City of Hope

THIRD ANNUAL
ISSPP Congress 2022
International Society for the Study of Pleura and Peritoneum

OVARIAN CANCER

Histologic and Molecular Implications on Ovarian Cancer Treatment

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Disclosures

- No relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Outcome differences depending on access to health care/socioeconomic status.

Histologic and Molecular Implications on Ovarian Cancer (OC) Treatment

Advancing innovative Therapies for Cancers that invade the Peritoneum and the Pleura

- Histology: OC is many diseases
- One therapy (Carboplatin + Paclitaxel) fits for all ?
- The challenge of chemoresistance in OC
- Prognostic factors: dealing with complexity
- New opportunities

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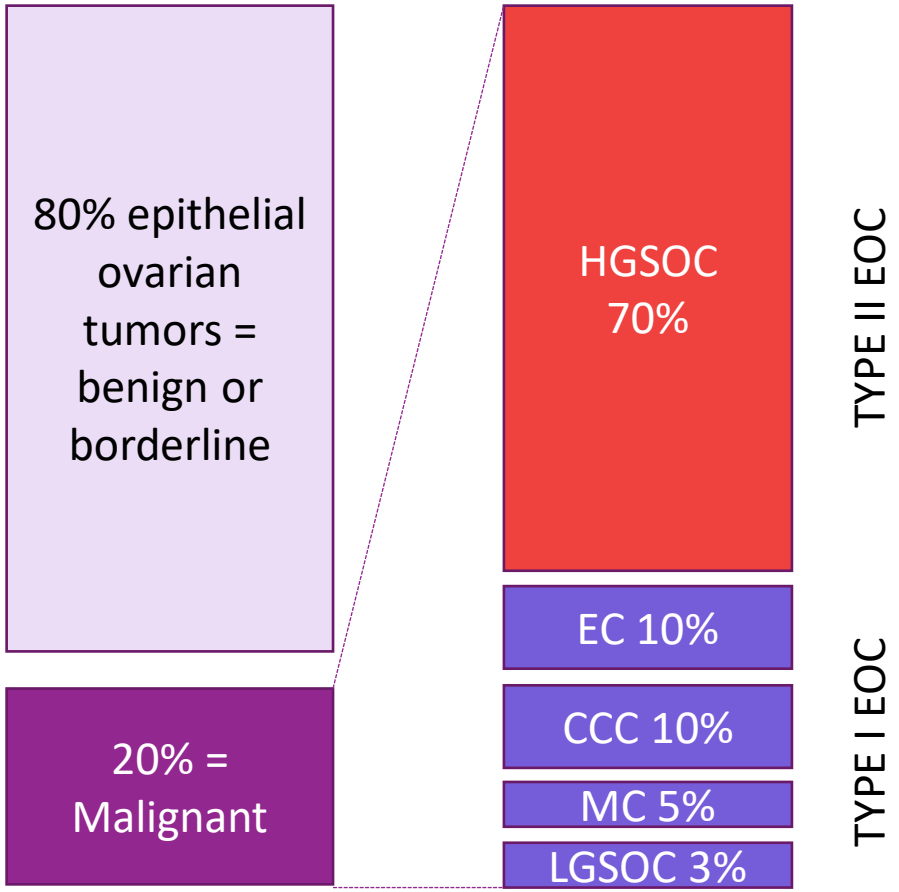
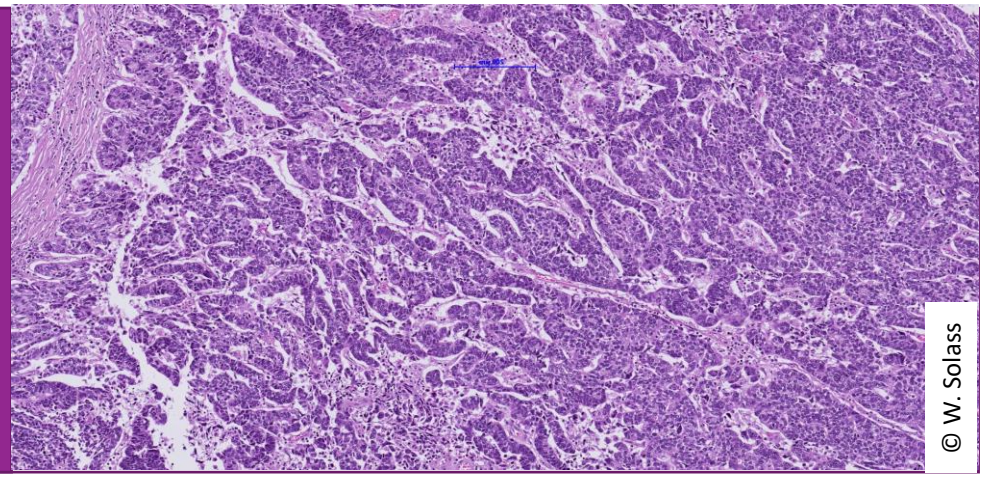
OC is many diseases



High-grade serous ovarian cancer (HGSOC)

70%

HISTOLOGY



GENOTYPE

> 95% TP53 mutations
50% homologous recombination DNA repair (HRR) pathway alterations
amplification of oncogenes: CCNE1, MYC, MECOM
deletion of tumor suppressors: PTEN, RB1, NF1

THERAPEUTIC ALGORITHM

All stages

↓

Carboplatin/Paclitaxel

Incl. Primary Peritoneal and Fallopian Tube

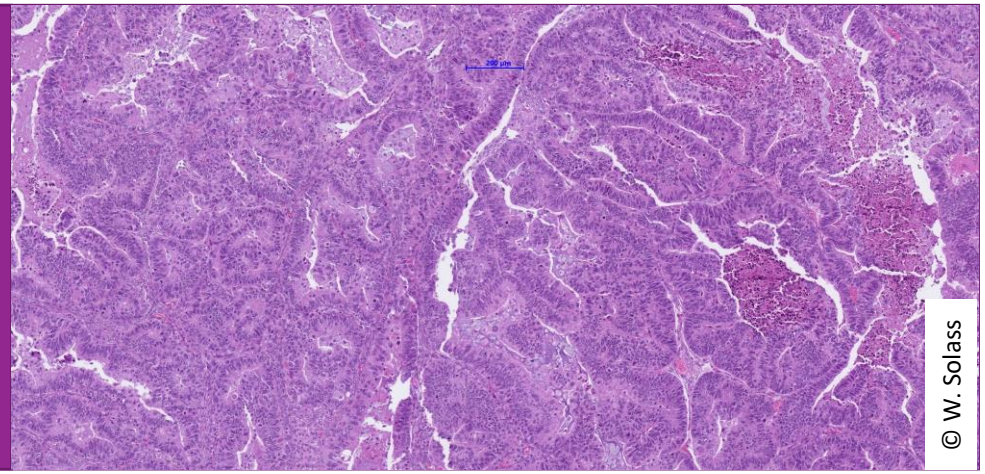
PROGNOSIS

Lacks a clear precursor
Aggressive phenotype
Develops platinum resistance
Poor prognosis

Endometrioid Ovarian Carcinoma (EC)

10%

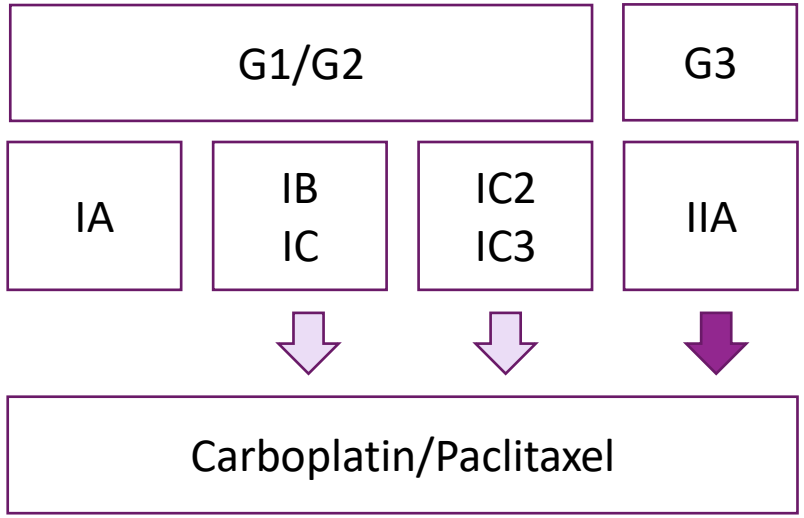
HISTOLOGY



GENOTYPE

- Mutational landscape
  - 30%–50% CTNNB1 (borderline)
  - 15%–40% PIK3CA, 30%–35% ARID1A, 10-30% KRAS (endometriosis)
  - 20-30% PTEN
  - 10 -25% TP53
- Four molecular subtypes
  - 60-70% NSMP (no specific molecular profile)
  - 10-25% TP53 mutated
  - 10-20% hypermutated with microsatellite instablility
  - 3-10% ultramutated POLE

THERAPEUTIC ALGORITHM



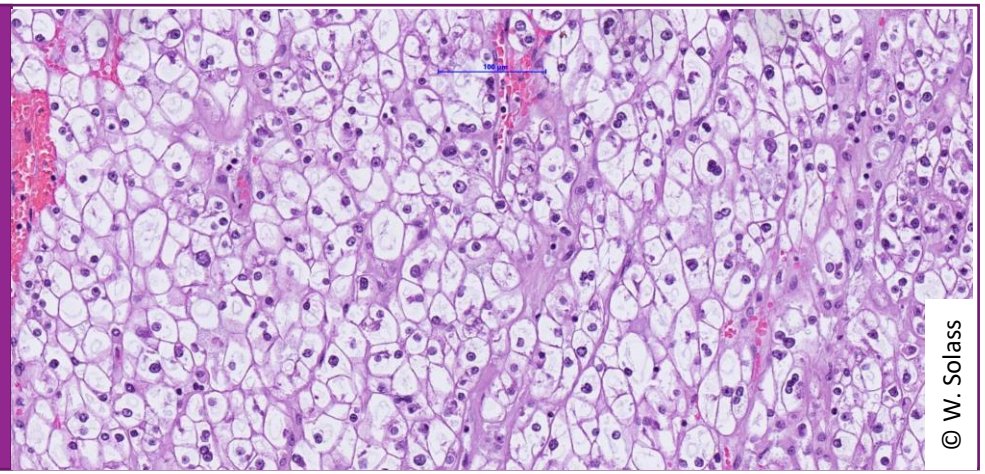
PROGNOSIS

Endometriosis is a risk factor for EC
Treatment response slightly better than HGSOC

Clear Cell Ovarian Carcinoma (CCC)

10%

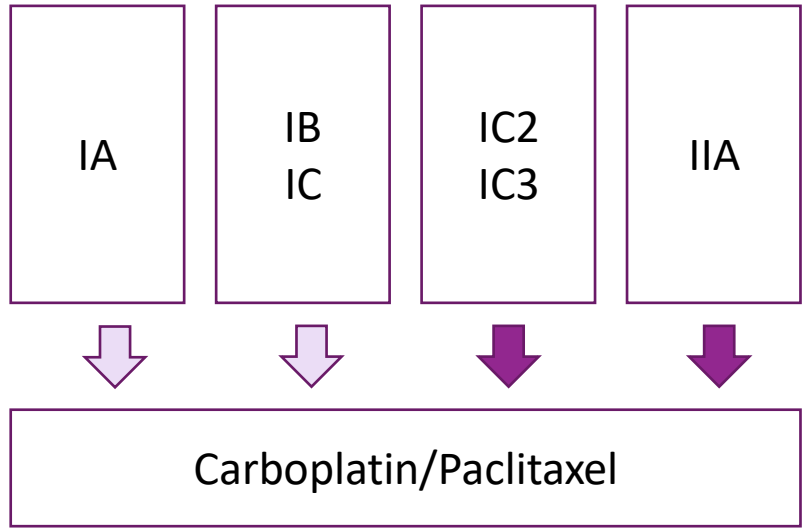
HISTOLOGY



GENOTYPE

- Mutational landscape
  - ARID1A (50%–75%), ARID1B (10%)- endometriosis
  - PIK3CA (40%–50%)- endometriosis
  - KRAS (15%)
  - PPP2R1A (15%)
  - TERT (15%)
  - TP53 (5%–20%)
  - PTEN (1%–5%)
- Significant overlap with EC

THERAPEUTIC ALGORITHM



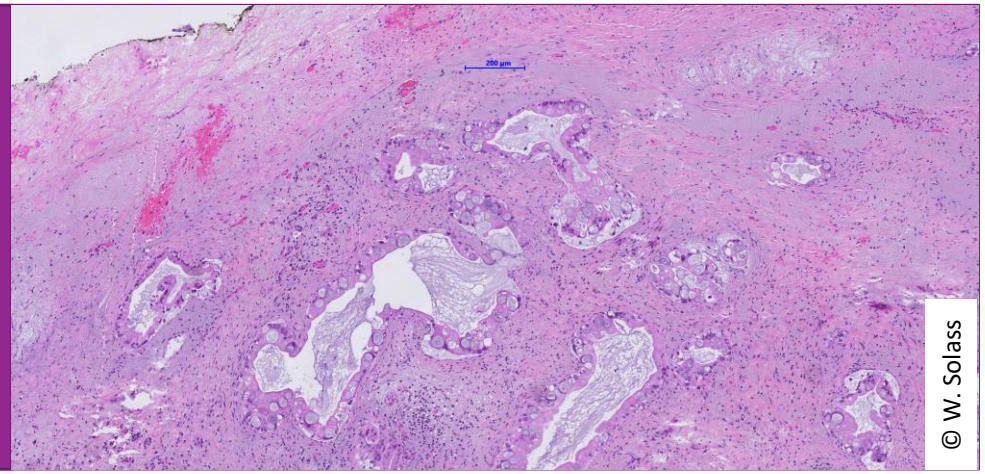
PROGNOSIS

Endometriosis is a risk factor for CCC

Mucinous Ovarian Carcinoma (MC)

5%

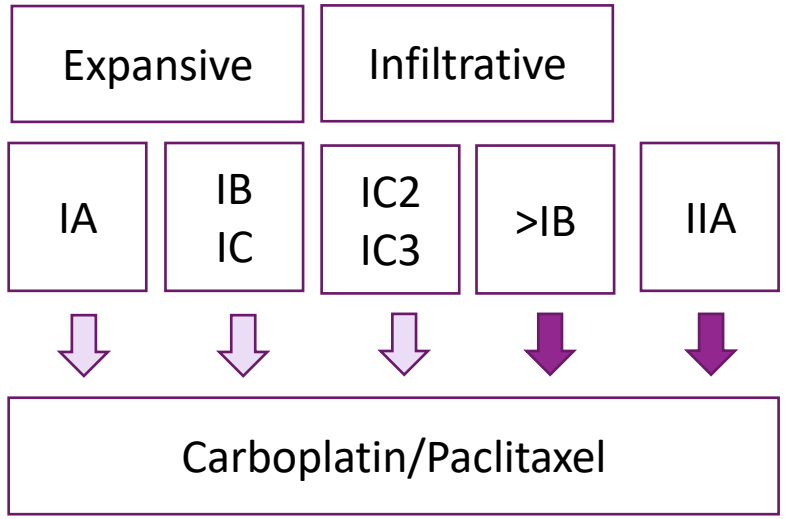
HISTOLOGY



GENOTYPE

- Mutational landscape
  - ARID1A (50%–75%), ARID1B (10%)- endometriosis
  - PIK3CA (40%–50%)- endometriosis
  - KRAS (15%)
  - PPP2R1A (15%)
  - TERT (15%)
  - TP53 (5%–20%)
  - PTEN (1%–5%)
- Significant overlap with EC and CCC

THERAPEUTIC ALGORITHM



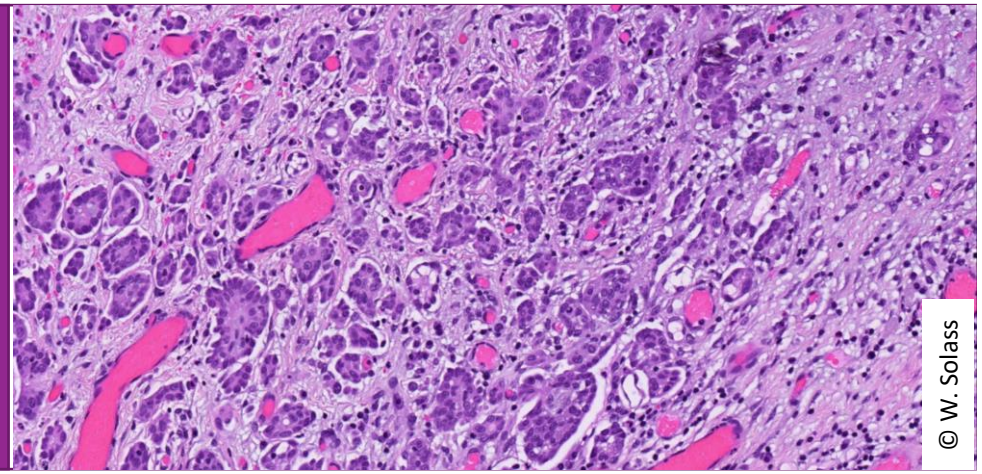
PROGNOSIS

Difficult to distinguish from metastatic mucinous GI tumors
When diagnosed early enough, prognosis is quite good.

Low-grade serous ovarian cancer (LGSOC)

3%

HISTOLOGY



GENOTYPE

- MAPK pathway gene mutations
  - 25% KRAS
  - 8% BRAF
  - 8% NRAS
- 15% EIFAX
- 11% USP9X
- P53 mutations << than HGSOC

THERAPEUTIC ALGORITHM

IA | IB | IC | IIA

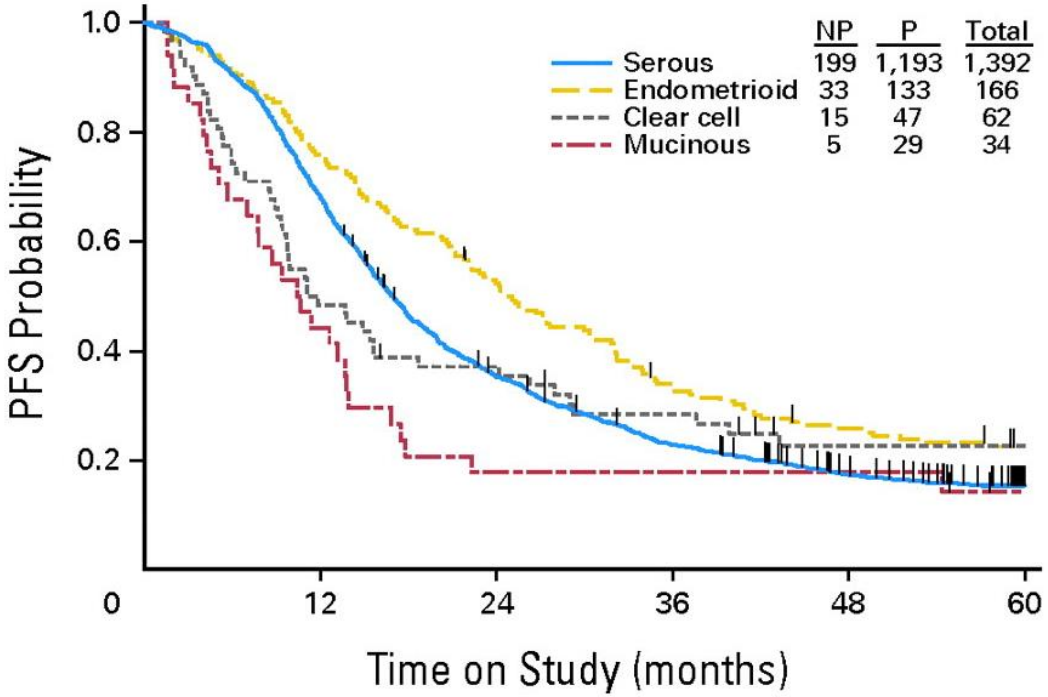
Carboplatin/Paclitaxel

PROGNOSIS

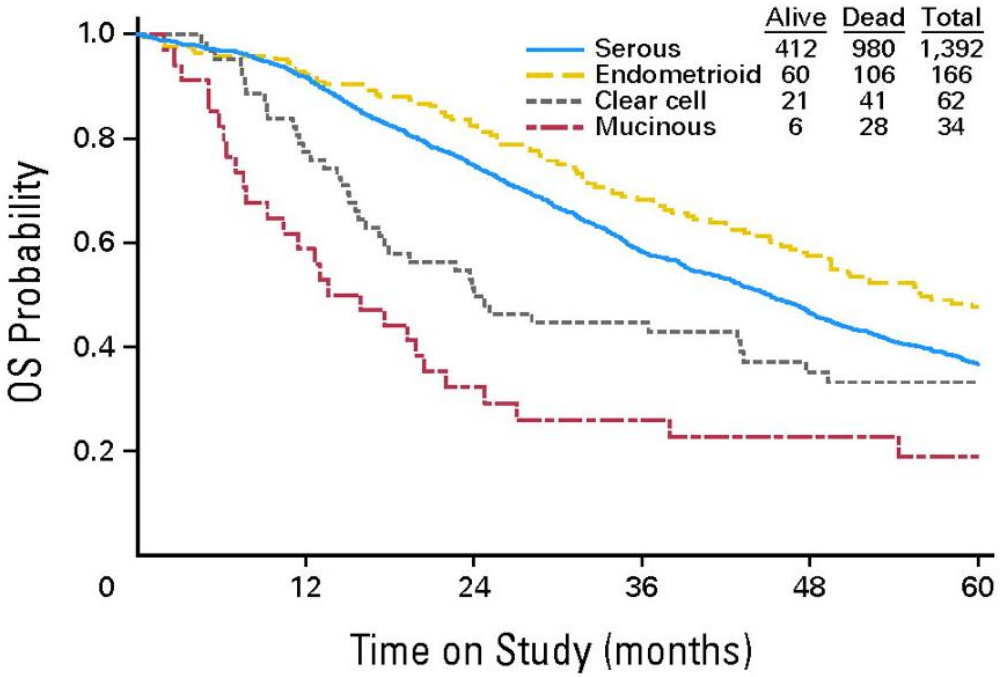
Less aggressive biological behavior
Lower sensitivity to chemotherapy
Good prognosis is detected early enough
Rarely develop into HGSOC

Prognosis of EOC depends on the histology

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



Winter WE 3rd et al, J Clin Oncol 2007

Histologic and Molecular Implications on Ovarian Cancer (OC) Treatment

Advancing innovative Therapies for Cancers that invade the Peritoneum and the Pleura

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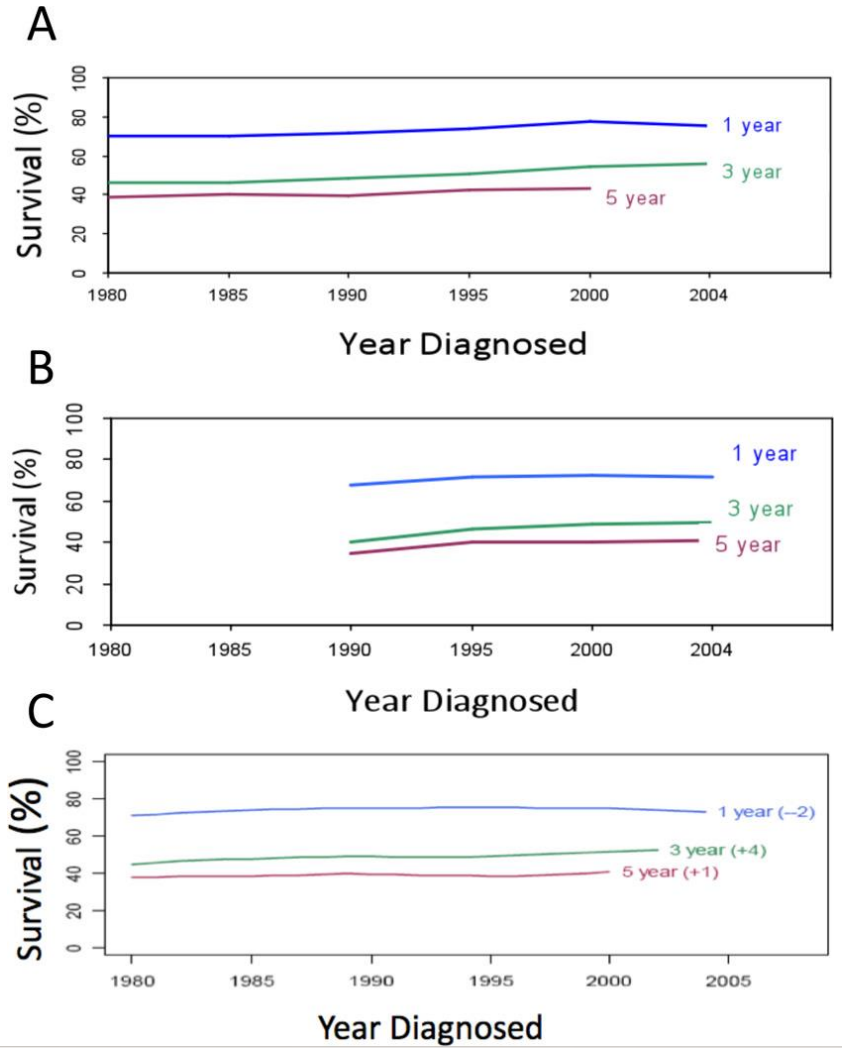
Treating ovarian cancer remains challenging

- The standard care for OC— a combination of surgery and chemotherapy — has remained almost unchanged since the 1960s
- No significant progress in overall survival
  - PARP-inhibitors: mature survival data expected 2023
  - Immune checkpoint inhibitors: disappointing in newly diagnosed OC



Vaughan et al, Nat Rev Cancer 2012

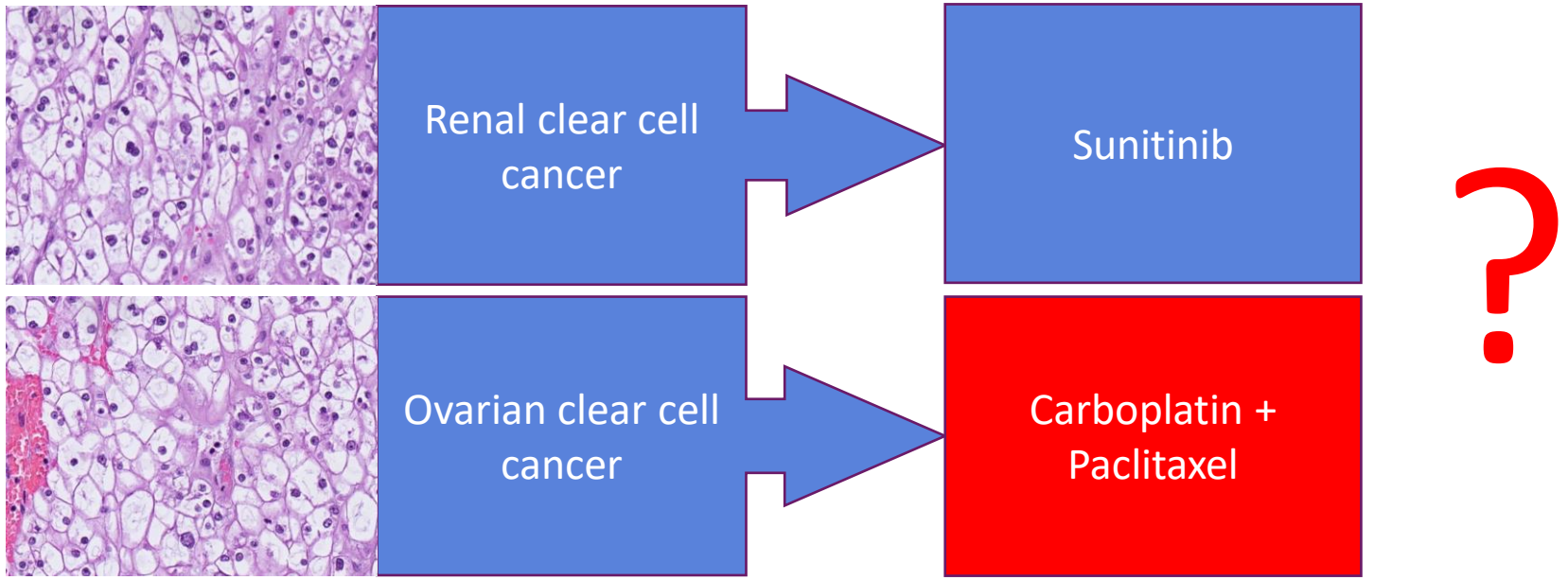
Does one therapy (Carboplatin + Paclitaxel) fit for all?

- Gold standard chemotherapy regimen (upfront) = Carboplatin + Paclitaxel
  - 70-80% of OC patients show initial response
  - 50-75% of responders relapse within 18 months after completing first-line therapy
  - Only 10% to 15% of patients who present with advanced disease experience long-term remission
- Lack of valid tools to predict whether they will be primary platinum resistant or not prior to chemotherapy

Paracchini et al, Oncotarget 2016; Herzog TJ, Clin Cancer Res 2004,
Arora et al Oncologist 2021, Li et al Front Oncol 2022

Does one therapy (Carboplatin + Paclitaxel) fit for all?

FOR EXAMPLE



"Taking a rigorous view, the ovarian histotypes should be regarded as distinct diseases, as their cell of origin, epidemiology, and driver mutations are quite different"

Vaughan et al, Nat Rev Cancer 2012,
Catopodis et al, Cancers 2019

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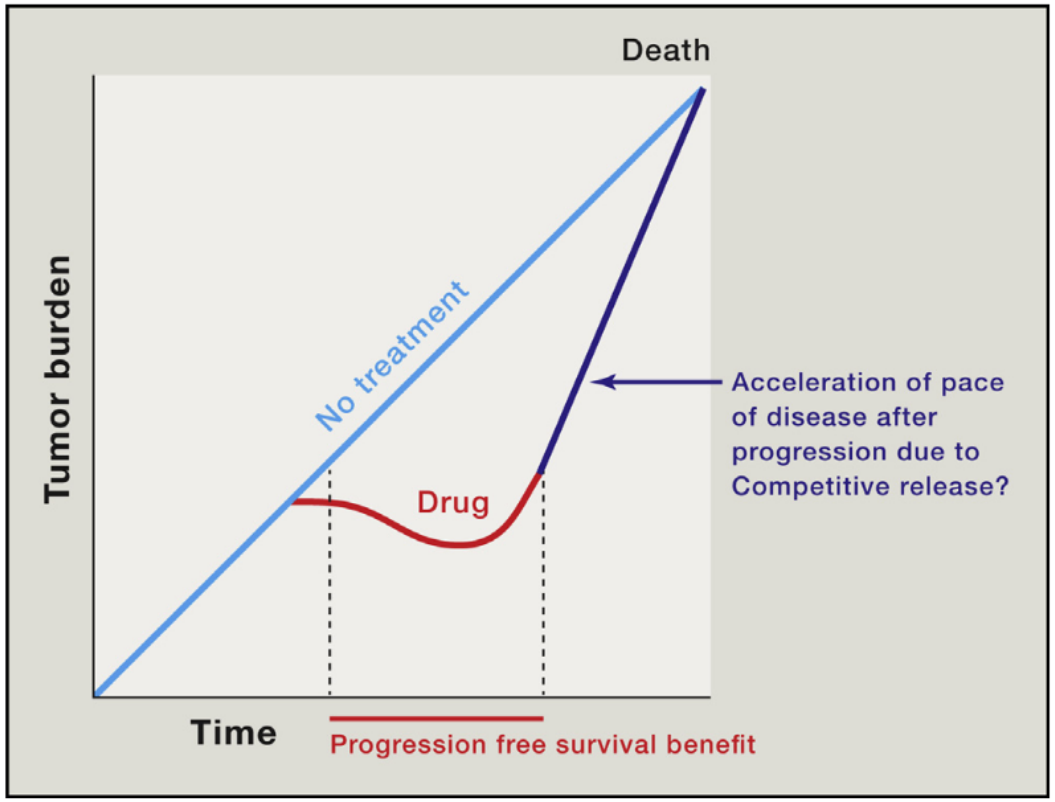
The challenge of chemoresistance in OC

Similar overall survival times, yet divergent progression-free survival times, between treated and untreated patients, may reflect the competitive release of aggressive subclones

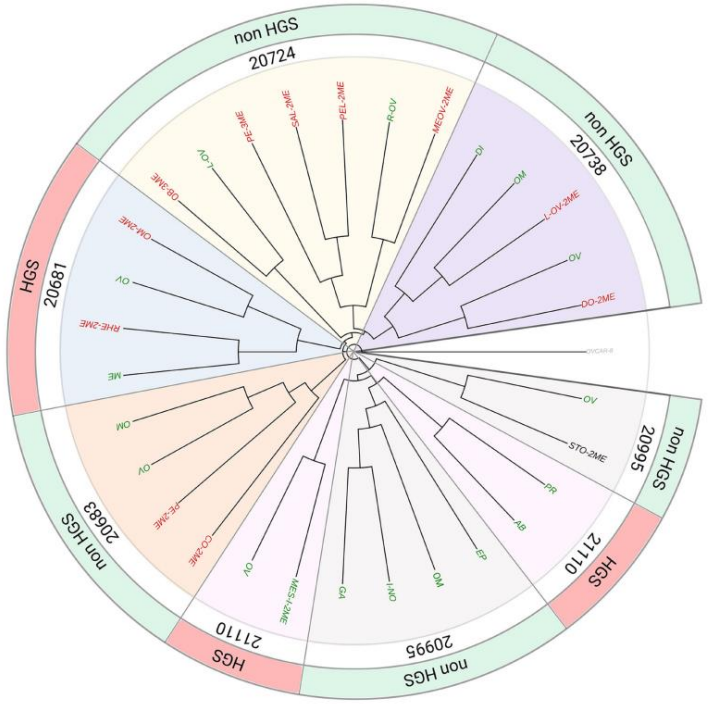
Platinum-resistant ovarian cancer has a median survival of 9–12 months and less than 15% respond to subsequent chemotherapy.



McGranahan et al, Cell 2017, Davis et al. Gynec Oncol 2014, Paracchini et al, Oncotarget 2021

Competitive Release of Resistance Subclones in OC

- In type 1 and Type 2 OC:
  - The genomic profile of a single tumor biopsy taken from the ovary is not representative
  - Relapsed disease arises probably **not from new mutations but from resistant clones originally present** in one of the primary lesions
  - The outgrowth of resistant subclones is favored by the selective pressure of standard chemotherapeutic treatment

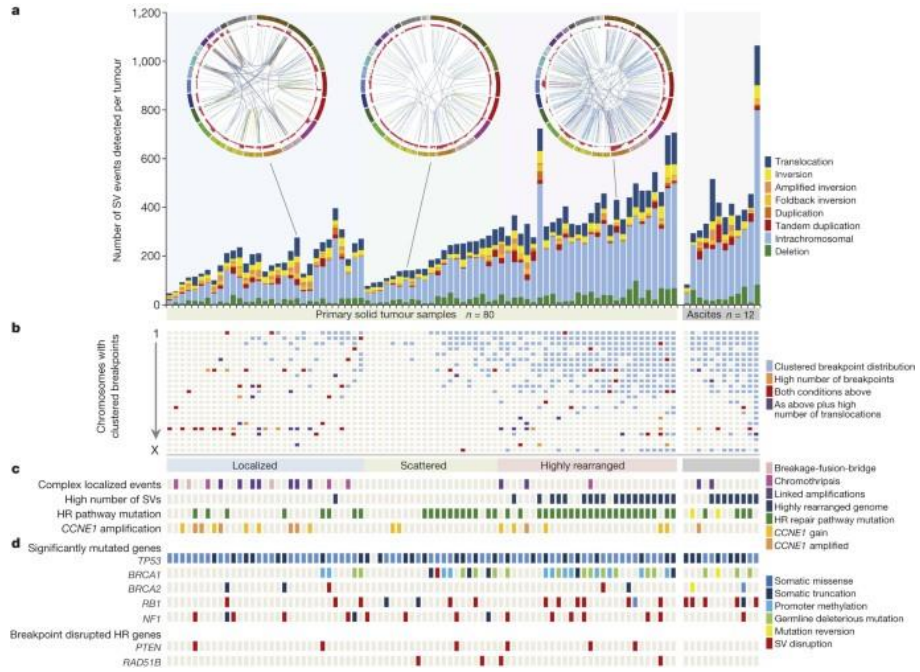


71 tumor biopsies taken from 12 HGSOC and 7 non-HGSOC, at the time of primary surgery (chemonaive tumor) and after chemotherapy. Targeted NGS sequencing (65 genes). Phylogenetic tree.

Paracchini et al, Oncotarget 2021

Whole-genome characterization of chemoresistant HGSOC

- Inactivation of the tumor suppressors RB1, NF1, RAD51B, and PTEN
- CCNE1 amplification common in refractory HGSOC
- Acquired resistance associated with:
  - reversions of germline BRCA1 or BRCA2 mutations
  - loss of BRCA1 promoter methylation
  - overexpression of the drug efflux pump MDR1



92 women with primary refractory, resistant, sensitive and matched acquired resistant HGSOC
Whole-genome sequencing of tumor and germline DNA samples

Patch et al, Nature 2015

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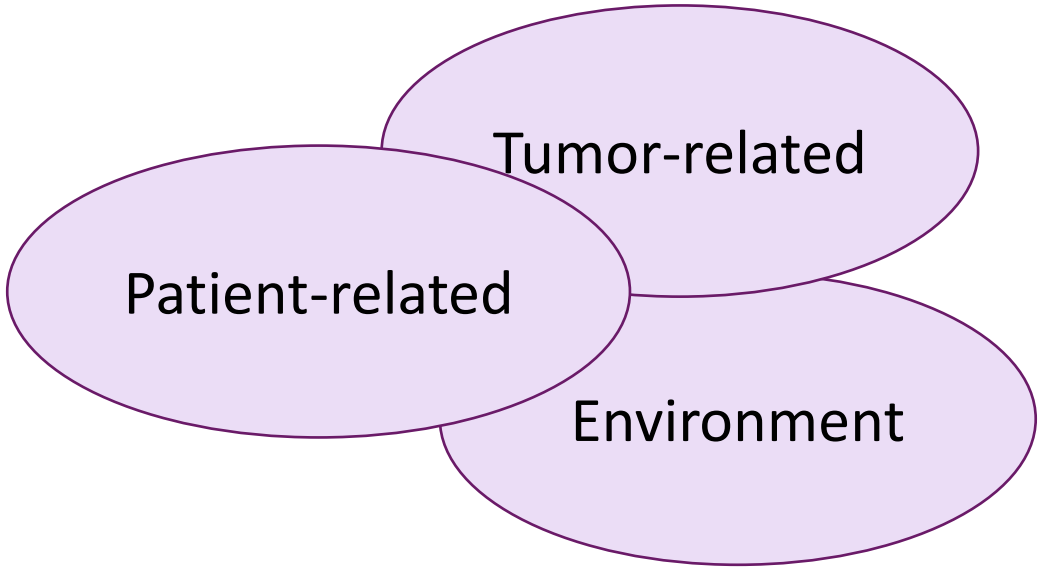
Diagnosis means generalization,
ignoring the individual

Prognosis means individualization,
looking at the individual

Prognostic factors: dealing with complexity

Prognostic factors



Intervention

Outcome

Endpoint : PFS, OS, Quality of life

New opportunities: AIML

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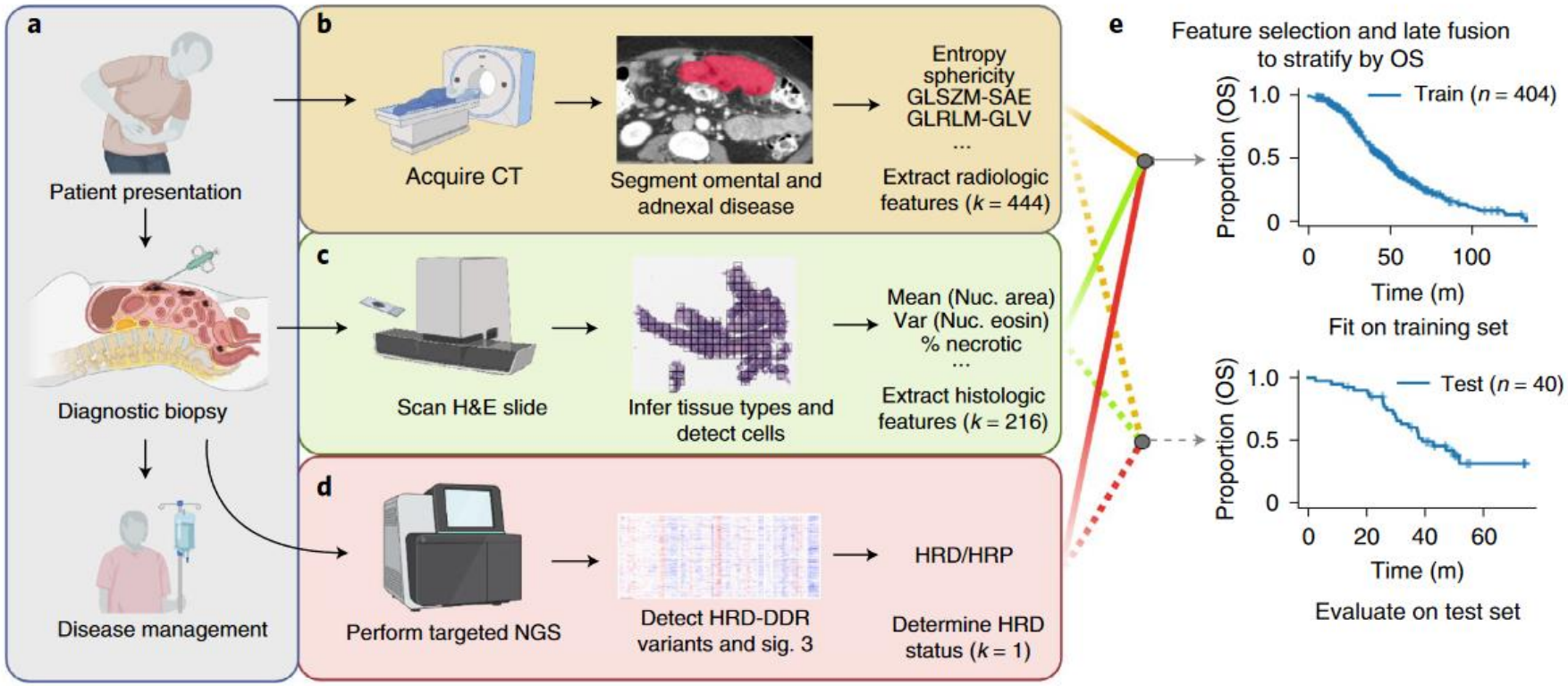
New opportunities: AIML

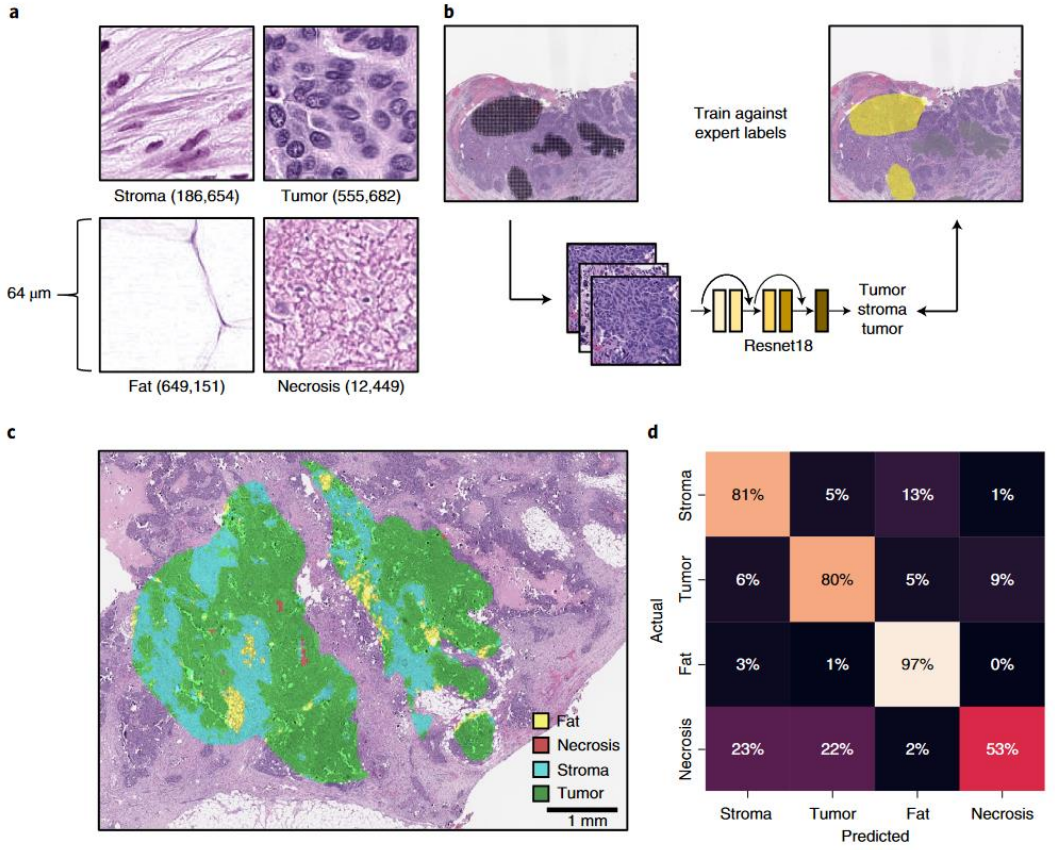
Multimodal data integration using machine learning improves risk stratification of HGSOC



Boehm et al Nature Cancer 2022

New opportunities: AIML

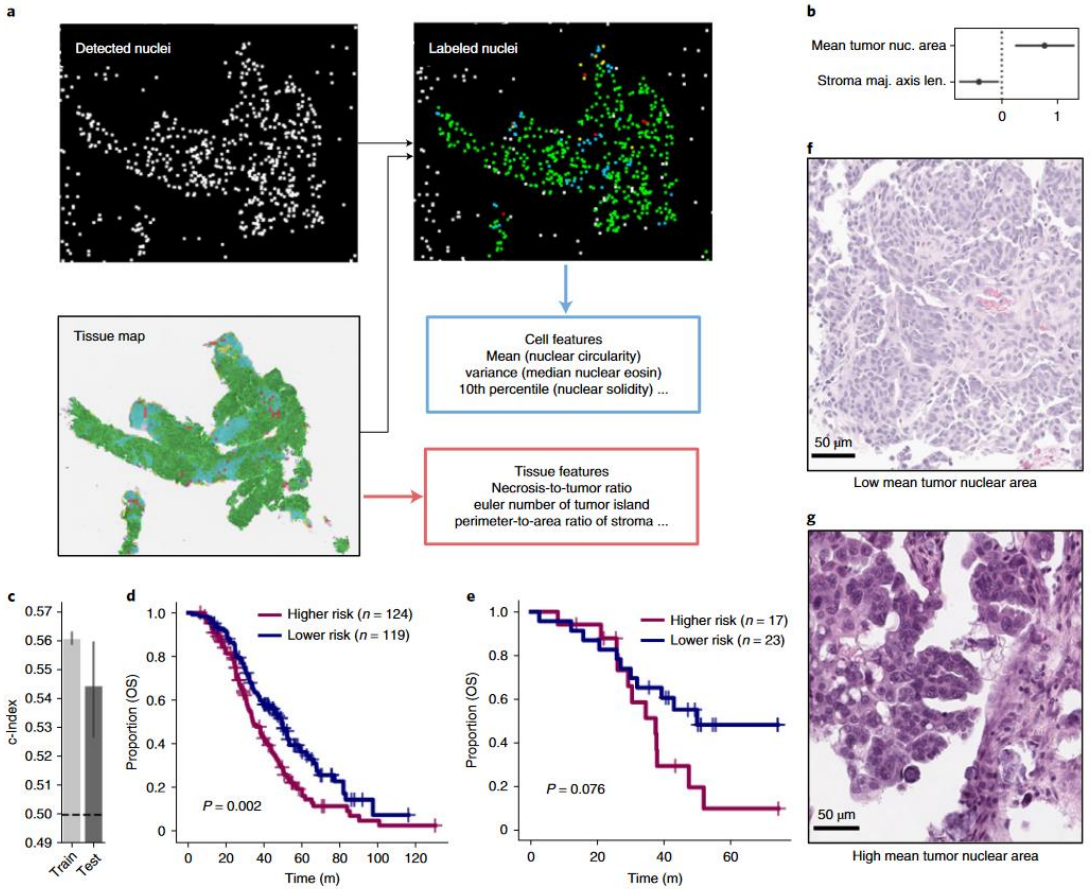
Weakly supervised deep learning accurately infers HGSOC tissue type on H&E



Boehm et al Nature Cancer 2022

New opportunities: AIML

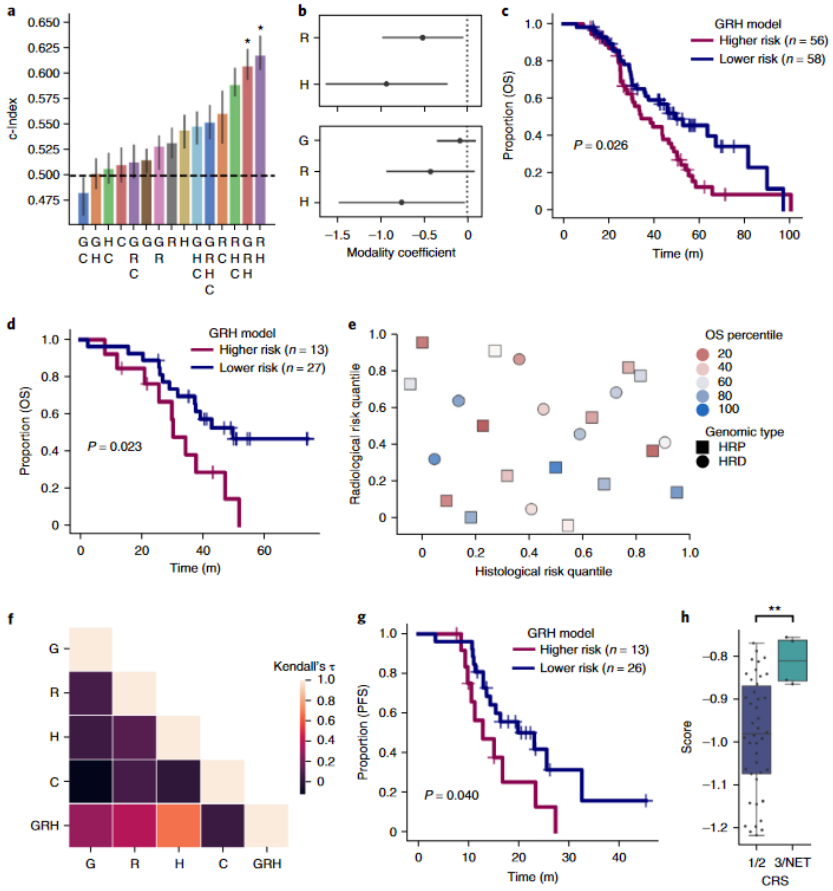
Interpretable histopathological features stratify HGSOC patients by OS



Boehm et al Nature Cancer 2022

New opportunities: AIML

Multimodal integration improves stratification and identifies clinically significant subgroups



Boehm et al Nature Cancer 2022

Conclusion

- The prognosis of OC depends on the histology and the molecular landscape
- Should start to adapt the treatment regimen according to that
- AIML can improve the stratification and identification of clinically significant subgroups

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