

**VILNIUS UNIVERSITY HOSPITAL  
SANTAROS KLINIKOS**

**RESEARCH AND INNOVATION**

**2020**

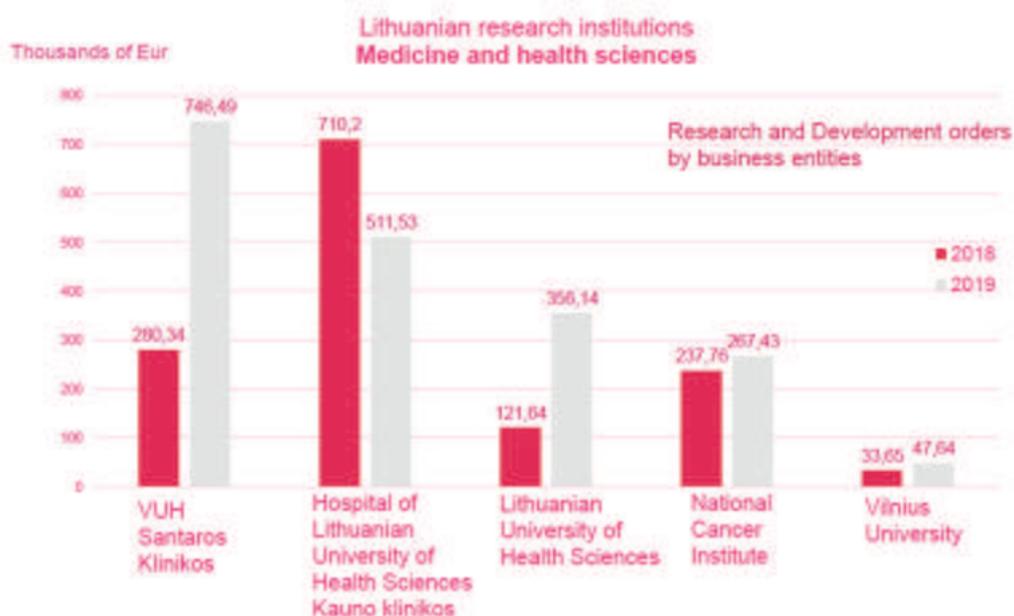
*The year 2020 will be remembered as a challenging time that demanded great courage and strength among members of the medical community at Vilnius University Hospital Santaros Klinikos. While fighting the COVID-19 pandemic, specialists from different medical fields continued to provide high-quality healthcare services, engage in the development of innovative diagnostic and treatment methods and participate in various international projects and biomedical studies. You are invited to discover achievements of 2020 for which Vilnius University Hospital Santaros Klinikos and its experts are valued both in Lithuania and internationally.*

*Yours Sincerely,  
Prof. A. Jankauskienė*

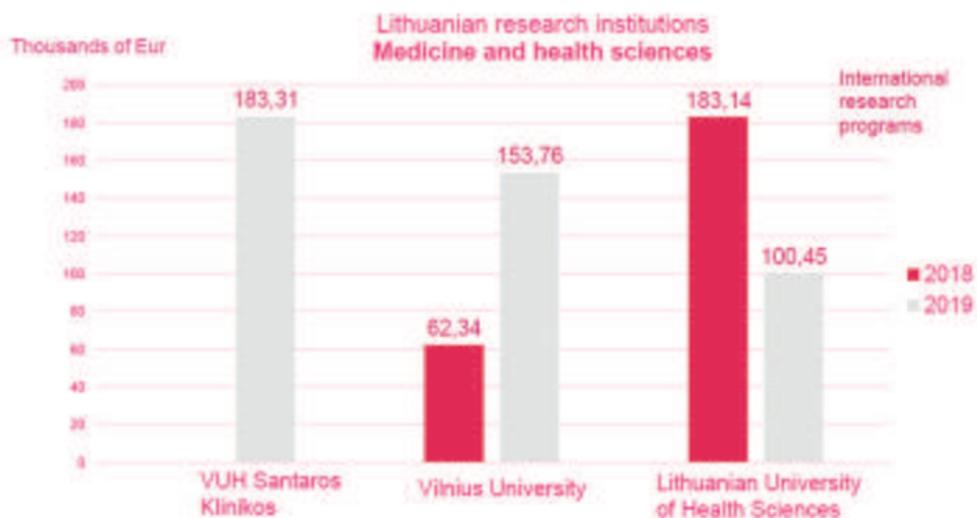
## Research and Development (R&D) at Vilnius University Hospital Santaros Klinikos

In 2020, there were 36 ongoing Research and Development (R&D) projects at Vilnius University Hospital (VUH) Santaros Klinikos, 43 more were submitted for evaluation. Researchers at VUH Santaros Klinikos participated in 209 commercial trials, 45 of which started in 2020. Further, 30 novel non-commercial biomedical and clinical studies were initiated as well.

Here we present data from the Research Council of Lithuanian.



When evaluating R&D-related data (projects, agreements and trials) provided by VUH Santaros Klinikos, the Research Council of Lithuanian recognized 764 490 EUR of revenue in 2019 – this estimate was 166% larger than in 2018.



In 2019, the Research Council of Lithuanian also acknowledged 183 310 EUR of revenue from international research programs (e.g., programs financed by the European Commission). This information has not been provided before and represents a great achievement for the hospital.

## Researchers from **Vilnius University Hospital Santaros Klinikos** contributed to the **WHO Solidarity trial**

On December 2 2020, interim results from the World Health Organization (WHO) Solidarity trial were published in the *New England Journal of Medicine*. With 405 healthcare institutions from 30 different countries participating in the study, the trial provided thorough evidence of how four repurposed antiviral drugs — remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a – may contribute to the management of patients with COVID-19.

Despite preexisting expectations, none of the drugs was shown to significantly reduce patient mortality, the duration of hospitalization or the need for mechanical ventilation. Researchers **Prof. Laimonas Griškevičius** and **Prof. Ligita Jančorienė** from Vilnius University Hospital (VUH) Santaros Klinikos contributed to the sample of 11 330 patients and were listed as co-authors of the interim study results. While the Solidarity trial did not prove any significant improvement of the outcomes of patients treated for COVID-19 with one any of the investigated drugs, there are indications that some of the latter may be beneficial in selected patient groups. For instance, remdesivir may be effective in persons hospitalized with less severe forms of COVID-19. Further, it should be noted that even after widespread vaccination, there might be individuals that do not develop immunity against SARS-CoV-2. Some members of society will decline to vaccinate as well. It is therefore important **to continue the Solidarity trial up to April 2020** and unceasingly search for effective treatment methods for those suffering from COVID-19. With new patients still being recruited in the study, the Solidarity trial is a unique and historical opportunity for specialists at VUH Santaros Klinikos to add to the large trial dataset that outlines how repurposed antiviral drugs may serve to fight a novel and burdensome infectious agent.

### Publications



1. WHO Solidarity Trial Consortium, Pan H, Peto R, [Griškevičius L, Jančorienė L], et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results [published online ahead of print, 2020 Dec 2]. *N Engl J Med*. 2020;10.1056/NEJMoa2023184. doi:10.1056/NEJMoa2023184

## A European study proved children deaths from **COVID-19** to be rare

With SARS-CoV-2 spreading across Europe in early 2020, most of the data concerning the novel infection emerged from adult studies. High mortality rates in Southern European countries led to significant worries among members of the medical community.

As little was known about the course of COVID-19 among children and adolescents, European members of the Paediatric tuberculosis network (Ptbnet) decided to invite the network's specialists for a common multicenter study and investigate COVID-19 cases in the pediatric population. It is noteworthy that Ptbnet is the largest international network that is dedicated to advance research and management of pediatric tuberculosis. Members of the network are specialists in pediatric pulmonology and infectious diseases – those fields in which expert opinion is crucial when providing care for children during the COVID-19 pandemic.

Because of a need for rapid results, the study was executed over the course of several weeks. Data was acquired from participants from 82 centers in 25 European countries: in Lithuania, the research team was composed of **Dr. Rimvydas Ivaškevičius, Assoc. Prof. Virginija Žilinskaitė, Daiva Vaičiūnienė** and the principal investigator **Dr. Inga Ivaškevičienė**. During the study period, 582 patients (aged up to 18 years) were recruited from various European countries. Six children were ill with COVID-19 at Vilnius University Hospital (VUH) Santaros klinikos' Children's Hospital and were included in the analysis. The Ptbnet initiative is a great example of how preexisting cooperation between researchers at VUH Santaros Klinikos and medical centers across Europe can serve to approach emerging global challenges – this time, the COVID-19 pandemic.

**The Ptbnet study revealed that children only rarely have severe forms of COVID-19:** just 8% (48 in total) of all study participants needed intensive care, none in the Lithuanian arm. Overall, from all patients admitted to intensive care units (ICUs), merely a half required respiratory support; one child was treated by using extracorporeal membrane oxygenation. There were four (0.69%) lethal outcomes among the 582 recruited patients.

Investigators reported the most frequent COVID-19 symptoms to be fever and cough (65% of cases), symptoms of upper and lower respiratory tract infections or pneumonia (54% and 25%, respectively) as well as gastrointestinal symptoms (22%). It was noted that the latter could occur with no symptoms of the respiratory system, as in cases of gastrointestinal infections. Asymptomatic cases were frequent (16%) and were diagnosed after contact with infected persons.

The Ptbnet initiative provided not only theoretical knowledge about COVID-19 infections in the pediatric populations, but was also useful to prepare effective healthcare services as well. For instance, the study showed that a child who requires intubation might be kept in an ICU for over a week.

The results of the Ptbnet study were published in *The Lancet Child and Adolescent Health*. Researchers of the Lithuanian arm are delighted with the opportunity to contribute to this important and relevant trial, which united pediatric specialists across Europe for a common cause.

## Publications



1. Götzinger F, Santiago-García B, Noguera-Julián A, [...] Ivaškevičienė I, Ivaškevičius R, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. doi:10.1016/S2352-4642(20)30177-2

## Digital Pathology for **Artificial Intelligence**

**Digital pathology images contain rich data on disease processes including the context of spatial tissue microenvironment.** This opens broad opportunities for artificial intelligence applications in disease diagnosis and predictive analytics. Major benefits come with extraction and quantification of novel features of pathology, often not visible by routine microscopy examination. The field is rapidly developing in many areas of medicine.

Researchers at the National Center of Pathology, the affiliate of Vilnius University Hospital Santaros Klinikos (**Director Prof. Arvydas Laurinavičius**) started digital pathology research in 2010 with image analysis-based quantification and began exploring the benefits of multivariate analytics of image analysis data to generate combined image-based biomarkers. Further, accuracy and calibration experiments for image analysis-based quantification were performed.

In 2015, a methodology based on hexagonal tiling of image analysis data was proposed to quantify intra-tumor heterogeneity of biomarker expression; this allowed to generate rich data set to compute spatial indicators. This approach was conceptualized as “comprehensive immunohistochemistry”. The heterogeneity indicators were demonstrated in later studies as independent prognostic factors, often exceeding the informative value of the average level of the biomarker expression.

**In 2020, another hexagonal grid-based methodology was published** – it allowed automatically detecting tumor-host interface zone and computing immune cell density profile across the zone. This actually measures the “willingness” of immune cells to enter the tumor (immunogradient) and provides independent prognostic value. Compared to other methods proposed to measure immune response in the tumor microenvironment, the interface zone immunogradient provides quantitative directional assessment in the very frontline of tumor-host interaction. PCT and Lithuanian patent applications have been submitted for this method.

## Publications

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1. Zilenaite D, Rasmusson A, Augulis R, et al. Independent Prognostic Value of Intratumoral Heterogeneity and Immune Response Features by Automated Digital Immunohistochemistry Analysis in Early Hormone Receptor-Positive Breast Carcinoma. *Front Oncol.* 2020;10:950. Published 2020 Jun 16. doi:10.3389/fonc.2020.00950
2. Rasmusson A, Zilenaite D, Nestarenkaite A, et al. Immunogradient Indicators for Antitumor Response Assessment by Automated Tumor-Stroma Interface Zone Detection. *Am J Pathol.* 2020;190(6):1309-1322. doi:10.1016/j.ajpath.2020.01.018
3. Nestarenkaite A, Fadhil W, Rasmusson A, et al. Immuno-Interface Score to Predict Outcome in Colorectal Cancer Independent of Microsatellite Instability Status. *Cancers (Basel).* 2020;12(10):2902. Published 2020 Oct 9. doi:10.3390/cancers12102902

## Specialists at the Center for Pediatric Oncology and Hematology are the main coordinators of a **Horizon 2020** project

In 2020, the Center for Pediatric Oncology and Hematology at Vilnius University Hospital (VUH) Santaros Klinikos won a tender to participate in the international Horizon 2020 Research and Education Cooperation Project, which aims to improve the survival of children with malignancies in Lithuania (**Twinning in Research and Education to improve survival in Childhood Solid Tumours in Lithuania, TREL**).

This is a particularly significant achievement of the VUH Santaros Klinikos Center for Pediatric Oncology and Hematology as its specialists participate in the project as key coordinators (**project coordinator Assoc. Prof. Jelena Rascon**) and one of the project's goals is to increase research experience at VUH Santaros Klinikos and create pathways for cooperation with potential project partners.

The main incentive to initiate the TREL project was the popular EURO CARE5 study, which previously studied the survival of European children with oncological diseases. It found that 10-20% fewer children with oncological diseases recover in Lithuania than in Western Europe. Worse treatment outcomes were associated with lower dedicated healthcare costs and insufficient funding for research. Unequal resources limited Lithuanian researchers' participation in international clinical trials and research projects – with the emergence of the latter, the survival of children increased from 10% to 80% since the end of the 20th century.

**The TREL project will focus on the most common molecular and genetic studies of solid tumors in children** (CNS, neuroblastoma and kidney tumors) and resistant forms of cancer. To achieve this goal, there will be cooperation with as many as eight research centers and hospitals in different countries around the world; 46 staff members from VUH Santaros Klinikos also be involved in the project.

**The project is divided into 7 main parts** - all of them will be carried out simultaneously, each having delegated specialists for their implementation. One of the cornerstones is the implementation of applied medical research and innovative diagnostics at the Center for Pediatric Oncology and Hematology by means of both retrospective and prospective sample analysis.

The activities envisaged in the next part of the project will allow VUH Santaros Klinikos to better prepare for early-stage clinical trials for the treatment of refractory solid tumors: special training will be provided for staff working in clinical trials. Another aim will be to improve the monitoring and quality of life of children who have survived cancer – this will be done by participating in the SurPass project, which will carry out research regarding future fertility of the children. The project intends to pay special attention to improving project management and administration skills at the Center for Pediatric Oncology and Hematology by adopting good management practices from the project's partners (for example, improving intellectual property protection skills).

**Thus, the TREL project will serve to exchange information**, share best practices and launch new research projects. We believe that the scientific knowledge acquired during the project together with the participating network of specialists will help to ensure better treatment results for children with oncological diseases.

## A trial for an effective treatment method for acute lymphoblastic leukemia has been completed

The **NOR-GRASPALL 2016 study** (principal investigator at the the Center for Pediatric Oncology and Hematology at Vilnius University Hospital (VUH) Santaros Klinikos – **Dr. Goda Elizabeta Vaitkevičienė**) was completed in 2020. It examined a treatment option for children with acute lymphoblastic leukemia (ALL) who cannot receive PEG-asparaginase. The study, which began in 2017, included 14 patients from the Department of Pediatric Oncohematology: their participation not only helped to investigate the positive effects of eriaspase, but also provided PEG-asparaginase-intolerant patients with an effective and innovative drug.

**Asparaginase is a particularly important chemotherapeutic agent for the treatment of ALL.** It works by breaking down asparagine: healthy cells in the body can produce this amino acid themselves, while leukemic cells cannot, so they starve and die. PEG-asparaginase is part of the standard treatment protocol in the Nordic and Baltic countries, but one of the common side effects of this medicine is allergic reactions. If the latter occur, PEG-asparaginase should be discontinued

Patients allergic to PEG-asparaginase require alternative treatment methods for ALL: one of them is eriaspase, a new form of asparaginase. With the new treatment, asparaginase is inserted into living blood donor erythrocytes and remains active in the recipient's body, breaking down asparagine and preventing tumor cells from surviving. In addition, erythrocytes protect the drug from being broken down in the body, so it can stay active for much longer than the aforementioned PEG-asparaginase. At the same time, asparaginase is also protected against antibodies in the patient's immune system, reducing the risk of an allergic reaction to the medicine. Asparaginase being present in erythrocytes is also thought to protect the body from its toxic effects, resulting in fewer side effects with eriaspase.

The NOR-GRASPALL 2016 study was commissioned by **Aarhus University Hospital, Denmark**. Researchers at the Center for Pediatric Oncology and Hematology at VUH Santaros Klinikos are pleased to have been able to contribute directly to the development of the new ALL treatment. The information gathered during the study and the drug is submitted to the U.S. Food and Drug Administration for approval.

### Publications

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1. Gottschalk Højfeldt S, Grell K, Abrahamsson J, [Vaitkevičienė G] et al. Relapse risk following truncation of PEG-asparaginase in childhood acute lymphoblastic leukemia [published online ahead of print, 2020 Nov 4]. *Blood*. 2020;blood.2020006583. doi:10.1182/blood.2020006583
2. Rank CU, Wolthers BO, Grell K, [Vaitkevičienė G, Griškevičius L] et al. Asparaginase-Associated Pancreatitis in Acute Lymphoblastic Leukemia: Results From the NOPHO ALL2008 Treatment of Patients 1-45 Years of Age. *J Clin Oncol*. 2020;38(2):145-154. doi:10.1200/JCO.19.02208

## International information integration - the way to the future of long-term patient monitoring



The goal of the Survivorship Passport (SurPass) project, which will start in March 2021, is to create a system that would allow the treatment and monitoring plan of recovering patients and patient recommendations to be translated into e-health systems so that they are visible and accessible to peripheral health care facilities.

Through programs initiated by the European Commission, an online European platform will be set up to provide data on cancer recovery. First, the intended system will transfer information about the disease the patient was suffering from and the way it was treated (e.g., chemotherapy, radiotherapy, surgery, transplantation). Based on the data entered, the system will automatically generate recommendations for patient monitoring. For example, it is known that some of the required treatment increases the risk of damage of certain organs, making patients likely to develop breast cancer, have endocrine complications or remain disabled. **The SurPass system** will make it possible to anticipate such risks. The initial patient monitoring plan will be created by adult and pediatric oncologists – the specialists who treated a distinct patient at first. They will provide the available data and the platform created will generate a ‘**survivorship passport**’ (SurPass). It will be linked to a patient’s medical report and the whole set of information will be transferred to the general SurPass system. International guidelines for the follow-up of the patient will be visible to personell in all treatment facilities that will use the system.

It is expected that the Electronic Medical History (ELI) system at Vilnius University Hospital (VUH) Santaros Klinikos will be compatible with the “survivor passport” system with the participation of specialists in the SurPass system, so that data provided by staff at VUH Santaros Klinikos will be automatically transferred to SurPass. In this way, VUH Santaros Klinikos can become one of the first institutions to apply the “survivor passport” system to patients who have agreed to enter the project.

**Physicians working on the project will have the opportunity to continually improve their knowledge** of long-term patient monitoring, its standards and requirements.

The SurPass system claims to be one of the latest breakthroughs in integrating patient data from individual healthcare facilities into an international network, ensuring standardized, evidence-based and long-term patient care.

## Patients with highly active multiple sclerosis receive **autologous hematopoietic stem cell transplantation**

Specialists at Vilnius University Hospital (VUH) Santaros Klinikos perform **autologous hematopoietic stem cell transplantation** (AHSCT) for patients with highly active relapsing-remitting multiple sclerosis (MS) who do not respond to second line therapy.

From 2013 to 2019, AHSCT was performed for 24 patients with relapsing-remitting MS, most of them had an assessment of cognitive functions and disability during a follow-up of 24 months. It was found that one year after AHSCT, selective improvement in cognitive functions could be noted and Expanded Disability Status Scale scores revealed improved disability in 76.9% of the study sample. Besides, no new lesions after magnetic resonance imaging were observed. Further, there were no lethal outcomes during the study period. Such results indicate that AHSCT might be a safe and effective procedure for the treatment of highly active relapsing-remitting MS. To evaluate the clinical course of MS and the patients' cognitive functions, a multidisciplinary cooperation between the Center for Hematology, Oncology and Transfusion Medicine (**Head Prof. Laimonas Griškevičius**) and the Center for Neurology (**Head Prof. Gintaras Kaubrys**) was necessary.

The results of the study were published in Nature Research's journal Scientific Reports.

### Publications



1. Giedraitiene N, Kizlaitiene R, Peceliunas V, Griskevicius L, Kaubrys G. Selective cognitive dysfunction and physical disability improvement after autologous hematopoietic stem cell transplantation in highly active multiple sclerosis. Sci Rep. 2020;10(1):21286. Published 2020 Dec 4. doi:10.1038/s41598-020-78160-1

## Complex heart surgery is now possible by using minimally invasive methods

In 2020, clinical trials aimed at effective and minimally invasive treatment of atrial fibrillation (AF) were carried out at the Center for Cardiology and Angiology (**Head Prof. Audrius Aidietis**) at Vilnius University Hospital (VUH) Santaros Klinikos.

During AF, the irregular atrial electrical activity and muscle tissue contractions leads to an increased risk of clotting and stroke. Previously, open-heart surgery was performed to treat AF; however, novel technologies allow specialists to isolate pulmonary veins by using a catheter, which serves to eliminate AF-triggered foci of excessive electrical heart activity. **Patients enrolled in one of the clinical trials at VUH Santaros Klinikos were the first patients in the world to receive one of these minimally invasive treatment procedures.** The difference between the system used in these clinical trials in 2020 and standard radiofrequency therapy is that the former is more effective because of pulse field ablation – the surface area affected by the balloon catheter is larger in comparison with the radiofrequency catheter; the current density is lower as well. In this way, unsafe tissue damage is prevented. During treatment, the tissues are prevented from high temperatures and the balloon catheter energy is titrated until the maximum surface temperature remains below 80°C. During the initial assessment of the safety of balloon ablation and its exploitation features, it has been established that it is a safe, convenient and promising treatment method for AF. For instance, after a follow-up of 270 days, 94.4% of all patients remained free of any atrial arrhythmias. In 2020, the project TriggersAF (financed by the Research Council of Lithuania) was further being implemented with aims not only to ensure effective AF treatment, but also to prevent strokes in patients with AF. Special wristband devices were developed to monitor patients with AF – they were created by engineers from Kaunas Technology University in collaboration with researchers from Vilnius University and Lund University. The wristbands help to detect dangerous AF as well as establish a precise diagnosis and promptly recommend the required treatment.

Specialists at the Center for Cardiology and Angiology (**Head Prof. Audrius Aidietis**) and the Center for Cardiac Surgery (**Head Prof. Kęstutis Ručinskas**) at VUH Santaros Klinikos are also constantly searching for better ways to perform minimally invasive mitral valve repairs. **In August 2020, the first-in-human transcatheter off-pump mitral valve (InnovHeart SAT-URN) implantation procedure was performed.** Previously, a surgical way was applied to repair the valve, whereas this novel technology allows to combine a transcatheter bioprosthetic valve with an annular structure to remodel the native annulus and seal the perimeter of the implant.

Off-pump minimally invasive repairs intended for the treatment of degenerative mitral valve regurgitation are being performed with NeoChord Artificial Chordae Delivery System by transapical placement of artificial chordae when natural chordae tendinae become ruptured due to degenerative mitral valve disease. From 2011, 115 replacements have already been performed (5 of them in 2020), the follow-up data analysis proves its effectiveness and allows an assessment of the predictive factors (for instance, during the echo, remodeling of left atrium or ventricle is being monitored) predicting the postoperative course of the disease.

## Publications



1. Anter E, Neužil P, Rackauskas G, [Aidietis A] et al. A Lattice-Tip Temperature-Controlled Radiofrequency Ablation Catheter for Wide Thermal Lesions: First-in-Human Experience With Atrial Fibrillation. *JACC Clin Electrophysiol.* 2020;6(5):507-519. doi:10.1016/j.jacep.2019.12.015
2. Reddy VY, Anter E, Rackauskas G, [Marinskis G, Aidietis A] et al. Lattice-Tip Focal Ablation Catheter That Toggles Between Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation: A First-in-Human Trial. *Circ Arrhythm Electrophysiol.* 2020;13(6):e008718. doi:10.1161/CIRCEP.120.008718
3. Reddy VY, Neužil P, Peichl P, [Rackauskas G, Aidietis A, Marinskis G] et al. A Lattice-Tip Temperature-Controlled Radiofrequency Ablation Catheter: Durability of Pulmonary Vein Isolation and Linear Lesion Block. *JACC Clin Electrophysiol.* 2020;6(6):623-635. doi:10.1016/j.jacep.2020.01.002
4. Weber A, Rucinskas K, Janusauskas V, [Zakarkaite, D] et al. Automated Implantation of Artificial Mitral Chords: Preliminary Results From the Feasibility Trial. *Ann Thorac Surg.* 2020;109(2):597-602. doi:10.1016/j.athorac-surg.2019.08.037
5. Drasutiene A, Janusauskas V, Speziali G, [Zakarkaite D, Budra M, Rucinskas K, Aidietis A]. Minimally invasive mitral valve repair with NeoChord system in patients with degenerative mitral disease: echocardiographic assessment and predictors for mid-term outcome. 2020. *European Heart Journal*, 41(Supplement\_2), ehaa946-2680.

## Medical services for patients with cardiovascular conditions during the COVID-19 pandemic

The availability of healthcare services changed greatly during the COVID-19 pandemic – it was more difficult to provide both diagnostic and treatment procedures at pre-pandemic levels. The fear of becoming infected deterred patients with urgent conditions from seeking timely and effective help, thus diminishing their chances of preventing severe complications or even lethal outcomes. Presuming that the pandemic influenced healthcare services for patients with cardiovascular diseases, specialists from Vilnius University Hospital (VUH) Santaros Klinikos tested this hypothesis by performing a case study from data of national databases.

The study was financed by the Research Council of Lithuania and led by **Prof. Giedrius Davidavičius**. Researchers analyzed and interpreted data from databases of the National Healthcare Insurance Fund, Emergency Services and a cluster for myocardial infarctions at VUH Santaros Klinikos. By comparing data from 2019 and 2020, the experts could provide evidence of both the socioeconomical damage and the direct harm to the public's health that was caused by strict lockdown measures and a subsequent decrease of the availability of healthcare services in Lithuania. **For instance, it was noted that only one in every two patients with cardiovascular conditions could receive appropriate medical services in May-June 2020.** In April 2020, there was a 50% decrease in the overall number of services provided with a drop of 71% and 86% when considering secondary or tertiary level services, respectively. Finally, the number of patients arriving with urgent cardiovascular conditions dropped by up to 32% during the study period.

**The data revealed that during the first half of 2020 there were 34% (or 35 000) more deaths among patients with cardiovascular conditions than in 2019.** The 30-day mortality of patients with coronary artery disease was 7.8% in January-August 2020 – higher than the value of 4.7% in 2019. Further, the rate of new diagnoses of coronary artery disease decreased 2.5 times and deaths outside of the hospital setting (mostly at home) increased by 14%.

The qualitative part of the study, a survey of patients and medical personnel, showed that the autumn of 2020 was marked by frequent hospitalizations of patients with poor status as many of them did not receive timely diagnostic tests and were not using appropriate drug therapy for their condition. Finally, specialists reported that remote consultations were not as effective as expected and did not meet the best standards of quality.

The conclusions of the project were used to outline recommendations for better implementation of cardiovascular care during the COVID-19 pandemic as well as for future crises.

## International participation to prepare guidelines for heart imaging

From 2016 to 2020, **prof. Jelena Čelutkienė** represented the Center for Cardiology and Angiology at Vilnius University Hospital (VUH) Santaros Klinikos by being a Board Member and co-coordinator of the Imaging Study Group at the Heart Failure Association (HFA) of the European Society of Cardiology. One of the activities during this term was to form a group of experts and prepare HFA guidelines for better practice of patient imaging.

The development of HFA guidelines is a highly dynamic and engaging process as every expert presents a proposition regarding a certain segment of the document and provides sound arguments by reminding those recent findings that are of the highest level of scientific evidence. Then begin active discussions between the specialists and a common position by the HFA emerges. In 2020, prof. J.Čelutkienė coordinated the preparation of acute heart failure and cardio-oncological statements on the behalf of the HFA.

### Publications



1. Čelutkienė J, Lainscak M, Anderson L, et al. Imaging in patients with suspected acute heart failure: timeline approach position statement on behalf of the Heart Failure Association of the European Society of Cardiology [published correction appears in Eur J Heart Fail. 2020 Jul;22(7):1287]. Eur J Heart Fail. 2020;22(2):181-195. doi:10.1002/ejhf.1678
2. Čelutkienė J, Pudil R, López-Fernández T, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(9):1504-1524. doi:10.1002/ejhf.1957

## High positions in the European Association of Preventive Cardiology and the International Atherosclerosis Society

**Prof. Žaneta Petrulionienė** has been elected to a high position as a nucleus member of the Primary Care Risk Factor Management Section of the European Association of Preventive Cardiology (EAPC) in August 2020. The professor will represent Lithuania and the entire EEC region in EAPC for the first time and will serve as a section nucleus member.

**Prof. Ž. Petrulionienė also represents Lithuania, the EEC region and Europe in the International Atherosclerosis Society (IAS) for the first time.** IAS Executive Board has appointed her as Member at Large (Europe). The professor is also an active National Coordinator of the global, world-wide project EAS-FHSC (The European Atherosclerosis Society Familial Hypercholesterolemia Studies Collaboration) and the National Coordinator of the international project ScreenProFH (Screening Project for Familial Hypercholesterolemia in Central, Southern and Eastern Europe). Further, she represents Lithuania in the International Lipid Expert Panel (ILEP) and is the current President Elect of the Baltic Atherosclerosis Society (BAS).

The professor is a member of a multidisciplinary team at Vilnius University Hospital Santaros Klinikos and, together with professor Aleksandras Laucevičius, leads the Lithuanian High Cardiovascular Risk (LitHir) Primary Prevention Program. According to the latest data, published in 2020 (analysis of 110370 Lithuanian adults from 2009 to 2018), the most common cardiovascular risk factor among both male and female subgroups was dyslipidemia (up to 90% among women and 86% among men). In contrast to men, there was no significant decrease in the prevalence of dyslipidemia among women throughout the years. The focus on the prevention of cardiovascular diseases remains particularly important and requires international cooperation as well as sharing best practices that would reduce the prevalence of dyslipidemia and atherosclerosis and increase the use of lipid-lowering medications among individuals at-risk.

### Publications



1. Laucevičius A, Rinkūnienė E, Petrulionienė Ž, Ryliškytė L, Jucevičienė A, Purnaitė R, Badarienė J, Navickas R, Mikolaitytė J, Gargalskaitė U, Dženkevičiūtė V, Kutkienė S, Gimžauskaitė S, Mainelis A, Šlapikas R, Gurevičius R, Jatužis D, Kasiulevičius V. Trends in cardiovascular risk factor prevalence among Lithuanian middle-aged adults between 2009 and 2018. *Atherosclerosis*. 2020 Apr;299:9-14. doi: 10.1016/j.atherosclerosis.2020.02.025.

## A rehabilitation program for patients with **pulmonary hypertension**

Pulmonary hypertension (PH) is a severe progressive disease that is associated with reduced exercise capacity and poor survival (the mean survival for patients without targeted treatment is about 5 years) and often occurs in young people. Even being on optimal targeted medication therapy, most of these patients remain with poor exercise capacity and low quality of life. Thus, scientists are searching for optimal care strategies, including non-pharmacological treatment possibilities, such as specialized rehabilitation programs, psychosocial support and education.

Since 2015, researchers at Vilnius University Hospital (VUH) Santaros Klinikos (**Principal investigator Dr. Lina Gumbienė, PhD student Eglė Palevičiūtė**) cooperate with scientists from Heidelberg University who have substantial experience in specialized PH rehabilitation.

PH-specialized cardiologists at VUH Santaros Klinikos together with rehabilitation physicians and physiotherapists visited the Thoraxklinik at Heidelberg University Hospital and Rehabilitation Clinic Königstuhl, where they learned to conduct a well-established exercise and respiratory training program for patients with PH. A training protocol was adapted to local conditions and the specialised rehabilitation program started in Vilnius in 2017.

Together with 11 centres across 10 European countries, researchers from VUH Santaros Klinikos participated in the first multicentre randomised controlled trial on feasibility, safety and efficacy of the specialized PH rehabilitation program. This treatment strategy was safe, well tolerated and effective – after a follow-up of 15 weeks, the change of 6-minute walking distance (the primary endpoint of the study) improved by  $34.1 \pm 8.3$  m in the training group as compared to study controls. A significant improvement in the trained patients' quality of life was demonstrated as well.

In the future, specialists are planning to adapt and adjust this rehabilitation program for patients with heart failure with preserved ejection fraction, complicated by pulmonary hypertension. These patients represent a large proportion of all persons with PH and no effective medications have yet been developed for their condition.

## Publications

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1. Grünig E, MacKenzie A, Peacock AJ, [Gumbiene L, Palevičiūtė E, Jurevičienė E] et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial [published online ahead of print, 2020 Nov 24]. *Eur Heart J.* 2020;ehaa696. doi:10.1093/eurheartj/ehaa696
2. Nagel C, Benjamin N, Egenlauf B, [Palevičiūtė E, Čelutkienė J] et al. Effect of supervised training therapy on pulmonary arterial compliance and stroke volume in severe pulmonary arterial hypertension and inoperable or persistent CTEPH. *Respiration*, 2020 (priimtas spaudai)

## Cardio-oncology consultations

The prevalence of oncological diseases increases in Lithuania and across the world. Thus, specialists of different medical fields encounter an increasing number of patients with cancer. Despite the advances in cancer treatment and the fact that there are many survivors from oncological diseases, some cardiological morbidity caused by cardiotoxic treatment regimens remains inevitable and may occur anytime during treatment or years afterwards. Further, some patients are diagnosed with cancer while having cardiovascular comorbidities and benefit from a thorough assessment of their condition before cancer therapy.

**After having understood that cardiology and oncology have to solve common problems, a new field of cardio-oncology emerged.** Its aim is to prevent or provide a timely diagnosis of cardiological comorbidity in patients with cancer in order to safely continue cancer treatment. The latter must be chosen with no delay as to increase the chances of better outcome. Even after treatment with cardiotoxic drugs is finished, all patients must be followed for symptoms of late onset cardiological dysfunction.

The increasing need of cardiological consultations for patients with cancer who are referred from the National Cancer Institute or Vilnius University Hospital (VUH) Santaros Klinikos determined that specialists at the Outpatient Department of Cardiology (**doctoral student Eglė Čiburienė and supervisor Prof. Sigita Aidietienė**) began to consider the field of cardio-oncology more actively by participating in related conferences, starting research projects and translating the knowledge into appropriate consultations for patients with cancer. For instance, after an internship at a Clinic for Cardio-oncology in London (United Kingdom), **E.Čiburienė** contributed to a joint publication regarding iron deficiency and anemia in cardio-oncology.

The main issues for which specialists in oncology refer their patients to cardiologists are:

- **The need for cardiovascular risk** assessment before undergoing drug therapy or surgery.
- **Cardiotoxicity**, which causes heart failure and is lethal for one in every two patients.
- **Persisting hypertension** among patients treated with vascular endothelial growth factor inhibitors.
- **Heart rhythm and conduction disorders** during cancer therapy.
- **Ischemia or coronary spasm** during chemotherapy
- **Diagnostics of heart tumors**
- Diagnostics and treatment of **pericardial effusion**

Specialists at VUH Santaros Klinikos have also created a local database that will serve for research purposes and analysis of problems that are most relevant for cancer patients in Lithuania.

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## The effect of arterial stiffness on the progression of pediatric chronic kidney disease

Children with chronic kidney disease have a significantly reduced life expectancy that is largely attributed to premature cardiovascular disease which also remains one of the leading causes of death in childhood and young adulthood. Premature cardiovascular morbidity, evident by markers of early atherosclerosis, increased arterial stiffness and left ventricular remodeling, has been reported even in young children with chronic kidney disease. Although the development of cardiovascular disease has been linked to various complications of chronic kidney disease, studies in the pediatric population are scarce, limited in sample sizes and mostly of cross-sectional nature.

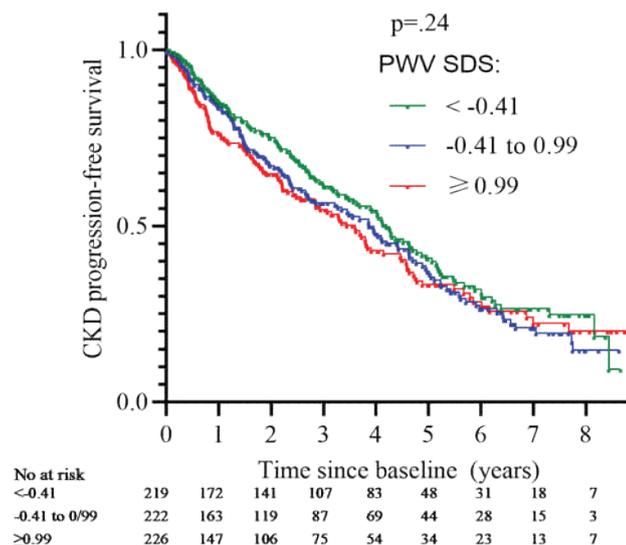
Chronic kidney disease is much less prevalent in children compared to adults and thus requires collaborative efforts such as the 4C Study (**Cardiovascular Comorbidity in Children with Chronic Kidney Disease; NCT01046448; [www.4c-study.eu](http://www.4c-study.eu)**) to reach adequately powered study samples. The 4C Study was initiated by prof. Franz Schaefer (Heidelberg University, Germany) and prof. Uwe Querfeld (Charite Hospital, Germany). One of the study sites since the beginning of the study was Vilnius University Hospital (VUH) Santaros Klinikos (study investigators: **prof. Augustina Jankauskienė, prof. Rimantė Čerkauskienė, Karolis Ažukaitis**).

The study prospectively followed children with chronic kidney disease stages 3-5 with six-monthly collections of various clinical data and annual comprehensive cardiovascular examinations. The study enrolled a total of 704 children from 55 pediatric nephrology centers in 12 European countries. Fourteen of the study participants were followed at VUH Santaros Klinikos. One of the regional coordinators for the 4C Study, responsible for the coordination of study and performing instrumental examinations in Lithuanian, Austrian, German, Italian and French centers was a pediatric nephrologist and doctoral student from VUH Santaros Klinikos **Karolis Ažukaitis**.

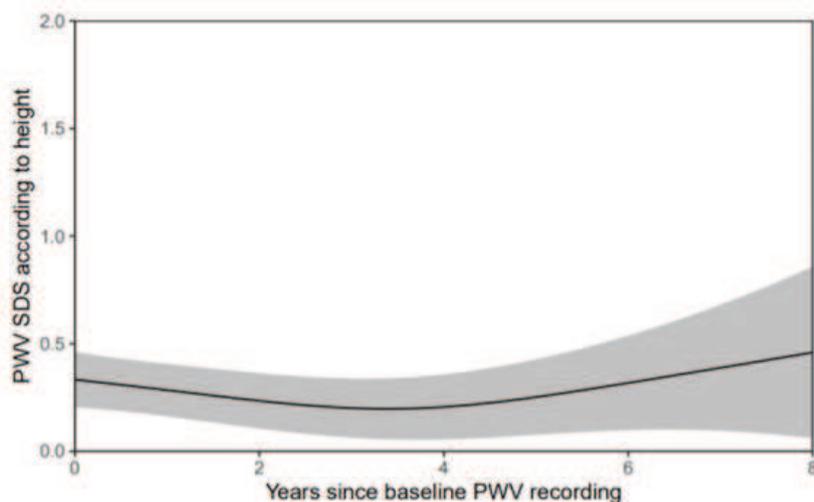
After more than eight years of prospective follow-up, analysis of the longitudinal data was started to elucidate the mechanisms leading to premature cardiovascular comorbidity and its consequences in pediatric chronic kidney disease. One of the central axis of cardiovascular disease development is accelerated arterial stiffness which was also selected as the topic of Karolis Ažukaitis thesis. Recently finished analysis is the largest attempt to date to study the prevalence, longitudinal dynamics and functional consequences of arterial stiffness in children with chronic kidney disease.

**Principal findings of the arterial stiffness analysis:**

- **Arterial stiffness is increased** in approximately one fifth of children with advanced pre-dialysis chronic kidney disease but is relatively stable over time.
- **Arterial stiffness is not related** to kidney function and its longitudinal dynamics, but is independently associated with younger age, female gender, shorter height, higher diastolic blood pressure, higher low-density lipoprotein cholesterol, higher proteinuria, lower vitamin D levels and lower ferritin levels.
- **Arterial stiffness is not related to** left ventricular mass or left ventricular hypertrophy but is independently associated with concentric left ventricular remodeling.
- **Arterial stiffness in children is not related to** chronic kidney disease progression.



**Figure 1.** Pulse wave velocity (arterial stiffness) and chronic kidney disease progression-free survival



**Figure 2.** The change in standard deviation score of pulse wave velocity over the years

The findings of the present analysis provided reliable evidence that arterial stiffness is increased in childhood chronic kidney disease and associated with chronic kidney disease complications, the patients' age and gender, but not kidney function per se. This is the first study to analyze the effects of arterial stiffness on chronic kidney disease progression and left ventricular geometry in children. In contrast to the adult population, arterial stiffness does not associate with chronic kidney disease progression in children but is independently associated with left ventricular concentric remodeling. The study not only allowed to elucidate early effects of accelerated arterial stiffness in pediatric chronic kidney disease but also to identify certain modifiable risk factors for its increase (such as low vitamin D levels, proteinuria and blood pressure). Collectively, study findings strongly support routine monitoring of pulse wave velocity as a marker of arterial stiffness in children with advanced chronic kidney disease.

### Publications



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## Innovative liver and coloproctology operations at the **Center for Abdominal Surgery**

At the Center for Abdominal Surgery at Vilnius University Hospital (VUH) Santaros Klinikos (**Head Prof. Kęstutis Strupas**) modern liver surgical techniques are being used to treat patients with advanced oncological diseases. Radical treatment methods such as multi-stage liver surgery are applied for inoperable liver tumors. A major part of the liver parenchyma is first separated and the portal and hepatic venous system blood vessels are ligated, upon observing sufficient liver parenchyma augmentation, the damaged part of the liver can be removed. Such methods often eliminate the disease and prevent postoperative complications'. At VUH Santaros Klinikos we use a world-standard liver metastasis treatment algorithm that provides a new opportunity for patients with oligometastatic and polymetastatic disease.

Besides, in 2020 a new palliative care method, electrochemotherapy, was introduced, which increases the concentration of the chemotherapeutic agent in the tumor tissue, thus inhibiting disease progression. This method is applicable for parenchymal organ malignancies, when surgical treatment is not possible.

**The center also conducts fundamental scientific research.** Together with the Center for Innovative Medicine and Vilnius University Life Sciences Centre specialists are participating in liver regeneration and tissue bioengineering research projects, which aim to find novel methods to compensate for impaired liver tissue function. The most recent project MITA Eureka, carried out together with the Medical University of Graz and a business partner, expands liver cell transcriptomics: a new generation microcircuit, so called liver-on-chip, which simulates liver function, is being developed (**Figure 1**).

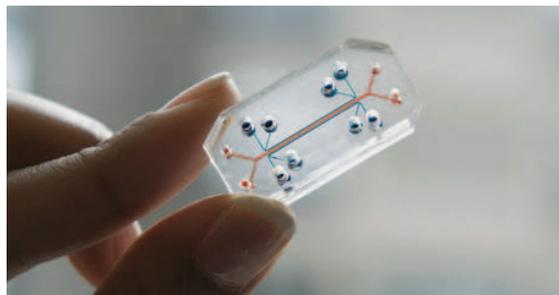
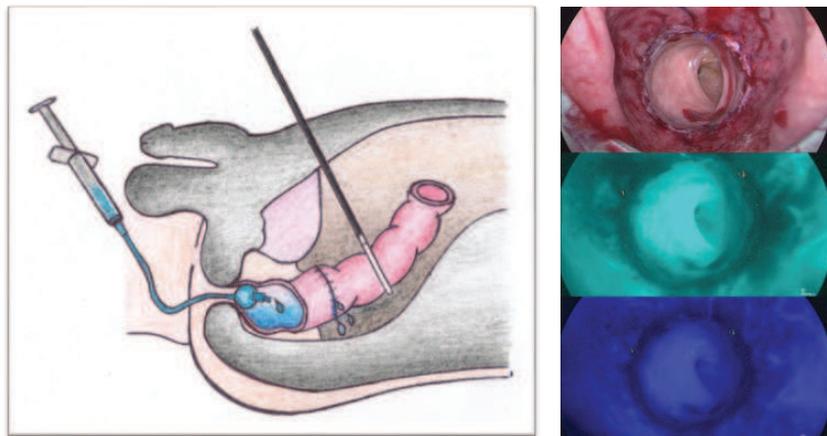


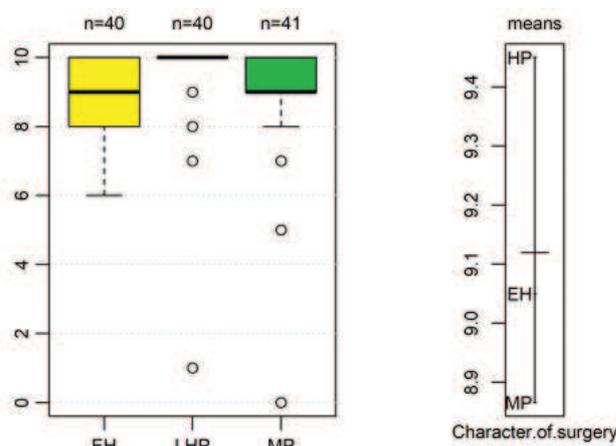
Figure 1. Liver-on-chip model

As a part of a clinical study, in 2020, a new standardized process to improve colorectal anastomosis safety was introduced. During this process, the mechanical anastomosis integrity and the vascular supply is tested by using Indocyanine Green Fluorescent imaging<sup>2-5</sup> (**Figure 2**). This assessment can be used during both laparoscopic and open surgery operations: once a safe colorectal anastomosis is identified, expectantly, less patients require preventive ileostomy.

**Figure 2.** Colorectal anastomosis mechanical integrity testing using methylene blue dye (left figure, sagittal view) and the formed colorectal anastomosis transanal blood flow evaluation using Indocyanine Green Fluorescent imaging (right figure).



In 2020, a research group from the Center for Abdominal Surgery published results of a double-blind randomized controlled trial comparing laser hemorrhoidoplasty with sutured mucopexy and excisional hemorrhoidectomy<sup>6</sup>. By analyzing our center data, it was found that laser hemorrhoidoplasty is less effective than excisional hemorrhoidectomy, but better evaluated by the patients, as it is less painful and less disruptive to patients' lives (**Figure 3**). **The laser surgery technique can be used to treat patients with hemorrhoids, anal fistulas and pilonidal disease.**



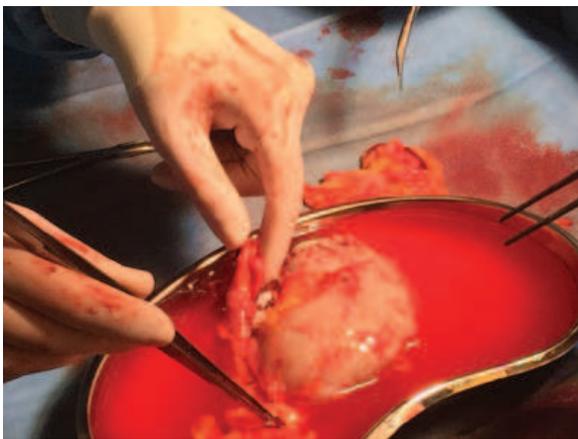
**Figure 3.** Evaluation of the operations by the patients: excisional hemorrhoidectomy (EH), laser hemorrhoidoplasty (LHP), sutured mucopexy (MP). LHP was evaluated by the patients as the best operation. Adapted (CC BY 4.0) from Poskus et al.<sup>6</sup>

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1. Račkauskas R, Baušys A, Sokolovas V, Paškoniš M, Strupas K. Short- and long-term outcomes of surgery for colorectal and non-colorectal liver metastasis: a report from a single center in the Baltic country. *World J Surg Oncol.* 2020;18(1):164. Published 2020 Jul 14. doi:10.1186/s12957-020-01944-2
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## A Decade of Experience in ABO-Incompatible Living-Donor Kidney Transplantation



Donor kidney preparation

In 2020, Centers for Nephrology (**Head Prof. Marius Miglinas**) and Urology (**Head. Assoc. Prof. Dr. Arūnas Želvys**) at Vilnius University Hospital (VUH) Santaros Klinikos marked a 10-year anniversary of ABO incompatible living donor kidney transplantation. Previously, only compatible blood type kidneys from deceased and living donors were accepted for donation.

Not infrequently, the mere finding of incompatible blood groups prevented kidney donation from otherwise acceptable living donors.

HLA antigen matching between the donor and recipient is paramount and is routinely performed prior to renal transplantation. Of particular importance are A, B, DR and DQ antigens. Blood type ABO antigens also play an important role as they are expressed by endothelial cells of the transplanted kidney. When kidneys that are incompatible by blood type are transplanted, preformed antibodies against ABO antigens trigger transplant rejection.

The first attempt of incompatible blood type kidney transplantation was published back in 1955. However, eight out of ten of the blood type incompatible transplants stopped functioning during the first few days after the surgery. Afterwards, only scattered reports of blood incompatible kidney transplantation followed and the survival was dismal reaching only about 4% after one year post-transplantation. Blood incompatible kidney transplants were abandoned until 1987, when an effective desensitization protocol was introduced and reducing the titers of the anti-A and anti-B antibodies became feasible and engendered transplantation success. The protocol involved repetitive pre-transplant plasmapheresis sessions, which are still in use today.

Currently, blood type incompatible kidney recipient candidates receive repetitive plasma exchanges until safe anti-A and anti-B antibody titers are attained. They also receive rituximab and oral immunosuppressants.

The first transplantation of this type at the Center for Nephrology at VUH Santaros Klinikos took place in 2010. A 39-year-old woman (blood type B) suffering from chronic kidney disease due to IgA nephropathy received a kidney from her mother (blood type AB). The procedure was a great success. Even today, 10 years after the transplantation, the allograft is functioning very well: the patient is working and leads an active life. The success inspired specialists to continue the practice. To date, 14 patients have received blood type incompatible transplants.

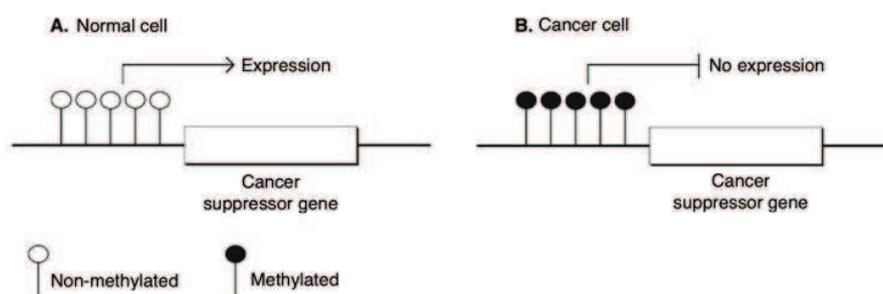


**Over 50 years have passed since the first kidney transplant surgery in Lithuania in 1970.** Since then, renal transplantation has become a routine treatment modality for patients suffering from chronic kidney disease, improves their outcomes and quality of life. At the Center for Nephrology at VUH Santaros Klinikos modern immunosuppression protocols are currently available and desensitization due to previously failed grafts is performed for those in need of a repeated transplantation. **The Center actively participates in the pancreatic beta cell replacement program targeting type 1 diabetic patients with end-stage kidney disease.** These patients require dialysis treatment and have an annual mortality rate of up to 10%. For them, kidney transplantation is a life-saving intervention that is also combined with transplantation of the pancreas, which increases surgical risk, but does not require additional immunosuppression. For these patients we recommend the kidney-pancreas transplantation to be performed simultaneously. Patients with type 1 diabetes who already received a kidney may benefit from pancreatic islet cell transplant. It reduces the risk of recurrence of diabetic kidney disease in the allograft. Patients with labile diabetes (e.g., having frequent hypoglycemic events) might benefit from islet transplantation alone.

## Epigenetic markers in prostate cancer diagnostics

Despite tremendous progress in radiological investigations, prostate cancer (PCa) diagnostics in modern-era of medicine still face significant problems. According to data from Vilnius University Hospital (VUH) Santaros Klinikos and other centres, **27%** of PCa patients are upgrading and **20%** are upstaging at the final pathological evaluation after radical prostatectomy. The total misclassification rate is as high as **40%**. Upgrading and upstaging after definitive therapy is associated with shorter biochemical recurrence-free survival, metastatic disease, shorter metastases-free survival and inferior cancer-specific survival rates.

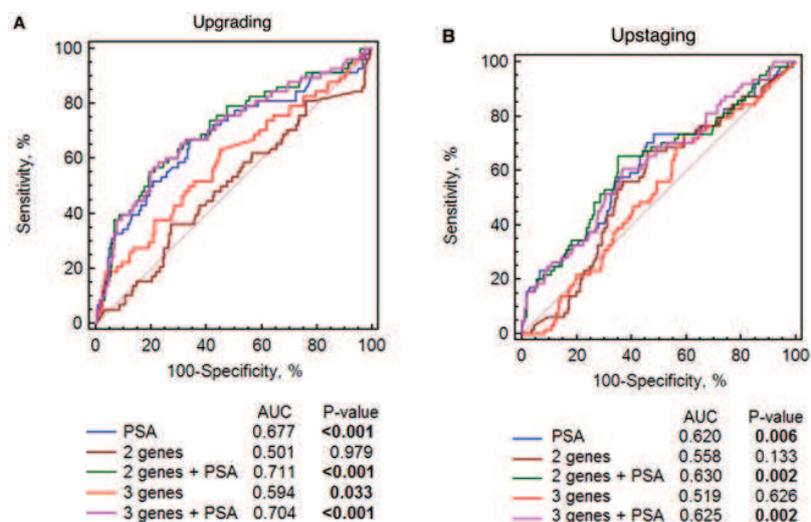
PCa is a heterogeneous disease. During the early phase of PCa carcinogenesis, DNA alterations are detected in gene regulatory areas – promoter regions (Figure 1). While these epigenetic alterations do not disrupt the normal sequence of DNA, normal gene expression is affected. Nucleic acids that circulate in body fluids contain information from all tumour foci and reflect genetic and epigenetic changes in PCa that may provide valuable information for improved diagnosis and timely prediction of the aggressiveness of PCa. According to **Prof. Feliksas Jankevičius, Dr. Arnas Bakavičius** and co-investigators from National Cancer Institute, significantly different promoter methylation frequencies of *RARB*, *RASSF1* and *GSTP1* genes are detected in cancerous and noncancerous prostate tissues.



**Figure 1.** Epigenetic alterations in prostate cancer. Promoter region of cancer suppressor gene are binded with methyl group (B).

A three-gene (*RARβ*, *RASSF1* and *GSTP1*) test combination with prostate-specific antigen is predictive for postoperative PCa upgrading, upstaging and risk increase – this finding confirms the utility of epigenetic markers in PCa diagnostics (Figure 2).

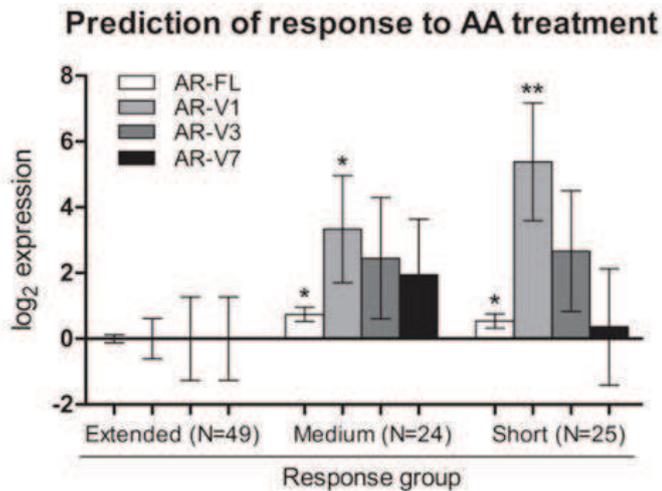
**Figure 2.** DNA methylation of *RARB*, *RASSF1*, *GSTP1* and prostate-specific antigen (PSA) as biomarkers of prostate cancer upgrading (A) and upstaging (B) after radical prostatectomy.



### Androgen receptor variants as predictive prostate cancer markers

Various treatment agents have been approved for treatment of PCa, however, scientific evidence is still scarce for selection of the most appropriate treatment strategy and drug sequencing, especially in castration resistant form of the disease.

Androgen receptor variants (AR-Vs) that lack ligand-binding domain and remain constitutively active are thought to be involved in the mechanisms responsible for developing resistance to androgen-pathway targeted agents. Reported result revealed that significantly higher expression of AR-V1 and AR-V7 was observed in PCa as compared to non-cancerous prostate tissue. AR-V1 upregulation was also significantly associated with shorter biochemical recurrence-free survival, primary and early *de novo* resistance to new generation hormone-pathway targeted therapy, as well as inferior overall survival rates (Figure 3).



**Figure 3.** Response to abiraterone acetate (AA) therapy according to different types of androgen receptor variants (AR-Vs).

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## CENTER-TBI: a deep look into brain injury

In 2020, the **Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study** was finished at the Center for Neurosurgery at Vilnius University Hospital (VUH) Santaros Klinikos (**Head Prof. Saulius Ročka**). The idea of the study appeared back in 2011, when EU and U.S. health institutions and delegates from non-governmental and patient institutions initiated a cycle of seminars and identified main questions regarding the management of patients after traumatic brain injury (TBI). Every year, around 50 million people suffer from TBI worldwide – it is also one of the leading causes of death among young adults. However, there was an additional need for sensitive and standardized epidemiological monitoring methods, evidence-based trauma markers and standardized treatment options.

During the project, clinical, radiological and laboratory data from 18 European countries and Israel were collected. After the inclusion phase had been finished in 2017, there were data of around 4500 patients who suffered from TBI in the CENTER-TB dataset. Patients treated at VUH Santaros Klinikos were included into the database as well and representatives from the Center for Neurosurgery are listed in the main publications of the study.

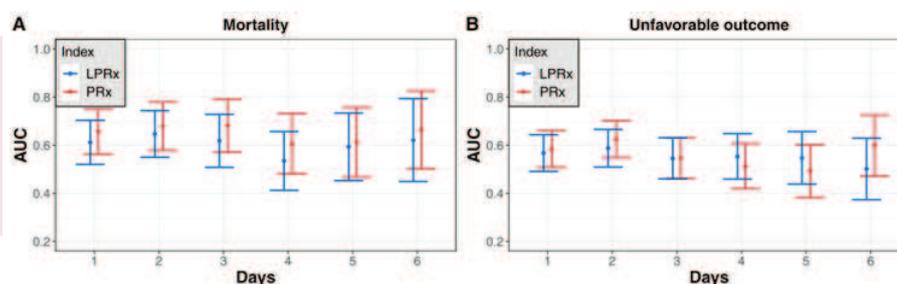
**One part of the study was aimed to explore changes in cerebrovascular reactivity after TBI.** It was confirmed that pressure-reactivity index (PRx) provides statistically significant information about mortality, independently from other clinical characteristics<sup>1</sup>. Monitoring of low-resolution PRx was also associated with mortality and could be used in centers without high-resolution signal monitoring (**Figure 1**)<sup>2</sup>. On the other hand, brain tissue oxygen (PbtO<sub>2</sub>) should not be used in cerebrovascular reactivity monitoring<sup>3</sup>. Association between high intracranial pressure during first 72 h after moderate or severe TBI and bad outcome was confirmed as well<sup>4</sup>.

The CENTER-TBI study was not limited to investigation of patient clinical data. Differences in medical systems, diagnostic algorithms, outcome evaluation and even legal questions were also addressed. Data from Lithuania was provided for comparison and included in the analysis as well.

**The CENTER-TBI study is a good example** of how collaboration of representatives from various countries with different health systems start a discussion concerning a specific topic that is relevant for the medical community. Subsequent big-data analysis is set to have a great impact when improving the diagnosis and management of TBI.

**More information:** <https://www.center-tbi.eu/>

**Figure 1.** AUCs for the prediction of mortality and unfavorable outcome over the early post-traumatic time course. Adapted (CC BY 4.0) from [2].



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1. Zeiler FA, Ercole A, Beqiri E, [Ročka S] et al. Association between Cerebrovascular Reactivity Monitoring and Mortality Is Preserved When Adjusting for Baseline Admission Characteristics in Adult Traumatic Brain Injury: A CENTER-TBI Study. *J Neurotrauma*. 2020;37(10):1233-1241. doi:10.1089/neu.2019.6808
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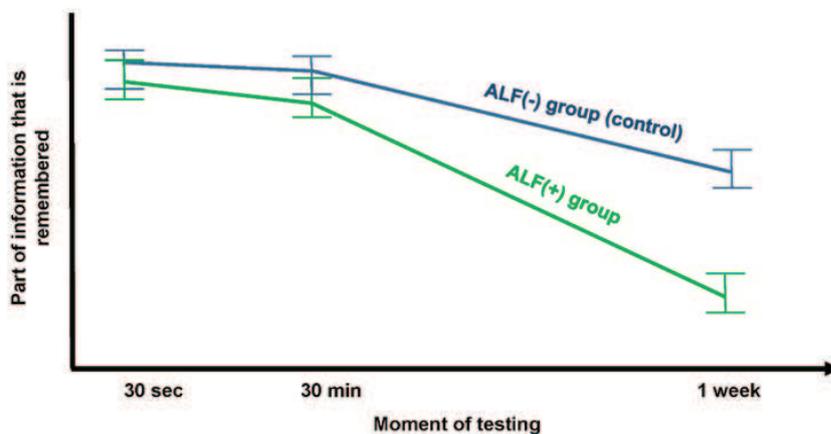
## Epilepsy studies help to understand the origins of seizures

In 2020, the main research focus at the Center for Rare Epilepsies at Vilnius University Hospital (VUH) Santaros Klinikos (**Head Prof. Rūta Mameniškienė**) was related to factors that either provoke or inhibit the manifestation of seizures in people with epilepsy (PWE). Recent results of a transcultural study that was started in 2016 and involved **researchers from Lithuania, Brazil, Guatemala and Turkey** revealed that both PWE (82.7%) and patients who experience migraines (91.6%) are able to identify factors that are associated with the exacerbation of their disease<sup>1</sup>. Despite different cultural environments in each study arm, PWE reported that a lack of sleep (56.6%), emotional stress (55.3%) and negative feelings (53.9%) provoke their seizures. Up to 31.4% of all PWE indicated that they are able to suppress the episodes. Further, another study at VUH Santaros klinikos provided early evidence that a subjective perception of factors that are associated with seizure provocation or inhibition is linked to objective epileptiform activity in electroencephalography (EEG) recordings<sup>2</sup>.

**It was also shown that different EEG techniques may activate discrete ictogenic neural networks (i.e., those important for the propagation of seizures)**, which are indirectly influenced by hormonal, emotional or diurnal factors. There are indications that the perception of being in control of one's disease is related to lower depression and anxiety levels among PWE and their ability to willfully suppress seizure activity<sup>3</sup>. Therefore, future research might help to better understand how the subjective information that PWE provide can serve to delineate the mechanisms of ictogenesis.

Historically, there are similar examples of how an interest in subjective patient complaints led to a better understanding of the pathogenesis of epilepsy. For instance, a modification of standard neuropsychological testing revealed the phenomenon of accelerated long-term forgetting (ALF). It is a memory disorder that is observed when some people with epilepsy forget new information faster than healthy individuals over days or weeks, but retain normal short-term memory (**Figure 1**).

In a review of 51 studies concerning ALF, **it was summarized that this phenomenon is most likely caused by long-term consolidation deficits**, presumably because of damage in hippocampal-neocortical networks or neocortical sites<sup>4</sup>. The review demonstrates how continuous attention to subjective patient memory complaints expanded general knowledge about the genesis of memory impairment in PWE.



**Figure 1.** Memory testing results in accelerated long-term forgetting (ALF) – the study group (ALF+) has similar initial memory patterns as the control group (ALF-), but starts to rapidly forget new information after days or weeks post-learning.

**The quality of life of PWE, their emotional state and seizure frequency are interrelated** – it is therefore essential to monitor different societal phenomena that may change the clinical situation of PWE and require additional attention from epileptologists. In 2020, the COVID-19 pandemic was the main event that transformed everyday life and had a significant impact on PWE. A survey at VUH Santaros Klinikos showed a decrease in self-reported mental and physical health among PWE during a national COVID-19 lockdown<sup>5</sup>. Further, remote consultations, which predominated during the pandemic, were valued less by patients with epilepsy than usual visits in-person. Even 32.2% of all respondents reportedly lost epilepsy-related medical services – such a loss was associated with seizure exacerbation. It was emphasized that improving the availability of antiepileptic drugs and ameliorating teleconsultations is essential during strict national lockdowns.

As the Lithuanian Parliament started considering the legal status of cannabis-related products, a survey at the Center for Neurology at VUH Santaros Klinikos revealed that 16.4% of PWE have already tried some form of cannabis preparations and 32.4% would be interested to try cannabis as a remedy for epilepsy<sup>6</sup>. It was noted that those interested in such opportunities were more willing to try cannabis and its preparations: it may therefore be important for specialists in neurology to discuss pharmacological interactions and prevent discontinuation of antiepileptic drugs when consulting PWE interested in trying cannabis products.

Finally, an international survey showed that there are great variation in the European Union when evaluating a patient's fitness to drive<sup>7</sup>. According to PWE, driving limitations are one of the most relevant everyday issues after being diagnosed with epilepsy. However, there are currently no specific guidelines of how EEG testing may provide better judgment about a patient's with epilepsy ability to drive safely.

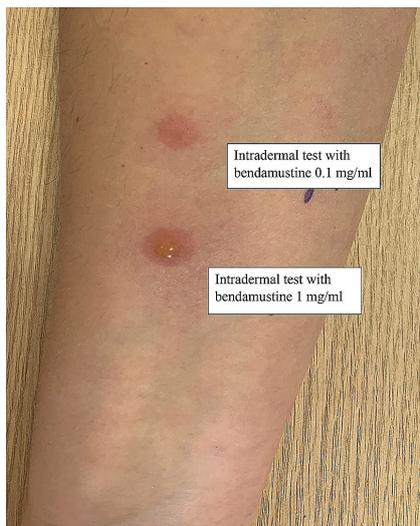
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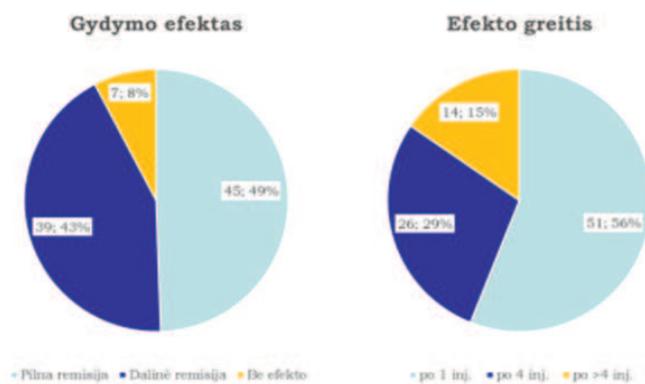
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## The Center for Pulmonology and Allergology

Specialists at the Center for Pulmonology and Allergology at Vilnius University Hospital (VUH) Santaros Klinikos (**Head Prof. Edvardas Danila**) conduct studies to detect drug allergies, discover new allergens and specify drug concentrations that might serve for provocation testing. In 2020, it was noted that non-standardized methods that examine allergic skin reactions may pose a threat for the patient (**Figure 1**)<sup>1,2</sup>



**Figure 1.** Skin reaction to bendamustine at 0.1 and 1 mg/ml after 10 days in one of the patients in a control group. Adapted (CC BY 4.0) from Malinauskienė et al. [1]



**Figure 2.** Experience of treating urticaria with omalizumab. Treatment efficacy, chart on the left – full remission (teal), partial remission (blue), no effect (yellow). Treatment speed, chart on the right – after one injection (teal), after four injections (blue), after more than four injections (yellow).

Experts at the Center for Pulmonology and Allergology also explore the efficacy of various treatment methods (e.g., biological therapy, plasmapheresis) for urticaria (**Figure 2**). Biomarkers that might be associated with better response to treatment are investigated as well.



**Figure 3.** In 2020, specialists at VUH Santaros Klinikos published a second edition of recommendations by experts in the field for the diagnosis and treatment of interstitial lung diseases.

## Publications

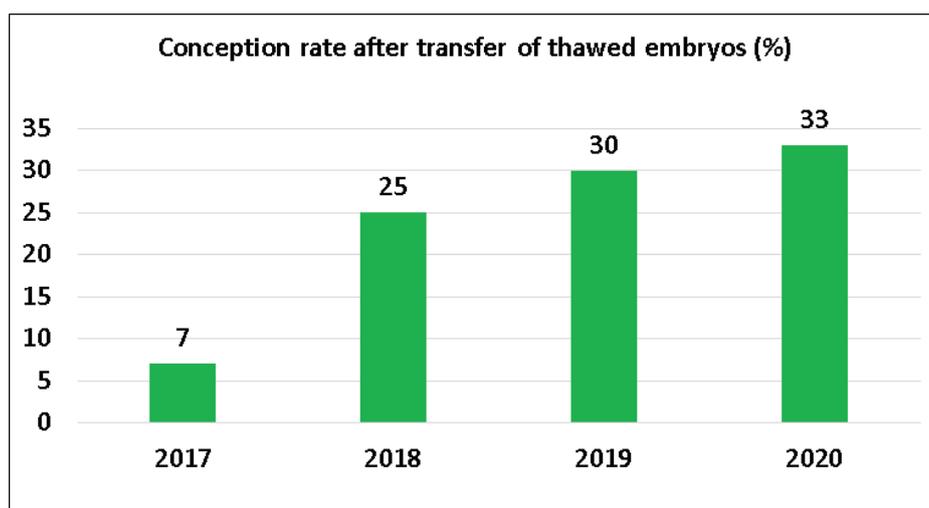


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## More couples receive innovative services of assisted reproduction at the **Center for Obstetrics and Gynecology**

In 2020, the Center for Obstetrics and Gynecology at Vilnius University Hospital (VUH) Santaros Klinikos marks its fourth year when novel assisted reproductive technologies (ART) are available for couples willing to conceive. The treatment is provided at the Santaros Fertility Center (**Head Obstetrician-Gynecologist Rimantas Gričius**) and the Subdepartment of ART and reproductive tissue bank (**Senior embryologist Dr. Živilė Gudlevičienė**).

In 2020, there were 80 thawed embryos at VUH Santaros Klinikos: 90% were transferred with a subsequently recorded conception in 24 (33%) cases – this result is the best since the start of providing such fertility services.



In vitro fertilization and intracytoplasmic sperm injection procedures at the Santaros Fertility Clinic are proved to be of adequate quality because of a high conception rate, which meets the standards of good clinical and laboratory practice. Pre-implantation genetic testing is performed as well: this allows early detection of genetic diseases, which would prevent the transfer of the embryo (**Figure 1**).



**Figure 1.** Pre-implantation genetic testing procedures: breaching of the zona pellucida and biopsy of a single blastomere.

From all patients who received services of **intrauterine insemination (IUI)**, 16% conceived in 2020. This is also the best result from all four years of IUI practice at VUH Santaros Klinikos.

According to data from the National Health Insurance Fund, VUH Santaros Klinikos remains the largest institution in Lithuania to provide services of fertility diagnostics, treatment and preservation as well as reproductive tissue donation.

**Around 40% of all fertility services in Lithuania were provided at VUH Santaros Klinikos.** Further, 97-98% of all couples that conceived after ART had a clinical confirmation of the pregnancy by ultrasound and the pregnancy concluded in the birth of a child. Results from 2020 reveal that ART services are constantly improving and there is now substantial help for couples willing to conceive in Lithuania.

To ensure that all patients receive care of the highest quality, this year the spectrum of practice at the Subdepartment of ART and reproductive tissue bank expanded as new specialists became members of the team. According to national and international guidelines to prevent occurrences of multiple pregnancy, a protocol of **“Single Embryo Transfer”** has been established as well.

## Publications

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1. R. Baušytė, R. Einikytė, J. Klimašenko, G. Stupelytė, I. Šiaudinytė, D. Žilovič. Recenzentai: V. Abraitis, D. Laužikienė, M. Minkauskienė, D. Ramašauskaitė. Pakartotinių persileidimų metodika. 2020 m.
2. Ž. Gudlevičienė, R. Baušytė, E. Dagtė, D. Balkelienė, A. Utkus, D. Ramašauskaitė. „The first live birth in Lithuania after application of preimplantation genetic testing“. Acta medica Lituanica. 2020 m.

## Human milk research is the basis of a newborn's rational diet

Human milk is the best food for newborns and infants. Donor human milk should be the second choice of nutrition for premature and ill newborns when own mother's milk is lacking. Such milk must be specially prepared in the donor human milk bank in compliance with appropriate safety requirements.

About **500 liters of the donor human milk** are collected and prepared annually in the donor human milk bank opened in 2017 at the Center for Neonatology of Vilnius University Hospital (VUH) Santaros Klinikos (**Head Assoc. Prof. Dr. Arūnas Liubšys**). The aim is to ensure that all premature and seriously ill newborns treated at VUH Santaros Klinikos who for various reasons do not have access to their own mother's milk, are fed with the donor human milk.



While there is no doubt about the benefits of human milk for the newborn, many unanswered questions remain. For example, how the composition of human milk changes throughout pregnancy or lactation and how it is influenced by the preparation and storage methods. In order to determine how these factors are related to the composition of the human milk, the nutritional composition of human milk by mid-infrared transmission spectroscopy was investigated at the Center for Neonatology of VUH Santaros Klinikos in 2017-2020 (**main researcher Ieva Jūra Paulavičienė**).

It was found that from two to six weeks after childbirth, the concentration of human milk proteins gradually decreases, the amount of carbohydrates increases, while the concentration of fat and the caloric value of human milk do not change significantly (Figure 1). In addition, the macronutrient composition of human milk is influenced by the duration of pregnancy, the method of childbirth, and the sex of the newborn, but not the age or the body mass index of the mother. The composition of human milk varies and depends on the time of the day: significant circadian fluctuations in protein, fat concentration, and caloric content were found, but there were no significant changes in the carbohydrate concentration. Various factor-dependent changes in the composition of human milk are likely to be important for the growth, development, and health status of the newborn.

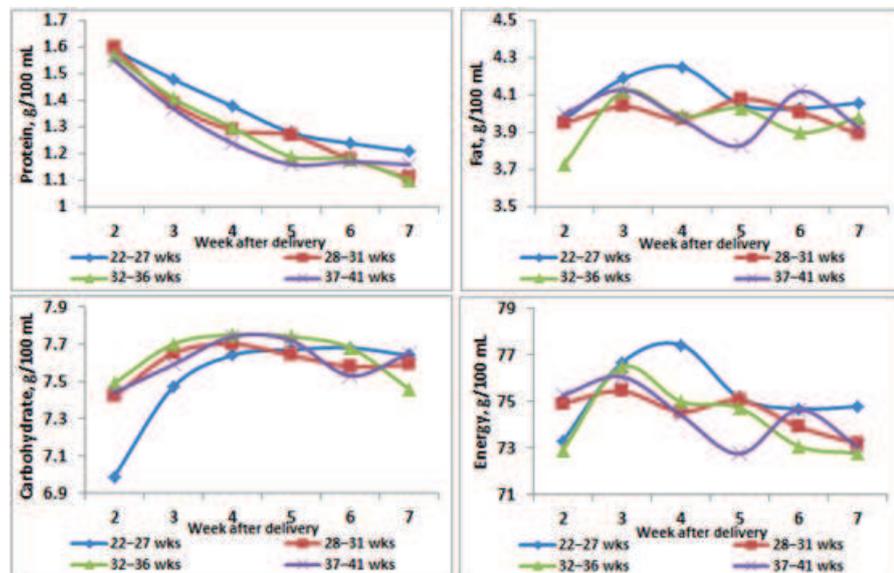


Figure 1. Changes in human milk macronutrient content and energy value depending on the duration of lactation

Another important part of the investigation was to evaluate how the composition of the donor milk is changed by its preparation (Holder pasteurisation) and storage (freezing). **Human milk freezing and Holder pasteurisation determined significant changes in the content of biologically active proteins (lactoferrin and lysozyme); however, they have no effect on the concentration of macronutrients, oligosaccharides and water-soluble metabolites in human milk.**

In collaboration with the researchers from the University of Cagliari (Italy), an innovative human milk metabolome analysis was also conducted. The analysis enabled assessment of pasteurisation impact on human milk metabolome composition and provided knowledge about oligosaccharide composition of human milk of women residing in Lithuania. The study revealed that **human milk freezing and Holder pasteurisation had no effect on the composition of oligosaccharides and water-soluble metabolites in human milk**. It was found that all participants belonged to the secretory type (Se+) according to oligosaccharides dominant in their milk; 17 out of 20 mothers (85%) had the type depending on the Lewis gene. These phenotypes determine the protective properties of the human milk.

## Publications

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## Recognition by the **International Atomic Energy Agency**: Regional courses were organized at **VUH Santaros Klinikos**



Dr. Mario Marengo (Bologna, Italy), Dr. Sigrid Leide Svegborn (Skane university, Sweden) and Dr. Birutė Gricienė (VUH Santaros Klinikos, Lithuania)

The International Atomic Energy Agency (IAEA) chose Lithuania as the country to organize the Regional Train-the-Trainers Course on Radiation Protection in Diagnostic and Therapeutic Nuclear Medicine in late 2019. Specialists from 17 different European countries attended the course, which was led by **the Head of the Department for Clinical Radiation Safety Assoc. Prof. Birutė Gricienė and the Direction for Management Aušra Bilotienė Motiejūnienė.**

This represented an opportunity for physics, radiation technology and safety specialists from Lithuania to participate in an accessible international training course. The lectures were provided by IAEA experts **Dr. Sigrid Leide Svegborn** (Skane university, Sweden) and **Dr. Mario Marengo** (Bologna, Italy).

Participants of the course visited Departments of Nuclear medicine at VUH Santaros Klinikos and the National Cancer Institute, where they had a chance to observe the local equipment, hear about the methods employed for optimization of radiation exposure and note the tools used for treatment of thyroid cancer.

The knowledge acquired throughout the course will serve to improve radiation safety in nuclear medicine centers across Europe and develop new methods that decrease the risk for patients and medical personnel.

In 2020, researchers at the Department for Clinical Radiation Safety at VUH Santaros Klinikos published results regarding radiation exposure among medical staff and the subsequent risk for oncological disorders. The specialists also participated in a survey by the IAEA – it revealed that low-exposure protocols are still rarely used in various European countries.

## Publications

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## New applications for Full Membership in European Reference Networks

The Center for Coordination of Rare Diseases brings together 38 specialized Centers of Excellence that provide multidisciplinary care for patients with various rare diseases from all across Lithuania as well as from foreign countries. **It is the largest center for the diagnosis, treatment, education and research in rare diseases in the country.**

Currently, Vilnius University Hospital (VUH) Santaros Klinikos holds **Full Membership in 8 European Reference Networks, ERNs** (with 13 Centers of Competence at VUH Santaros Klinikos) and is an **Affiliated Partner in 7 more ERNs** (with 11 Centers of Competence at VUH Santaros Klinikos). Participation in ERNs provides an opportunity to share knowledge on rare diseases with European experts: in 2020, cases of 7 patients with unclear diagnosis or treatment were presented for discussion. Ever increasing competencies of VUHSK experts in rare disease diagnosis and treatments provide means for further integration into ERNs: currently, four Centers of Competence are ongoing stringent assessment procedures to become the Full Members of existing ERNs.

## The first **Brain, Heart and Kidney Congress** in Vilnius proceeded in a hybrid fashion

From 22 to 24 October 2020 a multidisciplinary discussion among specialists in neurology, cardiology and nephrology took place in Vilnius in the form of the first **Brain, Heart and Kidney (BHK) Congress**, which attracted participants from Lithuania and various foreign countries. The conference was initiated with hopes of a closer relationship between experts of different medical fields.

The three-day-long conference was led by **Prof. Rūta Mameniškienė** and organized by representatives from the Faculty of Medicine of Vilnius University and specialists from Vilnius University Hospital Santaros Klinikos. The COVID-19 pandemic determined that a highly innovative way of hybrid conferences needed to be installed for the **44 invited speakers from 16 countries to easily participate in the event.**

It is noteworthy that the epidemiological situation changed almost constantly before and during the BHK Congress – the spread of SARS-CoV-2 was accelerating both in Lithuania and across Europe. For the safety of the event's participants, the conference proceeded in a hybrid fashion: attendees had the chance to take part in the lectures both in-person and online. Such a choice probably resulted in a larger number of specialists joining the BHK Congress as experts from various countries were able to share their knowledge and experience regardless of travel restrictions. Hopefully, such hybrid conferences will become an attractive way to increase engagement among members of the medical community and ease the dissemination of knowledge.

**The BHK Congress was oriented towards various medical fields** and invited to discuss issues that are important for most specialists in neurology, cardiology and nephrology. Among the subjects were ketogenic diet, the phenomenon of pain, transient loss of consciousness, the diagnosis and treatment of various cardiovascular and kidney disorders. Multidisciplinary lectures were predominant during the meetings and the existing relationship between discrete organ systems was emphasized: for instance, it was explored how migraines and stroke or stroke and myocardial infarction, or complications of the nervous system and kidney disorders are interrelated.

Further, special attention was also given to disorders that are rather rare, such as amyloidosis, mitochondriopathies, fibromuscular dysplasia, Fabry or Pompe diseases. Together with colleagues from the European Reference Network, members of the Congress discussed ways for implementing best care for patients with rare diseases and how multidisciplinary cooperation is set to solve many emerging issues in this patient group. Finally, new findings concerning clinical genetics, metabolomics were presented as well as they may underlie the future of diagnostics in some of the selected disorders.

Throughout the conference, participants could explore an exhibition of 14 virtual posters by junior investigators, seven more presented their findings during the oral session. The short reports of current research by the young attendees immersed into fruitful discussions about potential directions of new science projects and the feasibility of their applications in practice.

The first-ever BHK Congress revealed that it is highly productive to bring experts from different various fields together. A close connection between specialists in neurology, cardiology and nephrology may ensure better care for many patients – both those with very frequent and those with orphan conditions. After noticing an active involvement of Lithuanian scientists and members of the global medical community, the organizers are hopeful that future BHK meetings might begin a tradition of bi-annual international and multidisciplinary discussions in the light of substantial advances in neurology, cardiology and nephrology.

More information about the Congress is available at: [www.bhk2020.com](http://www.bhk2020.com)



## **Clinical trials and biomedical studies at VUH Santaros Klinikos in 2020:**

Commercial drug and medical device trials:  
**209 trials, 45 new (started in 2020).**

Non-surgical biomedical studies:  
**175 on-going, 30 new (including pediatric trials)**

Surgical biomedical studies:  
**23 on-going, 10 new (including trials in pediatric surgery)**

PhD candidate	Defense date	Dissertation theme	Supervisor
Giedrė Stundžaitė Baršauskienė	2020 01 23	Multivariate analysis of interrelations between facial anthropometric parameters, self-esteem, psychosocial wellbeing and body image after reconstruction of nasal soft tissue defects and aesthetic surgery	Prof. Dr. Jolanta Dadonienė
Arminas Skrebūnas	2020 03 19	Analysis of factors for abdominal aortic aneurysm growth after endovascular repair	Prof. Dr. Germanas Marinskis
Donatas Danys	2020 05 29	Lithuanian clinical trial of treatment of hemorrhoids. Double-blind randomized controlled trial comparing laser hemorrhoidoplasty with sutured mucopexy and excisional hemorrhoidectomy	Prof. Dr. Tomas Poškus
Jaroslav Tumas	2020 05 29	Effects of pancreatic and periamullar tumors, immunomodulation and surgical treatments on metabolism, systemic inflammatory response and outcomes	Prof. Dr. Audrius Šileikis
Agnė Drąsutienė	2020 06 11	Minimally invasive off-pump mitral valve repair procedure with NeoChord device to treat degenerative mitral regurgitation: patient selection and echocardiographic data assessment	Prof. Dr. Audrius Aidietis
Arnas Bakavičius	2020 06 22	The value of clinical and molecular markers in preoperative diagnosis of prostate cancer	Prof. Dr. Feliksas Jankevičius
Arijanda Neverauskienė	2020 06 22	Image quality and radiation optimization in children's nonsyndromic craniosynostosis computer tomography	Prof. Dr. Algirdas Edvardas Tamošiūnas
Marius Kurminas	2020 10 29	Study of ischemic stroke treatment results using mechanical thrombectomy and of factors affecting them	Prof. Dr. Dalius Jatužis
Jurgita Kuzmickienė	2020 11 20	The significance of cognitive and demographic indicators in predicting the response of Alzheimer's disease to treatment	Prof. Dr. Gintaras Ferdinandas Kaubrys
Virginija Rudienė	2020 12 17	Pulmonary hypertension related to congenital heart defects: prevalence, prognosis and the evaluation of treatment methods	Prof. Dr. Vytautas Jonas Sirvydis (emeritus)