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A.O. Mauriziano - Torino

TUMORE DELL'OVAIO: VERSO UNA NUOVA CLASSIFICAZIONE

3°Edizione

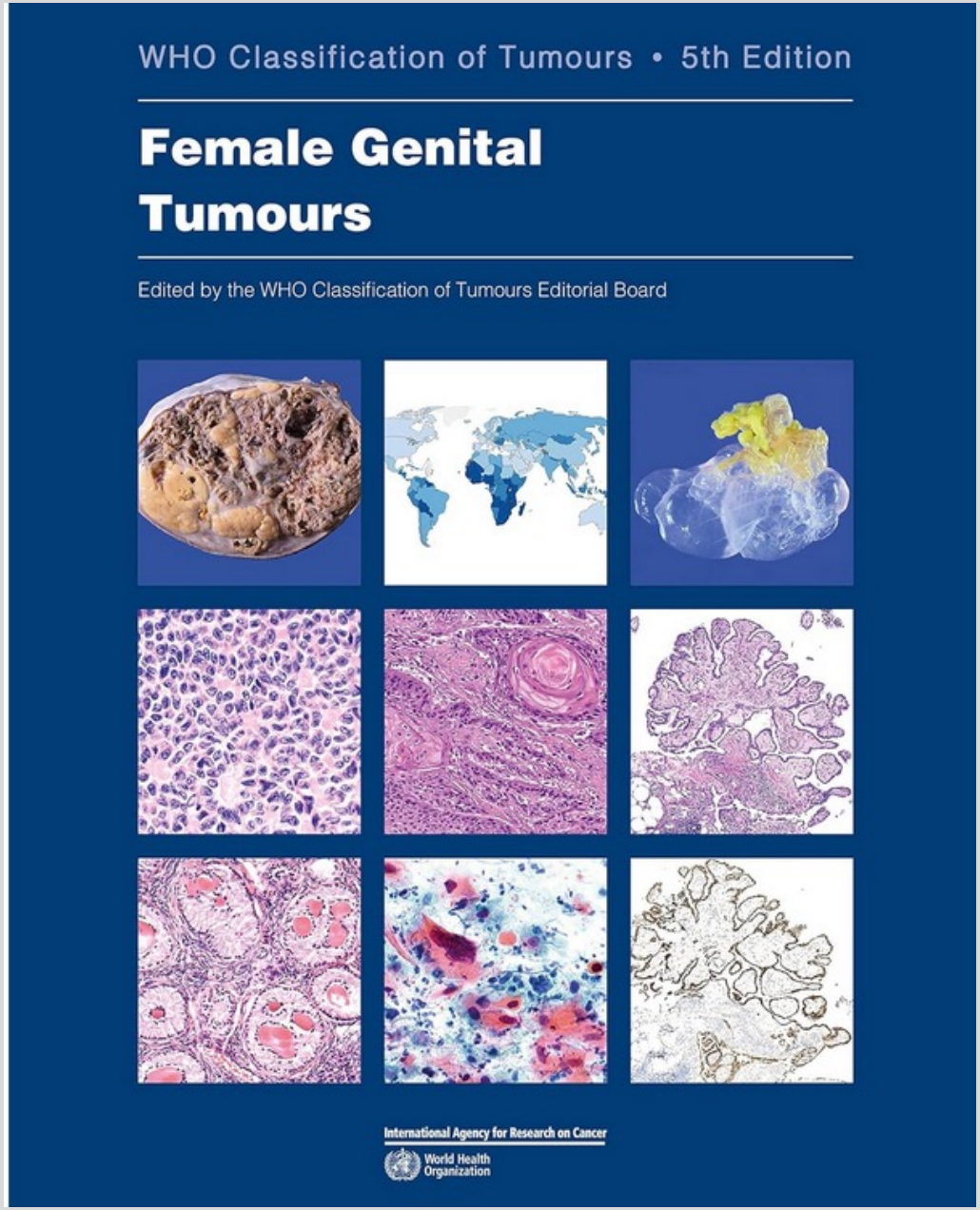
I tumori femminili

Dal gene profiling alla terapia personalizzata

22-23 Novembre 2023

Casale Monferrato, AL

Hotel Candiani


WHO Classification of Tumours • 5th Edition
Female Genital Tumours
Edited by the WHO Classification of Tumours Editorial Board
International Agency for Research on Cancer
World Health Organization

REVIEW

The Dualistic Model of Ovarian Carcinogenesis

Revisited, Revised, and Expanded

Robert J. Kurman and Ie-Ming Shih

Table 1 Clinicopathologic and Molecular Features of Type I and Type II Ovarian Carcinomas

Features	Type I	Type II
Stage	Frequently early stage	Almost always advanced stage
Tumor grade	Low grade*†	High grade
Proliferative activity	Generally low	Always high
Ascites	Rare	Common
Response to chemotherapy	Fair	Good (but recur later)
Early detection	Possible	Challenging
Progression	Slow and indolent	Rapid and aggressive
Overall clinical outcome	Good	Poor
Risk factors	Endometriosis	Lifetime ovulation cycles; BRCA germline mutations
Origin	See *Morphologic and Molecular Features of Precursor Lesions*	Mostly tubal
Precursors	Atypical proliferative (borderline) tumors	Mostly STICs
Chromosomal instability	Low	High
TP53 mutation	Infrequent	Almost always
Homologous recombination repair	Rarely defective	Frequently defective
Actionable mutations	Can be present	Rare

REVIEW

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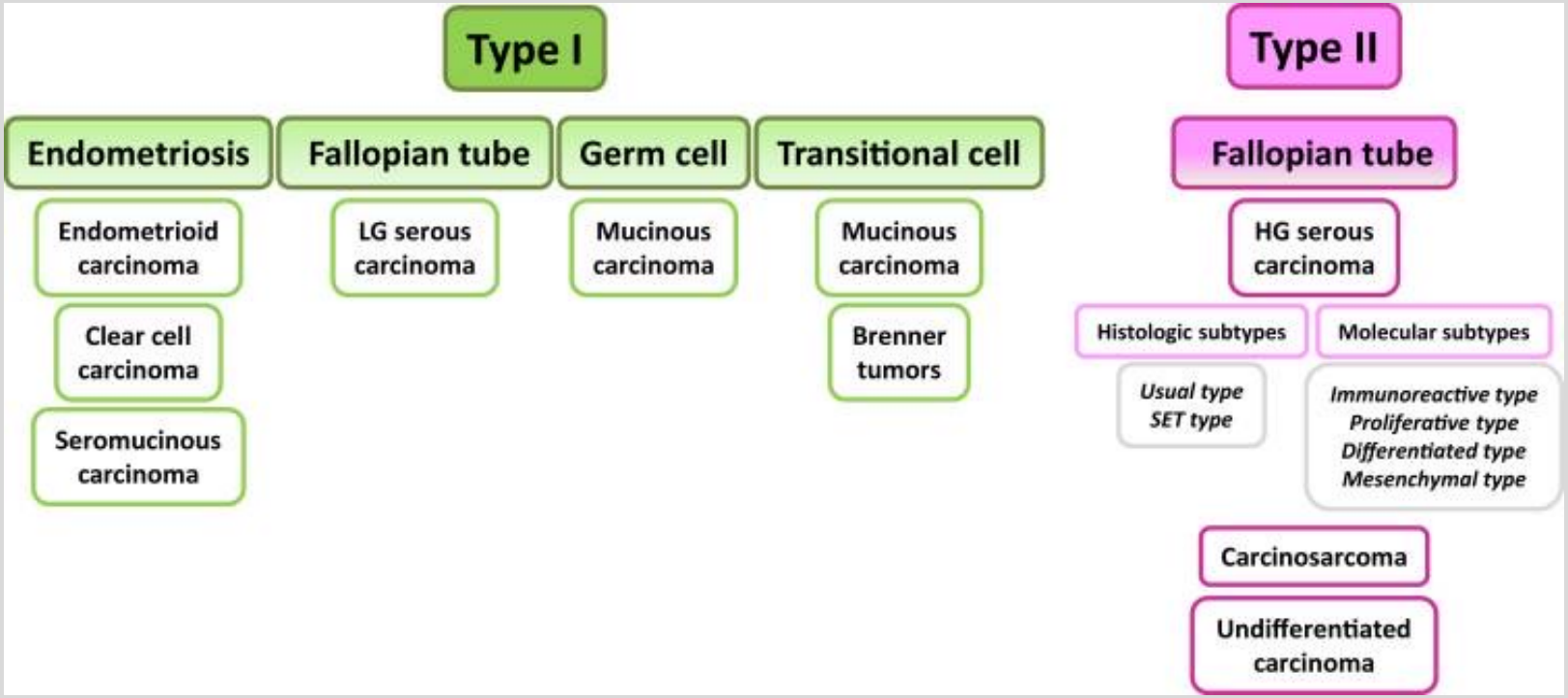
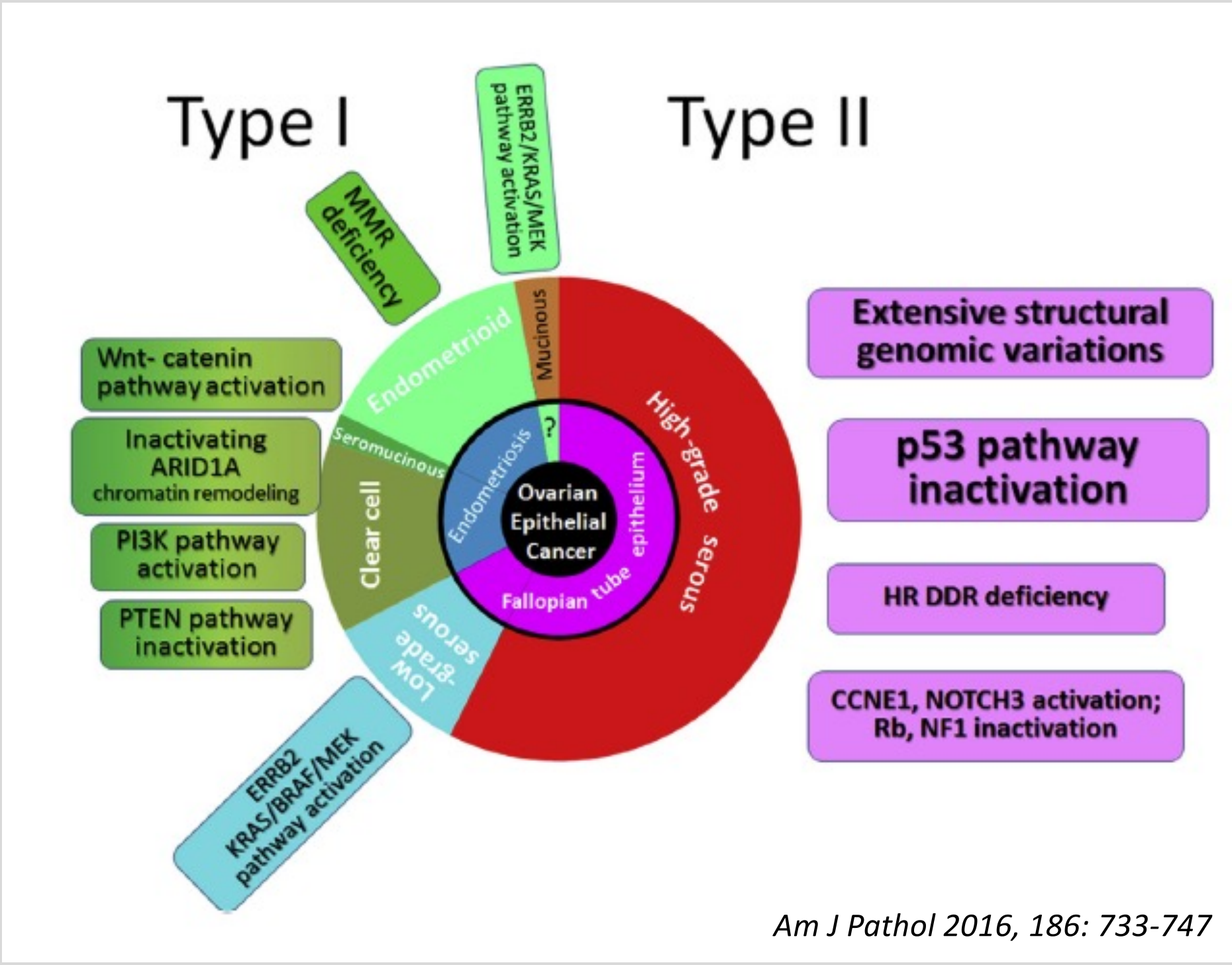
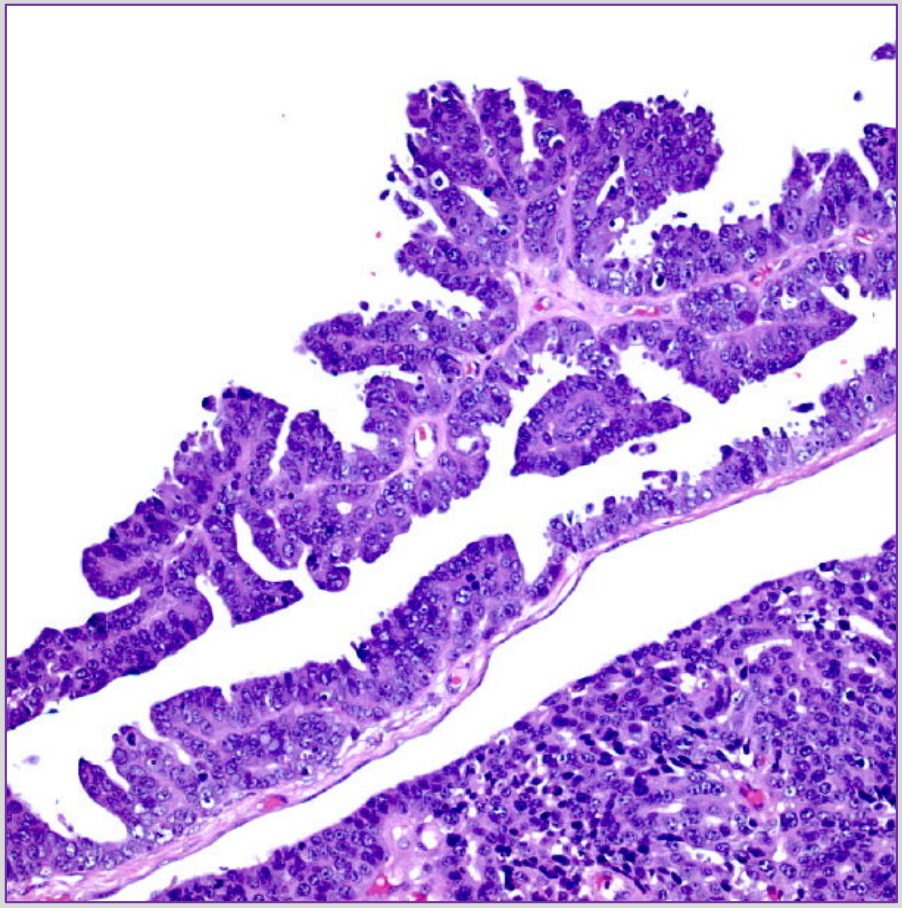




Am J Pathol 2016, 186: 733-747

HIGH GRADE SEROUS CARCINOMA

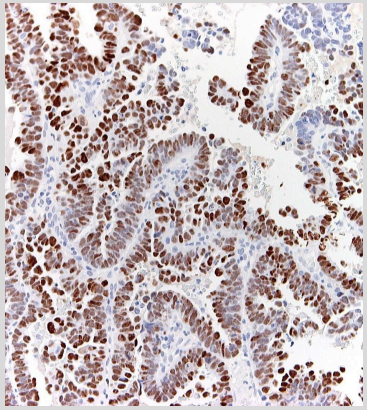
- Deriva dall'epitelio celomatico di superficie.
- 2 sottotipi: usuale (architettura papillare, ghiandolare o cribriforme) e SET variant (solido, pseudoendometrioide e transizionale).

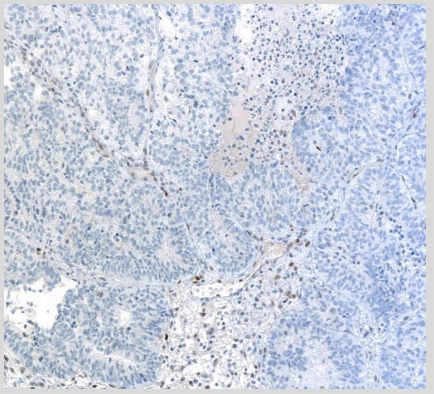


HIGH GRADE SEROUS CARCINOMA

IIC

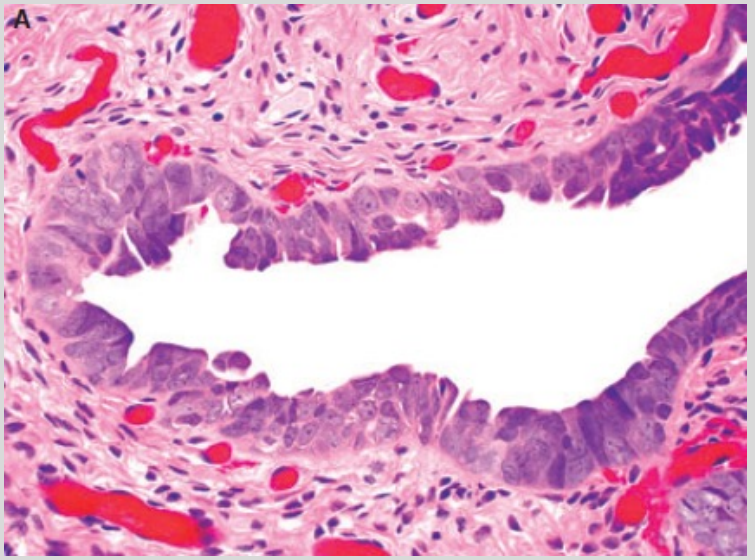
- WT1+
- CA125+
- ER+
- p16+
- p53 con pattern mutato (*“all or nothing”)*

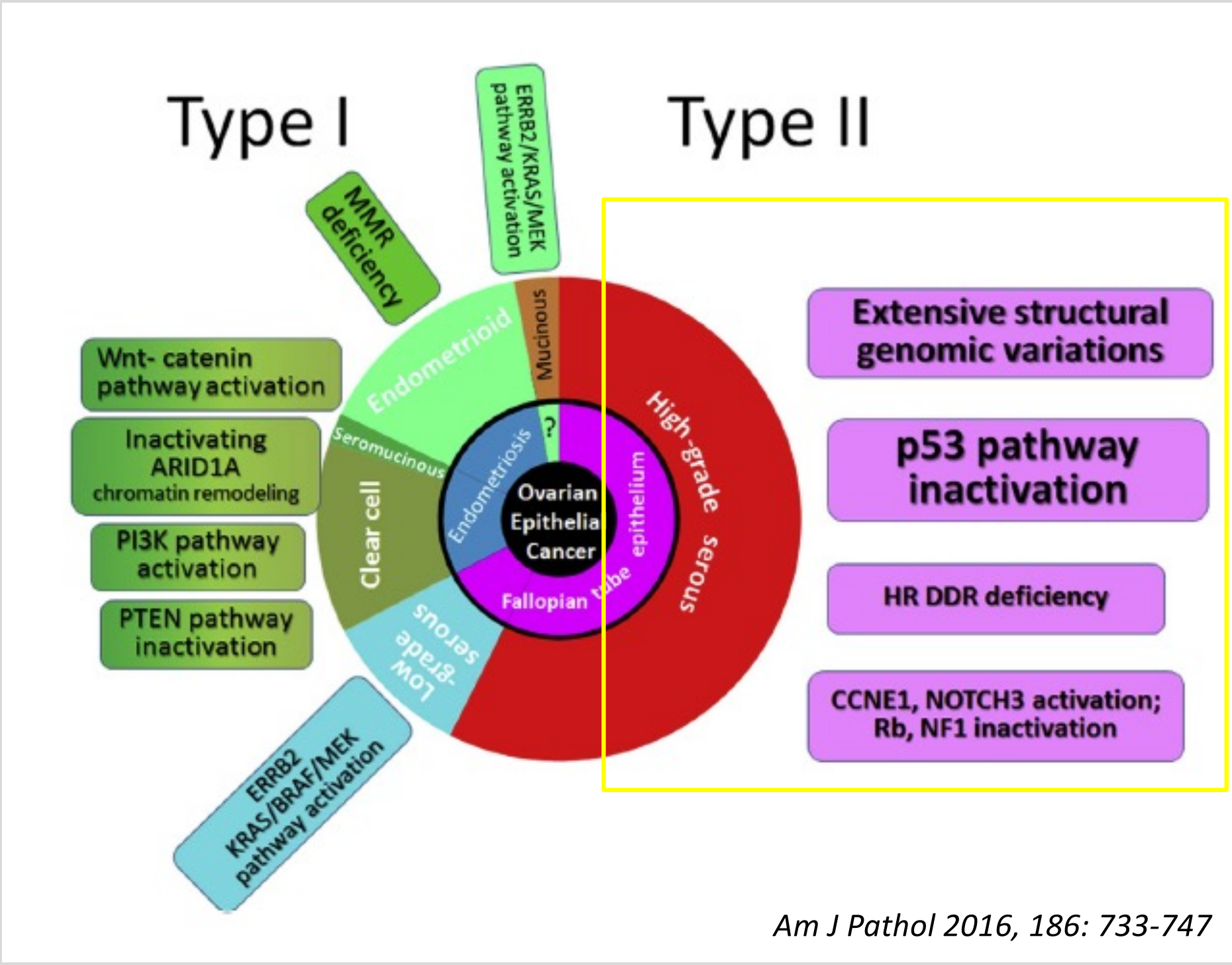




p53 mut

Riconosce come precursore il carcinoma intraepiteliale tubarico (STIC)

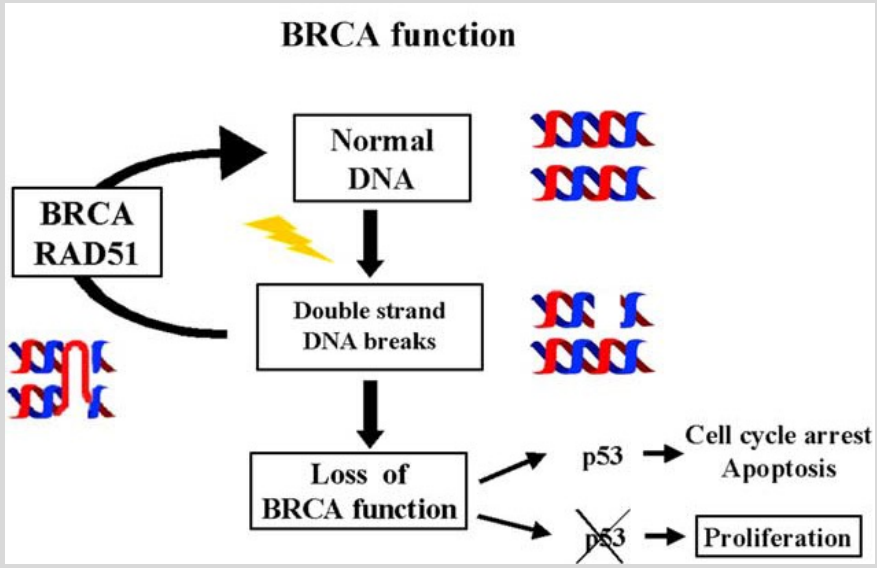




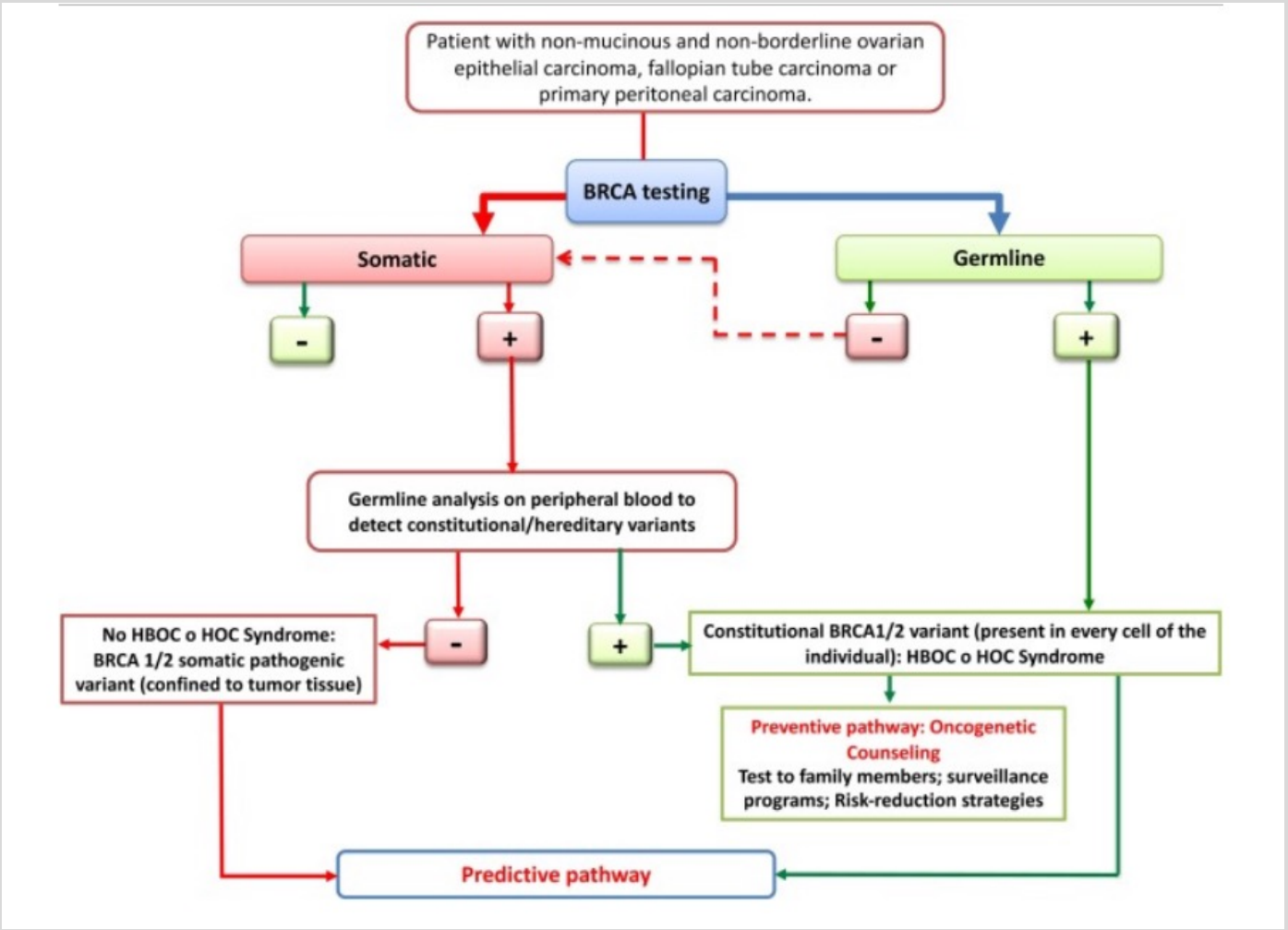
Am J Pathol 2016, 186: 733-747

CAUSE HRD (Homologous Recombination Deficiency)

1. MUTAZIONI SOMATICHE O GERMINALI *BRCA1* E *BRCA2*
2. MUTAZIONI DI ALCUNI GENI COINVOLTI NEL SISTEMA DI RICOMBINAZIONE OMOLOGA (*RAD51/ATM/BRIP1*)
3. METILAZIONE DI *BRCA1* O *RAD51* (mutualmente esclusivo con le mutazioni somatiche ma con gli stessi effetti prognostici e predittivi)



Human Pathology (2005) 36, 861– 870



- Dare la precedenza al test somatico vs germinale
- Permette di identificare il 7% circa di casi che rimarrebbero sconosciuti con il test germinale

Recommendations for the implementation of BRCA testing in ovarian cancer patients and their relatives. Crit Rev Oncol Hematol. 2019 Aug;140:67-72. AIOM-SIGU-SIBIOC-SIAPEC-IAP Working Group.

TEST SOMATICO

- Blocchetto FFPE
- Preparati istologici e/o citologici
- Cellularità tumorale >20%
- Fattori preanalitici (tempo di ischemia fredda, tipo di fissativo, tempo di fissazione)
- Preferire il materiale più recente
- Tecniche di NGS
- Laboratori di riferimento che effettuano CdQ

IMPLEMENTAZIONE DEL TEST DI BRCA

- IDENTIFICARE UN SET DI CARCINOMI A PROGNOSI MIGLIORE
- IDENTIFICARE UN SET DI CARCINOMI CHE RISPONDONO BENE AL PLATINO
- POSSIBILITA' DI UTILIZZARE PARP INIBITORI
- ATTIVITARE UNA SORVEGLIANZA CLINICO-GENETICA NEI CONFRONTI DEL PAZIENTE STESSO (predisposizione ad altri tumori) E DEI FAMILIARI.

Recommendations for the implementation of BRCA testing in ovarian cancer patients and their relatives. Crit Rev Oncol Hematol. 2019 Aug;140:67-72. AIOM-SIGU-SIBIOC-SIAPEC-IAP Working Group.

50% DEI CARCINOMI OVARICI SIEROSI DI ALTO GRADO MOSTRANO ALTERAZIONI DEL SISTEMA DI RICOMBINAZIONE OMOLOGA DEL DNA (HRD Homologous Recombination Deficiency)
… FENOTIPO BRCANESS…

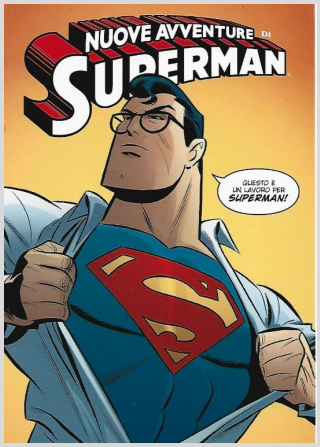
- HRD si correla con la risposta al trattamento con platino e PARP inibitori (meccanismo di letalità sintetica sulle cellule che sono prive di HR)
- Permette di stabilire entità del beneficio di PARP inibitori nei pz con BRCA wt

ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019 May 1;30(5):672-705.

Esistono delle *«reverse mutations»* che ristabiliscono il corretto funzionamento del sistema HR e che potrebbero essere correlate allo sviluppo delle resistenze ai trattamenti con platino o con PARP inibitori. Attualmente però non vengono ricercate

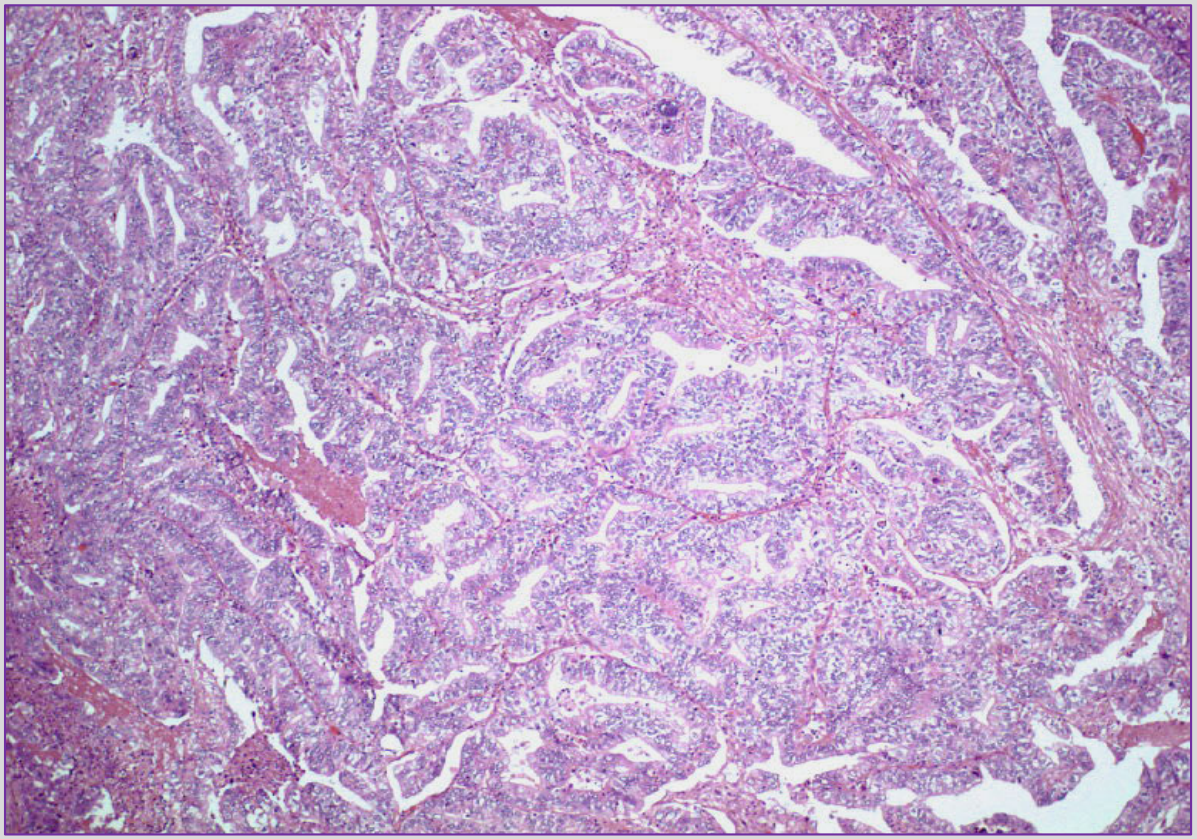
…PROSPETTIVE FUTURE…

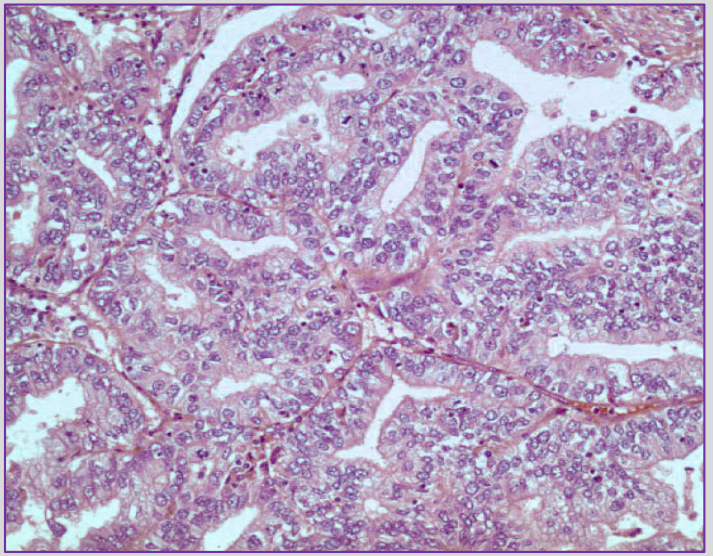
- Sviluppare un sistema composto di più marker che comprenda l'assetto mutazionale, le cicatrici genomiche e i test funzionali per valutare lo stato attuale di HRR per ciascun tumore ed eventuali reverse mutations.



Carcinoma endometrioide

- Frequenza del 9-11%.
- Architettura ghiandolare *back-to-back*, con invasione stromale.



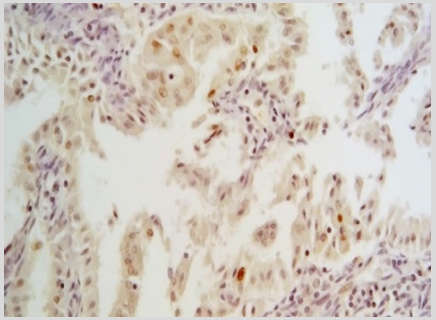


Carcinoma endometrioide

IIC

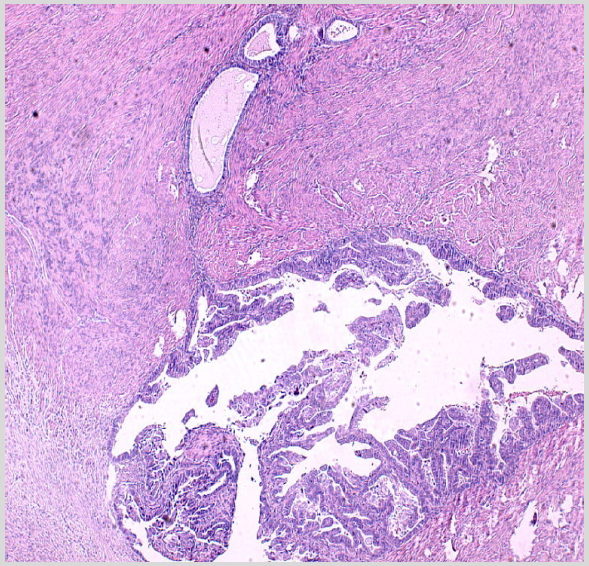
- ER+
- Ca125+

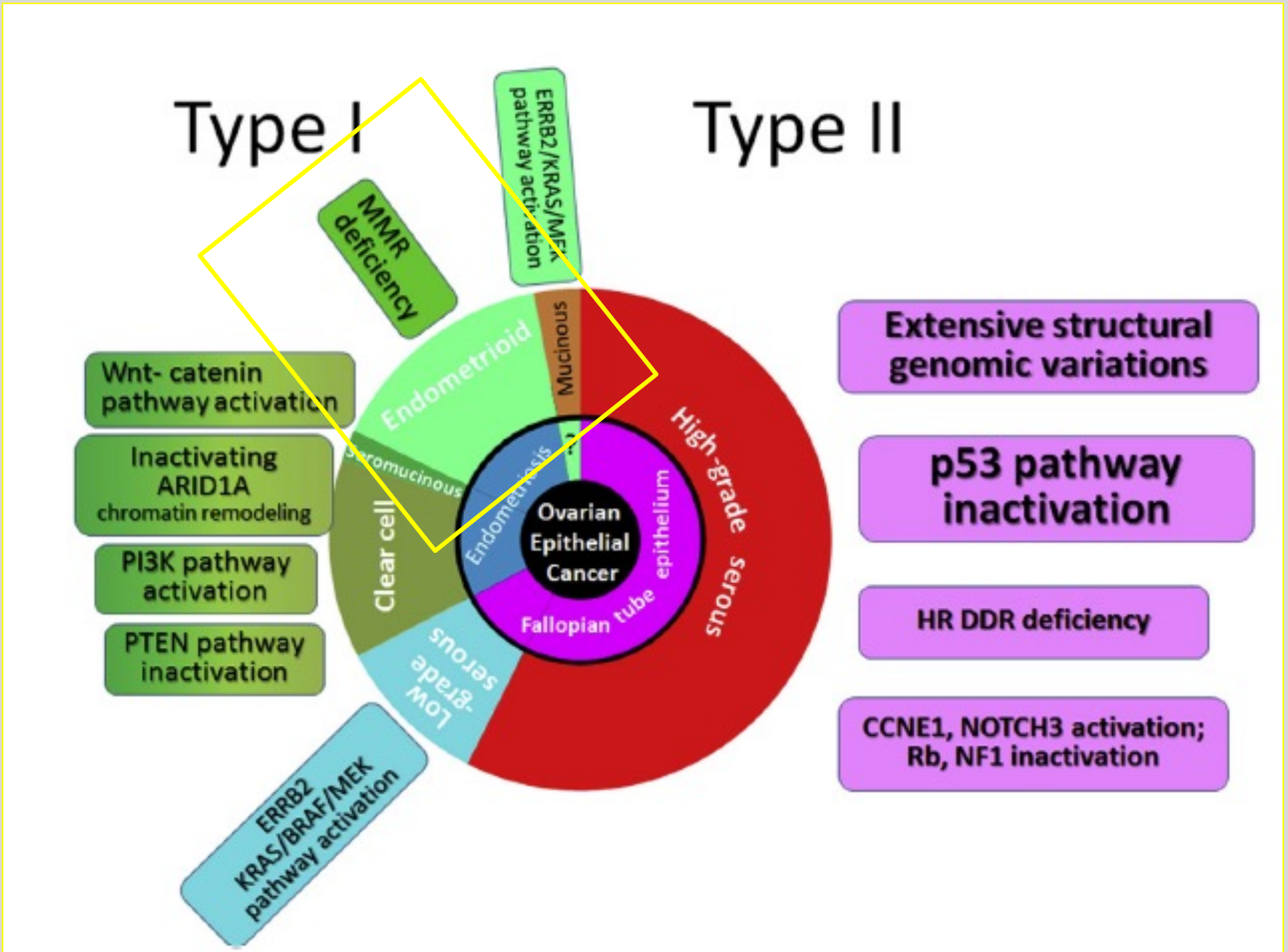
- WT1-
- P16-
- p53 con pattern *wild-type*



p53 wt

Riconosce come precursore l'endometriosi





Am J Pathol 2016, 186: 733-747

PROGNOSI

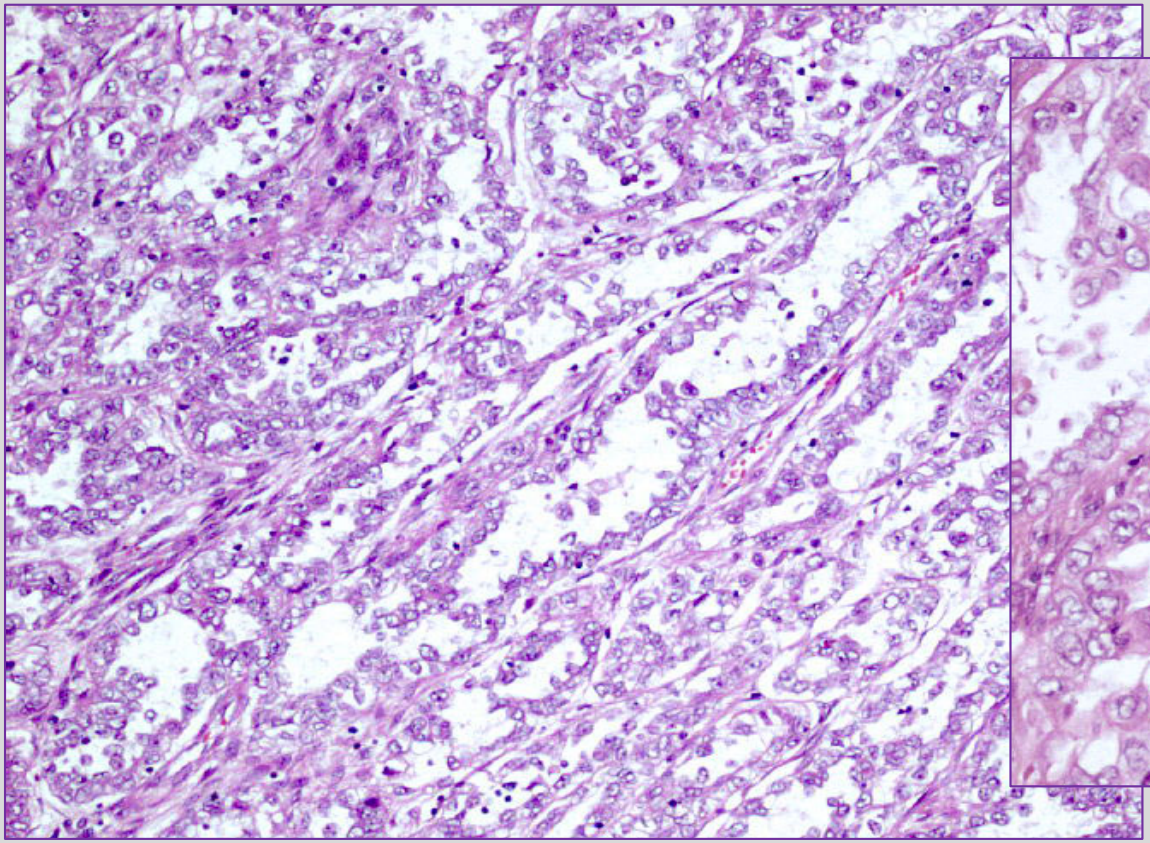
4 sottogruppi (analogia con k endometrio):

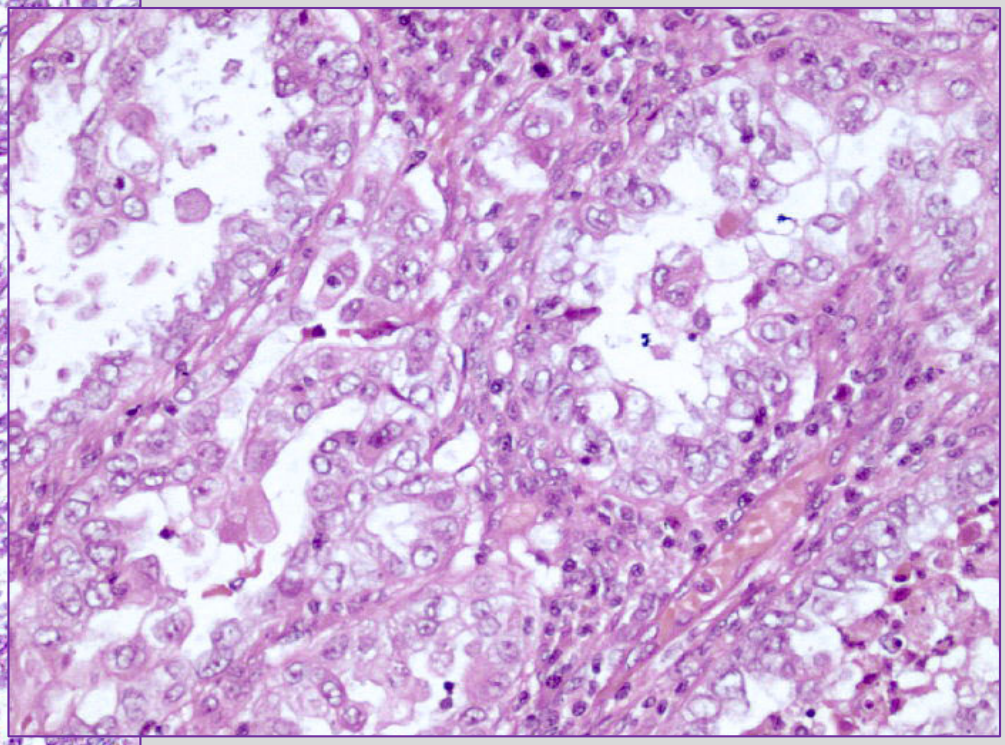
- POLE mutated
- MMRd
- No specific molecular profile
- P53 mutated

Krämer et all «Endometrial Cancer Molecular Risk Stratification is Equally Prognostic for Endometrioid Ovarian Carcinoma» Clin Cancer Res. 2020 Oct 15;26(20):5400-5410.

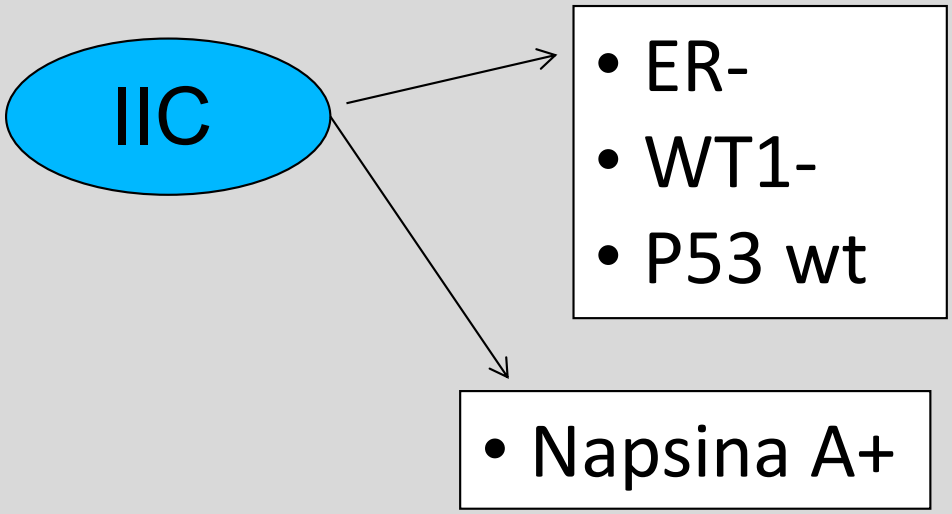
Carcinoma a cellule chiare

- Frequenza del 12-13%.
- Cellule con citoplasma chiaro con rinforzo di membrana opp eosinofilo o hobnail, disposte in pattern architetturali multipli e associati (tubulo-cistico, ghiandolare, solido, papillare).

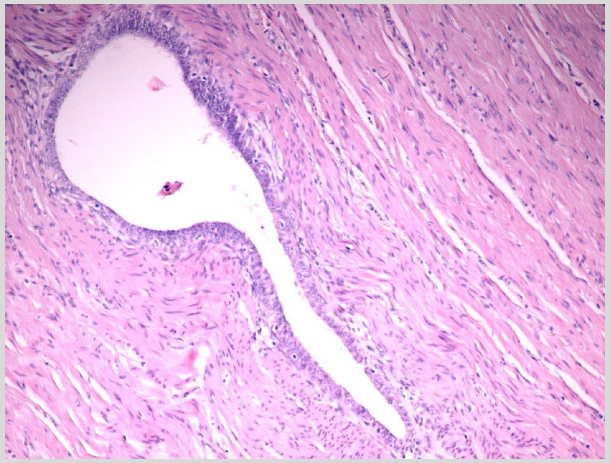


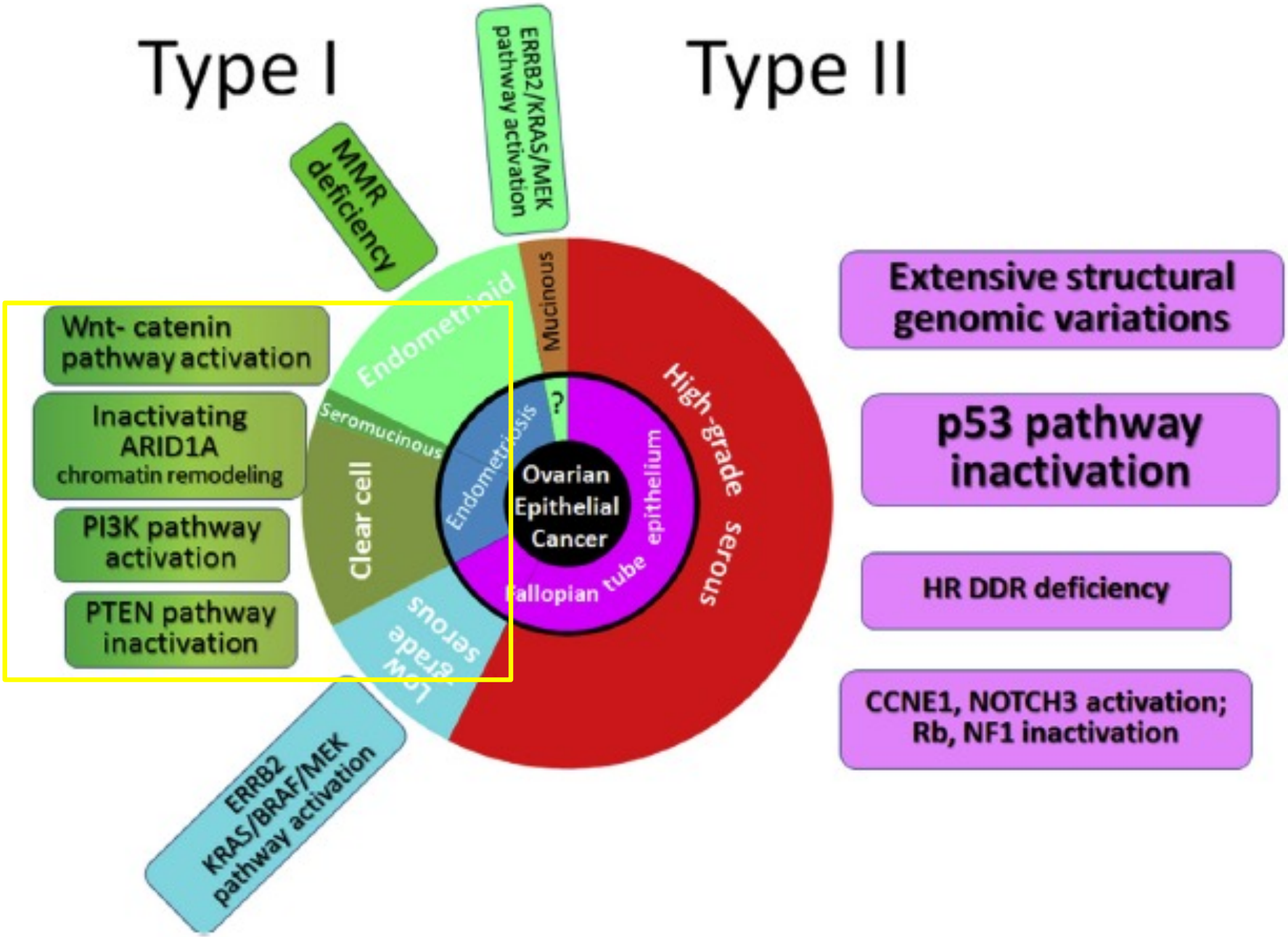


Carcinoma a cellule chiare



Riconosce come precursore l'endometriosi

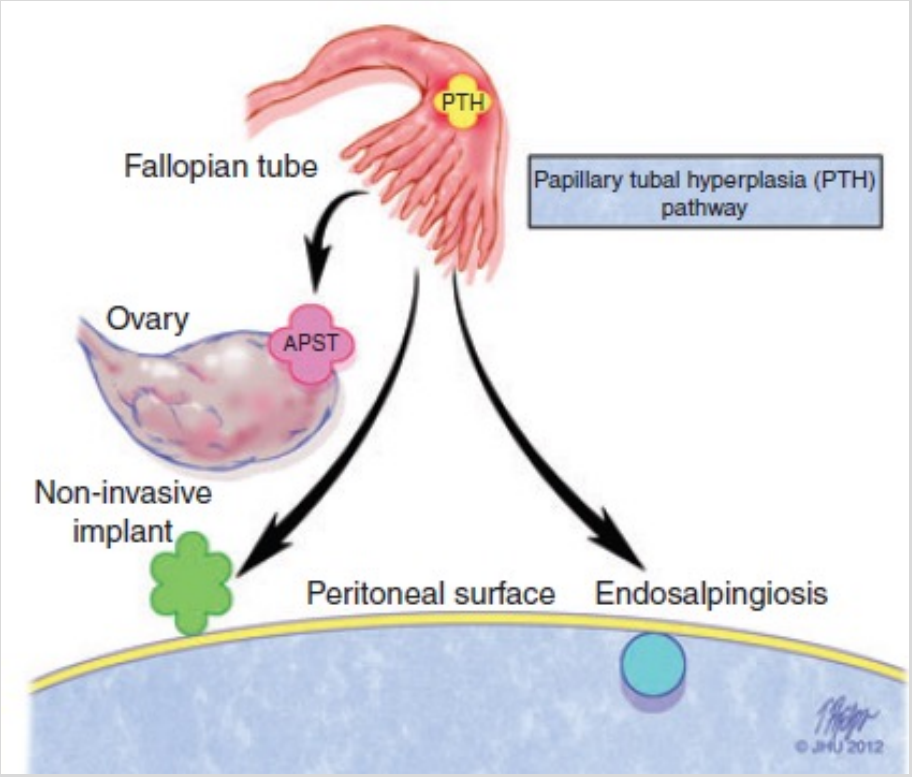




Am J Pathol 2016, 186: 733-747

LOW GRADE SEROUS CARCINOMA

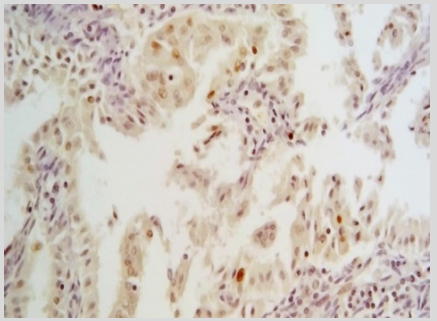
- E'una neoplasia poco frequente
- Riconosce come precursore l'iperplasia tubarica papillare e poi il tumore border-line.



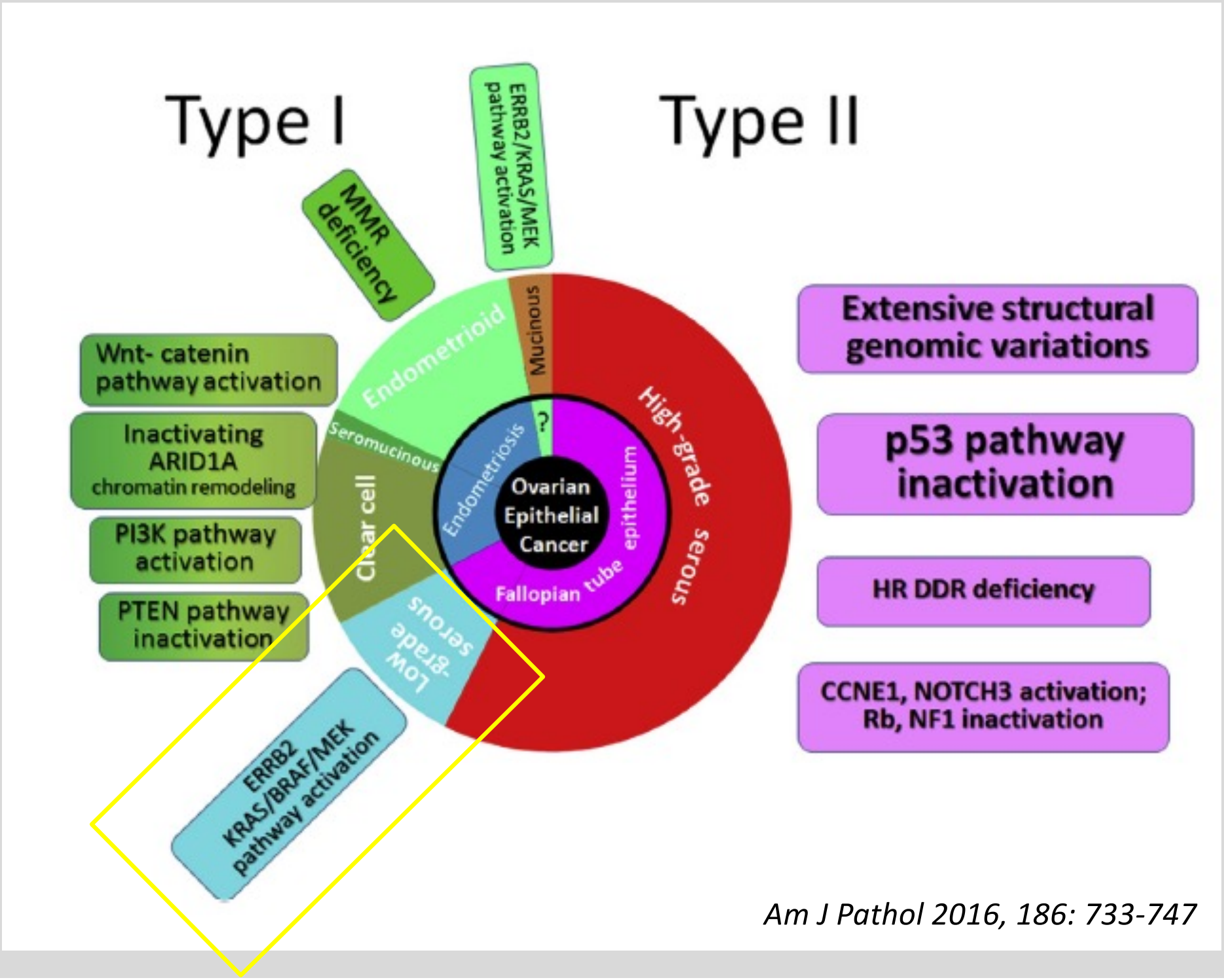
Histopathology 2013, 62, 44–58.

IIC

- WT1+, ER+
- P16 negativa
- p53 con pattern *wild-type*



P53 pattern wt



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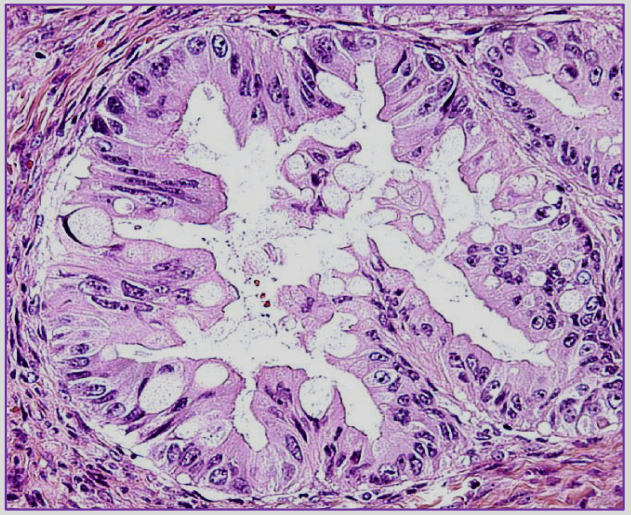
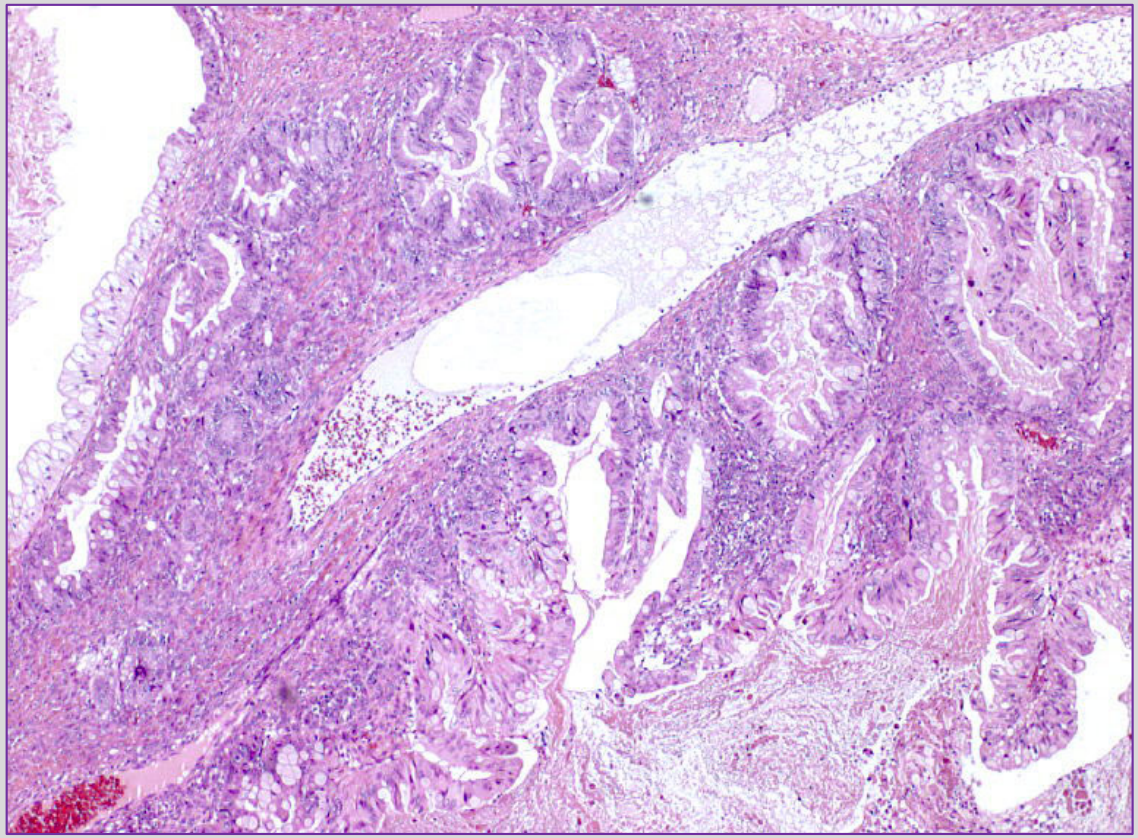
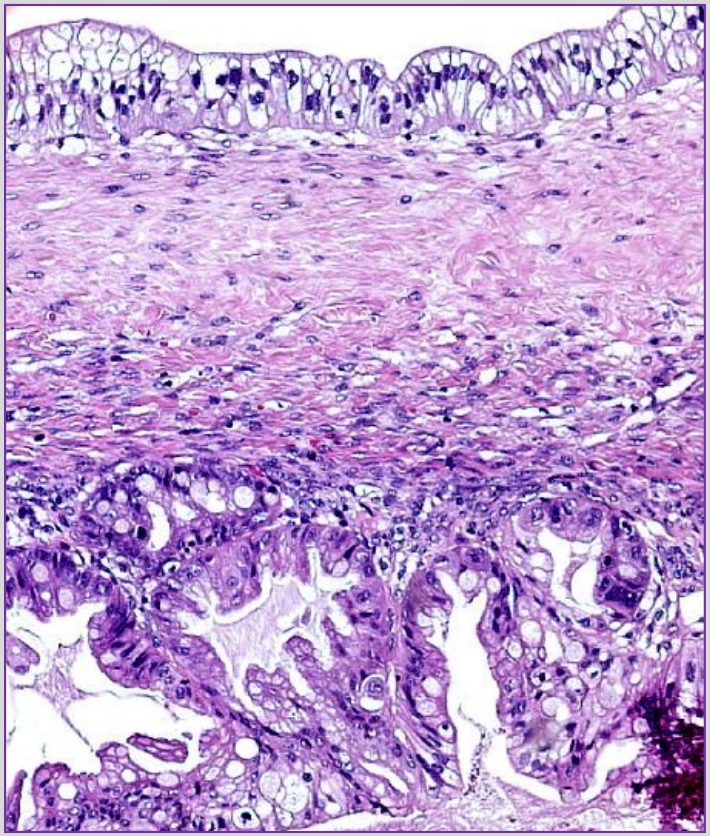
Carcinoma mucinoso

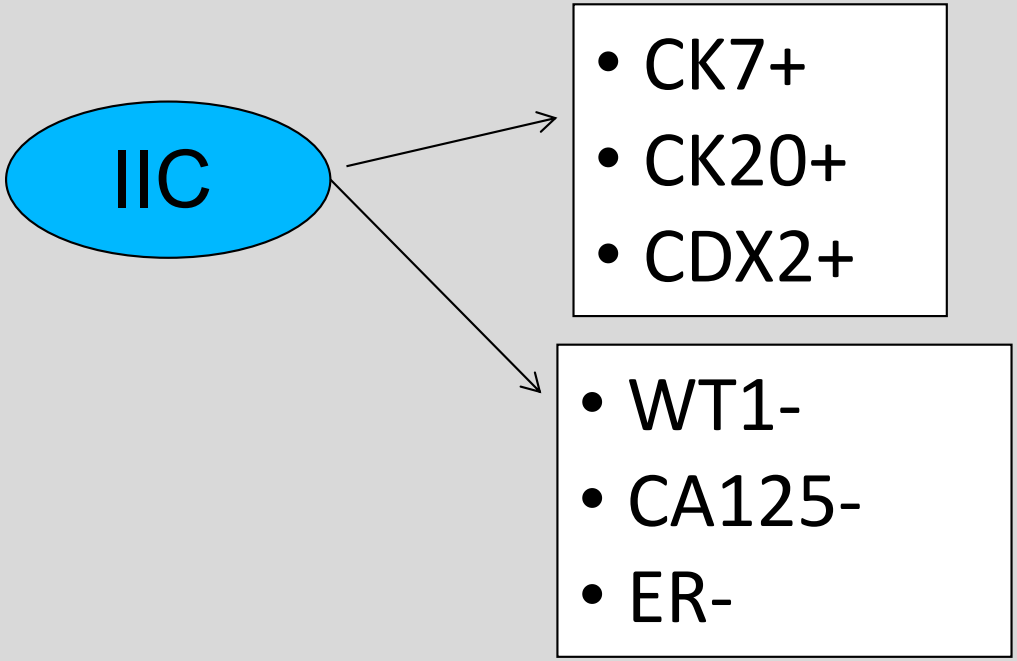
- Sono i tumori più rari (3%).
- Proliferazione di cellule mucinose (tipo intestinale o endocervicale) con disposizione ghiandolare *back-to-back* e invasione stromale.



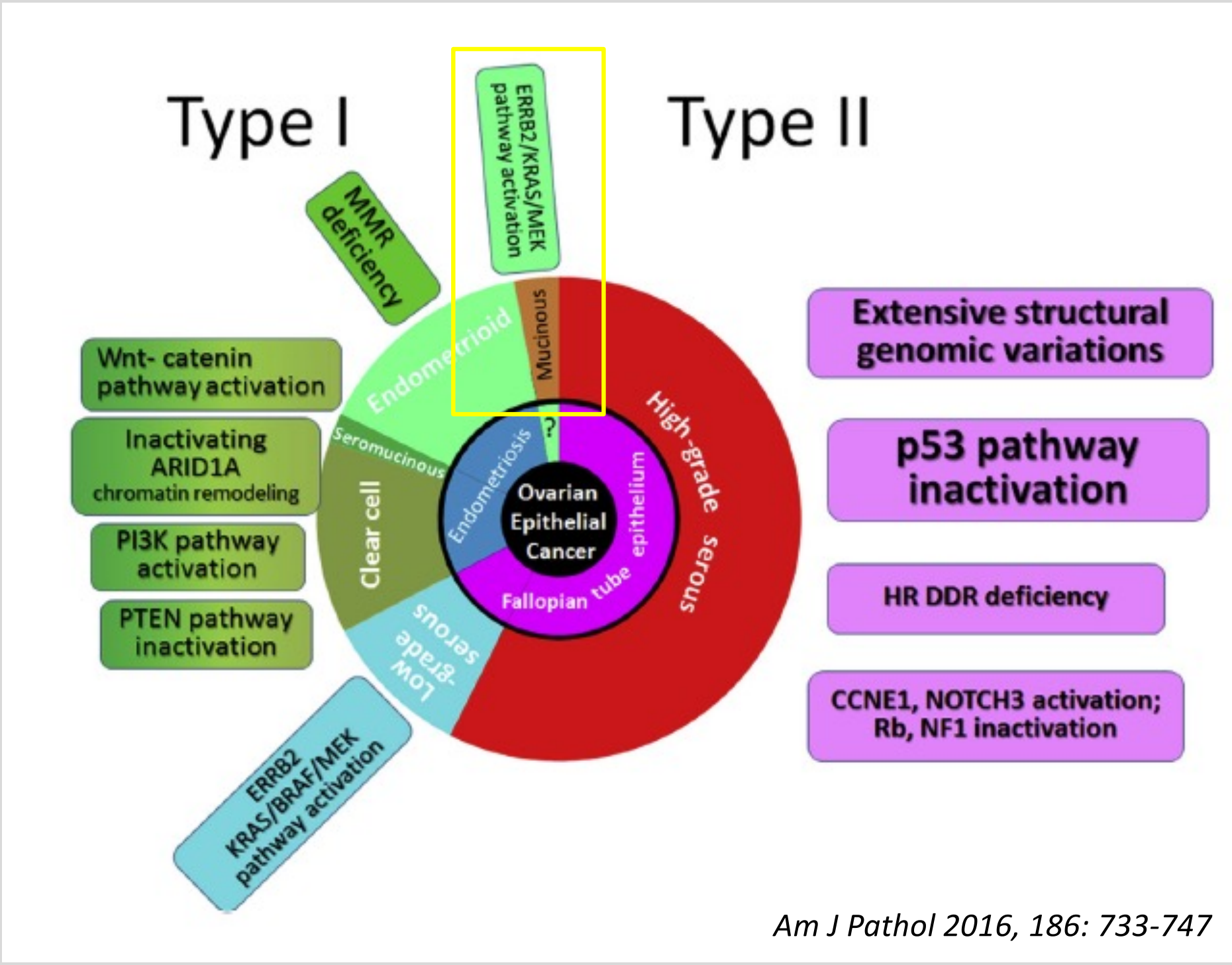




Carcinoma mucinoso



- D.D. con metastasi ovariche di adenocarcinoma mucinosi sulla base di criteri **clinico**-morfologici.



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Grazie