BRCA-analyses: Wie doet wat en waarom?

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14e bijeenkomst moleculaire diagnostiek in de pathologie 20200131

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BRCA1/2 mutations in ovarian cancer

Germline pathogenic variants in *BRCA1/BRCA2/BRIP1/RAD51C/RAD51D* lead to increased ovarian cancer risk

- ovarian carcinoma is an indication for genetic testing

Somatic mutations are restricted to the neoplastic cells

- germline and somatic *BRCA1/2* mutations associated with higher response to platinum- and PARP-based treatments

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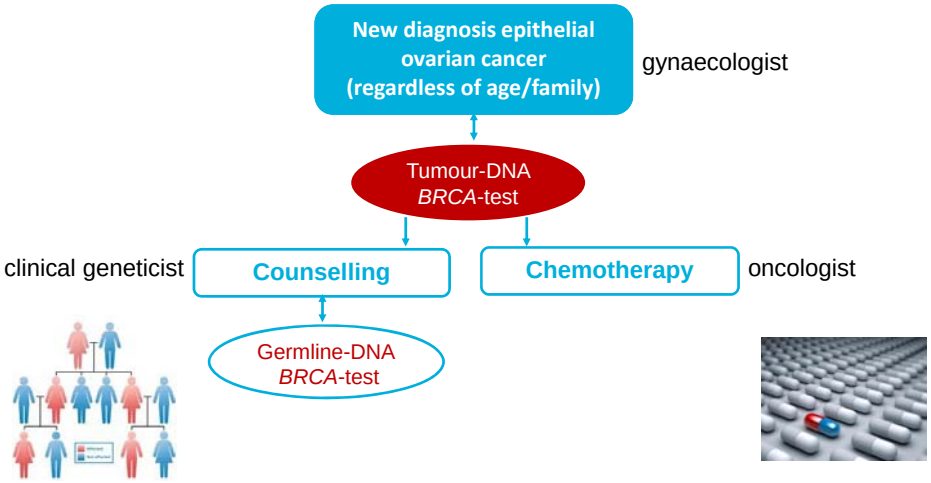
Tumour first



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smMIP-based tumour testing of *BRCA1/2*

- Efficient detection of all 193 blood-based and all 49 FFPE tumour-based germline mutations
- Accuracy per nucleotide based on 107 FFPE samples: 99.998%
- Sensitivity for detecting germline mutations on FFPE is similar to blood test
- Combined with MLPA *BRCA1* to detect exon deletions and duplications

Weren et al Human Mutation 2017 PMID: 27767231

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Regional implementation

Information for:
- Patients
- Gynaeco-oncologists
- Pathologists

https://www.cancergenetics.eu/en

Regular news letters

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Ordering of the test

- Gynaeco-oncologist informs patient about evaluation of tissue
- Pathologist initiates *BRCA1/2* test upon histological diagnosis of

  ovarian, fallopian tube or primary peritoneal carcinoma

  irrespective of subtype

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Performance and reporting

- Central laboratory with close collaboration between Pathology and Genetics
- Reporting
  - If tested **positive** for a clinically relevant *BRCA1/2* variant:
    - Relatively good response to PARP-inhibitors
    - May indicate a genetic predisposition for breast and ovarian cancer: referral to clinical geneticist is indicated
  - If tested negative for a clinically relevant *BRCA1/2* variant :
    - Less likely to respond to PARP-inhibitors
    - No indication for genetic predisposition
    - Only refer in case of family history of ovarian cancer

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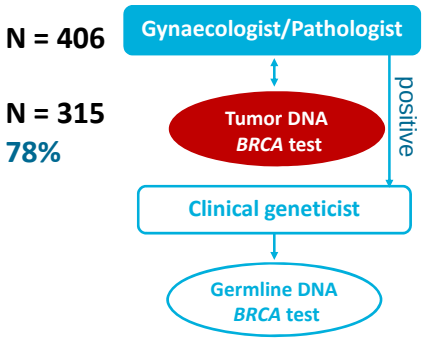
BRCA testing in Ovarian cancer by Pathologist (OPA)



N = 406

N = 315
78%

Inclusion Oct 2015 – June 2017

N = 51
17%

1 waiting for counselling
4 deceased
2 alive but not referred in our region

N = 44
Germline pathogenic *BRCA1/2* variant:
N = 25 57%
Extrapolation:
10% germline; 7% somatic

Vos et al Journal National Cancer Institute 2019 PMID: 31076742

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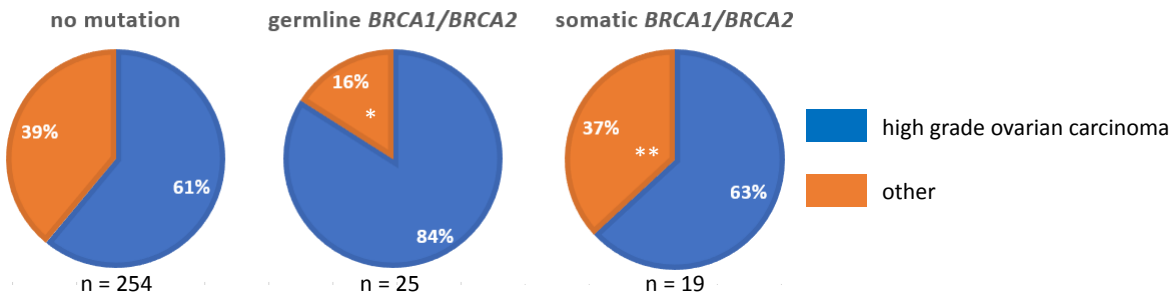
Ovarian carcinoma histology

Results from October 2015 to June 2017



* undifferentiated, clear cell, carcinosarcoma
** undifferentiated, low grade/unknown grade serous, mucinous, endometroid

Vos et al Journal National Cancer Institute 2019 PMID: 31076742

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OPA process data

Results from October 2015 to June 2017

Outcome of BRCA1/2 tumor test	No
Successful test	305 97%
Succesful after first test	292
Succesful after second test different sample	13
No test result available	10
Insufficient quality of DNA material	3
Low tumor cell percentage (<30%)	2
Lack of material	4
Test retracted	1

Vos et al Journal National Cancer Institute 2019 PMID: 31076742

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OPA process data

Results from October 2015 to June 2017

	Complete OPA tests (N = 305)
Median time from diagnosis to OPA request	14 days (IQR 8-21)
Median OPA turnaround time	14 days (IQR 12-16)
OPA on ovariectomy/debulking/staging surgery	247 (78%)
OPA on biopsy	64 (20%)
OPA on ascites	1 (0%)

Vos et al Journal National Cancer Institute 2019 PMID: 31076742

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Experiences of gynaeco-oncologists

- Survey response rate: 44% (18/41)
  - 9 hospitals
  - 1-3 responses per hospital
- **83%** is positive on the OPA workflow

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Patient experiences

- Semi-structured telephone interviews with 13 patients:
  - 4 women with germline *BRCA* mutation
  - 3 women with somatic *BRCA* mutation
  - 6 women with a normal tumour test

Experiences

- All appreciated the procedure
- All were satisfied with the information before and after the test

Vos et al Journal National Cancer Institute 2019 PMID: 31076742

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Similar study by LeidenUMC

- Oncomine *BRCA1/BRCA2* assay
  265 amplicons;
  median coverage of amplicons >100 (nb no unique coverage)

De Jonge et al, J mol diagn 2018, PMID 29936257

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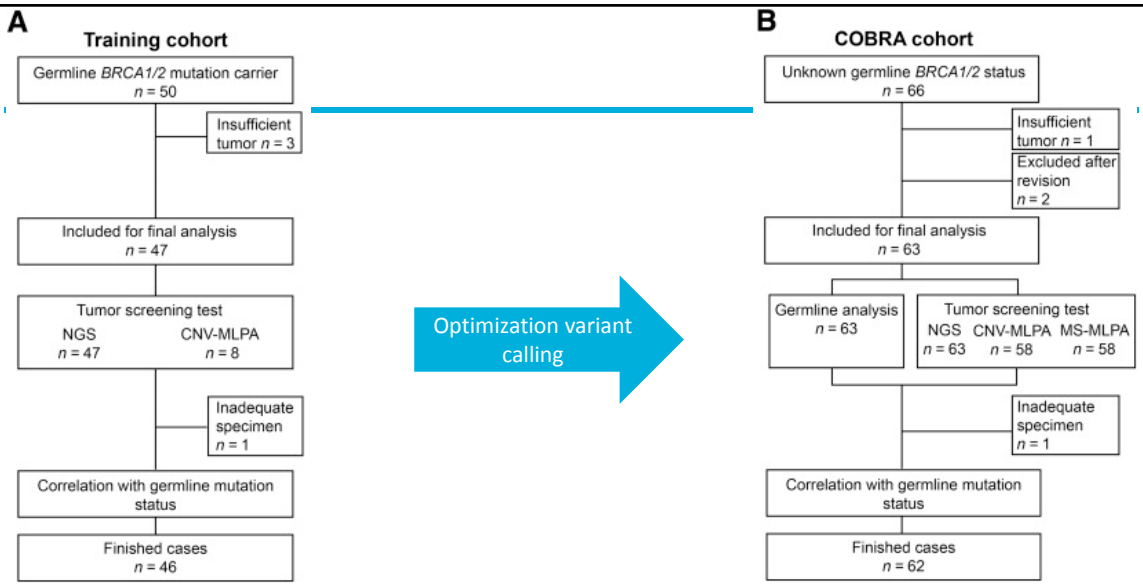

3 germline mutations missed
homopolymer stretch; 7- 11 bp deletions at end amplicon

All 6 germline mutations detected

De Jonge et al, J mol diagn 2018, PMID 29936257

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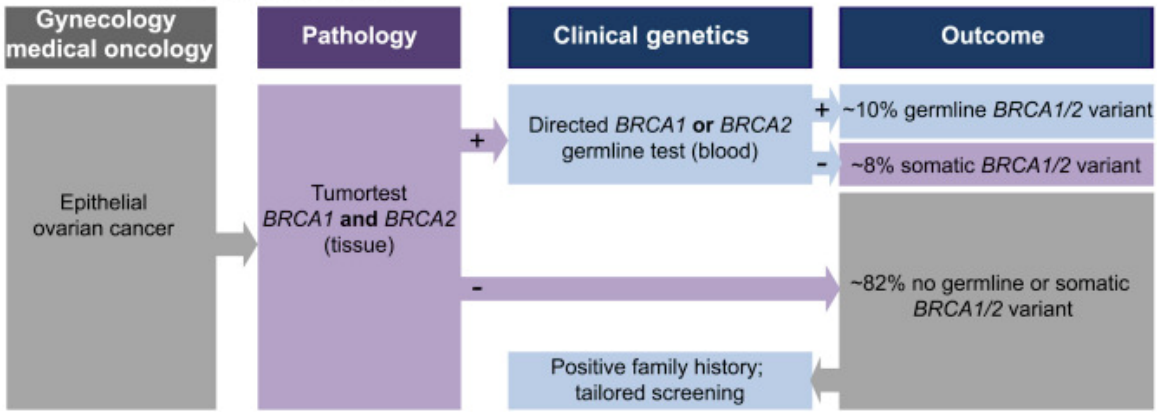
Current *BRCA1/2* screening



De Jonge et al, J mol diagn 2018, PMID 29936257

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Conclusions universal ovarian carcinoma testing

- Uptake by pathologists and referral rates are good
- About 50% of tumour-DNA-*BRCA*-mutations are somatic
- Patients are positive as long as quality and uniform interpretation is garanteed
- Gynaeco-oncologists are positive about tumour testing, although logistic problems occur for patients treated in multiple centers
- Multidisciplinary finetuning is essential
- Radboudumc test extended with *BRIP1*, *RAD51C, RAD51D;* Introduction MSI markers and HRD under discussion

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Nationwide implementation: KWF project

- Multidisciplinary:
  Gynaecologists, medical oncologists, clinical geneticists, pathologist, laboratory specialists
  Close collaboration with patient organisations

- Barriers/facilitators for implementation:
  - in daily practice of gynaecologists and gynaecological oncologists
  - of qualified tumor test and Tumor-First-workflow in pathology laboratories
  - of Tumor-First-workflow in multidisciplinary clinical genetics care pathway

Tjalling Bosse

- Stepwise implementation

- Integration in Dutch health care system:
  guidelines, SONCOS evaluations and financial solutions

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Tumour-first in other cancer types?

- Balance between germline and somatic mutations
- Systemic treatment choice based on germline and somatic BRCA mutations
- Proportion of tumours that need systemic treatment
- Necessity for testing other actionable mutations

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Tumour-first in other cancer types?

PARP inhibitors in other tumour types:

- Mamma carcinoma
  No? indication for locally advanced or metastasized HER2-negative tumours with germline BRCA mutation

- Pancreatic cancer
  No? positive clinical trial metastatic tumours with germline BRCA mutation (Golan et al NEJM 2019)

- Prostate cancer
  Yes?, but at time treatment is considered
  positive clinical trial metastatic tumours with germline or somatic BRCA mutation (ESMO meeting)

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Project group "tumor-/erfelijkheidsdiagnostiek"

- Representatives of:
  - VKGN (clinical geneticists)
  - VKGL (clinical molecular geneticists)
  - NVVP (pathologists and clinical scientists in molecular pathology)

- Advise to boards of professional organisation on
  - Design and organisation of clinical care pathways
  - Quality of tests, interpretation and reporting
  - Legal issues and financing of diagnostic strategies


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Organisation of tumor testing

Key points to consider

- Ovarian carcinoma tumor first-test
  - testing in “vergunninghoudende centra” in close collaboration with clinical molecular geneticists
  - a negative BRCA test withholds patients from germline genetic test
  - quality criteria of genetic lab (complete coverage of coding region and exon boundaries of all indicated genes and mutation types)

- Tumor types with less prominent heritable component
  - uniform reporting of different variants to prevent confusion in families
  - clear referral criteria and pathway to clinical geneticist

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