

Department of Gynecology

Chair of Obstetrics and Gynecology

Address

Universitätsstrasse 21–23
91054 Erlangen
Germany
Tel.: +49 9131 85-33451
Fax: +49 9131 85-33456
www.frauenklinik.uk-erlangen.de

Director

Prof. Matthias W. Beckmann, MD

Contact

Prof. Matthias W. Beckmann, MD
Tel.: +49 9131 85-33451
Fax: +49 9131 85-33456
fk-direktion@uk-erlangen.de

Main research topics

- Translational/clinical phase I–IV studies, health-care research, genetic studies (Central Research Unit)
- Biomaterials studies (whole blood, serum, tissue, body fluids) (Biobank Unit)
- Genome analyses, digitalization and artificial intelligence (Biostatistics and Informatics Unit)
- Molecular research (Laboratory for Molecular Medicine)
- Cryopreservation, artificial reproductive organs (Laboratory for Reproductive Medicine)

Structure of the department

Professorships: 3

Employees: 320

- Physicians: 50
- Scientists: 10 (8 of whom are externally funded)
- Doctoral candidates: 27

Main focuses of clinical care

- Minimally invasive and reconstructive surgery for genital and breast carcinomas
- Targeted therapies for genital and breast carcinomas
- Counseling for patients with high-risk breast and ovarian cancer
- Pre-, intra- and postpartum care for high-risk obstetric patients
- Prepartum diagnosis and care in cases of fetal malformation
- Conservative and surgical treatment in patients with extensive endometriosis (rASRM IV, deeply infiltrating endometriosis)
- Fertility-preserving therapy in cancer, including ovarian tissue cryopreservation
- Digitalization of care for gynecological/oncological and obstetric patients

Research

Research priorities in the Department of Gynecology are based on the clinical orientation of its seven certified centers (University Breast Center for Franconia, Familial Breast and Ovarian Cancer Center, University Gynecological Oncology Center

for Franconia, Continence and Pelvic Center, University Perinatal Center for Franconia, University Endometriosis Center for Franconia, University Reproductive Center for Franconia). Supplementary central infrastructure units are the Biostatistics and Informatics Unit, the Central Research Unit and the Institute for Women's Health, the Translational Biobank Unit, the Laboratory for Molecular Medicine, and the Laboratory for Reproductive Biology.

Biostatistics and Informatics Unit: Digitalization and artificial intelligence in the care of gynecological oncology and obstetrics patients

University Breast Center for Franconia, University Gynecological Oncology Center for Franconia, University Perinatal Center for Franconia

During the COVID-19 pandemic, the digitalization of care was further expanded for our gynecological oncology and obstetrics patients. An app was developed that ensures patient data sovereignty and anonymous data transfers to the Department. Recruitment channels were adapted to the "home care" situation using web-based research study information and eConsent. This is currently being used in the DEFenseCOVID-19 registry study (www.corona-register.de, with a direct link for study participation via <https://freeda.one>) to collect well-founded data from all cancer patients during the pandemic about their disease and treatment, as well as on mood and vaccination behavior.

Along with other goals, the digitalization of preventive medicine is being addressed using an integrated patient portal in the collaborative projects SMART-Start for pregnancy (a collaborative project along with IT-FAU, funded by the German Federal Ministry of Health, BMG) and in DigiOnko-Brustkrebs (funded by the Bavarian State Ministry of Health and Care).

With proper development and application in medicine, artificial intelligence (AI) has the potential to lead to improvements in prevention, early detection, diagnosis, and identifying novel treatments, and it can thus make a real contribution to personalized medicine. In the smart data project KDI, managed by Siemens and funded by the German Federal Ministry for Economic Affairs and Energy (BMWi), it has been possible to establish an initial basis for supporting tumor conferences using machine-learning algorithms. Further development of this is aimed for in the joint project Mlwin, funded by the Germany Federal Ministry of Education and Research (BMBF). The intention is that in the future, AI approaches should facilitate patient–doctor discussions as a documentation aid.

Laboratory for Molecular Medicine:

— Tumor biology and genetics, innate immunity and immunoediting

University Breast Center for Franconia, Familial Breast and Ovarian Cancer Center, University Gynecological Oncology Center for Franconia
Together with the Institutes of Pathology (Prof. A. Hartmann) and Urology (Prof. B. Wullich), the complete endogenous retroviral (ERV) expression

and regulation in relation to innate immunity are being analyzed for the three cancer entities bladder, kidney, and fallopian tube. Innate immunity in tumor cells is activated here using double-stranded ERV-RNA via TLR3 and MDAS receptors, and using ERV proteins via TLR4 receptors. For bladder tumors, a significant correlation has been demonstrated between high levels of ERV expression and inflammation, as well as longer survival. Secondly, kidney tumors were found to be associated with significantly better survival when there was high expression of specific ERV proteins. For fallopian tube carcinomas, the epigenetics of DNA and histones play a major role in ERV expression. This is being analyzed in collaboration with George Washington University (Washington, DC). The improved survival associated with activated inflammation might therefore be due to increased ERV expression. In summary, stimulation of ERV expression using epigenetic regulators might represent a new treatment method.

Using isolated human primary epithelial and mesenchymal breast tumor cells, it was possible to produce so-called spheroids — i.e., multicellular aggregates consisting of several thousand cells. In the process, these were identified as homo-spheroids (with a single cell type) or hetero-spheroids (with several cell types). With the help of 3D analyses (in collaboration with the Institute of Biophysics, Prof. B. Fabry), it has now been shown for proliferation and invasion that these spheroids behave like tumor fragments or biopsies. The complete sequencing of the RNA shows that specific transcription factors are overregulated in the tumor cells. Further experiments with more complex hetero-spheroids, especially with immune cells, as well as normal cell spheroids from healthy breast tissue, are expected to contribute to a better understanding of breast carcinogenesis.

— Genetic basis for pathological pregnancies

University Perinatal Center for Franconia, University Reproductive Center for Franconia
Molecular research in obstetrics is focusing on the detection of molecular causes and biomarkers for pathological changes during pregnancy and placental development. In the Franconian Maternal Health Evaluation Study (FRAMES), genetic variants in the aromatase gene CYP19A1, the progesterone receptor, and the estrogen receptor were analyzed and patients with preeclampsia were compared with healthy control individuals. In the Clinical Gravidity Association Trial and Evaluation (CGATE) program, molecular markers in the blood were investigated for their association with breast volume increases during pregnancy. Markers that are also associated with the occurrence and progression of breast cancer were found to have an influence on breast volume increases during pregnancy. In addition, in collaborative projects with the Erlangen Department of Pediatrics, molecular changes — especially in the retinoic acid signaling pathway and corticosterone metabolism — were analyzed in mouse and rat models of intrauterine growth restriction.

Central Research Unit: Clinical studies in gynecology

University Breast Center for Franconia, Familial Breast and Ovarian Cancer, University Gynecological Oncology Center for Franconia, University Endometriosis Center for Franconia

From 2001 to the end of 2020, more than 260 research projects were carried out in clinical phase I–IV studies, the objective of which is to achieve thorough individualization of therapy, increasing its effectiveness and minimizing side effects. Whole-genome sequencing and the very latest targeted therapies are being used for this purpose. The studies include curative and palliative treatment approaches.

One of the central projects is the Germany-wide PRAEGNANT registry for patients with metastatic breast cancer, which was first established in 2014. Tests for new biomarkers are being carried out. Among other things, these biomarkers provide information about the effectiveness and toxicity of treatment approaches and about the patients' quality of life. Using whole-genome sequencing makes it possible to identify innovative therapy targets, which can then be investigated in the framework of clinical studies or outside of the approval process. The data collected represent potential approval-procedure data — i.e., so-called real-world data.

In collaboration with Department of Medicine 5 — Hematology and Internal-Medical Oncology at Erlangen University Hospital, claudin-6 testing is being carried out on solid tumors as part of the Claudin-6 Study. If the test result is positive, patients can receive further targeted therapy using chimeric antigen receptor T cells (CAR-T) in the BNT211 study.

In addition to the projects developed by the Central Research Office and the Institute for Women's Health, the local center is taking part in numerous internationally important approval-procedure trials.

Biobank Unit: Collection of biomaterials

University Breast Center for Franconia, University Gynecological Oncology Center for Franconia, University Perinatal Center for Franconia, University Endometriosis Center for Franconia, University Reproductive Center for Franconia

The Biobank in the Department of Gynecology is one of the largest biobanks worldwide in the field of gynecological research. It includes not only patients from the hospital's own Breast Center (approx. 10,000 participants), Genital Cancer Center (approx. 6,400), Endometriosis Center (approx. 2,300), and Perinatal Center (approx. 1,800), but also patients from nationwide multicenter studies. Currently, biomaterials (132,000 blood samples, 16,500 tissue samples, 30,000 urine samples, and 150,000 serum/plasma and stool samples) are available from approximately 63,000 test persons. In a collaborative project with the Institute of Pathology, 10,500 tumor blocks from patients in clinical studies have now been acquired. The blood data can be compared with those from the tumor (for mutation analyses and expression patterns). Within the framework of a project funded by Horizon2020 and EraCoSysMed, markers in the peripheral immune system and in the tumor microenvironment are being analyzed to predict the treatment response and prognosis during immune checkpoint inhibitor therapy. The PRAEGNANT research network for patients with metastatic breast cancer (currently approx. 4,000 patients at 60 centers in Germany) represents an increasingly important component of the biomaterials collection. In this context, the use of

the PRAEGNANT registry study for patient selection based on clinical data and central testing of the biomarker heregulin for potential inclusion in a clinical study (SHERBOC) has been investigated, among other topics.

Laboratory for Reproductive Biology: Artificial organs and fertility preservation

University Endometriosis Center for Franconia, University Reproductive Center for Franconia, University Gynecological Oncology Center for Franconia

Although the results of fertility-preserving measures in cancer patients are good, with many pregnancies achieved, there is a group of patients whom it is not yet possible to help due to the nature of their disease. In these patients, there is a risk that the transplantation of preserved ovarian tissue may cause the cancer to recur, since malignant cells are present in the tissue. Helping these patients is an important focus of the research work. One approach is to create an artificial ovary using 3D electrospinning. In this process, follicles free of tumor cells are isolated from the removed ovarian tissue and inserted into artificial support scaffolds — produced by the Chair of Materials Science (Biomaterials) at Friedrich Alexander University (Erlangen–Nuremberg). The follicles are then further cultivated in the scaffolds, since follicles are unable to grow without the 3D structure of the stroma. In addition, the support scaffolds are rendered functional using growth factors.

In order to answer scientific research questions, the Endometriosis Center collects patient-history and clinical data for endometriosis patients, as well as biomaterials, in the framework of the International Endometriosis Evaluation Program (IEEP). The aim is to identify risk factors and predictive markers in relation to the diagnosis and recurrence of the disease, as well as on the effectiveness of treatment, relative to the patients' main symptoms. A sub-study forming part of the program compared different methods of obtaining circulating cell-free DNA.

In addition, a bioassay was set up in which the ingrowth of cells from endometriosis lesions into a collagen scaffold can be measured, allowing conclusions to be drawn regarding the invasiveness of these cells.

The staff of the Endometriosis Center are acting as coordinators for guideline development and for this purpose have carried out a systematic analysis of the literature from 2013 to 2018. This has made it possible to derive recommendations and statements for the diagnosis and treatment of patients with endometriosis.

Teaching

Since the end of 2010, the duty area of teaching in the Department of Gynecology has been one of the first university clinical institutions in Germany to have its own certified quality management system (now DIN EN ISO 9001:2015). This is regularly re-certified. Offering compulsory and elective subjects, the Department of Gynecology takes part in the curricular teaching of medicine and in interdisciplinary teaching in the framework of the cross-disciplinary subjects of general prevention, sexual medicine, and emergency medicine. The Department of Gynecology has its own Skills Lab, specially adapted to the requirements of teaching in obstetrics and gynecology, which is used for training as part of the block internship and the Practical Year. The Department of Gynecology also supervises medical doctorates.

Selected publications

Mark C, Grundy TJ, Strissel PL et al. Collective forces of tumor spheroids in three-dimensional biopolymer networks. *Elife*. 2020 Apr 30;9:e51912. doi: 10.7554/eLife.51912. Erratum in: *Elife*. 2020 Jun 02;9.

Fasching PA, Hartkopf AD, Gass P et al. Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: a multicentric analysis. *Breast Cancer Res Treat*. 2019 Jan;173(2):319–328. doi: 10.1007/s10549-018-5008-3.

Huebner H, Kurbacher CM, Kuesters G et al. Heregulin (HRG) assessment for clinical trial eligibility testing in a molecular registry (PRAEGNANT) in Germany. *BMC Cancer*. 2020 Nov 11;20(1):1091. doi: 10.1186/s12885-020-07546-1.

Pretscher J, Ruebner M, Ekici AB et al. Genetic variations in estrogen and progesterone pathway genes in preeclampsia patients and controls in Bavaria. *Arch Gynecol Obstet*. 2020 Sep 30. doi: 10.1007/s00404-020-05812-y.

Wunderle M, Ruebner M, Häberle L et al. RANKL and OPG and their influence on breast volume changes during pregnancy in healthy women. *Sci Rep*. 2020 Mar 20;10(1):5171. doi: 10.1038/s41598-020-62070-3.

Lux MP, Nabieva N, Hartkopf AD et al. Therapy landscape in patients with metastatic HER2-positive breast cancer: data from the PRAEGNANT real-world breast cancer registry. *Cancers (Basel)*. 2018 Dec 21;11(1):10. doi: 10.3390/cancers11010010.

Raffel N, Dittrich R, Bäuerle T, ..., Liverani L. Novel approach for the assessment of ovarian follicles infiltration in polymeric electrospun patterned scaffolds. *PLoS One*. 2019 Apr 29;14(4):e0215985. doi: 10.1371/journal.pone.0215985.

Burghaus S, Hildebrandt T, Fahlbusch C et al. Standards used by a clinical and scientific endometriosis center for the diagnosis and therapy of patients with endometriosis. *Geburtshilfe Frauenheilkd*. 2019 May;79(5):487–497. doi: 10.1055/a-0813-4411.

International collaborations

Prof. D. Easton, MD, Breast Cancer Consortium, Cambridge, United Kingdom

Prof. D. Lambrechts, MD, Catholic University of Leuven, Leuven, Belgium

Prof. D. Slamon, MD, University of California at Los Angeles (UCLA), Los Angeles, California, USA

Prof. R. Weinsilboum, MD, Mayo Clinic, Rochester, Minnesota, USA

Prof. S. Baylin, MD, Johns Hopkins Medical Center, Baltimore, Maryland, USA

Prof. K. Chiappinelli, George Washington University, Washington, DC, USA