Mermaid III
Early detection & screening; Biomarkers &/or Prognostic markers; Infection Theory
Evaluation of Scientific Progress
2018 report by the Independent Audit Committee (IAC)

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Mermaid-III follows on from two successful research programmes Mermaid-I and Mermaid-II which focused on ovarian and cervical cancer respectively. Mermaid-III has three work streams or work packages which together aim to impact ovarian cancer survival:

1. Early detection and Screening (Lead- Professor Susanne Krüger Kjær, University of Copenhagen, Rigshospitalet)
2. Biomarkers for ovarian cancer and/or Prognostic markers (Lead- Professor Claus Høgdall, University of Copenhagen, Rigshospitalet. Key Investigator - Dr Estrid Høgdall Dept. of Pathology, Herlev University Hospital)
3. The Infection theory (Lead- Professor Jan Blaakær, Århus University Hospital)

Outputs Reviewed- Submissions received from the three work-stream leads and Dr Bent Ottesen

On the basis of outputs reviewed the committee is happy to recommend continuation of the programme. Some comments have been listed at the end of each section.

EARLY DETECTION AND SCREENING

Prof Kjaer has assembled a strong team for her programme.
Collaborators include –

- The Ludwig Center for Cancer Genetics and Therapeutics; John Hopkins Medical Institutes,Baltimore, USA (Professor, consultant Bert Vogelstein; Professor,consultant Luis Diaz)
- Department of Pathology, John Hopkins Medical Institutes, Baltimore, USA (Professor, consultant Robert Kurman, Professor, consultant Ie-Ming Shih)
- Departments of Pathology and department of Gynecology, Denmark
- Department of Medical Epidemiol. & Biostatistics, Karolinska Institute, Stockholm, Sweden (Professor Joakim Dillner, Postdoc Karin Sundström)
- Ovarian Cancer Association Consortium (OCAC)

PROJECT-A: PAP-GENE STUDIES
A.1. Validation study:
Case control study for PAPSeek test in ovarian cancer showed very limited sensitivity of 33%. Paper has been submitted to Sci Transl Med (Wang et al)
A.2. PapGene on previously collected Danish LBC samples:

Validation study for PAPSeek on LBC samples in 40,000 Danish women (98 ovarian cancers identified in them). This work is ongoing.

A.3. Prospective collection of LBC samples to establish a Danish biobank

Prospective collection of LBC samples from 150,000 Danish women ages 23-60 undergoing cervical screening for bio-banking. This dataset will be linked to the Pathology Data Bank/the Danish Cancer Registry in order to identify women who have developed ovarian cancer. This collection has commenced. It is anticipated 50,000 will be collected per year.

B- Early detection focusing on serous borderline tumors (SBT)

B.1. Clinicopathologic and molecular features and behavior of SBT

This study is progressing well and generating extremely interesting and important data related to behaviour, biology and prognosis of SBTs.

3 publications in this review period.

B.2+B.3 Risk of borderline tumors and ovarian cancer following benign ovarian tumors

Outcomes show increased risk of borderline tumours following benign disease.

1 paper published.

C- Risk factors for ovarian borderline tumors and ovarian cancer (Collaboration with OCAC)

The team have confirmed the benefit of OCP use on risk of borderline tumours and contributed additional papers on OC risk (related to SSRI, menstrual cycle, aspirin, PCOS etc).

5 papers listed in this review period

D- Long-term survival of ovarian cancer

The well-established system of databases and linkages in Denmark provides a unique resource to undertake these long term analyses.

There are some interesting findings with 4 papers in this output period.

COMMENTS:

Using cervical screening specimens to predict future ovarian cancer risk is an exciting concept. However, preliminary data suggest the sensitivity of the test being used is limited for ovarian cancer. For ovarian cancer it may be prudent to have results from study A2 before focusing huge time and resource in study A3.

Depending on the age distribution of the cohort ascertained it could be many years before adequate number of events accrue in the A3 cohort. Resource for long term follow up needs to be considered. Of course Study A3 will also provide a bio-resource to study other cancers or diseases apart from ovarian cancer.

Studies B, C and D have progressed very well providing valuable data.

Overall, this stream has been extremely productive with 14 publications.

BIORMARKERS AND PROGNOSTIC MARKERS

A. Bio-banking Study: Collection of biological specimens

The collection comprises the Pelvic Mass Project 2004-2014 + GOVEC Study 2014+

The collection is ongoing. It has led to publications directly from the collection as well as (+) contribution to collaborative datasets and publications from these further enhancing academic outputs.
24 + 33 = 57 publications provided. Of these 7 + 5 are from within this period.
3 presentations + papers in progress from GOVEC.

B: Translational biochemical and molecular studies

RNA Stability Study
There were problems with sample collection but the work is now ongoing.
This has led to 2 presentations + 1 manuscript in preparation
Non-Epithelial Ovarian Cancer Study
Studies are ongoing. A paper on germ cell cancers has been submitted and one on granulosa cell tumours is in progress.
Methylation Studies
Current status- project is in WP-1 and work is ongoing
DNA Methylation an early event in Ovarian Clear Cell Carcinoma
Collaboration with Ellen Goode Mayo Clinic + Danish collaborators (2018-2020)
This work is in its initial stages.
Role of c-MET overexpression in the development of ovarian clear cell carcinoma
National collaborations have been established. The team encountered problems with sample collection but these have been overcome and work is now progressing.
P53 Studies (Ongoing collaboration with Bob Bast at MD Anderson in the US)
P53 auto-Ab analysis + IHC protein expression + NGS for p53
Testing for p53 Auto-Ab has been completed, P53 IHC is work has been completed and in May 2018 at GAP meeting. Sequencing of p53 has been undertaken. NGS and other Auto-Ab work are being extended.
LGSC Genomic and Proteomic characterisation
Collaboration established for proteomics with Prof de-Fazio at University of Sydney.
This work is planned for 2018
Patterns of Genomic Copy Number Aberrations predictive of malignant transformation of endometriosis into ovarian clear cell carcinomas
Sample collection is ongoing
Immune System and Clear Cell Carcinomas of the ovary
Analysis is ongoing. Results expected in 2019
One paper published.
PD-L1 expression in advanced ovarian cancer tissue
Work is ongoing
Outputs include two conference abstracts- ESMO 2017, ASCO June 2018
Patterns of Genomic Copy Number Aberrations predictive of malignant transformation of endometriosis into ovarian clear cell carcinomas
Problems with sample collection. Investigators are looking into this.

C: Data registration, validation, selection and description of study cohorts

Data are curated from different registers such as DGCD, NPR, Patobank and the death of cause register and Danish Cancer Biobank. There are data entry errors and missing data. This part of the programme relates to the necessary ongoing validation and data correction activity which in turn feeds into the translational MERMAID studies/ research programme.

This is an important part of the programme.

A combination of students and post-docs are involved in this

7 publications related to database register work during the 2017-18 period have been provided.

COMMENTS

The Bio-banking Study (A) is an extremely productive collection. It has led to number of translational studies which would not have been possible without it and also contributed to international collaborative research efforts.

The overall publication output over the years resulting from the biobank both from the investigators themselves and as part of international consortia/collaborations is commendable.

There have been some hiccups with sample collection in some of the translational studies (B) which are being addressed. Outputs from this work are largely expected to emerge over the next couple of years.

The bio-banking and technical analyses infrastructure provided by Dr Estrid Høgdall underpins significant parts of the overall programme and transgresses all three work-streams/work-packages. This central resource contribution should be acknowledged separately beyond just this work-stream.

INFECTION THEORY

This is a collaboration between Department of Obstetrics & Gynecology, Aarhus University Hospital, Denmark; Department of Obstetrics & Gynecology, Rigshospitalet, Denmark; Dept of Pathology, Herlev University Hospital, Denmark; and Department of Oncology, Lund University, Sweden.

This work-stream investigates a dogma challenging hypothesis.

Outputs- 1 presentation and 1 publication so far in this review period (2017+).

A STIC sub-study and NGS for virome and bacteriome are planned.

COMMENTS

This is the speculative (high risk) part of the programme. That infection is the primary driver is speculative.

Outputs so far are limited.

The committee looks forward to seeing more outputs over the next year as NGS data emerge.

On behalf of the Audit Committee
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