

VIRTUAL MOBILITY (VM)

GRANT REPORT

This report is submitted by the VM grantee to VNS Manager, who will coordinate the approval on behalf of the Action MC.

Action number: CA18117

VM grant title: Compilation of a comprehensive integrated classification for rare gynae cancers

VM grant start and end date: 01/10/2021 to 21/10/2021

Grantee name: Dr Miriam AZZOPARDI

<u>Description of the outcomes and achieved outputs (including any specific Action objective and deliverables, or publications resulting from the Virtual Mobility).</u>

OBJECTIVES OF THE PROJECT: In order to standardize and improve the quality of care of all rare gynae cancer and ensure an optimised access to clinical innovation, it is important to start with a unified classification for rare gynae cancers. Currently there are several classification systems of female genital tract tumours and rare gynae cancers. These include the WHO classification of tumours Editorial Board. Female Genital Tumours. Lyon (France) IARC 2020 (WHO classification of tumours series, 5th ed.; Volume 4), ICD-O-3 and RARECARENET classifications and ORPHANET classification for Rare Diseases. Through this VM grant, the main objective is to draw up a unified integrated classification of rare gynae cancers as a reference standard for future work related to this field. This work is fundamental for paving the way forward for the GYNOCARE COST Action. By having a unified classification of rare gynaecological cancers will lead to a harmonised approach when setting up cancer registries both on a local and a national level, and also when biobanking. This in turn will lead to better sharing of samples, especially when designing clinical trials.

DELIVERABLES: As shown in the Annex 1 and Annex 2, a harmonised classification has been created for malignant tumours of the female genital tract, and tumours of the female genital tract showing borderline behaviour.

<u>Description of the benefits to the COST Action Strategy (what and how).</u>

As pointed out in the GYNOCARE COST Concept paper published in January 2021 (*GYNOCARE Update: Modern Strategies to Improve Diagnosis and Treatment of Rare Gynecologic Tumors—Current Challenges and Future Directions. Di Fiore . et al, 2021; doi:10.3390/cancers13030493*), any strategy to improve on the available knowledge of rare gynaecological malignancies requires a clear classification of the cancers themselves and a definition of which of these cancers are considered rare. The term ‘rare tumour’ refers mostly to non-epithelial subtypes. However, histologically different epithelial sub-types of ovarian, endometrial and cervical cancers are also to be categorized as rare tumours (with

an annual incidence of six or fewer per 100,000) due to their different pathological behaviours. In total, rare gynaecologic tumours (RGT) represent more than 50% of the total number of gynaecologic tumours, with approximately 80,000 new cases per year in Europe. These involve more than 30 different histologic diagnoses, with a very limited number of patients in each diagnostic category.

Description of the virtual collaboration (including constructive reflection on activities undertaken, identified successful practices and lessons learned).

In the first week of the Virtual Mobility, a literature search was carried out about the female genital tract tumours classifications in use, together with a simultaneous literature search about the incidence rates of the female genital tract tumours and related databases. The latter was done to be able to use the incidence rates in order to determine whether a tumour is rare or not. Such databases include the EURO CARE 5 database and the RARE CARE NET database and the data from the CONCORD 3 study. An initial exercise was to finalise an exhaustive list as possible of all female genital tract tumours. The list was then subdivided into malignant tumours, tumours with borderline behaviour and finally benign tumours (Annex 1, 2 and 3 respectively). This was done as both benign and borderline behaviour tumours are important tumours that need to be considered in the differential diagnosis of rare gynae cancers. Finally, work is in progress on the malignant tumour list where the list is being mapped to the various classifications and coding systems in use, adding also other details such as the incidence rates of these gynae tumours.

Meetings organized: A number of meetings were organized in relation to the subject matter including an initial meeting that identified the need for the project, a subsequent meeting to discuss the available data sources and the experts to be consulted, followed by separate Zoom meetings held individually with Prof Simon Herrington from Cancer Research UK, Edinburgh Centre, who is an editor of the IARC publication the WHO Classification of Cancers of the Female Genital Tract (<https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Female-Genital-Tumours-2020>) and another meeting held with Prof Gemma Gatta from the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano and Work Package Leader of RARECARENET (<http://89.96.76.37/rarecarenet/index.php/wp1-5>). Further Zoom meetings were held on a weekly basis (every Tuesday afternoon) during the period of the virtual mobility to discuss progress with other members of the GYNOCARE COST Action, specifically Dr Bridget Ellul and Prof Charles Savona Ventura from Malta and Dr Sharon O'Toole and Dr James Beirne from Trinity College Ireland.

Further actions: The gynae cancer list (malignant only) has been mapped against the ICD-O-3 coding system and other coding systems including the newly proposed ICD-11 and other coding systems such as the ORPHACODE system for rare diseases. The estimates of the incidence rates of these gynae cancers will also be provided in order to create a harmonized list that can be mapped to most of the classifications in use by Cancer Registries and Rare Disease registries.

ANNEX 1: MALIGNANT TUMOURS OF THE FEMALE GENITAL TRACT

MALIGNANT TUMOURS OF THE FEMALE GENITAL TRACT
MALIGNANT TUMOURS OF OVARY
Serous tumours
8460/3 Low-grade serous carcinoma
8461/3 High-grade serous carcinoma
Mucinous tumours
8480/3 Mucinous adenocarcinoma
Endometrioid tumours
8380/3 Endometrioid adenocarcinoma NOS
8474/3 Seromucinous carcinoma
Clear cell tumours
8310/3 Clear cell adenocarcinoma NOS
Brenner tumours
9000/3 Brenner tumour, malignant
Other carcinomas
9111/3* Mesonephric-like adenocarcinoma
8020/3 Carcinoma, undifferentiated, NOS
8020/3 Dedifferentiated carcinoma
8980/3 Carcinosarcoma NOS
8323/3 Mixed cell adenocarcinoma
Mesenchymal tumours
8931/3 Endometrioid stromal sarcoma, low grade
8930/3 Endometrioid stromal sarcoma, high grade
8890/3 Leiomyosarcoma NOS

Mixed epithelial and mesenchymal tumours
8933/3 Adenosarcoma
Sex cord–stromal tumours
<i>Pure stromal tumours</i>
8810/3 Fibrosarcoma NOS
<i>Pure sex cord tumours</i>
8620/3 Adult granulosa cell tumour of ovary
<i>Mixed sex cord–stromal tumours</i>
8631/3 Sertoli–Leydig cell tumour, poorly differentiated
Germ cell tumours
9060/3 Dysgerminoma
9071/3 Yolk sac tumour NOS
9070/3 Embryonal carcinoma NOS
9100/3 Choriocarcinoma NOS
9085/3 Mixed germ cell tumour
<i>Monodermal teratomas and somatic-type tumours arising from a dermoid cyst</i>
9090/3 Struma ovarii, malignant
9084/3 Teratoma with malignant transformation
<i>Germ cell–sex cord–stromal tumours</i>
Miscellaneous tumours
9110/3 Adenocarcinoma of rete ovarii
8044/3 Small cell carcinoma, hypercalcaemic type
Small cell carcinoma, large cell subtype
8960/3 Wilms tumour
Tumour-like lesions
Metastases to the ovary
Tumours of the peritoneum
Mesothelial tumours
9050/3 Mesothelioma, malignant
9052/3 Epithelioid mesothelioma, malignant
9051/3 Sarcomatoid mesothelioma
9053/3 Mesothelioma, biphasic, malignant
Epithelial tumours (of Müllerian type)
8460/3 Low-grade serous carcinoma
8461/3 High-grade serous carcinoma
Mesenchymal tumours specific to peritoneum
8936/3 Gastrointestinal stromal tumour
8815/3 Solitary fibrous tumour, malignant
8931/3 Endometrioid stromal sarcoma, low grade
8930/3 Endometrioid stromal sarcoma, high grade
8806/3 Desmoplastic small round cell tumour
Tumour-like lesions
Metastases to the peritoneum
Carcinomas and sarcomas
8480/6 Pseudomyxoma peritonei
Gliomatosis
Tumours of the fallopian tube
Epithelial tumours
8461/3 High-grade serous carcinoma
8380/3 Endometrioid adenocarcinoma NOS
8980/3 Carcinosarcoma NOS

Mixed epithelial and mesenchymal tumours
8933/3 Adenosarcoma
Germ cell tumours
9080/3 Immature teratoma NOS
Gestational trophoblastic neoplasms
9105/3 Trophoblastic tumour, epithelioid
9100/3 Choriocarcinoma NOS
9101/3 Choriocarcinoma combined with other germ cell elements
Tumours of the uterine cervix
Squamous epithelial tumours
8085/3 Squamous cell carcinoma, HPV-associated
8086/3 Squamous cell carcinoma, HPV-independent
8070/3 Squamous cell carcinoma NOS
Glandular tumours and precursors
8140/3 Adenocarcinoma NOS
8483/3* Adenocarcinoma, HPV-associated
8482/3 Adenocarcinoma, HPV-independent, gastric type
8310/3 Adenocarcinoma, HPV-independent, clear cell type
9110/3 Adenocarcinoma, HPV-independent, mesonephric type
8484/3* Adenocarcinoma, HPV-independent, NOS
8380/3 Endometrioid adenocarcinoma NOS
Other epithelial tumours
8980/3 Carcinosarcoma NOS
8560/3 Adenosquamous carcinoma
8430/3 Mucoepidermoid carcinoma
8098/3 Adenoid basal carcinoma
8020/3 Carcinoma, undifferentiated, NOS
Mixed epithelial and mesenchymal tumours
8933/3 Adenosarcoma
Germ cell tumours
9064/3 Germ cell tumour NOS
9071/3 Endodermal sinus tumour
9071/3 Yolk sac tumour NOS
9100/3 Choriocarcinoma NOS
Tumours of the vagina
Epithelial tumours
8085/3 Squamous cell carcinoma, HPV-associated
8086/3 Squamous cell carcinoma, HPV-independent
8070/3 Squamous cell carcinoma NOS
8140/3 Adenocarcinoma NOS
8483/3* Adenocarcinoma, HPV-associated
8380/3 Endometrioid adenocarcinoma NOS
8310/3 Clear cell adenocarcinoma NOS
8482/3 Mucinous carcinoma, gastric type
8480/3 Mucinous adenocarcinoma
9110/3 Mesonephric adenocarcinoma
8980/3 Carcinosarcoma NOS
8140/3 Carcinoma of Skene, Cowper, and Littre glands
8560/3 Adenosquamous carcinoma
8098/3 Adenoid basal carcinoma
Mixed epithelial and mesenchymal tumours
8933/3 Adenosarcoma
Miscellaneous tumours
9064/3 Germ cell tumour NOS
9071/3 Yolk sac tumour, pre-pubertal type
Tumours of the vulva
Epithelial tumours

8086/3 Squamous cell carcinoma, HPV-independent
8070/3 Squamous cell carcinoma NOS
8090/3 Basal cell carcinoma NOS
9020/3 Phyllodes tumour, malignant
8500/3 Adenocarcinoma of anogenital mammary-like glands
Bartholin gland lesions
8070/3 Squamous cell carcinoma NOS
8200/3 Adenoid cystic carcinoma
8020/3 Carcinoma, poorly differentiated, NOS
8560/3 Adenosquamous carcinoma
8240/3 Neuroendocrine tumour NOS
8982/3 Myoepithelial carcinoma
8562/3 Epithelial–myoepithelial carcinoma
8085/3 Squamous cell carcinoma, HPV-positive
8542/3 Paget disease, extramammary
8400/3 Sweat gland adenocarcinoma
8401/3 Apocrine adenocarcinoma
8413/3 Eccrine adenocarcinoma
8409/3 Porocarcinoma NOS
8200/3 Adenoid cystic carcinoma
8144/3 Adenocarcinoma, intestinal type
Germ cell tumours
9064/3 Germ cell tumour NOS
9071/3 Yolk sac tumour NOS
Neuroendocrine neoplasia in the female genital tract
8240/3 Neuroendocrine tumour NOS
8240/3 Neuroendocrine tumour, grade 1
8249/3 Neuroendocrine tumour, grade 2
8041/3 Small cell neuroendocrine carcinoma
8013/3 Large cell neuroendocrine carcinoma
8045/3 Combined small cell neuroendocrine carcinoma
8013/3 Combined large cell neuroendocrine carcinoma
Haematolymphoid proliferations and neoplasia in the female genital tract
9680/3 Diffuse large B-cell lymphoma NOS
9699/3 Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
9690/3 Follicular lymphoma NOS
9687/3 Burkitt lymphoma NOS
Sporadic Burkitt lymphoma
Endemic Burkitt lymphoma
Immunodeficiency-associated Burkitt lymphoma
9930/3 Myeloid sarcoma
Mesenchymal tumours of the lower genital tract
Adipocytic tumours
8850/3 Liposarcoma NOS
8852/3 Myxoid liposarcoma
8851/3 Liposarcoma, well differentiated, NOS
8858/3 Dedifferentiated liposarcoma
8854/3 Pleomorphic liposarcoma
Fibroblastic and myofibroblastic tumours
8815/3 Solitary fibrous tumour, malignant
8832/3 Dermatofibrosarcoma protuberans, fibrosarcomatous
Vascular tumours
9140/3 Kaposi sarcoma
9120/3 Angiosarcoma
Smooth muscle tumours
8890/3 Leiomyosarcoma NOS
8891/3 Epithelioid leiomyosarcoma

8896/3 Myxoid leiomyosarcoma
Skeletal muscle tumours
8900/3 Rhabdomyosarcoma NOS
8910/3 Embryonal rhabdomyosarcoma NOS
8920/3 Alveolar rhabdomyosarcoma
8901/3 Pleomorphic rhabdomyosarcoma NOS
Peripheral nerve sheath tumours
9580/3 Granular cell tumour, malignant
Tumours of uncertain differentiation
8804/3 Epithelioid sarcoma
Classic epithelioid sarcoma
Proximal or large cell epithelioid sarcoma
9581/3 Alveolar soft part sarcoma
Undifferentiated small round cell sarcomas
9364/3 Ewing sarcoma
Melanocytic lesions in the female genital tract
8720/3 Malignant melanoma NOS
8745/3 Desmoplastic melanoma
8721/3 Nodular melanoma
8746/3 Mucosal lentiginous melanoma

ANNEX 2: TUMOURS OF THE FEMALE GENITAL TRACT SHOWING BORDERLINE BEHAVIOUR

TUMOURS OF THE FEMALE GENITAL TRACT SHOWING BORDERLINE/UNCERTAIN BEHAVIOUR
BORDERLINE TUMOURS OF OVARY
Serous tumours
8442/1 Serous borderline tumour NOS
Mucinous tumours
8472/1 Mucinous borderline tumour
Endometrioid tumours
8380/1 Endometrioid tumour, borderline
Clear cell tumours
8313/1 Clear cell borderline tumour
Seromucinous tumours
8474/1 Seromucinous borderline tumour
Brenner tumours
9000/1 Brenner tumour, borderline malignancy
Mesenchymal tumours
8897/1 Smooth muscle tumour of uncertain malignant potential
Sex cord–stromal tumours
<i>Pure stromal tumours</i>
8810/1 Cellular fibroma
<i>Pure sex cord tumours</i>
8622/1 Granulosa cell tumour, juvenile

8640/1 Sertoli cell tumour NOS
8623/1 Sex cord tumour with annular tubules
<i>Mixed sex cord–stromal tumours</i>
8631/1 Sertoli–Leydig cell tumour NOS
8631/1 Sertoli–Leydig cell tumour, moderately differentiated
8633/1 Sertoli–Leydig cell tumour, retiform
8590/1 Sex cord tumour NOS
8632/1 Gynandroblastoma
Germ cell tumours
<i>Monodermal teratomas and somatic-type tumours arising from a dermoid cyst</i>
9091/1 Strumal carcinoid
<i>Germ cell–sex cord–stromal tumours</i>
9073/1 Gonadoblastoma
Dissecting gonadoblastoma
Undifferentiated gonadal tissue
8594/1 Mixed germ cell–sex cord–stromal tumour NOS
Miscellaneous tumours
9110/1 Wolffian tumour
8452/1 Solid pseudopapillary tumour of ovary
Tumour-like lesions
Tumours of the peritoneum
Mesothelial tumours
Epithelial tumours (of Müllerian type)
8442/1 Serous borderline tumour NOS
Mesenchymal tumours specific to peritoneum
8890/1 Leiomyomatosis, peritonealis disseminata
8822/1 Abdominal fibromatosis
8815/1 Solitary fibrous tumour NOS
Fat-forming (lipomatous) solitary fibrous tumour
Giant cell–rich solitary fibrous tumour
Dedifferentiated solitary fibrous tumour
Tumours of the fallopian tube
Epithelial tumours
8442/1 Serous borderline tumour NOS

ANNEX 3; BENIGN TUMOURS OF THE FEMALE GENITAL TRACT

BENIGN TUMOURS OF THE FEMALE GENITAL TRACT
BENIGN TUMOURS OF OVARY
Serous tumours
8441/0 Serous cystadenoma NOS
8461/0 Serous surface papilloma
9014/0 Serous adenofibroma NOS
9014/0 Serous cystadenofibroma NOS
Mucinous tumours
8470/0 Mucinous cystadenoma NOS
9015/0 Mucinous adenofibroma NOS
Endometrioid tumours
8380/0 Endometrioid cystadenoma NOS
8381/0 Endometrioid adenofibroma NOS
Clear cell tumours

8443/0 Clear cell cystadenoma
8313/0 Clear cell cystadenofibroma
Seromucinous tumours
8474/0 Seromucinous cystadenoma
9014/0 Seromucinous adenofibroma
Brenner tumours
9000/0 Brenner tumour NOS
Mesenchymal tumours
8890/0 Leiomyoma NOS
8840/0 Myxoma NOS
Sex cord–stromal tumours
<i>Pure stromal tumours</i>
8810/0 Fibroma NOS
8600/0 Thecoma NOS
8601/0 Thecoma, luteinized
8602/0 Sclerosing stromal tumour
8590/0 Microcystic stromal tumour
8590/0 Signet-ring stromal tumour
8650/0 Leydig cell tumour of the ovary NOS
8670/0 Steroid cell tumour NOS
<i>Pure sex cord tumours</i>
<i>Mixed sex cord–stromal tumours</i>
8631/0 Sertoli–Leydig cell tumour, well differentiated
Germ cell tumours
9080/0 Teratoma, benign
<i>Monodermal teratomas and somatic-type tumours arising from a dermoid cyst</i>
9090/0 Struma ovarii NOS
9080/0 Cystic teratoma NOS
Miscellaneous tumours
9110/0 Adenoma of rete ovarii
Tumour-like lesions
Follicle cyst
Corpus luteum cyst
Large solitary luteinized follicle cyst
Hyperreactio luteinalis
8610/0 Pregnancy luteoma
Stromal hyperplasia and hyperthecosis
Fibromatosis and massive oedema
Leydig cell hyperplasia
Tumours of the peritoneum
Mesothelial tumours
9054/0 Adenomatoid tumour NOS
9052/0 Well-differentiated papillary mesothelioma, benign
Epithelial tumours (of Müllerian type)
Mesenchymal tumours specific to peritoneum
8817/0 Calcifying fibrous tumour
Tumour-like lesions
Mesothelial hyperplasia
9055/0 Peritoneal inclusion cysts
Transitional cell metaplasia
Endosalpingiosis
Histiocytic nodule
Ectopic decidua
Splenosis

Tumours of the fallopian tube
Epithelial tumours
9014/0 Serous adenofibroma NOS
Tubo-ovarian abscess
Salpingitis isthmica nodosa
Metaplastic papillary lesion
Placental site nodule
Mucinous metaplasia
Endosalpingiosis
Germ cell tumours
9080/0 Mature teratoma NOS
Tumour-like lesions
Exaggerated placental site reaction
Placental site nodule and plaque
Abnormal (non-molar) villous lesions
Molar pregnancies
9103/0 Partial hydatidiform mole
9100/0 Complete hydatidiform mole
Tumours of the uterine cervix
Squamous epithelial tumours
Squamous metaplasia
Atrophy
Condyloma acuminatum
8077/0 Low-grade squamous intraepithelial lesion
8077/0 Cervical intraepithelial neoplasia, grade 1
Glandular tumours and precursors
Endocervical polyp
Müllerian papilloma
Nabothian cyst
Tunnel clusters
Microglandular hyperplasia
Lobular endocervical glandular hyperplasia
Diffuse laminar endocervical hyperplasia
Mesonephric remnants and hyperplasia
Arias-Stella reaction
Endocervicosis
Tuboendometrioid metaplasia
Ectopic prostate tissue
8932/0 Adenomyoma NOS
Mesonephric-type adenomyoma
Endocervical-type adenomyoma
Germ cell tumours
9080/0 Mature teratoma NOS
9084/0 Dermoid cyst NOS
Tumours of the vagina
Epithelial tumours
Condyloma acuminatum
8052/0 Squamous cell papilloma NOS
Vestibular micropapillomatosis
Solitary vaginal papilloma
Atrophy
8560/0 Tubulosquamous polyp
8077/0 Low-grade squamous intraepithelial lesion
8077/0 Vaginal intraepithelial neoplasia, grade 1
8261/0 Villous adenoma NOS
8263/0 Tubulovillous adenoma NOS
Müllerian papilloma
Vaginal adenosis
Endocervicosis
Cysts
8940/0 Mixed tumour NOS

Mixed epithelial and mesenchymal tumours
Miscellaneous tumours
9080/0 Mature teratoma NOS
9084/0 Dermoid cyst NOS
Tumours of the vulva
Epithelial tumours
Condyloma acuminatum
8077/0 Low-grade squamous intraepithelial lesion
8077/0 Vulvar intraepithelial neoplasia, grade 1
Differentiated exophytic vulvar intraepithelial lesion
Vulvar acanthosis with altered differentiation
8405/0 Papillary hidradenoma
8940/0 Chondroid syringoma NOS
9010/0 Fibroadenoma NOS
9020/0 Phyllodes tumour, benign
<i>Bartholin gland lesions</i>
8140/0 Adenoma NOS
8932/0 Adenomyoma NOS
Haematolymphoid proliferations and neoplasia in the female genital tract
Florid reactive lymphoid hyperplasia
Mesenchymal tumours of the lower genital tract
Adipocytic tumours
8850/0 Lipoma NOS
8881/0 Lipoblastoma-like tumour
Fibroblastic and myofibroblastic tumours
Postoperative spindle cell nodule
Fibroepithelial stromal polyp
8810/0 Fibroma NOS
8825/0 Myofibroblastoma
9160/0 Cellular angiofibroma
8826/0 Angiomyofibroblastoma
NTRK-rearranged spindle cell neoplasm (emerging)
Smooth muscle tumours
8890/0 Leiomyoma NOS
8891/0 Epithelioid leiomyoma
8896/0 Myxoid leiomyoma
Skeletal muscle tumours
8905/0 Genital rhabdomyoma
Peripheral nerve sheath tumours
9540/0 Neurofibroma NOS
9560/0 Schwannoma NOS
9580/0 Granular cell tumour NOS
Tumours of uncertain differentiation
8841/0 Superficial angiomyxoma
8841/0 Aggressive angiomyxoma
Melanocytic lesions in the female genital tract
8720/0 Naevus NOS
8740/0 Junctional naevus NOS
8750/0 Intradermal naevus
8760/0 Compound naevus
8761/0 Congenital melanocytic naevus NOS
8780/0 Blue naevus NOS

8790/0 Cellular blue naevus
8720/0 Atypical melanocytic naevus of genital type
8727/0 Dysplastic naevus