RICERCA TRANSLAZIONALE NEGLI STUDI MANGO-ENGOT

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MaNGO
Mario Negri Gynecologic Oncology

MaNGO-ENGOT studies

Cervical cancer (n=5)

- INTERLACE
- KEYNOTE-A18
- SENTICOL III
- eVOLVE-Cervical
- BEAT cc

Ovarian cancer (n=25)

- NItCHE
- ARTISTRY-7
- SRTO-002- GM3
- ANITA
- NEWTON
- UP-NEXT
- LUPPA-1
- GLORIOSA
- LEPRE
- PROPi
- LATER-OC
- BOP-Trial
- EPIK-O
- DUO-O
- TRUST
- NIRVANA
- AGO-OVAR 28
- N-Plus
- IOlanTHe
- MIRASOL
- INNOVATE-3
- EPIK-O
- ENGOT-ov65
- ENGOT-ov57
- ARAVIVE-ov66

Endometrial cancer (n=10)

- KEYNOTE-B21
- AtTEnd
- POD1UM-204
- DOMENICA
- GOG-3064
- EQ132
- XPORT-EC
- NAVTEMADLIN
- RAINBO BLUE
- REALITY

MaNGO-ENGOT studies and liquid biopsy

AtTEnd

Randomized study (phase III)
Paclitaxel-Carboplatin-Placebo
Paclitaxel-Carboplatin-Atezolizumab
Endometrial cancer (stage III/IV or recurrent)

NIRVANA

ENGOT-ov57

Randomized study (phase III)
Paclitaxel-Carboplatin → mantainance Niraparib
Paclitaxel-Carboplatin-Beva → manteinance Niraparib-Beva
Advanced Ovarian cancer patients

LEPRE

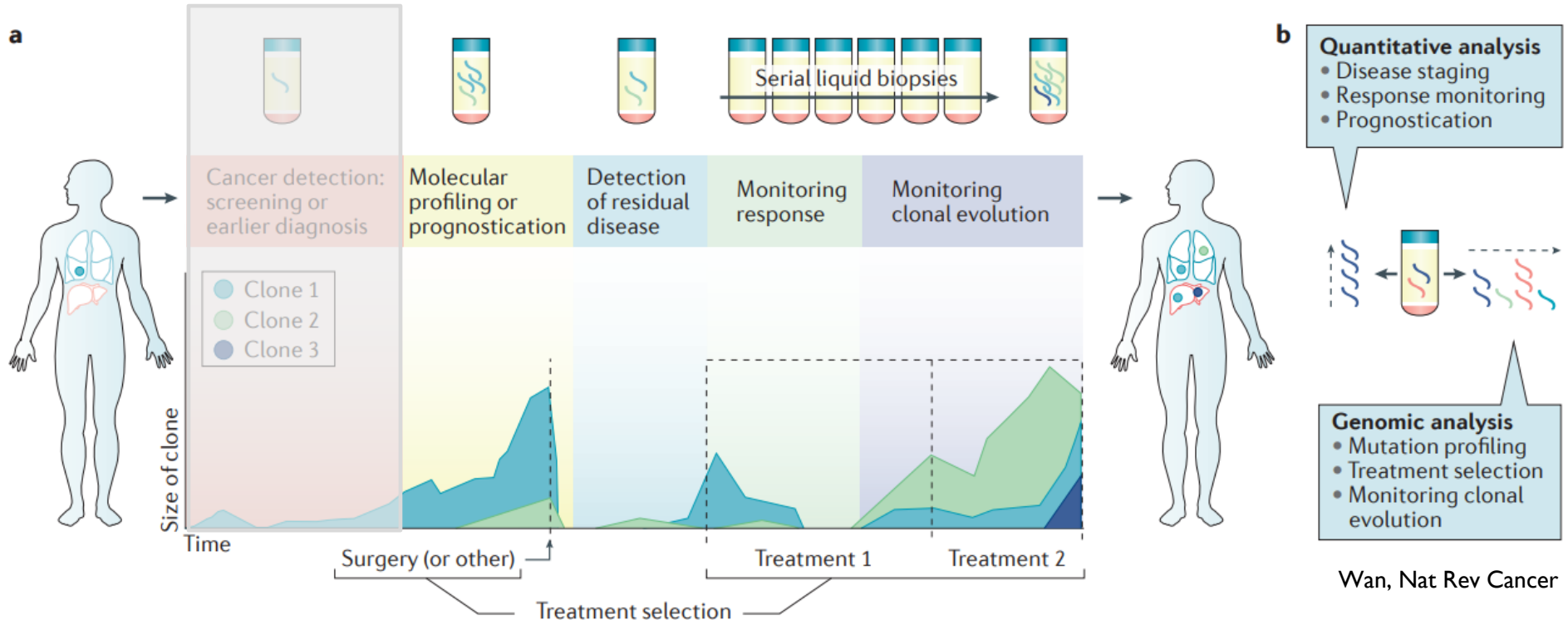
Randomized study (phase III)
Paclitaxel-Carboplatin
Letrozole
Low Grade Serous OC (stage III/IV, ER/PGR +)

IOlAnTHe

Phase IV trial
Advanced stage (stage III/IV), Pt sensitive, HRD +

MaNGO-ENGOT studies and liquid biopsy

- AtTEnd
- LEPRE
- NIRVANA
- ENGOT-ov57
- IOlAnTHe



Wan, Nat Rev Cancer

- ctDNA prognostic biomarker
- Monitoring the disease and therapy response
- Molecular analysis of the relapse → treatment rationalization

MaNGO-ENGOT studies and liquid biopsy

- AtTEnd
- LEPRE
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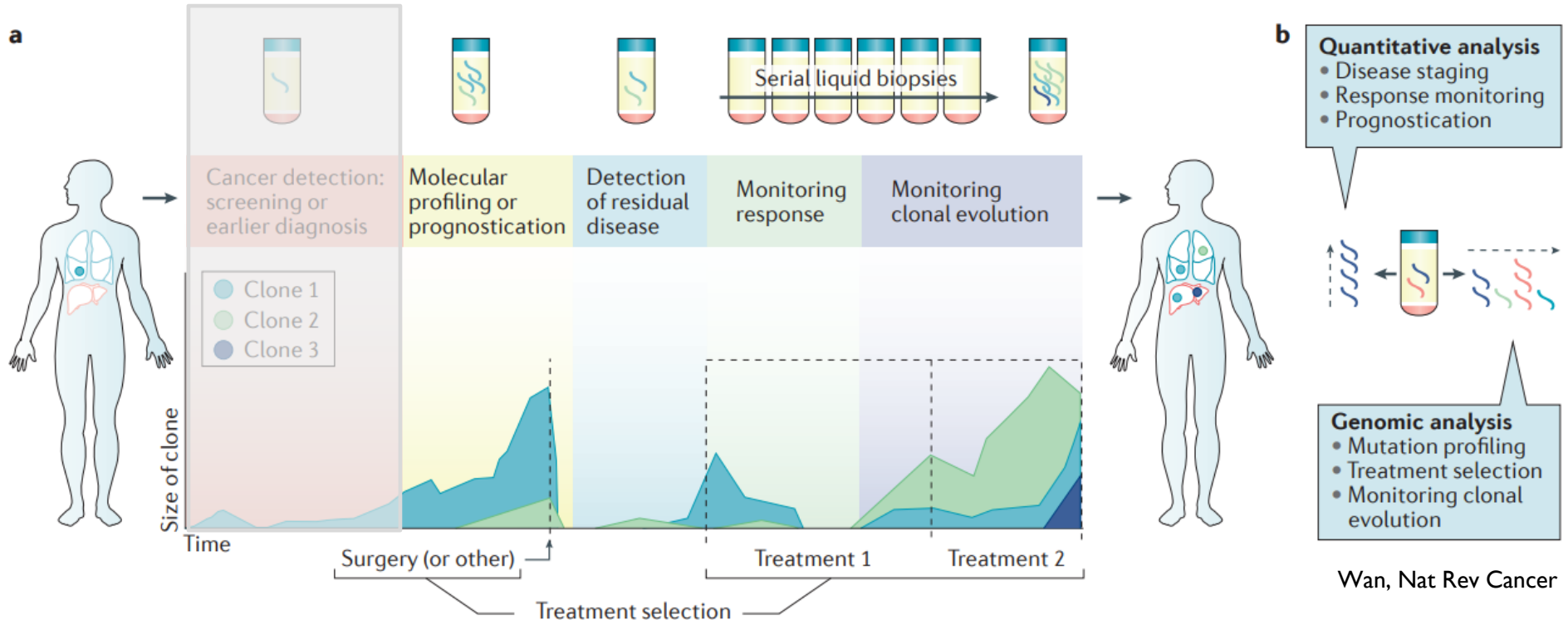

Wan, Nat Rev Cancer

- ctDNA prognostic biomarker
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IOlAnTHe

AtTEnd

LEPRE

NIRVANA

ENGOT-ov57

IOlAnTHe

Phase IV trial to confirm the efficacy of Olaparib in combination with bevacizumab as maintenance frontline treatment of HRD positive ovarian tumors

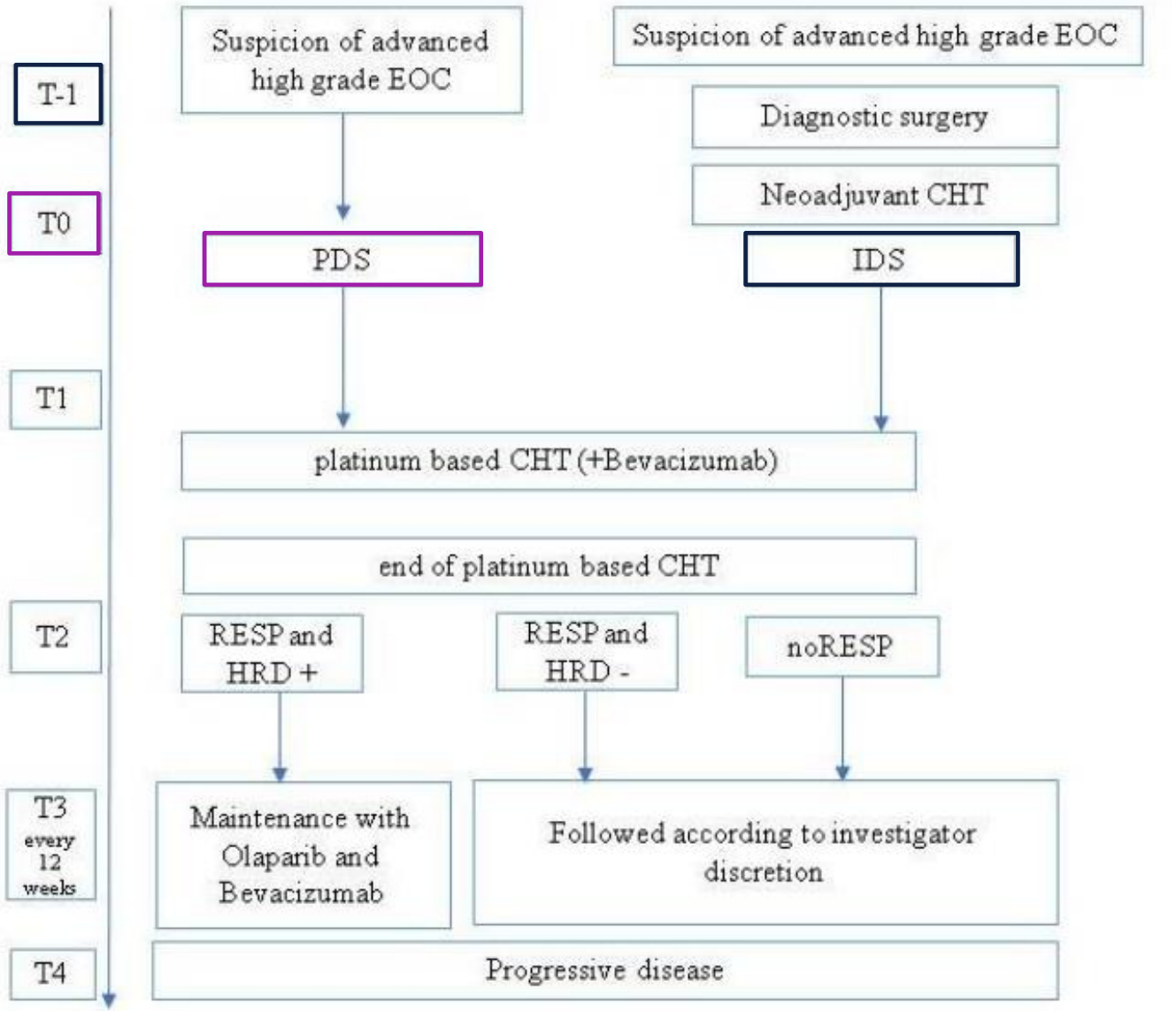
Translational study I
(D'incalci's group)

Longitudinal analysis of ctDNA to monitor disease evolution and mutational analysis of HR-related genes

Translational study II
(Cavallaro's group)

Organotipic models to predict PARPi response

IOlAnTHe



Primary tumor tissue
Accademic HRD test vs Myriad Mychioce CDxPlus

Association between residual tumor and tumor fraction (TF)

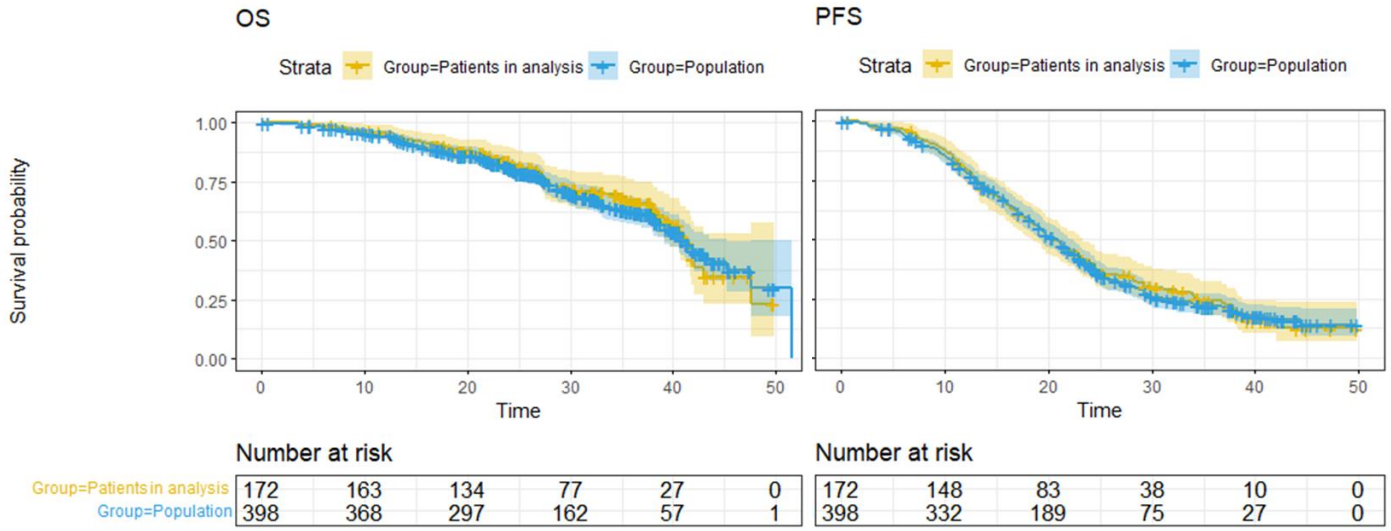
Longitudinal monitor: TF levels → anticipation of recurrence

Longitudinal monitor: mutational status of HR-related genes

Mito16a-MaNGO-ov2a-engot ov17

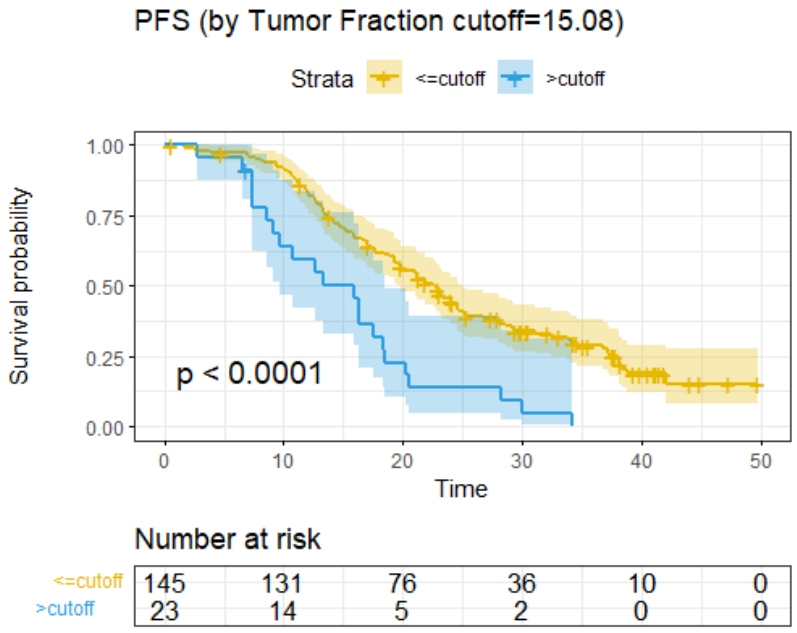
- Type of Study: phase IV, single-arm, multicentric study
- Study population: stage III/IV epithelial ovarian cancer patients
- Treatment: Carboplatin + Paclitaxel + Beva

	Patients in analysis (n=172)	MITO16A Population (n=398)
Median age (IQR)	58.4 (49.9;65.9)	59.2 (49.9;66.5)
Age category		
<65	124 (72)	278 (70.0)
≥65	48 (28)	120 (30)
ECOG performance status		
0	134 (78)	315 (79.2)
1	34 (20)	69 (17.3)
2	4 (2)	14 (3.5)
Residual disease		
None	68 (40)	153 (38.4)
≤ 1 cm	35 (20)	72 (18.1)
> 1 cm/ not operated	69 (40)	173 (43.5)
FIGO stage		
IIIB	14 (8)	36 (9.1)
IIIC	125 (73)	275 (69.1)
IV	33 (19)	87 (21.9)
Tumor histology		
High Grade serous	147 (86)	333 (83.7)
Low Grade serous	4 (2)	13 (3.3)
Endometrioid	7 (4)	9 (2.3)
Clear Cell	4 (2)	11 (2.8)
Mucinous	2 (1)	3 (0.8)
Mixed	0 (0)	4 (1.0)
Other	8 (5)	25 (6.3)

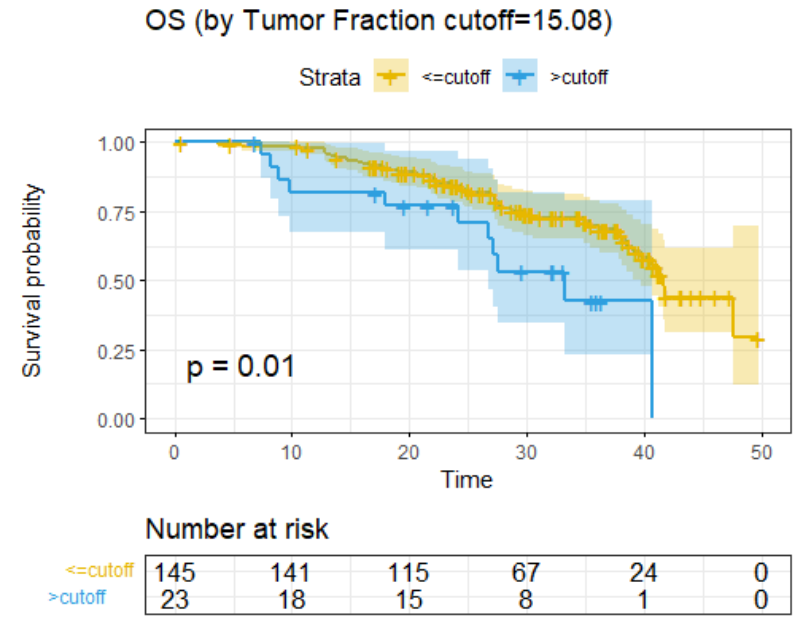


Mito16a-MaNGO-ov2a-engot ov17

PFS



OS

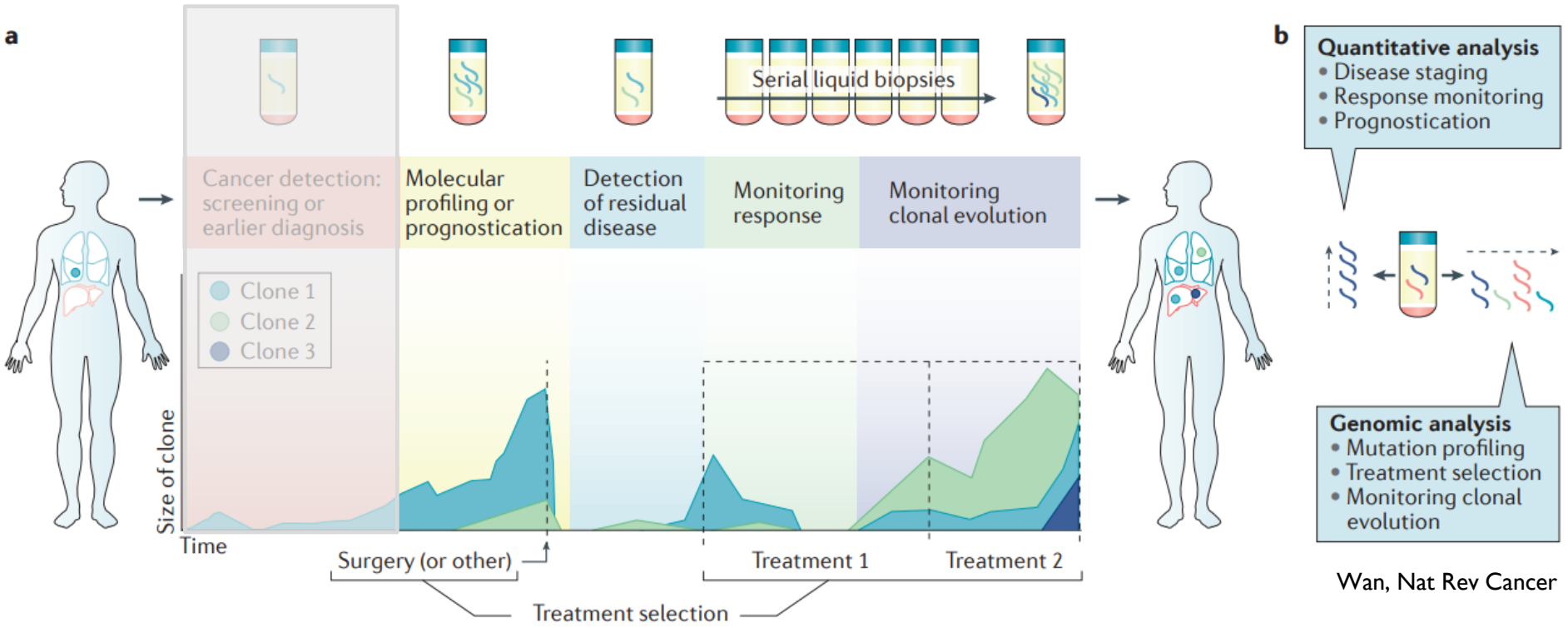


Events PFS: 125/168
Events OS: 57/168

Multivariate Analysis

Cox-model for HRD Patients	HR (IC 95%) for PFS	p-value	HR (IC 95%) for OS	p-value
Tumor Fraction	1.021 (1.00-1.04)	0.031	1.028 (1.01-1.06)	0.011
Residual	1.239 (1.00-1.53)	0.047	1.190 (0.88-1.61)	0.262
PS 0 vs 1-2	1.640 (1.07-2.52)	0.023	1.686 (0.92-3.09)	0.091
Stadio 3 vs 4	2.662 (1.72-4.12)	<0.001	1.630 (0.88-3.02)	0.120
Isto cat	1.359 (0.81-2.27)	0.243	1.182 (0.56-2.51)	0.664
Age elderly	0.915 (0.61-1.38)	0.671	0.808 (0.44-1.47)	0.484

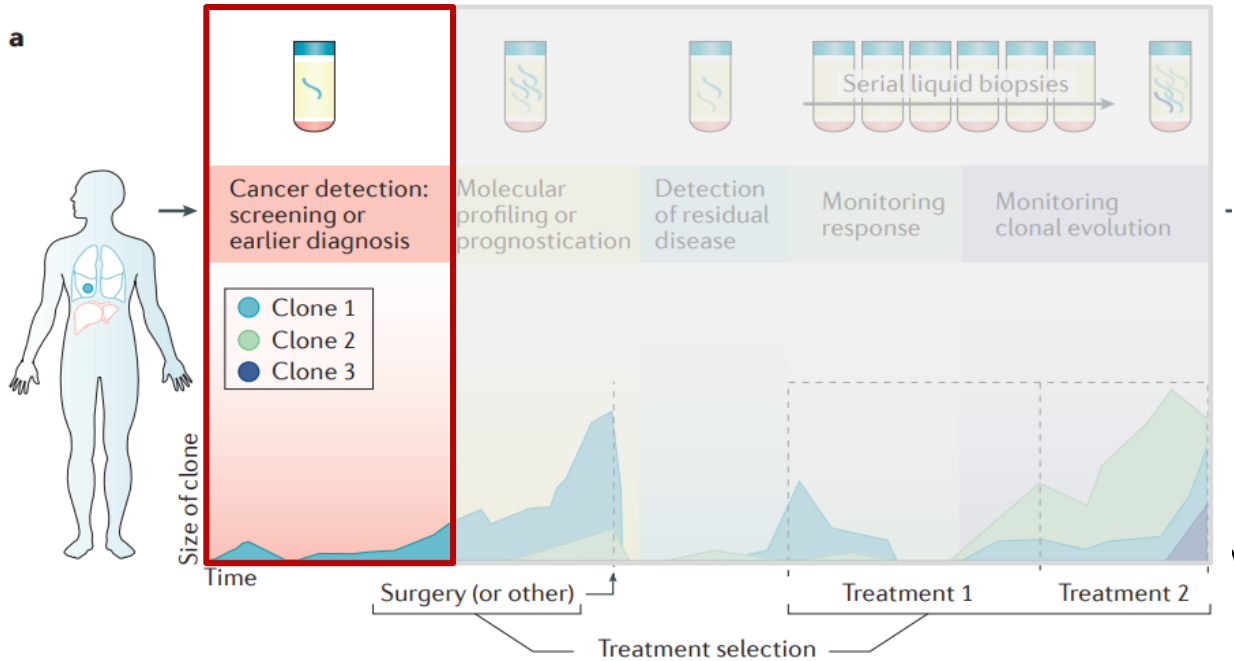
Mito16b-MaNGO-ov2b-engot ov17



Wan, Nat Rev Cancer

- **TF at time of surgery is a prognostic biomarkers**
- Monitoring the disease and therapy response
- Molecular analysis of the relapse

Liquid biopsy and early diagnosis



Wan, Nat Rev Cancer

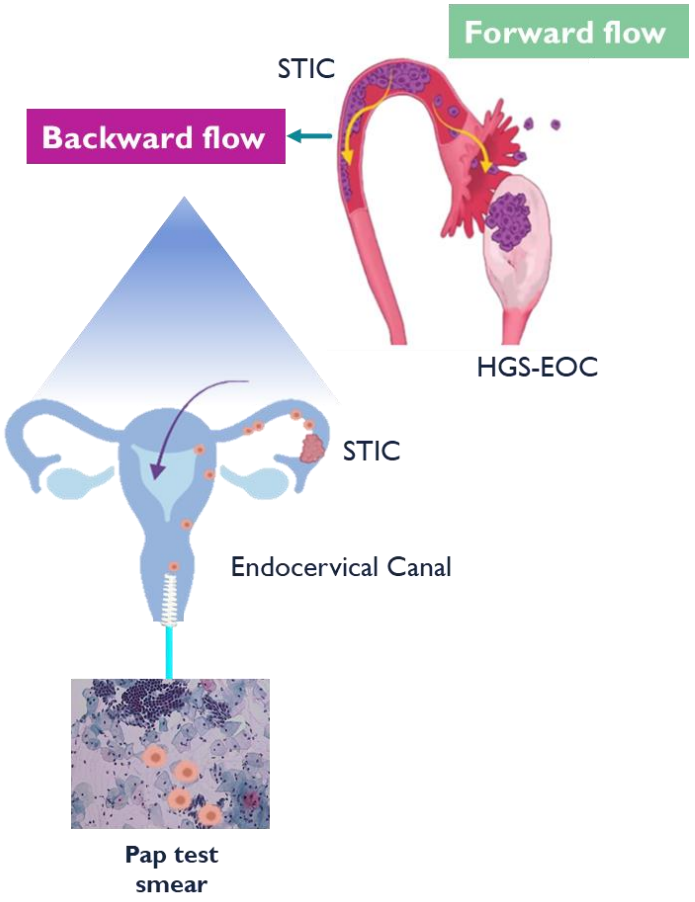
Multi-cancer early detection using liquid biopsy
(GRAIL and National Institute for Health and Care Research)

?

- Low specificity. 79 out of 323 (25%) false positive
- Low sensitivity for early stage (stage I) of disease (24%)
- Economical and psychological consequences

Pap test for the early diagnosis of HGS-EOC

HYPOTHESIS

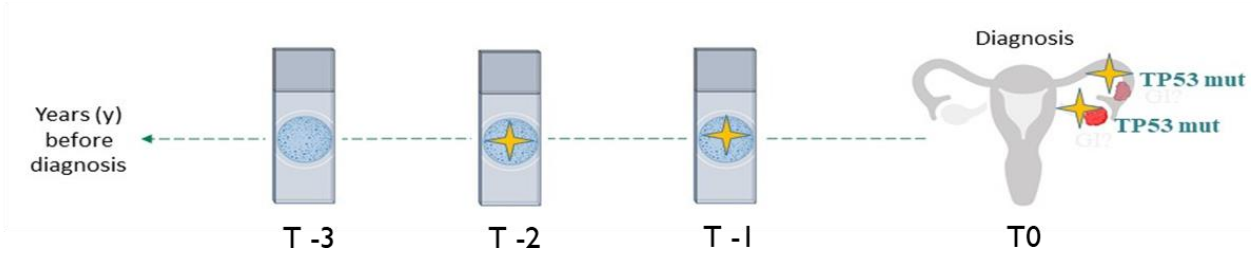


AIM

To evaluate Pap test smear as a source of DNA suitable for HGS-EOC early detection

APPROACH

TP53-based

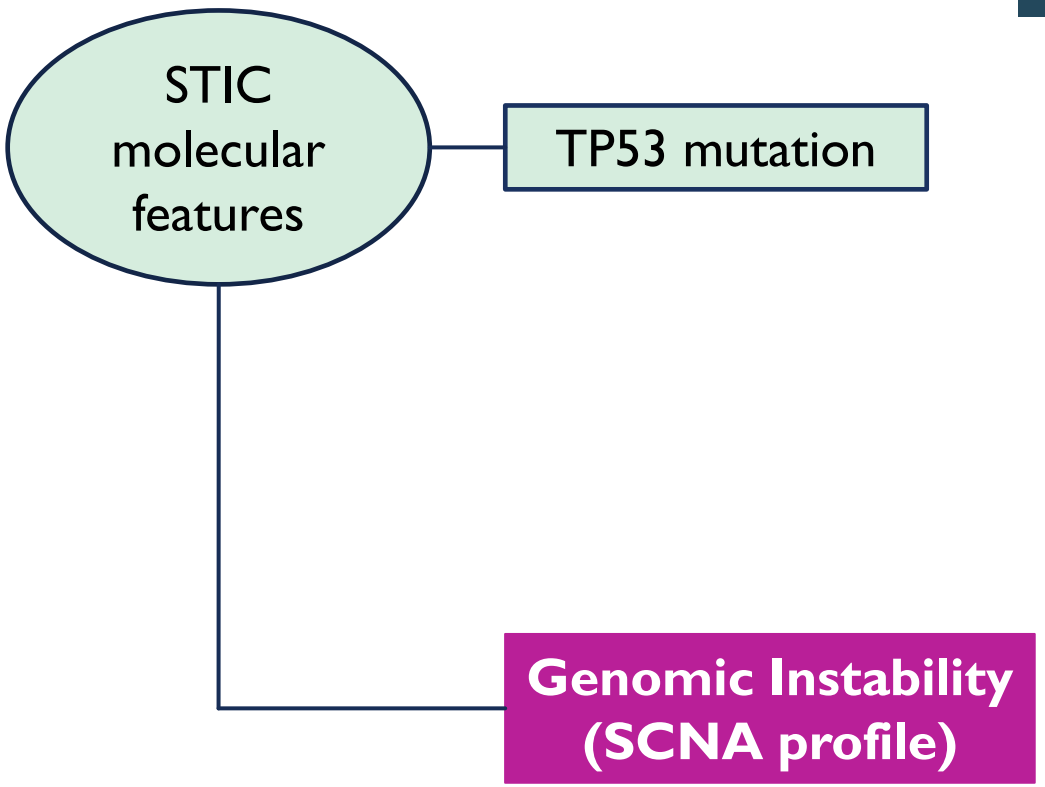


Pap test for the early diagnosis of HGS-EOC

RESULTS

In two independent cohorts (tot n= 68) of patients we confirmed that Pap test smear is a suitable source of material to longitudinally monitor molecular feature (TP53 mutations) characterizing early phase of malignancy up to 10 years before diagnosis.

LIMITATION



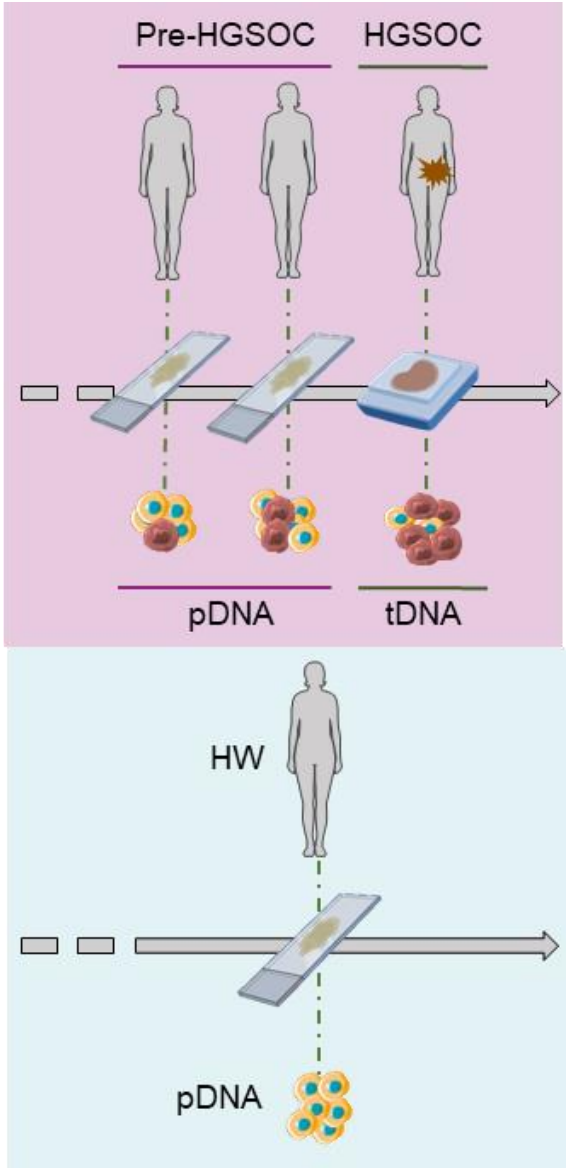
- ❖ Previous knowledge about tumor-related pathogenic TP53 mutation
- ❖ Normal tissue could have somatic TP53 mutations that do not trigger neoplastic transformation
  - Age
  - Tissue-specific cell proliferation rate
  - Benign conditions (i.e. p53 signature)

L. Paracchini et al., JAMA Network Open 2020
L. Paracchini et al., under second revision

Pap test for the early diagnosis of HGS-EOC

AIM

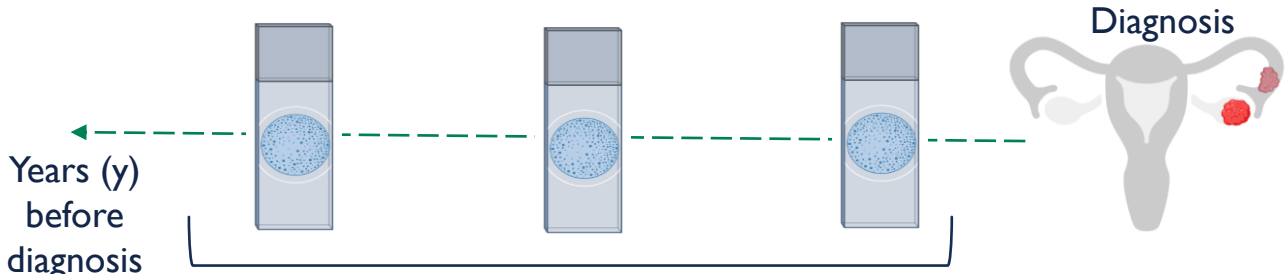
To test Pap test genomic instability pattern as a new method for the early diagnosis of STIC



- Restrospective and Multicentric
- N. of HGS-EOC patients analyzed: 62
- N. of Pap test sample: 99
- Δ temp before diagnosis (y): 0-13
- N. of Healthy Donor: 77

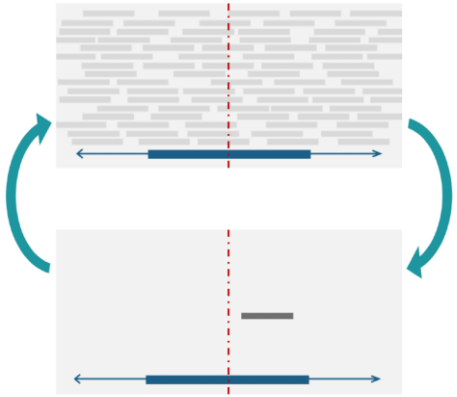
L. Paracchini, L. Mannarino et al., under second revision

Pap test for the early diagnosis of HGS-EOC



DNA extracted from Pap test

Genomic Instability analysis (shallow whole genome sequencing)



Somatic Copy Number Alterations (SCNAs)

Copy number Profile Abnormality score **CPA score**

Pap test for the early diagnosis of HGS-EOC

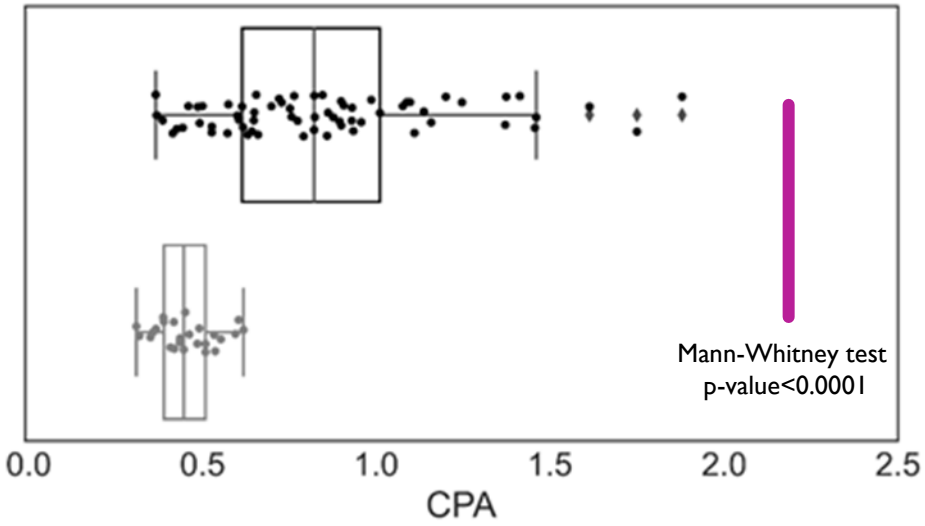
Women who progressed toward malignancy

CPA score

vs

Healthy women

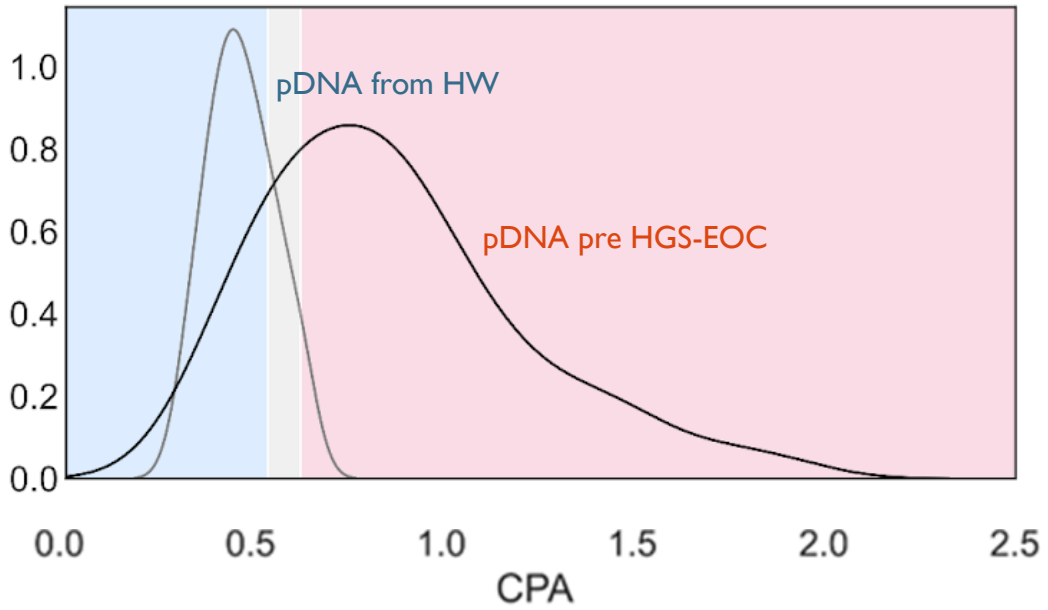
Statistically different CPA distribution



L. Paracchini, L. Mannarino et al., under second revision

Pap test for the early diagnosis of HGS-EOC

CPA distribution defines 3 different intervals



Blue Zone — **negative for genomic alterations**
0<CPA<0.52372

Gray Zone — **area of uncertainty**
0.52372<CPA<0.61

Red Zone — **positive for genomic alteration**
CPA>0.61

In this setting

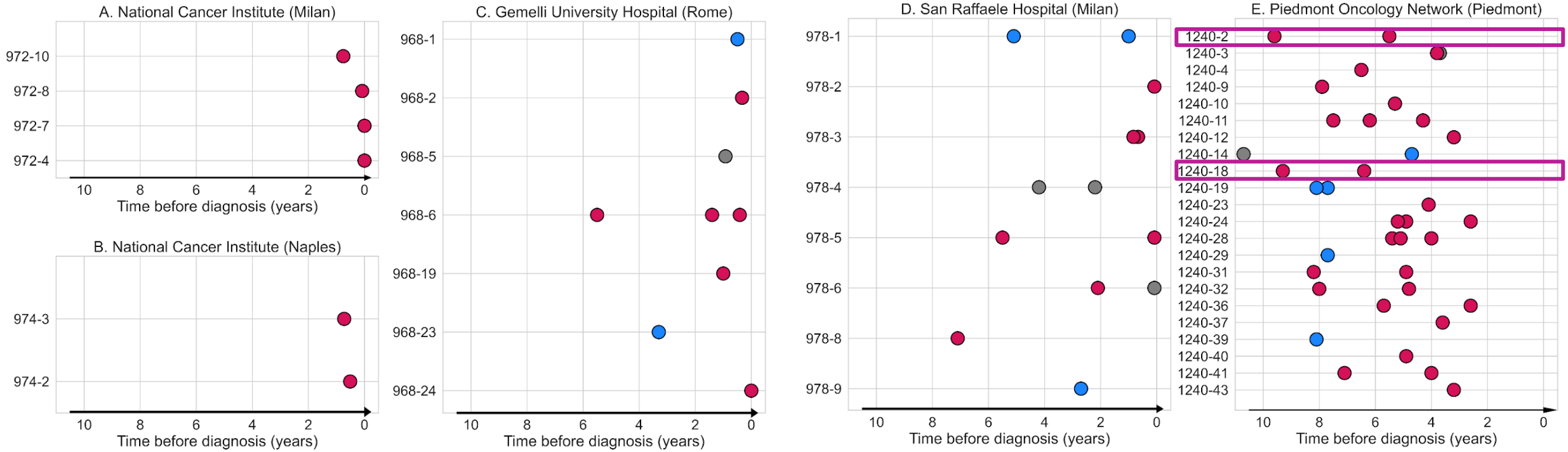
Specificity: 96%

Sensitivity: 75,38%

Accuracy: 81,11%

L. Paracchini, L. Mannarino et al., under second revision

Pap test for the early diagnosis of HGS-EOC



- **aneuploid genome** (red circles) 75.4% (49/65)
- **diploid genome** (blue circles) 15.4% (10/65)
- **uncertain** (gray circles) 9.2% (6/65)

Pap test for the early diagnosis of HGS-EOC

Our findings indicate that **early detection of HGS-EOC is potentially feasible by examining the genomic instability profile in DNA derived from endocervical swab**

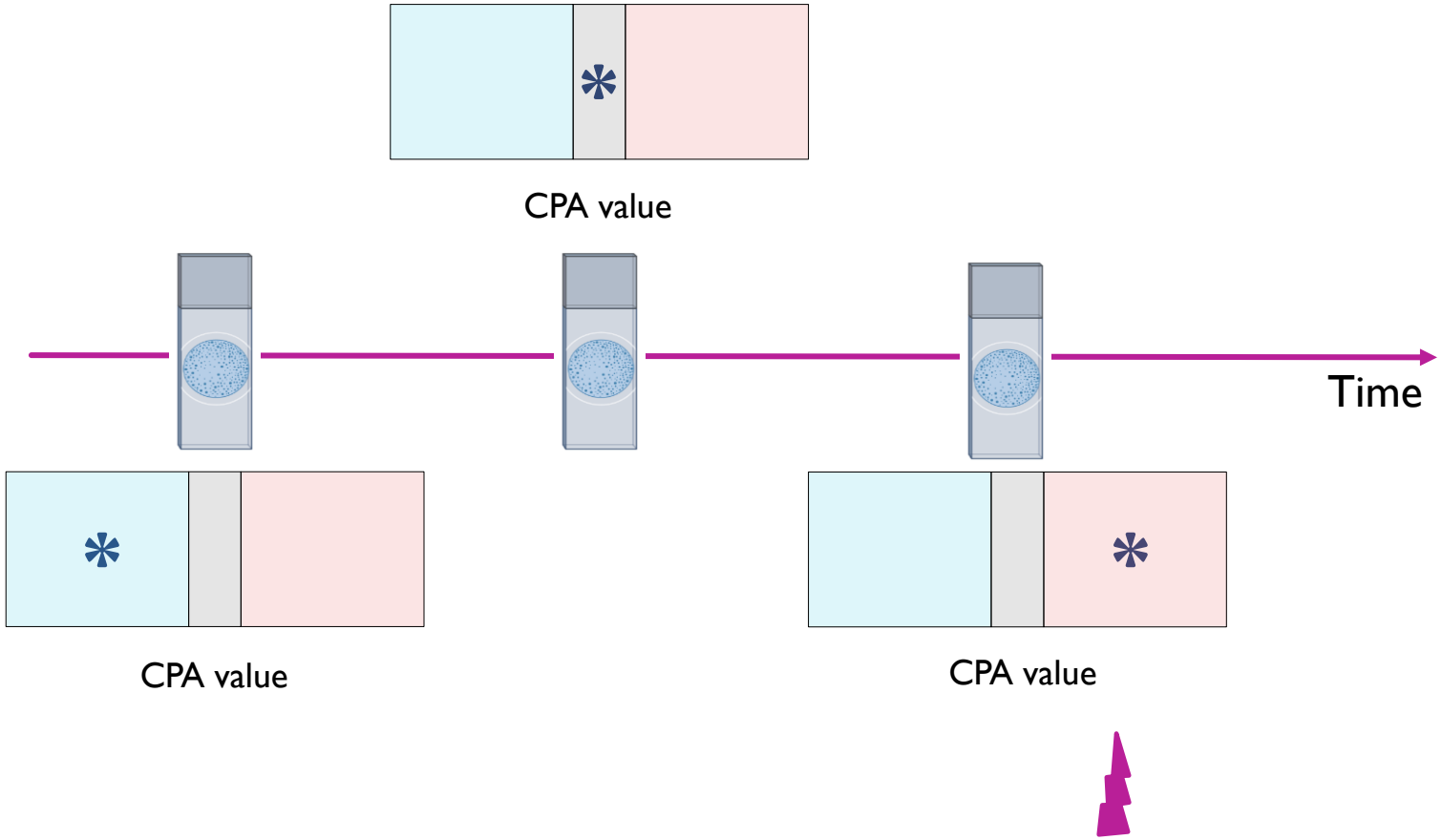
Pap test for the early diagnosis of HGS-EOC

Future perspectives

Population: gBRCA women

Type of study

- Perspective
- Longitudinal
- Multicentric



AIM

To monitor the high risk population, to suggest the proper time for prophylactic surgery

HUMANITAS
RESEARCH HOSPITAL

Cancer Pharmacology group

Prof. Maurizio D'Incalci
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Dr. L. Beltrame
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All the centres that have partecipated