction of new drugs to treat castration-resistant prostate cancer (CRPC) over the past decade, up to one-third of CRPC patients face primary resistance to the new generation of compounds. Therefore, sensitive molecular tools are urgently needed to reliably select treatment and predict response. The aim of this study, conducted at the VUH SK Centre for Urology, was to assess urinary miRNA and circulating androgen receptor (AR) transcript levels as a predictor of outcome in non-invasive CRPC patients receiving abiraterone acetate (AA) treatment. After analysis of the study results, it is concluded that urinary miRNAs can be used as prognostic biomarkers in CRPC patients to predict the response to AA therapy, especially in cases with high AR levels in the blood.[4]

Vibrational spectroscopy provides the possibility for sensitive and precise detection of chemical changes in biomolecules due to development of cancers. At the VUH SK Urology Centre, interstitial fluid was analysed, and Surface Enhanced Raman Spectroscopy (SERS) was applied to distinguish between cancerous and healthy human bladder tissue.[5] Correct identification of 80% of the samples was achieved even with a limited dataset and can be further improved. Further development of such a detection method could be implemented in clinical practice to help surgeons to identify the boundaries of malignant tumours during surgery.

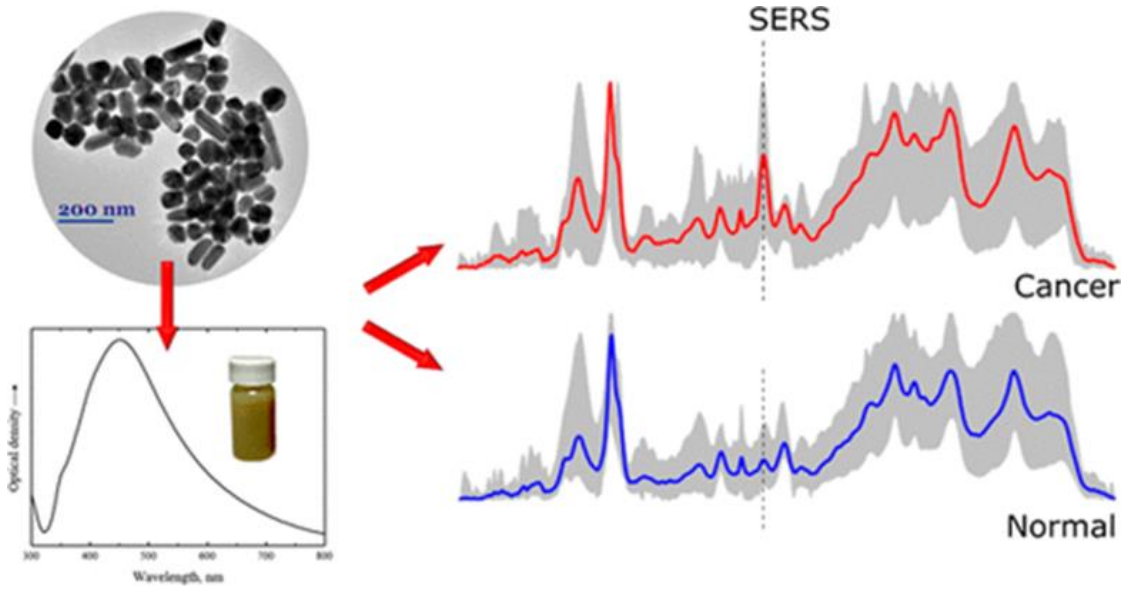

Figure 2: Enhanced Raman spectroscopy (SERS) results comparing healthy and cancerous bladder tissue.[5]

Urolithiasis is a common disease worldwide, but its causes are still not well understood. In most cases, crystalluria is an early sign of urinary stone formation, and characterisation of urinary deposits can help clinicians take early preventive measures to stop further progression of stones. In view of the need for a more reliable method, we used Raman spectroscopy to determine the chemical composition of urinary sediments and urinary stones in 15 patients with urolithiasis to see if there is a direct correlation between the composition of the respective stones and the sediments.[6] We found that the main chemical compounds that normally make up urinary stones also make up sediment, and that their composition correlated in eleven out of fifteen cases. According to the authors of the study, Raman spectroscopy is an informative and reliable method that can be used to analyse urinary sediment for the early diagnosis of urinary stone formation.

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Centre for Pediatric Oncohematology

VUH SK – a leader in pediatric hematopoietic stem cell transplantation in the Baltic region

2022 marks the 20th anniversary of pediatric hematopoietic stem cell transplantation (HSCT) at Vilnius University Hospital Santaros Klinikos (VUH SK). For two decades, the Centre for Pediatric Oncohematology at VUH SK – the only specialised pediatric centre in the Baltic States – has been performing HSCT (also known as bone marrow transplantation) for children with blood cancer, congenital immunodeficiencies, severe blood or metabolic diseases. HSCT is performed from a related donor (brothers, sisters), an unrelated donor (searches are carried out in Lithuanian and global registries), and also transplantation of the donor's own stem cells (autologous transplantation).

Due to their complexity, HSCTs services are considered as one of the indicators of progress in overall health service delivery. The number of HSCTs in Europe is steadily increasing, but pediatric HSCTsare specific in several ways:

- Pediatric HSCT is only performed for very rare diseases or conditions (< 1:200 000).
- Worldwide, the need for HSCT in children is about 10 times lower than in adults.
- More allogeneic (more complex and riskier) than autologous HSCTs are performed in children, because of a different morbidity pattern between children and adults. Diseases such as primary immunodeficiencies and congenital haematopoietic deficiencies are already present in childhood and these patients would not survive without transplantation.

Given the anniversary of pediatric HSCT, the results of these procedures performed at the VUH SK between 2002 and 2021 were evaluated and summarized.[1] From 2012 to 2021, the average number of allogeneic HSCTs performed per year is 11, and the overall average number of HSCTs is 17 per year. Since 2011, VUH SK has also become a reference centre for Latvian children in need of HSCT. Thus, one centre now fully covers the need for HSCT services for children in two countries. Latvian citizens account for 22.2% of recipients under the age of 18 (Figure 1). Since 2018, regular monthly patient discussions with Latvian colleagues have been taking place once a month, which allows optimising patient care.

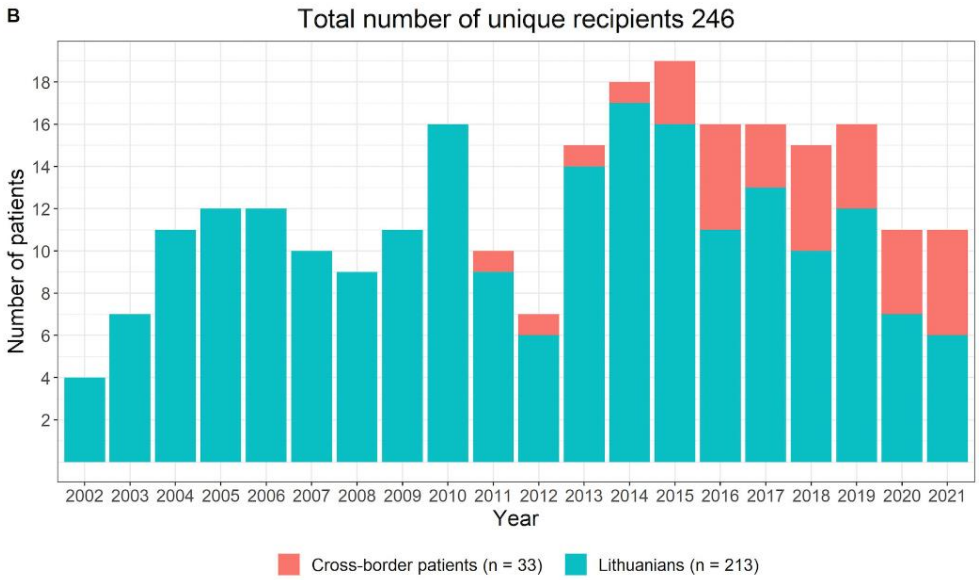

Figure 1. Pediatric HSCT performed at VUH SK for Lithuanian and foreign nationals 2002-2021.

There has been a remarkable improvement in allogeneic transplant outcomes over the two decades. The 5-year overall survival rate increased statistically significantly from 38.0% in 2002-2011 to 77.8% in 2012-2021, p<0.0001 (Figure 2A), while early mortality (up to 100 days after HSCT) due to toxic complications decreased from 24.0% to 9.7% in the respective years, p<0.0001 (Figure 2B). The improvement was due to the introduction of modern diagnostics for infectious markers and minimal residual disease, the standardisation of treatment and nursing protocols, the continuous improvement of the work of the Lithuanian registry of allogenic bone marrow donors and the Lithuanian bone marrow donor service, the acquisition of the knowledge, skills and experience of a dedicated team of physicians and nurses, and the continuous learning and international cooperation. In March 2022, in collaboration with the National Cancer Institute, for the first time in Lithuania, total body irradiation was introduced before HSCT for patients with acute lymphoblastic leukaemia. This new technology has already been used in two children and will help to reduce the likelihood of recurrence after HSCT and improve transplantation outcomes.

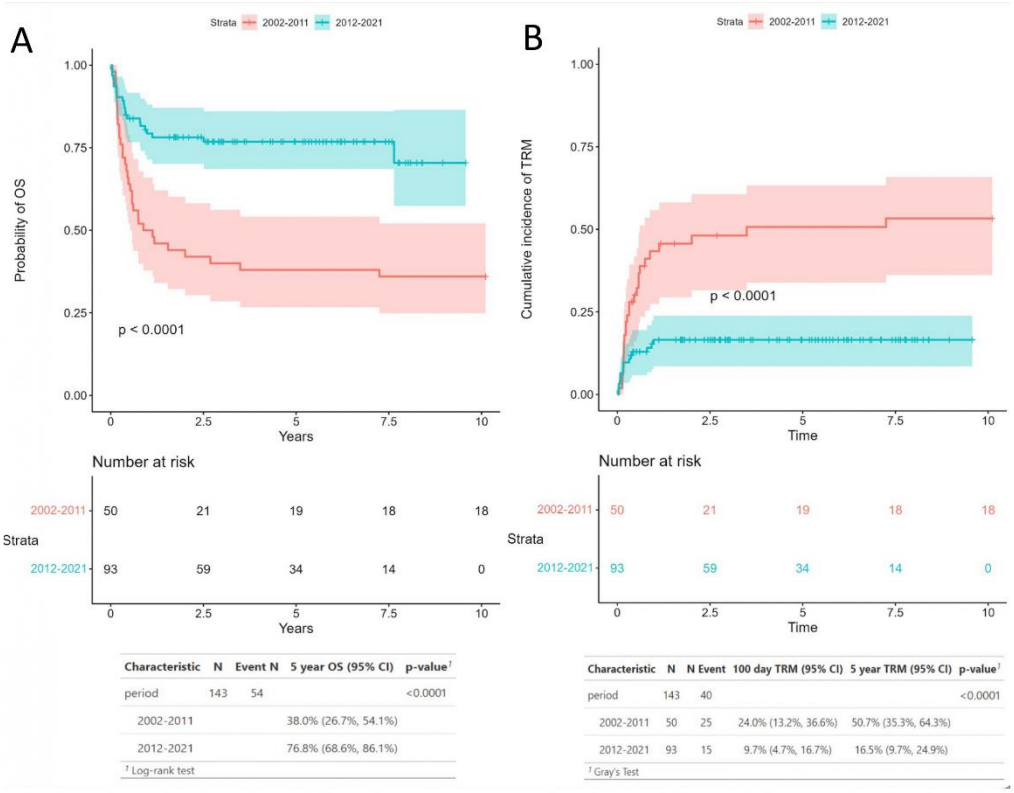

Figure 2. Outcomes of pediatric HSCT (n = 143): overall survival (A) and mortality due to toxic complications (B).

The international conference "Pediatric Haematopoietic Stem Cell Transplantation in Lithuania - 20 Years of Progress and Cooperation" was also dedicated to the 20th anniversary of HSCT at VUH SK. During the event, colleagues from Lithuania, Latvia and Estonia shared their experience, foreign experts shared the latest scientific achievements and reviewed future research directions. Young doctors had the opportunity to present their papers, which were published in Acta Medica Lituanica.[2] A doctor from Ukraine, who had spent a year of training at the Centre for Pediatric Oncohematology of VUH SK, also gave a presentation at the conference. A separate session was organised for nurses from the Baltic States and Ukraine, who shared their experiences and discussed issues of concern. The progress of the VUH SK Centre for Pediatric Oncohematology was also disseminated to the public.[3]

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Skills to improve the care of children with malignant tumours

In 2022, the international HORIZON 2020-funded Research and Education Collaboration project, coordinated by Vilnius University Hospital Santaros Klinikos (VUH SK), was continued with the **Twinning in Research and Education to improve survival in Childhood Solid Tumors in Lithuania (TREL)** (duration 2021-2023).

This is a particularly significant initiative of the Centre for Pediatric Oncohematology of VUH SK, as its specialists are participating in the project as the main coordinators of the nine-institution consortium (**project leader – Prof. Dr. Jelena Rascon**), and one of the project's objectives is to improve the reputation of VUH SK as a scientific institution, opening new avenues for collaboration with potential project partners.[1]

In 2022, the project continued its activities on fertility risk assessment in collaboration with the Dutch project partner Princess Maxima Centrum. Together with partners in Lithuania, a specific questionnaire was adapted for counselling children with oncological diseases to assess the risk of fertility damage. The work has been summarised in a joint publication[2] and at several international conferences. At the International Baltic Pediatric Conference, the **paper presented by Eglė Stukaitė-Ruibienė**, a 5th year student at the Faculty of Medicine of Vilnius University, was **recognised as the best oral presentation**. Two research funding grants have been awarded by the Research Council of Lithuania to continue the work. Thanks to the cooperation, a fertility damage assessment tool has been put into practice, and informational material on fertility preservation (Figure 1) has been prepared for children undergoing treatment for oncological disease and their parents.

Figure 1. Patient information material on fertility damage in childhood cancer treatment.

In 2022, several multidisciplinary teams of VUH SK specialists had the opportunity to get acquainted with the organisation of the project partners' work, to acquire innovative knowledge in the field of clinical pharmacology, molecular-genetic and pathological diagnostics, and biobanking. A multidisciplinary team of specialists (pediatric oncohematologists, pathologists, biologists, laboratory specialists, project coordinators) undertook an internship at the Gustave Roussy Institute in Paris, France, a European leader in early phase clinical trials in adults and children (first in human and first in child, Figure 2). Thanks to this collaboration, several international clinical trials are being initiated at VUH SK to improve the personalised treatment of resistant pediatric tumours and the efficacy of high-risk neuroblastoma treatment.

The VUH SK project management and clinical trial administration team had the opportunity to improve their competences in the field of international project management, application administration, legal and data protection regulation in collaboration with the St. Anna Children's Cancer Research Institute in Vienna, Austria (Figure 2). The work is expected to continue in 2023.

In 2022, VUH SK bioinformaticians and clinical geneticists had regular training sessions with specialists from the University Hospital of Region Hovestaden in Copenhagen (Denmark). The joint activities culminated in the publication of a case report on a family history of pediatric renal tumours.[3]

Figure 2. VUH SK multidisciplinary team placements in Paris at the Gustave Roussy Institute (left) and in Vienna at the St. Anna Children's Cancer Research Institute (right).

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International integration of information – the way forward for the future of long-term patient monitoring

The Horizon 2020 funded project **"Study on the development and implementation of the PanCare Digital Survivorship Passport to improve the care of childhood cancer survivors (PanCareSurPass)", continued at** Vilnius University Hospital Santaros Klinikos (VUH SK) in 2022. The project started in March 2021 and will run until 2024. Its aim is to develop a system using information technology to transfer the recommendations for monitoring childhood cancer survivors into the eHealth system, so that they can be visible and accessible to peripheral health care facilities. The Centre for Pediatric Oncohematology (project **leader Prof. Dr. Jelena Rascon)** together with the Information Systems Unit of the Center for Informatics and Development **(leader Dr. Justas Trinkūnas)** are responsible for the implementation of the project at the VUH SK.

Several initiatives funded by the European Commission have led to the development of the **Survivorship Passport (SurPass)**, a web-based platform that generates recommendations for monitoring a person's recovery from cancer, based on the data on the cancer disease and the treatment given. For example, it is known that the treatment required may increase the risk of damage to certain organs, such as breast cancer, endocrine complications etc. The increased risk of late complications varies depending on the specific diagnosis and the intensity of treatment. The **SurPass** platform assesses such risks based on the above data and generates patient-specific monitoring recommendations.

On 7 April 2022, a remote Open Space Meeting was held to bring together survivors of childhood cancer (both former patients and their parents/guardians), physicians from different specialties, IT specialists, and healthcare administrators to discuss the barriers and facilitators of SurPass implementation. Similar meetings have been organised in other partner institutions involved in the project (Austria, Belgium, Spain, Italy, Lithuania, Germany). The meetings identified common and country-specific barriers and facilitators to SurPass implementation. The IT barriers were analysed and summarised in a joint publication.[1]

The implementation of SurPass in VUH SK – leveraging information technology and national eHealth capabilities and best practices – aims to develop the digitalisation of SurPass and ensure its availability to other healthcare facilities where the patient may be visiting after recovery.

The project will involve the addition of data to the Pediatric Oncohaematology Treatment Passport (F5767) form, which will need to be transmitted to the SurPass platform. It also requires the development and implementation of integration interfaces to automatically transfer data to the SurPass platform. The use of the SurPass platform will be carried out in accordance with the use cases below.

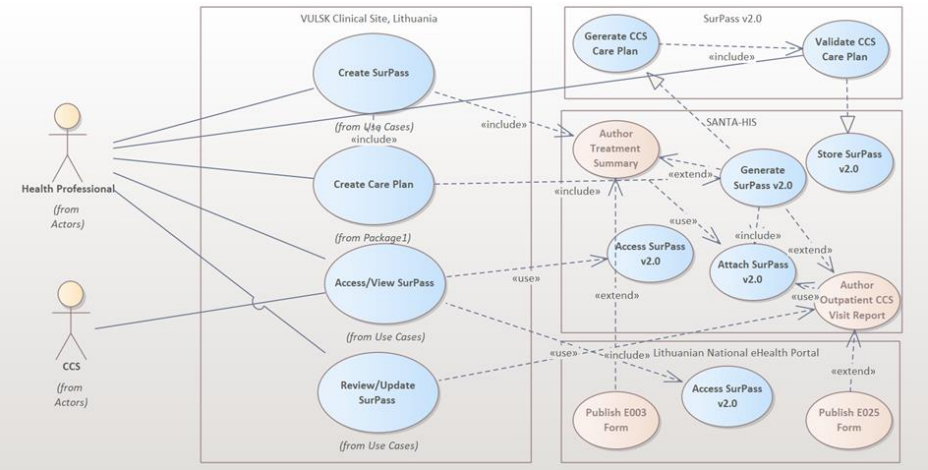

Figure 1. Diagram for the principles of use of SurPass.

In 2022, the Pediatric Oncohaematology Treatment Passport (F5767) was updated with new data: diagnoses of ICO-3 and ICCC, surgery, stem cell transplantation, chemotherapy and radiotherapy data. A summary form for the Pediatric Oncohaematology Treatment Passport (F5767) was created, which will allow to see all the forms created for patients and to automatically transfer patient data to the SurPass platform. Testing work is underway to prepare for the implementation of the changes to the electronic medical record, the production environment of the system and to transfer the data to the production environment of the SurPass platform. Test scenarios for ten clinical cases have been developed. Testing will be carried out with anonymised patient data.

Until now, SurPass has been available mainly in Italy and Austria, and was only available to specialists at the hospital where the person recovered**.** **The PanCareSurPass project** aims to roll out SurPass in six EU countries (including Lithuania) and to use information technology and national eHealth capabilities to extend the digitalisation of SurPass and make it available to other healthcare facilities that a person may be visiting after recovery from cancer. In this way, information on past illness, treatment and, most importantly, follow-up recommendations will be available to all healthcare professionals. This specific information can only be made available with the consent of the person.

It is expected that the electronic medical record (EMR) system of the VUH SK, as part of the **PanCareSurPass project**, will be able to be aligned with the "passport" system, so that the data provided by VUH SK staff to **the SurPass system** is automatically transmitted. In this way, VUH SK may become one of the first institutions to apply the passport system to patients who have agreed to enter the project.

Doctors working in the project will have the opportunity to continuously improve their knowledge of lon-"term patient monitoring, its standards and requirements. The **PanCareSurPass** project activities are expected to lead to a breakthrough in the monitoring of recovered patients by integrating patient data from individual healthcare facilities into an international network, thus ensuring standardised, evidence-based and sustainable patient care.

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International Course in Clinical Pharmacology

The team of the Centre for Pediatric Oncohematology of Vilnius University Hospital Santaros Klinikos (VUH SK), in collaboration with Vilnius University, organised a clinical pharmacology course for pediatric oncohematologists from the Baltic and Northern European countries. The course took place in Vilnius from June 2 to 3 June, 2022. The course was part of the Nordic Society of Pediatric Oncohematology (NOPHO) course series. **Assoc. Prof. Dr. Goda Elizabeta Vaitkevičienė,** Chair of the organising committee of the course, has been the head of the Pharmacology Group of the Nordic Society of Pediatric Oncohaematology for eight years. The **fact that the NOPHO Society's Clinical Pharmacology Course has been entrusted to Lithuania is the result of many years of work.**

The course is aimed at young professionals (PhD students, recently graduated medical doctors) wishing to work in pediatric oncohematology. The lecturers of the course are top specialists from the major pediatric oncohematology centres in the Nordic countries (University Hospitals of Lund, Stockholm, Uppsala, Copenhagen) and are widely recognised outside Europe. Among the guest lecturers were internationally renowned specialists from Vilnius University (Prof. Dr. Jolanta Gulbinovič) and the Lithuanian University of Health Sciences.

Although clinical pharmacology has been taught as a university discipline in Lithuania for many years, the development of this field in clinical practice (including pediatric oncohematology) is not sufficient. In Western countries, clinical pharmacology is an integral part of clinical practice and research. Therefore, such courses are an opportunity to mobilise Lithuanian forces and attract leaders in clinical pharmacology from our region, to gain first-hand experience and establish new contacts with renowned foreign lecturers and scientists, who not only lead research groups in their centres, but are also leaders in international clinical pharmacology research. Young colleagues from the VUH SK Centre for Pediatric Oncohematology also participated in the course alongside students from Northern Europe and other Baltic countries.

The course included lectures, clinical case studies, and discussions on the principles of clinical pharmacology in pediatric oncohematology, including pharmacogenetics, pharmacodynamics, drug interactions and toxicity of the main drugs used in pediatric oncology, early phase clinical trials, and the use of off-label drugs for pediatric age groups in pediatric oncohematology (Figure 1). The course is planned to be repeated regularly every 3 years.

Figure 1. Moments from the Clinical pharmacology course.

In the development of clinical pharmacology, the study “Dynamics of 6-mercaptopurine metabolite concentrations during maintenance therapy in children with acute lymphoblastic leukaemia” was initiated at the VUH SK Centre for Pediatric Oncohematology in collaboration with partners from the University of Copenhagen's Rigshospitalet Hospital (principal investigator – Assoc. Prof. Dr. Goda Elizabeta Vaitkevičienė). Preliminary data show that 6-mercaptopurine metabolite concentrations remain stable and do not fall before the drug is taken. This property would allow the use of the 6-mercaptopurine metabolite concentration study to assess adherence to the treatment regimen.

In September 2022, Lauryna Aukštikalnė, a clinical pharmacologist, also started working at VUH SK. She focuses on pediatric clinical pharmacology and pediatric oncohematology, advising children and adults on a wide range of drug-related issues, such as the rationality of treatment, the causes of ineffectiveness of treatment, adverse drug reactions, dosing of drugs according to the patient's age, gender, race, various organ dysfunctions and drug/drug-food interactions, and the testing and interpretation of drug concentrations.

National Center of Pathology

Tumour immune microenvironment studies

In 2022, a team of pathology, urology and bioinformatics specialists from Vilnius University Hospital Santaros Klinikos (VUH SK) demonstrated independent significance of CD8+ lymphocyte density gradient across the epithelium-stroma interface of non-muscle-invasive papillary urothelial carcinoma (NMIPUC) to predict recurrence free survival in patients treated with BCG immunotherapy (Figure 1). Importantly, only the CD8+ lymphocyte density gradient but not absolute densities in the tumor tissue compartments provided the prognostic information. The prognostic models will support better NMIPUC patient risk stratification for clinical decision making.

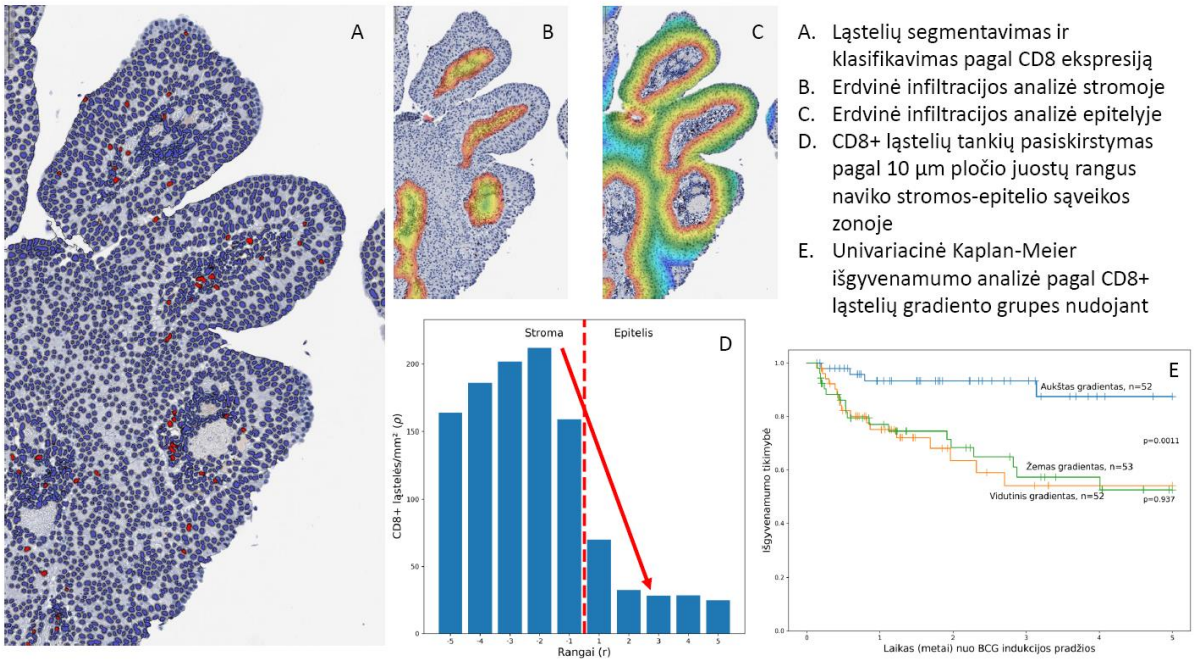

Figure 1. Flowchart of CD8+ lymphocyte density gradient assessment and impact on patient survival (Drachneris J, Rasmusson A, Morkunas M, Fabijonavicius M, Cekauskas A, Jankevicius F, Laurinavicius A. CD8+ Cell Density Gradient across the Tumor Epithelium-Stromal Interface of Non-Muscle Invasive Papillary Urothelial Carcinoma predicts Recurrence-free Survival after BCG Immunotherapy (submitted for publication)).

In collaboration with the Centre for Abdominal and Onco-Surgery at VUH SK a retrospective study of hepatocellular carcinoma (HCC) patients who underwent surgical liver resection is being conducted. The prognostic value of computational indicators of tissue immune response generated from digital immunohistochemistry images in context of conventional clinical and pathology data was explored in 2022.[2] To our knowledge this study is the first to introduce a computational method for assessing the combined impact of independent CD8+ distributions across automatically detected malignant and non-malignant epithelial – stromal interface zones within the same resected liver tissue specimen (Figure 2).

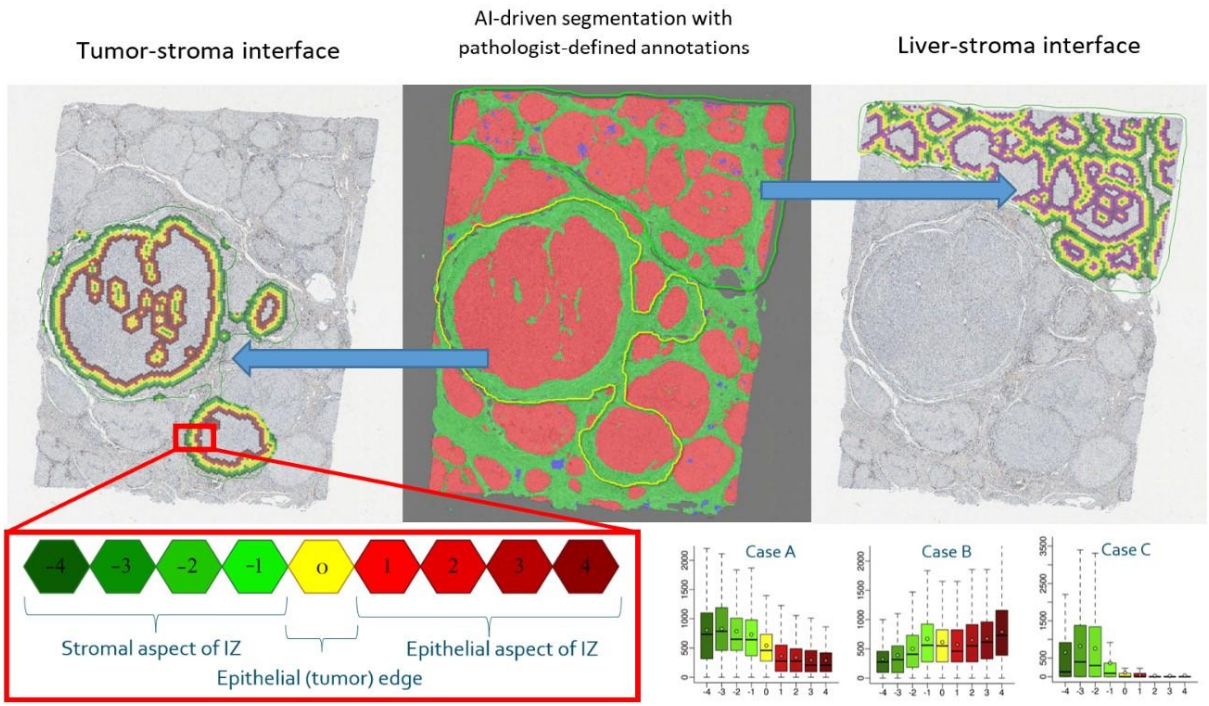

Figure 2. Flowchart of the study – AI assesses the boundary between tumour and healthy tissue .

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Centre for Cancer Coordination

Europe's fight against cancer – what can we do?

Despite rapid scientific advances and innovations in diagnosis and treatment, cancer remains a major public health problem, with an estimated 2.7 million people in Europe diagnosed with cancer in 2020, and a further 1.3 million dying from it. By 2035, cancer is expected to increase by as much as 25% in Europe and may become the leading cause of death. **The need to find effective ways to tackle the growing burden of cancer led to the publication of the European Union's (EU) Beating Cancer Plan in 2021.**[1] Together with a budget of €4 billion, the plan outlines four key areas for action on which European doctors and researchers are encouraged to focus:

- Cancer prevention. Emphasis is placed on tackling the main risk factors for cancer – tobacco use, harmful alcohol consumption, environmental pollution and harmful substances – and on preventing infectious cancers through vaccination of both genders.
- Early detection – promoting better access to quality cancer screening services, calling for breast, cervical and colorectal cancer screening programmes to be offered to 90% of the target population by 2025.
- Diagnosis and treatment. The aim is that by 2030, 90% of patients will receive cancer care at National Comprehensive Cancer Centres (CCCs). A European Initiative to Understand Cancer (UNCAN.eu) has also been developed to increase access to innovative cancer diagnostics and treatments.
- To improve the quality of life among cancer patients and survivors, as well as to provide rehabilitation services, reduce recurrence rates and promote social integration and reintegration of patients into the labour market.

Vilnius University Hospital Santaros Klinikos (VUH SK) provides comprehensive care for patients with all types of oncological diseases, their relatives and cancer survivors. It is estimated that more than 4,000 new patients diagnosed with cancer are treated each year at VUH SK, and specialised oncology diagnosis and treatment services are provided to patients from other countries. In addition, VUH SK is a full member of twelve European Reference Networks (ERNs), including EuroBloodNet (Rare Blood Diseases ERN, https://eurobloodnet.eu/), PaedCan (Pediatric Oncology ERN, https://paedcan.ern-net.eu/), EURACAN (Rare Adult Solid Tumours, https://euracan.eu/), and Genturis (Rare Inherited Oncology ERN, https://www.genturis.eu/l=eng/Home.html). VUH SK specialists provide state-of-the-art cancer diagnostics, including imaging, interventional radiology and telepathology. Many of the world's most advanced cancer treatments, such as chemotherapy, oncological surgery, radiotherapy, stem cell and solid organ transplantation, and cellular immunotherapy, are used to ensure comprehensive and high-quality care for patients with any type of oncological disease. One of the latest developments in cancer care at VUH SK is the introduction of CAR T-cell therapy in September 2022.

Of the 36 VUH SK centres, at least one third routinely provide healthcare services to cancer patients and participate in cancer-related research with Vilnius University. In order to clarify the governance of cancer services, to strengthen interdisciplinary cooperation between specialists from different medical fields in the areas of cancer prevention, clinical services and research, and thus to increase the quality of services for cancer patients and to develop research activities, a **Cancer Coordination Group (chaired by Prof. Dr. Tomas Poškus) and a Centre for Cancer Coordination (headed by Prof. Dr. Jelena Rascon) have been established in VUH SK in 2022.** The Cancer Coordination Group is composed of representatives of the VUH SK centres providing services to cancer patients and acts as an advisory body to find common solutions for the development of cancer services and science, regardless of the different profiles of services provided. The administrators, specialists, auditors, data experts and programmers working in the Centre for Cancer Coordination are looking for ways to technically implement the objectives of the VUH SK in relation to the comprehensive care of cancer and the advancement of science. It is

hoped that the newly created Cancer Coordination Units and the joint efforts of the different units of VUH SK will help the institution not only to effectively improve services to cancer patients in line with the EU strategic directions in the fight against cancer, but also to develop a close cooperation with clinical and scientific partners such as Vilnius University and the National Cancer Institute.

From 2022, VUH SK specialists will also participate in the European initiative "UNderstand CANcer" (UNCAN.eu). The ambition of this project is to develop a strategic plan for a common European platform, UNCAN.eu, a federal data centre for cancer research, bringing together high-quality scientific data from the countries participating in the initiative, after a 15-month coordination and support activity called "4.UNCAN.eu". This initiative is expected to lead to new directions in the development of cancer science and to increase the scientific potential in many EU Member States, despite preexisting inequalities between countries. VUH SK's commitment to increasing attention to oncological diseases was also symbolically demonstrated during the scientific-practical conference "Cancer challenges for medical professionals: how to overcome them?", held on 15 September 2022, where specialists from VUH SK, the National Cancer Institute, the National Centre of Pathology and the Žalgiris Clinic of Vilnius University Hospital, as well as patients' representatives from the Lithuanian Cancer Patient Coalition, shared their experiences, cancer diagnosis, treatment and scientific innovations of the past years. It is expected that the activities of VUH SK in 2022 will become a new starting point for a targeted and integral fight against oncological diseases of all localizations and will allow discovering new opportunities for cooperation with colleagues in Lithuania and abroad.

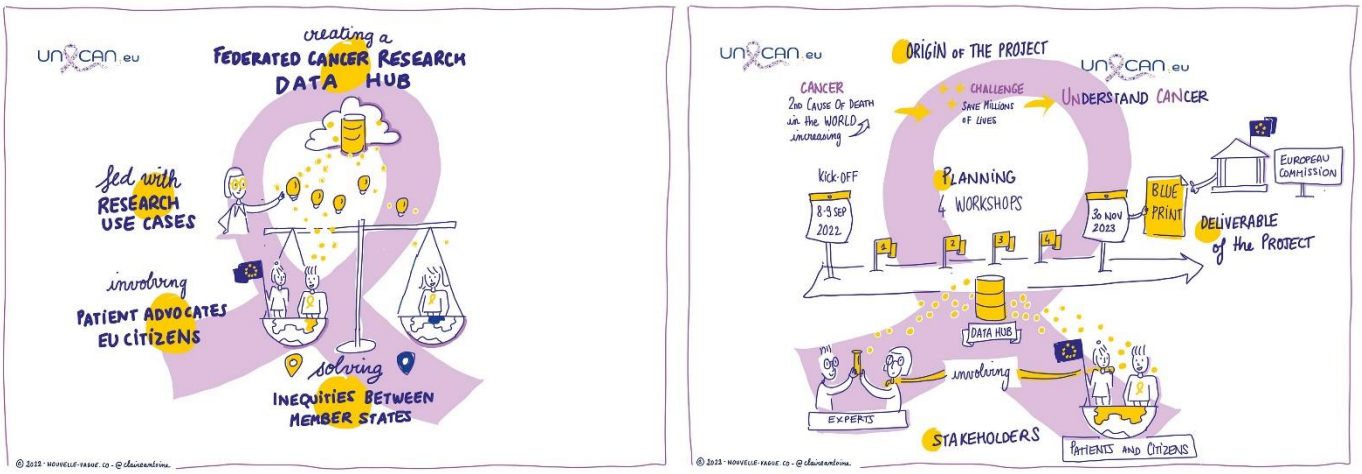

Figure 1. Concept of the European initiative UNCAN.eu.

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Doctoral dissertations defended by VUH SK staff at Vilnius University in 2022

Doctoral student	Date of defense	Dissertation topic	Supervisor
Benediktas Kurlinkus	2022 01 21	Search for diagnostic and prognostic biomarkers of pancreatic adenocarcinoma	Prof. Dr. A. Šileikis
Vytautas Juknevičius	2022 02 25	Evaluation of patients with resistant arterial hypertension before and after pharmacological treatment correction or a renal artery sympathetic denervation procedure	Prof. Dr. A. Laucevičius
Skaistė Sendžikaitė	2022 03 24	Early vascular aging and arterial hypertension in children after correction of coarctation of the aorta	Prof. Dr. A. Jankauskienė
Kotryna Linauskienė	2022 03 24	Contact allergy to heavy metals: risk factors and pathogenesis	Assoc. Prof. Dr. L. Malinauskienė
Eglė Puncevičienė	2022 03 25	Associations of rheumatoid arthritis etiopathogenesis and clinical course with genetic and epigenetic factors	Prof. Dr. I. Butrimienė
Tomas Baltrūnas	2022 03 25	Value of near infrared spectroscopy in detecting tissue perfusion changes during the revascularization of peripheral arteries and its prognostic value	Prof. Dr. K. Ručinskas
Mindaugas Budra	2022 03 25	Long-term results of transventricular mitral valve repair for degenerative mitral regurgitation	Prof. Dr. K. Ručinskas
Greta Balčiūnienė	2022 04 08	The importance of inflammatory markers in maternal blood and amniotic fluid for the diagnosis of chorioamnionitis	Prof. Dr. (HP) G.S. Drąsutienė

Romena Laukienė	2022 06 08	miRNA expression analysis and prognostic significance in thyroid carcinomas	Prof. Dr. L. Cimbalistienė
Marija Svetikienė	2022 06 17	Effects of postoperative immunonutrition on cellular and systemic immune responses and outcomes in low-risk cardiac surgery	Prof. Dr. J. Šipylaitė
Raminta Lukšaitė-Lukštė	2022 06 21	Optimizing the diagnosis of acute appendicitis – a prospective clinical study	Prof. Dr. T. Poškus
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