

## MEETING REPORT

# BRIDGING THE GAP BETWEEN RESEARCH AND CURE IN RARE GYNECOLOGICAL CANCERS: WHERE DO WE STAND? REPORT FROM THE GYNOCARE CONFERENCE IN NAPLES (17<sup>TH</sup>-18<sup>TH</sup> FEBRUARY 2023)

Jean Calleja-Agius \*

Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

\* Correspondence to: ✉ [jean.calleja-agijs@um.edu.mt](mailto:jean.calleja-agijs@um.edu.mt), <https://orcid.org/0000-0001-6369-0297>.

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The **European Network for Gynecological Rare Cancer Research: from Concept to Cure (GYNO-CARE COST Action CA18117)** organized a two-day hybrid conference entitled: *"Bridging the gap between Research and Cure in Rare Gynecological Cancers: where do we stand?"*. This conference was held in the historic Aula Botazzi at the Luigi Vanvitelli University of Campania in Naples, Italy.

The aim of this conference was to showcase new approaches to improve the diagnosis and treatment of rare gynecological cancers. There were 24 invited talks by high-profile international speakers organized over 3 sessions, followed by a final roundtable. The current state of the art, and even beyond the state of the art, in the field of basic and translational research in rare gynecological cancers have been presented. Ongoing and future innovative clinical trials for rare gynecological cancers have been also discussed with the aim of designing personalized cure. The basis of and advances in pathological diagnosis of rare gynecological cancers have been outlined. The ultimate aim was to bridge the gap between the pharmaceutical industry and biotechnology companies and translational research in rare gynecological cancers, to overcome challenges in this area. The conference focused on the complex interplay of factors that contribute to susceptibility, prevention, and

management of gynecological cancers, providing an excellent discussion forum on the key challenges and the latest advancements that mostly promise to propel this field forward.

Gynecological oncology has a paradoxical high prevalence of rare cancers, especially in ovarian tumors, characterized by small number of cases, long trial accrual times, few interested investigators, low funding/pharma priority, fewer patient advocates and lack of trial designs. **Gian Franco Zannoni**, from the Department of Pathology, Fondazione Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy explained how clear cell, low grade serous, mucinous, undifferentiated carcinoma, carcinosarcoma, small cell carcinoma hypercalcemic type and mesonephric-like adenocarcinoma can all be considered rare epithelial types of ovarian cancer, distinct for morphology and molecular background. Advances in understanding their heterogeneity should improve pathologic diagnostic criteria, molecular characterization, and hypothesis-generating clinical studies. Gynecological neuroendocrine neoplasms (NENs) are also rare (NET/NEC). Sex cord-stromal tumors represent a heterogeneous group, mostly indolent, with wide range in incidence age, often associated with endocrine manifestations. Peculiar genetic mutation has been revealed. A clinical-histo-molecular

approach: FATWO (no recurrent alterations) STK11 adnexal tumors (STK11), sex cord-stromal tumors (FOXL2, DICER1), is necessary for a better definition and highly diagnostic reproducibility. Germ cell tumors are another type of rare ovarian tumors, occurring in young age. Second opinion, multidisciplinary staff and biology research are fundamental in management of these rare ovarian cancers.

The role of antibody-drug conjugate (ADC)-based treatments in epithelial ovarian cancer was described by **Neil Conlon** from the National Institute for Cellular Biotechnology, Dublin City University, Ireland. His research team showed that a TROP2-directed ADC displayed potent *in vitro* activity against epithelial ovarian cancer cell lines and demonstrated synergy when combined with other approved DNA damaging drugs. Analysis of publicly available data showed that TROP2 gene expression was correlated with poorer progression-free and overall survival, especially in advanced disease and in those treated with carboplatin/paclitaxel or topotecan.

Therefore, these drug combinations warrant further investigation. In support of this, **Francesco Legge**, from the Obstetric and Gynecology Unit, F. Miulli General Regional Hospital, Bari, Italy, explained how personalized treatment algorithms, including debulking surgery, chemotherapy and maintenance therapy, for advanced ovarian cancer should take into account the specific molecular fingerprint of the disease as well as the individual risk of complications.

Endometrial cancer is overall common in postmenopausal women; however, a small proportion of women are diagnosed with endometrial cancer under the age of 40 years (5%). Immunohistochemical predictive markers of response to conservative treatment of endometrial hyperplasia and early endometrial cancer were outlined by **Antonio Raffone** from the University of Naples Federico II, Naples, Italy. In endometrial cancer, research carried out based on clinical-morphological and molecular-genetic studies revealed new pathogenetic mechanisms and predictors of the recurrence, such as the presence of the c.389G > A (p.R130Q) PTEN gene, promoter methylation MLH1, the proliferation marker Ki-67.

This led to the development of a mathematical model for predicting the evolution of the endometrial cancer in patients from different risk groups which was presented by **Irina Tripac** from the Department

of Gynecology, Institute of Oncology of Moldova. Standard surgical treatment of women with endometrial cancer precludes further fertility, therefore if fertility sparing treatment is desired, especially in the rarer cases of endometrial cancer in younger women, an attempt for medical treatment is done.

The state of the art and future perspectives in fertility sparing management in patients with endometrial cancer was presented by **Valeria Masciullo**, Department of Gynecology, Fondazione Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy.

This was followed by further insights into translational science in fertility sparing procedures for endometrial cancer by **Monika Sobocan** from the Division for Gynecology and Perinatology, University Medical Center Maribor, Maribor, Slovenia. Candidates for fertility sparing treatment are selected based on histological and clinical criteria. The integration of molecular classifiers into risk assessment has led to new venues of clinical assessment also in fertility sparing treatment. Molecular classifiers, which classify endometrial cancer into subgroups of POLE mutated, mismatch repair deficient (MMRd), p53 abnormal (p53 abn) and of no specific mutational profile (NSMP) can be used to additionally provide therapy individualization. In fertility sparing treatment therefore first data show, that women with MMRd endometrial cancer have shown worse response to fertility sparing treatment. However, studies focusing on fertility sparing treatment and molecular classifiers are lacking. Initial data also point towards lower complete response rates at 6 months and overall complete response in MMRd tumors than NSMP tumors. Yet most young women still classify into the NSMP subgroup of endometrial cancer requesting additional characterization and more robust data. Studies suggest also the need for integration of additional refinement and analysis of carcinoma in women with endometrial cancer using markers such as PI3K/Akt/mTOR markers and other interconnected signaling pathways.

In addition, while medical assisted reproductive therapies may pose risk of gynecological cancer, such treatment also needs to be accessible for patients who experienced gynecological cancer. This was stressed by **Vera Dimitrievska** from the University of American College, North Macedonia and **Gligor Tofoski** from the Gynecology and Obstetrics Department at Ss. Cyril and Methodius University in Skopje, North Macedonia.

As early detection is crucial for successful treatment outcomes, there is a need for effective screening methods. However, currently, there is no mass screening available for endometrial cancer in asymptomatic individuals. In a study carried out by **Jacopo Troisi** from the Scuola Medica Salernitana, University of Salerno, Italy, the diagnostic accuracy of an ensemble machine learning algorithm that uses serum metabolomics signatures for screening of endometrial cancer was evaluated. The results showed that the proposed metabolomics signature was not affected by the stage and grading of endometrial cancer or the presence of other comorbidities. However, it was influenced by different endometrial cancer histotypes, providing additional substratification. These findings suggest that metabolomics could be a promising and novel screening tool for endometrial cancer.

Multi-omics, which is the integration of various omics technologies, including genomics, transcriptomics, proteomics, and metabolomics provides a more comprehensive understanding of the molecular mechanisms underlying diseases, including rare gynecological cancers. In the context of studying rare gynecological cancers, multi-omics can help identify key molecular pathways and potential biomarkers associated with the development and progression of these cancers. By analyzing multiple omics data sets, researchers can gain a more comprehensive view of the genomic, epigenomic, transcriptomic, proteomic, and metabolic alterations associated with rare gynecological cancers and gain insight into the functional consequences of these molecular alterations. As outlined by **Yashwanth Subbannayya**, from the School of Biosciences and Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK; and **Sureyya Ozcan Kabasaka** from the Department of Chemistry, Middle East Technical University, Ankara, Turkey, integrated approaches such as proteogenomics can help identify variants such as mutant peptides, fusion proteins, and alternative splicing events and provide evidence for the translation of pseudogenes, long non-coding RNAs, and micropeptides. These, in turn, can serve as biomarkers for diagnosis, prognosis, or aid as potential therapeutic targets. Overall, multi-omics approaches can provide a more comprehensive understanding of the molecular mechanisms underlying rare gynecological cancers, which can help identify potential therapeutic targets and biomarkers for early detection and personalized treatment.

In cervical cancer, Human Papillomavirus (HPV) 16 and 18 genotypes cause 70% of cases. A new method was described by **Anna De Filippis** from the Department of Experimental Medicine, L. Vanvitelli University of Campania, Naples, Italy, long DNA regions modified with biotinylated oligos, called "Long Regions of DNA Pull-down" (LDP) were generated. Approximately 4350 proteins have been identified by the mass spectrometric analysis, of which 310 interact with a single oligo. Gene Ontology studies were conducted to analyze the biological processes, molecular functions, and cellular components in which these proteins are involved. Most of them play a role in DNA replication, transcription, and translation. Some interactors were already known and implicated in HPV-associated diseases, while others had never been described. These data may pave the way for further studies to find new potential and effective therapies to combat HPV16 infection, progression, and pathogenicity. Cervical screening is a way of preventing cancer by detecting high risk HPV can cause cervical cells to become abnormal.

**Cristina Clare Gallego de Largy** from Marqués Valdecilla University Hospital, Santander, Spain described how a cervical cancer screening project began in March 2022, using digital colposcopy with guidance from Spain to Uganda. The incidence of cervical cancer in Uganda is one of the highest in the whole world, with a relative risk of 4.4 in this country.

**Aljoša Mandić** from the Oncology Institute of Vojvodina, University of Novi Sad, Serbia gave an overview on the rare neuroendocrine cervical cancer, which accounts for 1.4% of all invasive cervical cancers. Even in this rare cervical tumor, HPV has an important role. Despite a small number of studies that had examined mutational hotspots in these neoplasms and attempted to characterize them from a molecular/somatic mutation standpoint the most frequently altered genes were PIK3CA (19.6% of cohort), MYC (15.5%), TP53 (15.5%), and PTEN (14.4%). The most common primary treatment was radical surgery combined with chemotherapy. There was no standard chemotherapy regimen but platinum and etoposide was the most commonly used treatment. Radiotherapy-based treatment schemes were also commonly utilized in the upfront setting for early-stage disease. Multimodal therapy for all stages of neuroendocrine tumors of the cervix is recommended, and the majority of patients receive a combination of surgery, radiation, and chemotherapy.

For early stage disease (tumors  $\leq 4$  cm) and negative nodes on imaging, radical hysterectomy and pelvic lymphadenectomy followed by chemotherapy with platinum and etoposide is the primary management recommended with consideration for additional radiotherapy. Large studies in patients with uncommon or rare tumors are difficult with limited prospective data with which to guide decisions.

■ To date, the best chemotherapy regimen in cervical cancer has a response rate of 48% with an overall survival of 17 months, and limited options for second-line chemotherapy. Immunotherapy can induce a strong immune response in cervical cancer due to retained viral antigens. Although the response rates to programmed cell death 1 (PD-1) inhibition alone have been modest, the landmark survival reported in the recently published trials suggests that immunotherapy will represent a paradigm shift in the treatment of advanced and recurrent cervical cancer.

■ **Domenica Lorusso** from the Department for Obstetrics and Gynecology, Catholic University of Sacred Heart of Rome, Italy demonstrated how, in the Empower Cervical 1 trial, the anti PD1 inhibitor *cemiplimab* provides better outcome in comparison to single agent chemotherapy in second and third line setting of advanced disease. The KEYNOTE-158 trial has led to the approval of pembrolizumab in recurrent programmed cell death ligand 1 (PD-L1) positive cervical cancer based on a significant increase in overall and progression free survival when combined to platinum-based chemotherapy plus or minus bevacizumab. Combinations of programmed cell death 1 and anticytotoxic T-lymphocyte-associated protein 4 inhibitors (CTLA4) inhibitors have shown promising and durable activity. There is active research with new combinations of checkpoint inhibitors, as well as combinations of these drugs with chemotherapy and radiation, and other novel approaches. Responses to immunotherapy can be dramatic and durable. Continued work to find the optimal combination and setting for immunotherapy is ongoing and all these aspects were discussed during the COST conference.

■ Vulvar cancer is a rare disease that requires multimodal treatments including surgery, radiotherapy, and chemotherapy. The disease often relapses, and treatment options are limited, especially for elderly women with comorbidities. **Anna Myriam Perrone** from the Division of Gynecologic Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna,

University of Bologna, Italy explained how electrochemotherapy with bleomycin has proven to be a valid alternative, and our studies have demonstrated an efficacy of around 80% in local control. These results were validated in a large scale with a multicenter study called Elechtra, which confirmed the findings of the first studies with low toxicity and minimal side effects. The quality of life of these patients was evaluated and those who responded to the therapy experienced a significant reduction in pain, particularly for smaller lesions located in the posterior vulva. A new study is currently ongoing, using bleomycin associated with platinum-based chemotherapy.

■ The holistic care of patients with rare gynaec cancer was highlighted by **Francesco Pegreff**, from the Department for Life Quality Studies, University of Bologna, Italy in his lecture on the Impact of Sarcopenia and Exercise Training on Skeletal Muscles in Patients with Rare Cancer. In cancer patients, low muscle mass and function due to sarcopenia has been identified as negative prognostic factor predisposing to falls and fractures. Furthermore, muscle wasting, and weakness caused by cancer-related inflammation, significantly affect quality of life in everyday living activities. Because the pathophysiology is not yet fully understood, therapeutic options remain limited and physical activity remains a viable modality to enhance muscle function in older sarcopenic adults. Lifestyle interventions, especially exercise and nutritional supplementation, prevail as mainstays of treatment, concerning rarer forms of gynecological tumors. However, not enough studies have currently been conducted to estimate the prevalence of sarcopenia and how it can affect clinical and functional outcomes in everyday clinical practice and life. COST is an excellent starting point for future research studies and interdisciplinary collaborations.

■ Identification of early stage disease markers and a fast detection of markers accompanying disease development play a crucial role in modern personalized medicine. Novel biotechnology, such as antibody-modified nanomembrane as specific ultrasensitive detectors for clinical application was presented by **Evzen Amler** from the Department of Biophysics, Charles University, Prague, Czech Republic. Preparation of nanofiber-based detectors functionalized on nanofiber surface with relevant antibodies, aptamers or other bioactive substances are the key steps towards highly sensitive and specific bionanosensors and also towards smart targeted and controlled drug delivery

systems. Nanofibers are unique due to their extremely large ratio between the surface and volume. Thus, the probability of the disease marker interaction with the nanofiber is also very large. Consequently, the application of the smart gynecological tampon based on nanofibers functionalized on the surface with a specific antibody against the disease marker could lead to the specific interaction of the specifically modified nanofiber surface with the disease markers even at their very low concentration and, thus, to identification and possible even treatment of the disease at its early stage.

Smart clinical trials, especially those intended to design cures for rare gynecological cancers, are crucial in order to allow advances to be made. The European Union enacted a new Clinical Trials Regulation in 2014, replacing the previous Clinical Trials Directive of 2001, in a bid to create a level playing field across EU member states, whilst simplifying the application process for researchers and providing more visibility and more transparency to the general public on clinical trials. As explained by **Neville Calleja** from the Department of Public Health, University of Malta, Malta, the European Medicines Agency has introduced the Clinical Trials Information System (CTIS), an IT infrastructure through which all clinical trial applications are to be processed, by applicants and regulatory authorities, and which also includes a public interface for the general public to be informed of what research is happening, together with documentation pertaining to such clinical trials.

Characteristics of clinical trials investigating pharmacological treatments for rare gynecological cancers were described by **Klejda Harasani** from the Department of Pharmacy, Faculty of Medicine, University of Medicine Tirana, Albania. There was only little variation in the design of completed clinical trials, where most were open-label (no masking) with single group assignment and allocation was not applicable as they were single-arm trials. Only one completed clinical trial had a calculated Jadad score higher than 2 (Jadad score = 3) which indicates higher quality. Results were unpublished in 65 % of the completed clinical trials and 45 % of them had neither publications, nor had posted any results. These findings highlight the need for higher-quality clinical trials and better reporting of data from the current ones.

As discussed by **Riccardo Audisio**, from the University of Göteborg, Sweden, although modern clinical decision-making rests on evidence-based med-

icine, where Randomized Controlled Trials (RCTs) and meta-analyses are considered unequivocal, such undisputable truth is often equivocal. Young and fit patients are more frequently enrolled, while older and frail ones are excluded as well as those on polypharmacy, deprived and dependent ones. Individuals with poor literacy are preferred to unlearned patients. Negative trials are frequently unpublished, therefore meta-analytic investigations present biased results as they rest on skewed data. Moreover, RCTs are extremely expensive.

Now that real-time, good quality data can safely be harvested, the scientific community should look forward to relying more consistently on Cancer Registry data. There are numerous examples of their effectiveness and their clinical impact. Consecutive and real-life information provides extremely reliable and sound results. It is very important to collect robust data to steer clinical research. As explained by **Gemma Gatta**, former director of the Evaluative Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, different objectives characterize clinical and population-based studies. For instance, in survival studies, clinical study evaluates the effectiveness of treatment and indicates the highest achievable survival in selected patient groups. By contrast population-based study evaluates the effectiveness of the health care systems and estimates the average survival actually achieved in the general population. Clinical studies require an ad hoc design and data collection while in population-based studies, data are currently collected by disease (cancer) registries (PBCR). The definition of the disease needs to follow international classification, the variables collected are few and of high quality to permit the comparison between populations. In high income countries PBCR collect more clinical variables, which follow strict rules given by the IARC. PBCR with their data on incidence are able to provide estimation on number of new diagnoses per year or incidence rates by country then make available those for rare gynecological tumors. Also, PBCR indicates time trends then to know if there is an increment/reduction of diagnosis or if incidence remains stable. The correct pathological diagnosis, which for rare cancers needs sometimes of a second opinion, have to be acquired and correctly codified by registry. To provide survival by type of tumour, PBCR have to access to reliable and complete sources to know the life status of cases included in the registry. For the majority of rare gynecological tumors, this contribution will show in-

cidence and survival differences by type of tumors, country, time period, hospital.

While RCTs are the gold standard in novel therapy development, in rare diseases the low patient numbers as well as the cost involved in interventional clinical trials represent a significant barrier. As such, a more efficient research approach through real world evidence (RWE) and pragmatic (combining interventional and real-world arms) studies would leverage the abundant historical patient data in patient journals and databases and bypass the need for large numbers of real-time patients and high financial burden. **Stephanie Darmanin** and **Ylva Kaiser**, working for private pharma companies in Sweden, gave their perspective from the industry experience. Identifying relevant key opinion leaders, establishing relationships at a local, national, and global level and engaging in international collaborations around RWE to create bigger data collections is critical. When approaching pharmaceutical company medical affairs teams and patient organizations for industry-sponsored research grants and joint projects, researchers should have a clear, clinically relevant idea, with a connection to patient data/samples, a correlation to parameters of disease/clinical phenotypes, and outcomes that can eventually be applied in the clinic, or at least be of clear relevance to clinicians and patients. The opportunity presented by investigator-sponsored studies (ISS), where the investigator is the instigator of the study proposal as well as the principal owner of the data, but resources are provided by a partner within the pharmaceutical industry, should be further explored. A collaborative approach involving clinicians is preferable in order to gain company interest and create a platform for future investment in the disease area. Innovative protocols for personalized one-patient clinical trials, designed around the individual patient's genomic, proteomic and histological profile are an appealing option, which will however require consideration of regulatory and ethical implications.

Gynecological cancer is a leading cause of morbidity and mortality worldwide. Considering the huge diversities in etiological factors, the complexity of cancer progression and the accessibility of treatments only well organized and massive translational and clinical research can improve global outcomes. **Mariela Vasileva-Slaveva** from the Bulgarian Breast and other gynecological Cancers Association, Sofia, Bulgaria; and Medical University Pleven, Pleven, Bulgaria presented data supporting the fact that access

to education and training as well as access to appropriate networking are key limiting factors in developing clinical research by healthcare professionals.

In conclusion, rare gynecological tumors are not so rare, characterized by various clinical presentations and different natural histories. Further collaborative efforts will implement new trials design, and care pathway organization at all levels, in order to better molecular classification, improve prognosis and define possible new molecular targets. The GYNOCARE Conference in Naples has been an outstanding experience, with over 140 participants. It has favoured several new collaborations with experienced and committed colleagues working in several disciplines in a lot of countries within and outside Europe. Despite the intense schedule of inspiring talks, the conference provided many opportunities for discussions and interactions with leading scientists from around the globe in a very pleasant atmosphere. The next GYNOCARE conference will be held in Sofia, Bulgaria in July 2023.

## COMPLIANCE WITH ETHICAL STANDARDS

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Dr. Jean Calleja-Agius is the only Author of this article.

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#### Plagiarism

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#### Data falsification and fabrication

N/A.

## APPENDIX - MEETING PROCEEDINGS

## Bridging the gap between research and cure in rare gynecological cancers: where do we stand? Report from the GYNOCARE Conference in Naples (17<sup>th</sup>-18<sup>th</sup> February 2023)

### LOCAL ORGANIZERS:

- Antonio **Giordano**  
University of Siena and Temple University
- Maurizio **Guida**  
Federico II University of Naples
- Francesca **Pentimalli**  
LUM University Giuseppe Degennaro
- Renato **Franco**  
Luigi Vanvitelli University of Campania

### SCIENTIFIC COMMITTEE:

- Jean **Calleja-Agius**  
(CA18117 Chair) University of Malta
- Riccardo **Di Fiore**  
University of Malta
- Michelino **De Laurentiis**  
National Cancer Institute of Naples IRCCS Pascale
- Michele **Caraglia**  
Luigi Vanvitelli University of Campania

All the data correspond to the real. The **European network for Gynecological Rare Cancer Research: from Concept to Cure (GYNOCARE COST Action CA18117)** organized a two-day hybrid conference entitled: 'Bridging the gap between Research and Cure in Rare Gynecological Cancers: Where do we stand?'. This conference was held in the historic Aula Botazzi at the Luigi Vanvitelli University of Campania in Naples, Italy.

The aim of this conference was to showcase new approaches to improve the diagnosis and treatment of rare gynecological cancers (RGCs). The current state of the art, and even beyond the state of the art, in the field of basic and translational re-

search in RGCs, have been presented. Ongoing and future innovative clinical trials for RGCs have been also discussed with the aim of designing personalized cure. The basis of and advances in pathological diagnosis of RGCs have been outlined. The aim was to bridge the gap between industry and biotechnology companies and translational research in RGCs, to overcome challenges in this area. The conference focused on the complex interplay of factors that contribute to RGC susceptibility, prevention, and management, providing an excellent discussion forum on the key challenges and the latest advancements that mostly promise to propel this field forward, hosting high-profile speakers.

## SESSION 1.

### BASIC AND TRANSLATIONAL RESEARCH: PRESENT AND FUTURE

#### Presentation 1.1. Investigation of antibody-drug conjugate-based treatments in epithelial ovarian cancer

- Neil **Conlon**  
National Institute for Cellular Biotechnology,  
Dublin City University, Dublin, Ireland  
(neil.conlon@dcu.ie)

Antibody drug conjugates (ADCs) allow for the targeted delivery of cytotoxic agents to increase anti-cancer efficacy and minimize toxicities. ADCs are biotherapeutics composed of an antibody specific to an extracellular antigen, a linker molecule that

conjugates the toxic payload that is then trafficked into the target cell. Mirvetuximab soravtansine, a folate receptor alpha-targeting ADC, gained FDA approval for folate receptor alpha-positive advanced epithelial ovarian cancer in 2022. In addition, several other ADCs are in clinical testing for the treatment of ovarian cancer. This work focused on the potential of ADCs with DNA-damaging payloads. We showed that a TROP2-directed ADC displayed potent *in vitro* activity against epithelial ovarian cancer cell lines and demonstrated synergy when combined with other approved DNA damaging drugs. Analysis of publicly available data showed that TROP2 gene expression was correlated with poorer progression-free and overall survival, especially in advanced disease and in those treated with carboplatin/paclitaxel or topotecan. We believe that these drug combinations warrant further investigation.

### Presentation 1.2. Proteomics: A road map towards a clinical test

- Sureyya Ozcan **Kabasaka**  
Department of Chemistry, Middle East Technical University (METU), Ankara, Turkey  
(sozcan@metu.edu.tr)

Proteomics is comprehensive research of proteins that facilitates development of novel biomarkers for diagnostic applications and exploration of prospective therapeutic targets. Changes in protein profile reflect biological changes. Thus, protein-based biomarkers can be used for both diagnostic and prognostic purposes. A roadmap towards a protein-based biomarker clinical test starts with well-designed clinical study. Candidate markers obtained from the study should then be analyzed in an independent clinical set to verify the finding and subsequently validated. A robust, reliable, and accurate clinical test requires comprehensive workflows that need are further evaluated by regulatory bodies.

### Presentation 1.3. Integrated omics analysis to identify biological mechanisms of gynecological cancers

- Yashwanth **Subbannayya**  
School of Biosciences and Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK  
(y.subbannayya@surrey.ac.uk)

Multi-omics refers to the integration of various omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, to provide a more comprehensive understanding of the molecular mechanisms underlying diseases, including rare gynecological cancers. In the context of studying rare gynecological cancers, multi-omics can help identify key molecular pathways and potential biomarkers associated with the development and progression of these cancers. By analyzing multiple omics data sets, researchers can gain a more comprehensive view of the genomic, epigenomic, transcriptomic, proteomic, and metabolic alterations associated with rare gynecological cancers and gain insight into the functional consequences of these molecular alterations. Integrated approaches such as proteogenomics can help identify variants such as mutant peptides, fusion proteins, and alternative splicing events and provide evidence for the translation of pseudogenes, long non-coding RNAs, and micropeptides. These, in turn,

can serve as biomarkers for diagnosis, prognosis, or aid as potential therapeutic targets. Overall, multi-omics approaches can provide a more comprehensive understanding of the molecular mechanisms underlying rare gynecological cancers, which can help identify potential therapeutic targets and biomarkers for early detection and personalized treatment.

### Presentation 1.4. Personalized clinical management of ovarian cancer

- Francesco **Legge**  
Mother and Child Department, Obstetric and Gynecology Unit, F. Miulli General Regional Hospital, Acquaviva delle Fonti, Bari, Italy  
(f.legge@miulli.it)

Ovarian cancer (OC) represents the most challenging gynecological cancer, with approximately 70% of patients presenting advanced stage of disease and among those with peritoneal disease about 70% relapsing within 3 years from the end of first line therapy. The survival benefit of maximal primary cytoreductive surgery must be balanced with the risk of serious complications delaying chemotherapy initiation. OC is a heterogeneous disease with specific molecular alterations characterizing clear cell (*e.g.*, PTEN, PIK3CA, ARID1A), mucinous (*e.g.*, KRAS), low grade serous (*e.g.*, BRAF, KRAS, ER, PR) and high grade serous (*e.g.*, p53, wt-1, BRCA1/2) histotypes influencing sensitivity to specific drugs as well as the surgical management. In particular, half of high-grade serous OC exhibit a high degree of genomic instability due to deficiencies in homologous recombination including somatic and germline BRCA mutation, which are associated to sensitivity to platinum-based chemotherapy and PARP-inhibitors. Personalized treatment algorithms, including debulking surgery, chemotherapy, and maintenance therapy, for advanced OC should consider the specific molecular fingerprint of the disease as well as the individual risk of complications.

### Presentation 1.5. Personalized clinical management of endometrial cancer using molecular approach

- Irina **Tripac**  
Department of Gynecology, Institute of Oncology of Moldova, Moldova (i\_jacovlev@yahoo.com)

Endometrial cancer (EC) is the sixth most common cancer in females. Roughly, 382,000 new cases are



diagnosed each year and EC accounts for 90,000 deaths worldwide. The estimated five-year survival rate in developed countries is about 80% with primary treatment. The median age at uterine cancer diagnosis is 62 years. The estimated number of new endometrial carcinoma cases in Europe in 2021 was 134,578 with 41,638 deaths, and the incidence has been rising with aging and increased obesity of the population. The adequacy of risk stratification systems in EC have recently been compared and challenged. There are 5 major risk stratification systems in EC, of which the modified European Society of Medical Oncologists (ESMO) classification was demonstrated to best discriminate for recurrence and nodal metastases in early-stage disease. Considering the high number of possible markers, only a few have been included in internationally recommended guidelines for risk stratification. However, none of the existing schemes was deemed highly accurate. In addition, all current systems stratify women based on pathologic data obtained after surgical staging (stage is a component of risk assignment). There is great need to obtain earlier and more biologically informative data from EC tumors that could assist in planning the optimal course of treatment for the individual.

The results of the complex study performed on a group of 269 patients with EC in stages I-II revealed clinical-morphological predictors of the recurrences: rare uterine cancers such as clear cell carcinoma, mucinous carcinoma, serous carcinoma; invasion of more than 50% in the myometrium; the depth of tumor invasion in the myometrium >1 cm and in the stroma >0.5 cm; the presence of lymphovascular invasion and the presence of necrosis in the tumor. The level of the Ki-67 expression estimated in the immunohistochemical examination in 50 patients with EC in stages I-II, was imposed by its predictive value on survival, so that with its increase, the survival rate decreases. In patients with a Ki-67 level close to a proliferative activity of 0-33%, the survival rate was 80.8 ± 3.3%, and with a proliferative activity greater than 34%, the survival rate decreased to 57.9 during the 3-year follow-up period.

DNA testing in 50 patients with EC in stages I-II detected mutations in the MLH1 gene in 10 (20%) cases and is to be used to determine the risk of disease recurrence. The analysis of the obtained results showed that in EC patients the presence of the MLH1 epimutation significantly affects overall survival regardless of the risk group stratification. The mean time to EC progression in patients with the MLH1 epimutation was 14.6 months.

The mutation c.389G > A (p.R130Q) of the PTEN gene was detected in 12 (24%) patients. The 3-year follow-up of patients (n = 12) carrying the mutation in PTEN gene, regardless of the risk group, revealed a poor prognosis of the disease, which was occurred either by the recurrence of endometrial adenocarcinoma (n = 8), or by the appearance of metastases (n = 4). Research based on clinical-morphological and molecular-genetic studies revealed new pathogenetic mechanisms and predictors of EC recurrence, such as the presence of the c.389G > A (p.R130Q) PTEN gene, promoter methylation MLH1, the proliferation marker Ki-67, which allowed the development of a mathematical model for predicting the evolution of the disease in EC patients from different risk groups over a 3-year period.

### **Presentation 1.6. Fertility sparing in endometrial cancer: state of the art and future perspectives**

→ **Valeria Masciullo**  
Unit of Hysteroscopic Surgery, Fondazione Policlinico A. Gemelli, Rome, Italy  
(valeriamasciullo@yahoo.com)

Endometrial cancer is the most common gynecologic malignancy in developed countries and approximately 10% of the women with endometrial cancer (EC) are below the age of 45. Management of endometrial cancer in young women who desire to maintain fertility presents a unique set of challenges since the standard surgical treatment based on hysterectomy and salpingo-oophorectomy is often not compatible with the patient's goals. A fertility sparing approach can be considered in selected patients with early stage and low-grade endometrial cancer or atypical hyperplasia (EAH). Oral therapy with megestrol acetate is recommended based on extensive experience, although without consensus on dosages and treatment length. However, Levonorgestrel intrauterine device appears an alternative treatment, particularly in patients who are not planning to conceive soon or do not tolerate oral therapy. The pooled complete response rate, recurrence rate, and pregnancy rate of EC were 76.3%, 30.7% and 52.1%, respectively. In a randomized controlled trial, megestrol acetate plus metformin guaranteed an earlier complete response rate than megestrol acetate alone for endometrial hyperplasia, however some other studies failed to show the same efficiency. Hysteroscopic lesion resection increases efficiency of megestrol acetate and prognostic outcome in patients with EAH and EC who wish to preserve their fertility.

Treatment of grade 2 cancers seems feasible however it should only be allowed as part of clinical trials. Molecular characterization of EC could probably model a tailored treatment in the future. However, fertility preservation is not the standard approach for staging and treatment, potentially worsening oncologic outcomes and hysterectomy should always be performed once the conceiving plan is completed.

### **Presentation 1.7. Translational science in fertility sparing procedures for endometrial cancer**

- **Monika Sobocan**  
Division for Gynecology and Perinatology, University Medical Center Maribor, Maribor, Slovenia; Faculty of Medicine, University of Maribor, Maribor, Slovenia (Monika.sobocan@ukc-mb.si; monika.sobocan3@um.si)

Endometrial cancer (EC) is a common gynecological cancer with peak incidence at the age of 60 years. Although most women with endometrial cancer are postmenopausal a small proportion of women are diagnosed with EC under the age of 40 years (5%). Standard surgical treatment of women with EC precludes further fertility, therefore if fertility sparing treatment is desired an attempt for medical treatment is done. Candidates for fertility sparing treatment are selected based on histological and clinical criteria. The integration of molecular classifiers into risk assessment has enabled us new venues of clinical assessment also in fertility sparing treatment. Molecular classifiers, which classify EC into subgroups of POLE mutated, mismatch repair deficient (MMRd), p53 abnormal (p53 abn) and of no specific mutational profile (NSMP) can be used to additionally provide therapy individualization. In fertility sparing treatment therefore first data show, that women with MMRd endometrial cancer have shown worse response to fertility sparing treatment. However, studies focusing on fertility sparing treatment and molecular classifiers are lacking. Initial data also point towards lower complete response rates at 6 months and overall complete response in MMRd tumors than NSMP tumors. Yet most young women still classify into the NSMP subgroup of EC requesting additional characterization and more robust data. Studies suggest also the need for integration of additional refinement and analysis of carcinoma in women with endometrial cancer using markers such as PI3K/Akt/mTOR markers and other interconnected signaling pathways.

### **Presentation 1.8. Gynecological cancer risk associated with ART-technologies - prevention and management strategies**

- Presented by Gligor **Tofoski**  
Department of Gynecology and Obstetrics, Ss. Cyril and Methodius University in Skopje, North Macedonia (gligor.tofoski@gmail.com)

There is concern that assisted reproductive technology (ART) may increase gynecological cancer risk, such as ovarian cancer. However, to date most studies are inconclusive, due to multiple confounding factors. Such factors include infertility itself and older age. Observational studies overall found that women treated with fertility medications may have no greater risk of ovarian cancer than untreated infertile women. While steps have been taken to minimize bias, the conclusions are limited because they are based on observational data and do not account for confounding factors such as treatment regimen, parity and specific infertility diagnosis. Many prospective and retrospective studies were carried out on this topic, but no relevant randomized clinical trials. Fertility-sparing treatments with safe oncological outcomes are feasible in endometrial, cervical, and ovarian cancer cases. After fertility-preserving treatment for gynecological cancers, ART can enable pregnancy to be achieved with apparent oncological safety. The success of such procedures should directly impact clinical practice and management of those patients who require fertility-sparing treatment.

### **Presentation 1.9. Medical Assisted Reproduction (MAR) for patients who experienced gynecological cancer - how accessible is it?**

- Presented by Vera **Dimitrievska**  
University of American College, North Macedonia (vdimitrievska@gmail.com)

In 2015, the World Health Organization (WHO) estimated that cancer is a main cause of death worldwide and a significant cause of morbidity, loss to productivity, and rising cost of healthcare. According to the Centers for Disease Control and Prevention (CDC), in 2016, 14 million new cases of cancer were diagnosed worldwide with 8.2 million deaths attributed to cancer.

Gynecological cancers have a prevalence of 15%-20% of the total neoplasms involving women.

About 20% of gynecological cancer affects women under 40 years of age, who often have not completed parity or are before their first pregnancy. Infertility is a global health issue affecting around 48 million couples and 186 million individuals worldwide. There are significant social inequalities in the prevalence, diagnosis, and treatment of infertility, as well as health risks for women, men and their offspring associated with these treatments.

As part of the European B<sup>2</sup>-InF project, with the main aim to explore young adults' knowledge, perceptions and concerns about infertility and Assisted Reproduction Technology (ART), and to contrast it with the information provided by ART providers in 8 countries (Albania, Belgium, Spain, Italy, Kosovo, Northern Macedonia, Slovenia, Switzerland), we examined 33 medical centers (3 to 5 centers per country). The transcripts of the clinics' information collected were analyzed following qualitative approaches from a socio-cultural and gender perspective. The objective is to describe and analyze, from a

gender perspective, the social representations that these different centers make visible on their websites, through the texts and images posted.

Regarding the information provided by clinics, the explored websites present a large amount of information with an excess of technical and scientific terms without plain language interpretations, thus hindering its understanding by the general population. In addition, information about risk and success rates is not always available or it is presented in an unspecific or unclear way. Furthermore, information about infertility treatment services, and the marketing resources used to present this information, are primarily directed towards white and heterosexual couples, and skewed towards women, which may contribute to the unequal social burden of female infertility.

To better inform European citizens about infertility and MAR treatments, clinics must align the information they provide with the concerns and expectations of the public, by all means meeting the legal standards for truthful advertising.

## SESSION 2.

### CLINICAL TRIALS: DESIGNING CURES 2.0

#### Presentation 2.1. The Clinical Trials Regulation in a Nutshell

→ **Neville Calleja**  
Department of Public Health, University of Malta, Malta (neville.calleja@um.edu.mt)

The European Union enacted a new Clinical Trials Regulation in 2014, replacing the previous Clinical Trials Directive of 2001, in a bid to create a level playing field across EU member states, whilst simplifying the application process for researchers and providing more visibility and more transparency to the general public on clinical trials. Indeed, following the publication of this regulation, applicants need only to apply to one competent authority in one of the involved member states, as opposed to two competent authorities (scientific and ethical) in each member state where the clinical trial is expected to occur. In addition, the European Medicines Agency has introduced the Clinical Trials Information System (CTIS), an IT infrastructure through which all clinical trial applications are to be processed, by applicants and regulatory authorities, and which also includes a

public interface for the general public to be informed of what research is happening, together with documentation pertaining to such clinical trials.

#### Presentation 2.2. New treatments for advanced metastatic cervical cancer

→ **Domenica Lorusso**  
Department for Obstetrics and Gynecology, Università Cattolica del Sacro Cuore, Rome, Italy (domenica.lorusso@policlinicogemelli.it)

Novel therapies are needed for the treatment of recurrent cervical cancer. The best chemotherapy regimen to date has a response rate of 48% with an overall survival of 17 months, with limited options for second-line chemotherapy. Immunotherapy can induce a strong immune response in cervical cancer due to retained viral antigens and is reviewed in this article. Although the response rates to programmed cell death 1 (PD-1) inhibition alone have been modest, the landmark survival reported in the recently published trials suggests that immunotherapy will represent a paradigm shift in the treatment of advanced and recurrent cervical cancer. The Empower Cervical 1 trial has demonstrated that anti PD1 inhibitor Ceimprimab provide increased outcome in comparison to single agent chemotherapy in sec-

ond and third line setting of advanced disease. The KEYNOTE-158 trial has led to the approval of pembrolizumab in recurrent programmed cell death ligand 1 (PD-L1) positive cervical cancer based on a significant increase in overall and progression free survival when combined to platinum-based chemotherapy plus or minus bevacizumab. Combinations of programmed cell death 1 and anticytotoxic T-lymphocyte-associated protein 4 inhibitors (CTLA4) inhibitors have shown promising and durable activity. There is active research with new combinations of checkpoint inhibitors, as well as combinations of these drugs with chemotherapy and radiation, and other novel approaches. Responses to immunotherapy can be dramatic and durable. Continued work to find the optimal combination and setting for immunotherapy is ongoing and all these aspects were discussed during the COST meeting that represents an excellent network for future research collaborations.

### Presentation 2.3. Neuroendocrine cervical cancer: do we made step forward in treatment?

→ **Aljoša Mandić**  
Oncology Institute of Vojvodina, University of Novi Sad, Novi Sad, Serbia  
(aljosa\_mandic@yahoo.com)

Neuroendocrine cervical cancer first was described by Albores-Saavedra in 1972, these tumors account for 1.4% of all invasive cervical cancers. The term neuroendocrine refers to the fact that the tumor cells originate from the embryonic neuroectoderm and display an immunohistochemical profile consistent with endocrine glandular cells. The small-cell neuroendocrine tumor is the most common (80%), than large-cell neuroendocrine carcinoma (12%), and other histologic types such as undifferentiated neuroendocrine tumors (8%). NECC are aggressive tumors with a high tendency for nodal involvement and distant metastases. Independent prognostic factors are age, lymph node metastases, smoking, pure small-cell histology, tumor size. Overall, the 5-year survival rate is 36% and the median overall survival ranges between 22 and 25 months and 2–15% for patients with Stage III-IV disease. In 2017–18, the WHO and International Agency for Research on Cancer (IARC) convened introduce new terminology incorporated into the 5th edition of WHO classification of tumor. Low-grade cervical NETs are very rare and encompass Grade 1 (typical carcinoid) and Grade 2 (atypical carcinoid). Using the 5th edition WHO terminology, the poorly dif-

ferentiated (high grade) include small and large cell variants. The difference in grading of cervical NETs is based on mitotic index and Ki-67. Even in this rare cervical tumor HPV has an important role. In Castle P et al meta-analysis in SCNC, 85% were HPV positive, 78% were HPV16 and/or HPV18 positive, 51% were singly HPV18 positive, and 10% were singly HPV16 positive. In a subset of 5 SCNC studies (75 cases), 93% were positive for p16INK4a by immunohistochemistry and 100% were HPV positive. For LCNC, 88% were HPV positive, 86% were positive for HPV16 or HPV18, 30% were singly HPV18 positive and 29% were singly HPV16 positive. Despite a small number of studies that had examined mutational hotspots in these neoplasms and attempted to characterize them from a molecular/somatic mutation standpoint the most frequently altered genes were PIK3CA (19.6% of cohort), MYC (15.5%), TP53 (15.5%), and PTEN (14.4%). Also comparing with another neuroendocrine tumors, it was identified PI3-kinase or MAPK pathway activating mutations in 67% of NECC. When compared to NECC, lung and bladder small cell carcinomas exhibited a statistically significant higher rate of coding mutations ( $P < .001$  for lung;  $P = .001$  for bladder). Mutation of TP53 was uncommon in NECC (13%) and was more frequent in both lung (103 of 110 tumors [94%],  $P < .001$ ) and bladder (18 of 19 tumors [95%],  $P < .001$ ) small cell carcinoma. These comparative genomics data suggest that NECC may be genetically more similar to common cervical cancer subtypes than to extra-cervical small cell neuroendocrine carcinomas of the lung and bladder. Comparing HGNECC with small cell lung cancer (SCLC), significant differences in TMB, microsatellite instability, HPV-positive status, and in PIK3CA, MYC, PTEN, TP53, ARID1A, and RB1 alteration rates were found. These results may have implications for the selection of cytotoxic and targeted therapy regimens for this rare disease. The most common primary treatment was radical surgery combined with chemotherapy. There was no standard chemotherapy regimen, but platinum and etoposide were the most commonly used treatment. Radiotherapy-based treatment schemes were also commonly utilized in the upfront setting for early-stage disease. Both the SGO and the Gynecologic Cancer Intergroup (GCIg) recommend multimodal therapy for all stages of neuroendocrine tumors of the cervix, and the majority of patients receive some combination of surgery, radiation, and chemotherapy. For early-stage disease (tumors  $\leq 4$  cm) and negative nodes on imaging, radical hysterectomy and pelvic lymphadenectomy followed by chemotherapy with platinum and

etoposide is the primary management recommended with consideration for additional radiotherapy. Frumovitz and colleagues presented the results from a retrospective NeCTuR registry study of topotecan, paclitaxel, and bevacizumab (TPB) in patients with neuroendocrine cervical cancer. This analysis included 62 women who had received TPB and 56 who had non-TPB-based treatments, with the caveat that some patients had received those drugs individually. Results showed that the median PFS with TPB was 8.7 months vs. 3.7 months without TPB (HR: 0.27), and at 1 year, 26% of patients remained on TPB regimens vs. 9% with non-TPB regimens. However, no significant OS difference was seen between the TPB vs. non-TPB groups (median OS: ~15 months; HR: 0.87). Nevertheless, the authors concluded that TPB should be considered an option for recurrent, high-grade neuroendocrine cervical cancer. In multiple resistance immune checkpoint inhibitors and targeted therapies may be beneficial however, the literature is limited. In Caroll M et al study the checkpoint inhibitors, was with no responders. high-grade neuroendocrine cervical tumors are almost always PD-L1-negative and microsatellite-stable so checkpoint inhibitors should be used with caution. Large studies in patients with uncommon or rare tumors are difficult with limited prospective data with which to guide decisions. For women with small- and large-cell neuroendocrine cervical carcinoma there currently exists a rich network on social media sites, making recruitment to protocols much more feasible. In 2013, The University of Texas MD Anderson Cancer established a Neuroendocrine Cervical Tumor Registry (NeCTuR) where data are prospectively entered.

#### **Presentation 2.4. Cancer registries and clinical practice**

→ **Riccardo A. Audisio**  
University of Göteborg, Göteborg, Sweden  
(raudisio@doctors.org.uk)

Modern clinical decision-making rests on evidence-based medicine, where Randomized Controlled Trials (RCTs) and meta-analyses are considered unequivocal. Such undisputable truth is often equivocal: young and fit patients are more frequently enrolled, while older and frail ones are excluded as well as those on polypharmacy, deprived and dependent ones. Individuals with poor literacy are preferred to unlearned patients. Negative trials are frequently unpublished, therefore meta-analytic investigations

present biased results as they rest on skewed data. More on, RCTs are extremely expensive, with phase III RCTs costing several tenth of millions of euros. At a time when real-time, good quality data can safely be harvested, the scientific community should look forward to relying more consistently on Cancer Registry data. There are numerous examples of their effectiveness and their clinical impact. Consecutive and real-life information provides extremely reliable and sound results.

#### **Presentation 2.5. The importance of robust data collection to steer clinical research**

→ **Gemma Gatta**  
Evaluative Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy  
(gemma.gatta@istitutotumori.mi.it)

Different objectives characterize clinical and population-based studies. For instance, in survival studies, clinical study evaluates the effectiveness of treatment and indicates the highest achievable survival in selected patient groups. By contrast population-based study evaluates the effectiveness of the health care systems and estimates the average survival actually achieved in the general population. Clinical studies require an ad hoc design and data collection while in population-based studies, data are currently collected by disease (cancer) registries (PBCR). The definition of the disease needs to follow international classification, the variables collected are few and of high quality to permit the comparison between populations. In high income countries PBCR collect more clinical variables. However, the additional variables follow strict rules given by the IARC. PBCR with their data on incidence are able to provide estimation on number of new diagnoses per year or incidence rates by country then make available those for rare gynecological tumors. Also, PBCR indicates time trends then to know if there is an increment/reduction of diagnosis or if incidence remains stable. The correct pathological diagnosis, which for rare cancers needs sometimes of a second opinion, have to be acquired and correctly codified by registry. To provide survival by type of tumor, PBCR have to access to reliable and complete sources to know the life status of cases included in the registry. For the majority of rare gynecological tumors, this contribution will show incidence and survival differences by type of tumors, country, time period, hospital.

## Presentation 2.6. Electrochemotherapy in vulvar cancer

- **Anna Myriam Perrone**  
Division of Gynecologic Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, University of Bologna, Italy (myriam.perrone@unibo.it)

Vulvar cancer is a rare disease that requires multimodal treatments including surgery, radiotherapy, and chemotherapy. Unfortunately, the disease often relapses, and treatment options are limited, especially for elderly women with comorbidities. Therefore, we aimed to find a low-impact and effective therapy for these patients. Electrochemotherapy with bleomycin has proven to be a valid alternative, and our studies have demonstrated an efficacy of around 80% in local control. The first study was conducted in 2012, evaluating only eight cases. Subsequent studies in 2014 with 25 cases confirmed the initial findings and showed that the therapy could be repeated, resulting in further response. In 2019, we validated these results on a large scale with a multicenter study called Elechtra, which confirmed the findings of the first studies with low toxicity and minimal side effects. In 2021, we evaluated the quality of life of these patients and found that those who responded to the therapy experienced a significant reduction in pain, particularly for smaller lesions located in the posterior vulva. In Bologna, we are conducting a new study that uses Bleomycin associated with platinum-based chemotherapy. After ten years, the European Society of Gynecological Oncology guidelines have recognized electrochemotherapy as an alternative in palliative treatments of vulvar tumors.

## Presentation 2.7. The Impact of Sarcopenia and Exercise Training on Skeletal Muscles in patients with rare cancer

- **Francesco Pegreffi**  
Department for Life Quality Studies, University of Bologna, Bologna, Italy (f.pegreffi@unibo.it)

Sarcopenia is frequently encountered in the elderly, and more frequently in subjects with cancer. In these patients, low muscle mass and function due to sarcopenia has been identified as negative prognostic factor predisposing to falls and fractures. Furthermore, muscle wasting, and weakness caused by cancer-related inflammation, significantly affect quality of life in everyday living activities. Because

the pathophysiology is not yet fully understood, therapeutic options remain limited and physical activity remains a viable modality to enhance muscle function in older sarcopenic adults. Despite lifestyle interventions, especially exercise and nutritional supplementation, prevail as mainstays of treatment, concerning rarer forms of gynecological tumors, not enough studies have currently been conducted to estimate the prevalence of sarcopenia and how it can affect clinical and functional outcomes in everyday clinical practice and life. COST is an excellent starting point for future research studies and interdisciplinary collaborations.

## Presentation 2.8. The rehabilitation of women with incontinence

- **Francesca Gimigliano**  
Department of Mental and Physical Health and Preventive Medicine, Luigi Vanvitelli University of Campania, Naples, Italy (francesca.gimigliano@unicampania.it)

Rehabilitation has been defined by the WHO as a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment. Urinary incontinence affects 25% to 45% of women worldwide. The most common forms are: 1. Mixed urinary incontinence that is the involuntary loss of urine associated with both stress and urgency; 2. Stress urinary incontinence that is the involuntary loss of urine through physical exertion or effort, coughing or sneezing; and 3. Urgency urinary incontinence that is the involuntary loss of urine associated with a sudden and compelling desire (urgency) to urinate that is difficult to delay. The person with urinary incontinence should undergo a multidisciplinary treatment including rehabilitation. There are several treatments that might be proposed, including: pelvic floor muscle training with or without biofeedback, electrical stimulation, magnetic stimulation, vaginal cones, bladder training, prompted voiding, anti-incontinence devices, lifestyle interventions such as weight reduction, and complementary alternative techniques such as acupuncture. Evidence on the effectiveness of the management of urinary incontinence are still scarce in quality and quantity. Larger, well conducted trials, using CONSORT guidelines for data reporting, and addressing important clinical outcomes should be performed.

## SESSION 3.

### THE DIFFICULT DIAGNOSIS: FROM CLASSIC METHOD TO DIGITAL PATHOLOGY

#### Presentation 3.1: Rare ovarian tumors: a pathological point of view

- Gian Franco **Zannoni**  
 Department of Pathology, Fondazione Policlinico Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy (Gianfranco.Zannoni@unicatt.it)

Gynecological oncology has a paradoxical high prevalence of rare cancers, especially in ovarian tumors, characterized by small cases number, long trial accrual times, few interested investigators, low funding/Pharma priority, fewer patient advocates and lack of trial designs. Clear Cell, Low Grade Serous, Mucinous, Undifferentiated carcinoma, Carcinosarcoma, Small cell carcinoma hypercalcemic type and Mesonephric-like adenocarcinoma can be considered rare epithelial entities, distinct for morphology and molecular background. Advances in understanding their heterogeneity should improve pathologic diagnostic criteria, molecular characterization, and hypothesis-generating clinical studies. Gynecological Neuroendocrine neoplasms (NENs) are rare (NET/NEC) and more frequent in mixed forms (NECs more frequent than NETs).

Sex cord-stromal tumors represent a heterogeneous group, mostly indolent, with wide range in incidence age, often associated with endocrine manifestations. Peculiar genetic mutation has been revealed. Sex cord like architectural features can be frequently observed in other NO SEX-CORD tumors. A clinical-histo-molecular approach: FATWO (no recurrent alterations) STK11 adnexal tumors (STK11), Sex cord-stromal tumors (FOXL2, DICER1) is necessary for a better definition and highly diagnostic reproducibility.

Germ cell tumors are rare ovarian tumors, occurring in young age. Since introduction of modern chemotherapy, cure rate is 95%. Second opinion, multidisciplinary staff and biology research are fundamental. Questions open for the medical treatment.

Finally, rare gynecological tumors are not so rare, characterized by various clinical presentations and different natural histories. Further collaborative efforts will implement new trials design, and

care pathway organization at all levels, in order to better molecular classification, improve prognosis and define possible new molecular targets.

#### Presentation 3.2. From colposcopy to digital colposcopy with guidance from Spain to Uganda

- Cristina Clare **Gallego de Lary**  
 Marqués Valdecilla University Hospital, Santander, Spain  
 (crisitnaclare.gdl@hotmail.com)

Cervical screening is a way of preventing cancer. It tests for a virus called high risk human papillomavirus (HPV). High risk HPV can cause cervical cells to become abnormal. This virus is present in 90% of young women since the first sexual intercourse. However, the immune system is able to wash away the virus in the majority of cases under 25 years, this is why the screening begins at this age approximately in first world countries. For some unknown reason, the incidence of cervical cancer in Uganda is one of the highest in the whole world, with a relative risk of 4,4 in this Country. In 2020 the World Health Organization (WHO) said the incidence of cervical cancer is 97,5% with a mortality for this cause of 66%. The cervical cancer screening project began in March 2022 and will go on every six months by the Association Idivaka. It consists of giving out information and engaging with the community. For this, regular meetings with women in the area are held in order to say who Idivaka is and what the aim is of the project in order to get their approval. Once the patients are at the hospital, the screening begins with more information about cervical cancer and the importance of prevention. They then fill in and sign the consents and HIV and HPV tests are performed. If HPV tests positive, they then are performed a diagnostic colposcope as a triage test according to (WHO) guidelines. The colposcope is a stereoscopic low-power microscope used to detect an abnormality, to determine the extent of the lesion and the severity of the lesion, and to guide biopsy from the most appropriate area. Excisional treatment of cervical precancerous lesions is performed under colposcopic visualization.

A way to improve the guidance from Spain to Uganda and to continue doing training from the distance is the digital colposcopy. It is an Internet-enabled portable colposcope designed to simplify the workflow during and after a colposcopy

procedure. User-friendly configuration for easy adoption by novice and experienced clinicians. Video of the procedure in real time with an Iwaka cervical expert is possible and so the colposcopy can be remotely monitored in real time, directing the clinician to the point of care throughout the entire consultation. Moreover, pictures to store in the patient's clinical record to revise in future consults. This way, apart from having regular training campaigns in Uganda, online guidance can improve their practices around the rest of the year with full support from the team.

### **Presentation 3.3. Development and validation of a serum metabolomic signature for endometrial cancer screening in postmenopausal women**

- **Jacopo Troisi**  
Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Baronissi, Salerno, Italy; Theoreo Srl, Montecorvino Pugliano, Salerno, Italy; Department of Chemistry and Biology, A. Zambelli University of Salerno, Fisciano, Salerno, Italy (troisi@theoreosrl.com)

Endometrial cancer (EC) is a type of cancer that develops in the glandular lining of the uterus and is the most prevalent gynecological cancer globally. It accounts for about 50% of all female urogenital tumors and is the sixth most commonly diagnosed cancer in women. As early detection is crucial for successful treatment outcomes, there is a need for effective screening methods. However, currently, there is no mass screening available for asymptomatic individuals. We conducted a study to evaluate the diagnostic accuracy of an ensemble machine learning algorithm that uses serum metabolomics signatures for EC screening. The algorithm was trained using metabolomics profiles from 88 EC patients and 80 controls and validated on 1430 women with unknown EC status. The study revealed that the algorithm accurately identified 16 out of 18 true-positives, with only two false-positives and no false-negatives. We further validated the model on a cohort of 871 subjects undergoing hysterectomy, of which 126 were diagnosed with EC. The results showed that the proposed metabolomics signature was not affected by the stage and grading of EC or the presence of other comorbidities. However, it was influenced

by different EC histotypes, providing additional EC-linked substratification. These findings suggest that metabolomics could be a promising and novel screening tool for EC.

### **Presentation 3.4. Antibody-modified nanomembrane as specific ultrasensitive detectors for clinical application**

- **Evzen Amler**  
Department of Biophysics, Charles University, Prague, Czech Republic  
(evzen.amler@lfmotol.cuni.cz)

Identification of early-stage disease markers and a fast detection of markers accompanying disease development play a crucial role in modern personalized medicine. Preparation of nanofiber-based detectors functionalized on nanofiber surface with relevant antibodies, aptamers or other bioactive substances belong among the key steps towards highly sensitive and specific bionanosensors and also towards smart targeted and controlled drug delivery systems. Nanofibers are unique due to their extremely large ratio between the surface and volume. Thus, the probability of the disease marker interaction with the nanofiber is also very large. Consequently, the application of the smart gynecological tampon based on nanofibers functionalized on the surface with a specific antibody against the disease marker could lead to the specific interaction of the specifically modified nanofiber surface with the disease markers even at their very low concentration and, thus, to identification of the disease at its early stage. Such a layer could, in addition, serve also as the active part of the bionanosensors in microchips or, alternatively, can be applied for nanotheranostic application.

### **Presentation 3.5. Immunohistochemical predictive markers of response to conservative treatment of endometrial hyperplasia and early endometrial cancer**

- **Antonio Raffone**  
Department of Neuroscience, Reproductive Sciences and Dentistry, Gynecology and Obstetric Unit, School of Medicine, Federico II University of Naples, Naples, Italy  
(anton.raffone@gmail.com)

Progestogens are widely used for the conservative treatment of endometrial hyperplasia and early



endometrial cancer. However, they do not always achieve the regression in all cases. Although several immunohistochemical markers have been assessed to predict the response to treatment, their usefulness is still unclear. We carried out a systematic review to analyze the usefulness of each immunohistochemical marker studied in predicting the response to progestogens in endometrial hyperplasia and early endometrial cancer. After reviewing 27 studies with a total of 1360 women; 43 immunohistochemical markers were identified and assessed. The most studied predictive markers in the pretreatment phase were progesterone and estrogen receptors. Progesterone receptor B appeared more promising. Further studies are needed to confirm the usefulness of mismatch repair proteins, Dusp6, GRP78 and PTEN combined with other molecules such as phospho-AKT or phospho-mTOR. In the follow-up phase, Nrf2 and survivin showed the stronger evidence; a role may also be played by Bcl2 and Ki67. Further studies are necessary for Fas, NCoR, AKR1C1, HE4, PAX2 and SPAG9. In conclusion, several immunohistochemical markers might be helpful in predicting the response to conservative treatment of endometrial hyperplasia and early endometrial cancer on pretreatment and follow-up specimens. Further studies are needed to confirm their usefulness and possibly integrate them in a predictive immunohistochemical panel.

### **Presentation 3.6. Identification of the first map describing the human and the HPV-16 viral genome interaction**

→ **Anna De Filippis**  
 Department of Experimental Medicine, Luigi Vanvitelli University of Campania, Naples, Italy  
 (anna.defilippis@unicampania.it)

Human Papillomavirus (HPV) infects actively proliferating cells such as epithelial cells, and its replication cycle is associated with host cell differentiation. Therefore, it can cause asymptomatic infections or clinical manifestations, ranging from slight to severe diseases. HPV16 and 18 genotypes

cause 70% of cervical cancers worldwide. The aim of this work is the identification of human proteins that interact with the HPV16 genome in infected cells, to search for new potential therapies through an innovative approach. A new method was developed to generate long DNA regions modified with biotinylated oligos, called "Long Regions of DNA Pull-down" (LDP). Hybrid oligos were designed using Primer3 software and the whole genome of the HPV16 sequence. Primers contain a specific part for each sequence and the other part corresponding to unique sequences do not present in the human and viral genome. The pHPV-16 *Escherichia coli* plasmid (ATCC® 45113™) was amplified, extracted, and used as a template for the first amplification step by pull-down PCR. The 500 bp amplifications were used as templates in the second round to obtain fragments with biotinylated 5' ends. SiHa cells, containing integrated copies of HPV16, were grown, and nuclear extraction was performed. Subsequently, DNA pull-down was carried. The biotinylated dsDNA fragment interacted with the streptavidin beads; then, the SiHa nuclear extract was added to this complex and incubated to promote interaction. In this way, it was possible to isolate specific interacting proteins that was processed by mass spectrometry. Approximately 4350 proteins have been identified by the mass spectrometric analysis, of which 310 interact with a single oligo. Gene Ontology (GO) studies were conducted to analyze the biological processes, molecular functions, and cellular components in which these proteins are involved. Most of them play a role in DNA replication, transcription, and translation. Some interactors were already known and implicated in HPV-associated diseases, while others had never been described. For example, chromodomain-helicase-DNA binding protein 4 (CHD4) is a component of the NuRD complex that participates in chromatin remodeling by deacetylating histones. These data may pave the way for further studies to find new potential and effective therapies to combat HPV16 infection, progression, and pathogenicity.

## SESSION 4:

### ROUND TABLE. PHARMA-BIOTECH: CHALLENGES IN THE 21ST CENTURY

#### PANEL MEMBERS:

- Francesco **Cosentino**
- Danica **Cujic**
- Massimiliano **Galdiero**
- Carlo **Ronsini**
- Vanda **Salutari**
- Sergio **Sandrucci**
- Klejda **Harasani**

#### Presentation 4.1. Characteristics of clinical trials investigating pharmacological treatments for rare gynecological cancers

- Klejda **Harasani**  
Department of Pharmacy, Faculty of Medicine,  
University of Medicine, Tirana, Albania  
(klejda.harasani@umed.edu.al)

Members from Working Group 5 “*Coordination of interactions between clinical trials, translational research, and basic research*” have focused on developing a clinical trial reference depository and systematically reviewing clinical trials for rare gynecological malignancies. Master protocols are classified into basket trials, umbrella trials, and platform trials.

The PRISMA 2020 guidelines for systematic reviews and meta-analysis were followed and two different databases were searched. The WHO’s International Clinical Trials Registry Platform (ICTRP) and the clinicaltrials.gov databases were consulted, as well as the articles published in PubMed/MEDLINE reporting on results of the included clinical trials on rare gynecological cancers. A total of 212 records, covering trials recorded during the period 1993-2022, were included in the final review.

The number of clinical trials investigating therapies for rare gynecological cancers (RGC) has steadily increased over the years, reaching 79 clinical trials initiated in the period from 2017 to 2022. Moreover, the most evident finding is the increment in trials involving targeted therapies. Indeed, 35 new clinical trials on targeted therapies started in the last five years compared to just 26 from 2000 to 2016. Furthermore, during the last five years (2017-2022) there has been

an increase in clinical trials investigating a combination of therapies (targeted therapies plus chemotherapy) and a decrease in clinical trials focused on chemotherapeutic agents only. Our review revealed that overall, the majority of clinical trials included predominantly chemotherapy (41.98%), followed by targeted therapy (30.19%) and a combination of therapies (23.11%). A paradigm shifts in oncology drug expenditure from chemotherapy and hormonal therapy to targeted approaches has occurred over the past 25 years.

More than half of the trials were phase II trials (110; 51.89%), followed by phase I (53; 25.00%), and phase III (32; 15.09%). The status of recruiting was mainly completed (80; 37.74%), recruiting (59; 27.83%), and active, not recruiting (25; 11.79%). There were 26 (12.26%) terminated or withdrawn clinical trials due to various reasons such as low accrual (reported in 8 clinical trials), lack of approval by the ethics committee, sponsor decision to withdraw funding, principal investigator departure from institution or due to toxicity. Funding was public in 101 clinical trials (47.64%), private in 66 (31.13 %), private, non-profit in 40 (18.87%). Most of the trials were international and multi-center.

Basket trial: combination immunotherapy with the anti-programmed cell death protein 1 (anti-PD-1) antibody nivolumab and the anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibody ipilimumab has demonstrated significant clinical efficacy across a range of common malignancies, justifying evaluation of this combination in rare gynecological cancers.

There was only little variation in the design of completed clinical trials, where most were open-label (no masking) with single group assignment and allocation was not applicable as they were single-arm trials. Only one completed clinical trial had a calculated Jadad score higher than 2 (Jadad score = 3) which indicates higher quality. This phase III clinical trial of carboplatin and paclitaxel with or without bevacizumab in women with stage III or IV epithelial ovarian, primary peritoneal or Fallopian tube cancer was randomized, double blind and included a description of withdrawals and dropouts. Results were unpublished in 65% of the completed clinical trials and 45% of them had neither publications, nor had posted any results. These findings highlight the need for higher-quality clinical trials and better reporting of data from the current ones.

### Presentation 4.2. MCCR alumni club survey on tackling hurdles in front of young clinical investigators in oncology

- Mariela **Vasileva-Slaveva**  
 Bulgarian Breast and other Gynecological Cancer Associations, Sofia, Bulgaria; Shterev Hospital, Sofia, Bulgaria; Medical University of Pleven, Pleven, Bulgaria  
 (sscvasileva@gmail.com)

Cancer is a leading cause of morbidity and mortality worldwide. Considering the huge diversities in etiological factors, the complexity of cancer progression and the accessibility of treatments only well organized and massive translational and clinical research can improve global outcomes. Methods in clinical cancer research Alumni Club (MAC) created a survey to identify the main challenges in front of young clinical investigators in oncology.

An anonymized survey was spread in social media between April and November 2022. Target population were health-care professionals involved in any aspect of oncology – physicians, nurses, and researchers. We divided participants to young - below the age of 40, and more experienced –  $\geq 40$  years; and according to country of practice to Europeans and non- Europeans. Results: we received 121 responses from 36 different countries. 89 participants were from European countries and 32 were from non-European. 87 (72% of the participants) were below 40 years. Older, more experienced professionals and Europeans are more likely to be involved in clinical trials in every aspect. The main source of funding – independently of geographic location – were Pharma grants. Investigators out of Europe have less participation in international grants. Over 50% of participants dedicate time for clinical research from their personal time and are not paid for it. Almost 50% of investigators don't have access to an experienced mentor in conducting clinical trials in their institution.

In conclusion, despite the limited number of participants, our data support the fact that access to education and training as well as access to appropriate networking are key limiting factors in developing clinical research by healthcare professionals.

### Presentation 4.3. Pharma-Biotech collaboration in biomarker discovery

- Danica **Ćujić**  
 Institute for the Application of Nuclear Energy INEP, University of Belgrade, Serbia  
 (danicac@inep.co.rs)

Laboratory testing is quite economical compared to other medical procedures: up to 60% of medical decisions is based on laboratory results, which account for 5 to 10% of medical expenses. There are several interested parties, who might benefit from reliable clinical biomarker: 1) patient who expect as little invasive and unpleasant medical tests as possible, 2) clinicians who need reliable disease indicator, 3) scientists who are focused on focused on discovering disease mechanisms and identifying a sensitive and specific disease markers, 4) government that aims to reduce the costs of diagnostics and treatment and 5) industry that is seeking for new and innovative diagnostic products.

Biomarker discovery is complex, long-lasting, and expensive process. There is substantial difference between biomarker research in science laboratory and their clinical use in medical labs or even next to the patient's bed. Biomarker discovery usually requires expensive equipment, procedures that might be not always easy to perform or are based on custom made protocol, but not always appropriate for large scale testing and high throughput analysis. On the other hand, biomarker is suitable for clinical use if it is: reproducible, easy to perform, with affordable price, provides result in a short time, method is convenient for automatization.

Clinicians are an indispensable party in the biomarker discovery pipeline. While during initial processes of disease mechanism revealing and biomarker identification, tight collaboration between doctors and scientist is essential, later during validation, doctors are included in clinical studies, mainly supported by industry.

The research excellence is based not just on researchers' idea, but also greatly depends on available funding. Nowadays, the collaboration between SROs and industry, particularly life science, clinical diagnostics, and IT industry, is very important. Scientific institutions usually do not have potential to launch their invention on the market but could collaborate with industry in different ways: outsourcing R&D sectors from industry to SRO, submitting joint project application (e.g., Horizon Europe 2021-2027), technology

transfer from science to industry through licensing or spin-off companies. This collaboration is not always smooth and there are few obstacles that could hinder this cooperation: researchers' fear of leaving basic research, administrative procedures reject industry to collaborate, regulation of IP rights and profit share. In the last few years, significant efforts are made to improve the research infrastructure in Serbia. The Serbia Accelerating Innovation and Growth Entrepreneurship Project (SAIGE Project), supported by the World Bank, aims to improve excellence of scientific research and to promote innovative and entrepreneurial thinking among researchers. The establishment of BIO4 campus tends to unite institutes and faculties involved in biomedicine, biotechnology, bioinformatics, and biodiversity and stimulate exchange of knowledge and expertise. Beside the most up-to-date research infrastructure equipment organized, through several thematic facilities that will push forward basic research, the idea of the campus is also to stimulate innovative research and bring together research and industry knowledge and capacities.

#### Presentation 4.4: Perspective from industry experience

- Stephanie **Darmanin**, independent contributor  
Global lead Site Activation and Contracts - Clinical Operations, IQVIA Sweden
- Ylva **Kaiser**, independent contributor  
Medical Advisor and Medical Affairs, Sanofi, Sweden

*Disclaimer: this content was prepared by Stephanie Darmanin and Ylva Kaiser in their personal capacity, with a genuine interest to support the efforts being made to improve research outcomes and cure of rare gynecological cancers. The views, information and opinions expressed are solely those of the authors and do not reflect the view of their employers or anyone else.*

While randomized controlled trials are the gold standard in novel therapy development, in rare diseases the low patient numbers as well as the cost involved in interventional clinical trials represent a significant barrier. As such, a more efficient research approach through real world evidence (RWE) and pragmatic (combining interventional and real-world arms) studies would leverage the abundant historical patient data in patient journals and databases and bypass the need for large numbers of real-time patients and high financial burden.

Identifying relevant key opinion leaders, establishing relationships at a local, national, and global level and engaging in international collaborations around RWE to create bigger data collections is critical. When approaching pharmaceutical company medical affairs teams and patient organizations for industry-sponsored research grants and joint projects, researchers should have a clear, clinically relevant idea - with a connection to patient data/samples, a correlation to parameters of disease/clinical phenotypes, and outcomes that can eventually be applied in the clinic, or at least be of clear relevance to clinicians and patients. The opportunity presented by investigator-sponsored studies (ISS), where the investigator is the instigator of the study proposal as well as the principal owner of the data, but resources are provided by a partner within the pharmaceutical industry, should be further explored. A collaborative approach involving clinicians is preferable in order to gain company interest and create a platform for future investment in the disease area.

Innovative protocols for personalized one-patient clinical trials, designed around the individual patient's genomic, proteomic, and histological profile are an appealing option, which will however require consideration of regulatory and ethical implications.

## AWARD CEREMONY

- Prof. Jean Calleja-Agius **GYNO CARE COST Action Chair**, has been presented with the **Giovan Giacomo Giordano NIAF Lifetime Achievement Award for Ethics and Professionalism in Medical Research** ([https://www.ilmattino.it/napoli/cronaca/premio\\_giordano\\_riconoscimento\\_a\\_due\\_ricercatori\\_della\\_federico\\_ii-7246479.html](https://www.ilmattino.it/napoli/cronaca/premio_giordano_riconoscimento_a_due_ricercatori_della_federico_ii-7246479.html)).

This award was established in 2010 in honor of the late Prof. Giovan Giacomo Giordano, renowned pathologist and former chair of the Department of Pathology, National Cancer Institute of Naples and Professor at the Federico II University of Naples, who dedicated more than sixty years of his life to the study of cancer and the role of environmental factors in the onset of this disease. Prof. Giovan Giacomo Giordano was also a major advocate against corruption in the Italian medical community and the driving force for the establishment of medical ethical standards among his colleagues. The award was presented to Prof. Jean Calleja-Agius by Prof Antonio Giordano, son of the late Prof. Giovan Giacomo Giordano, and who himself is a Professor of Molecular Biology at Temple University in Philadelphia and a 'Chiara Fama' Professor in the Department of Pathology and Oncology at the University of Siena, in Siena, Italy. Prof. Antonio Giordano is also the Director of the Sbarro Institute for Cancer Research and Molecular Medicine and the Center for Biotechnology

at Temple's College of Science & Technology in Philadelphia, USA. This was the first time that this award was ever awarded to a non-Italian or Italian-American professional. The other two recipients of the award this year are: Prof. Orlando Paciello and Prof. Roberto Ciarcia from the Faculty of Veterinary Medicine at the Federico II University of Naples, Naples, Italy.

Prof. Orlando Paciello, Professor of Veterinary Pathological Anatomy of the Federico II University of Naples has a PhD in "Environmental Pathology". He has been involved in the study of animal pathologies tumors related to environmental pollution and the possible role of animals as sentinels of the state of health of the environment from the point of view of One Health.

Professor Ciarcia is an Associate Professor in Veterinary Pharmacology and Toxicology, also at the Federico II University of Naples. From 2016 to 2021, he was the coordinator responsible for the international agreement between the Sbarro Health Research Organization (S.H.R.O.) of Philadelphia and the Federico II University of Naples. This award recognizes the merit of having studied the role of various bioactive substances for the treatment of oncological and chronic degenerative diseases, as well as the study of the potential role of natural compounds included in animal diets in mitigating the toxicity of food contaminants, such as mycotoxins, which represent a danger and a threat to human health and to various animal species. The studies of environmental contaminants, conducted by Professor Ciarcia, have become part of the so-called "One Health" approach, including food safety, the control of zoonoses and the fight against antibiotic resistance.



## CONCLUSIONS

The GYNOCARE Conference in Naples has been an outstanding experience. It has favored several new collaborations with experienced and committed colleagues working in several disciplines in a lot of countries within and outside Europe. Despite the

intense schedule of inspiring talks, the meetings provided many opportunities for discussions and interactions with leading scientists from around the globe in a very pleasant atmosphere. The next GYNOCARE conference will be held in Sofia, Bulgaria in July 2023. More information can be found on the GYNOCARE website: [www.gynocare.net](http://www.gynocare.net).

