Il carcinoma ovarico: approccio multidisciplinare e prospettive terapeutiche

Dall' istologia alla caratterizzazione biomolecolare

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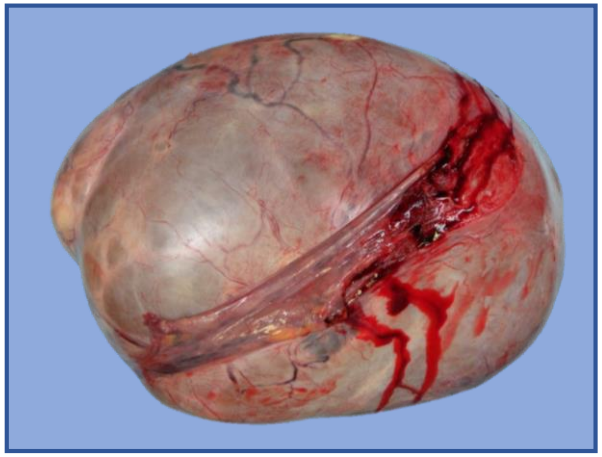
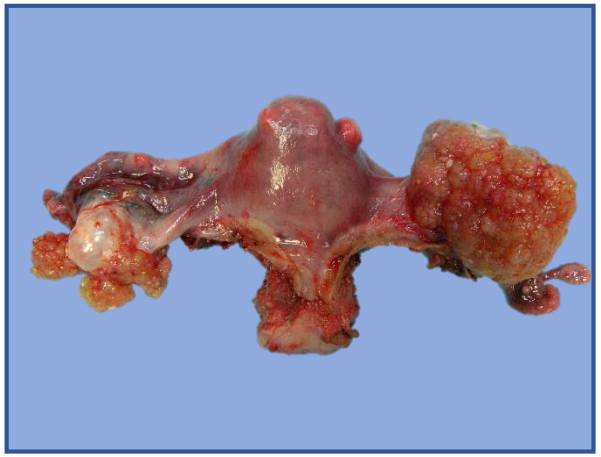
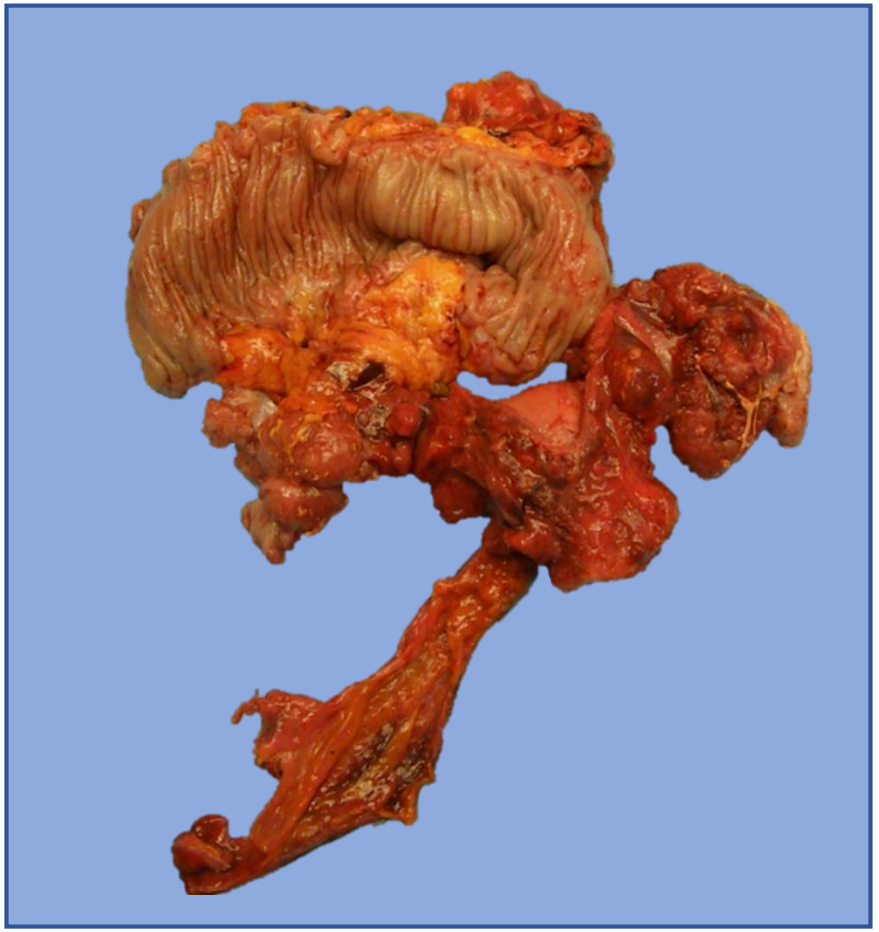
Ovarian cancer is a general term for a series of distinct diseases that simply share an anatomical location







The dualistic model clusters ovarian carcinoma into two groups



Type I

Low grade
Low stage at presentation
Favorable outcome

Endometrioid Carcinoma EOC
Clear Cell Carcinoma CC
Low grade serous carcinoma LGSC
Mucinous Carcinoma MC
Brenner tumor

Genetic stability

Type II

High grade
High stage at presentation
Dismal prognosis

High Grade Serous Carcinoma HGSC
Carcinosarcoma
Undifferentiated Carcinoma

Genetic caos (p53 mutation)

Am J Pathol 2004, 164:1511-1518

REVIEW

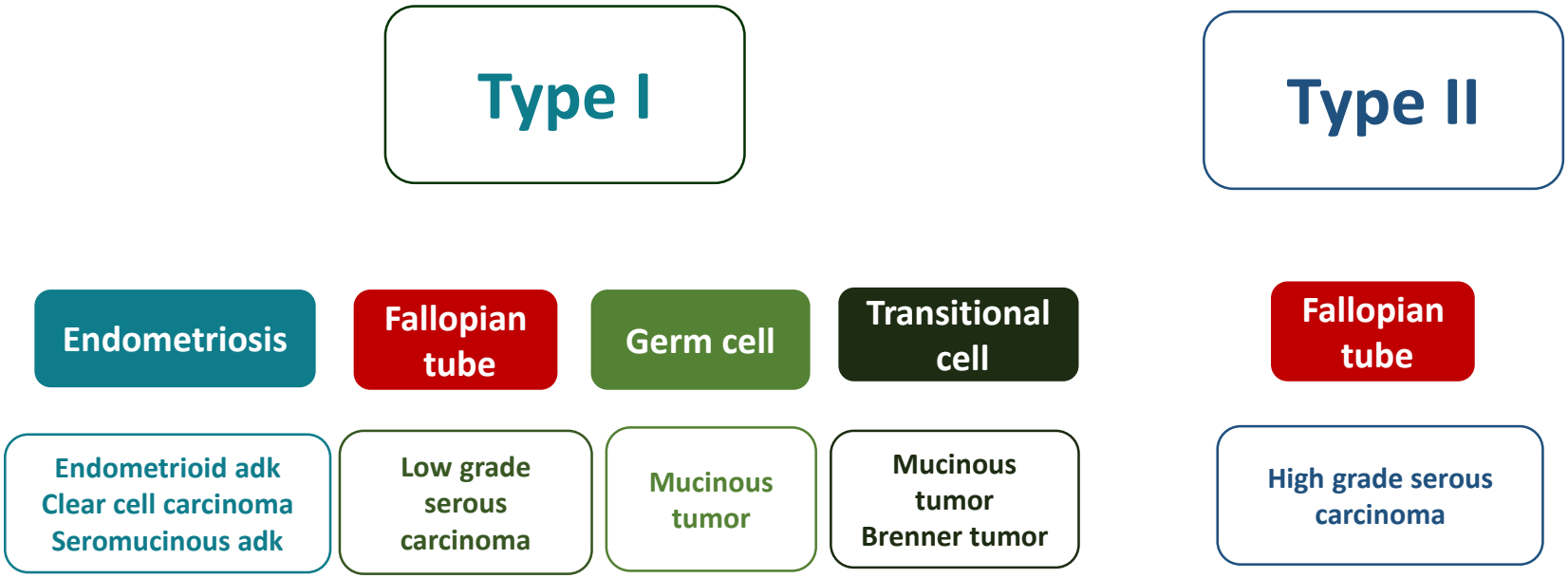
The Dualistic Model of Ovarian Carcinogenesis

Revisited, Revised, and Expanded

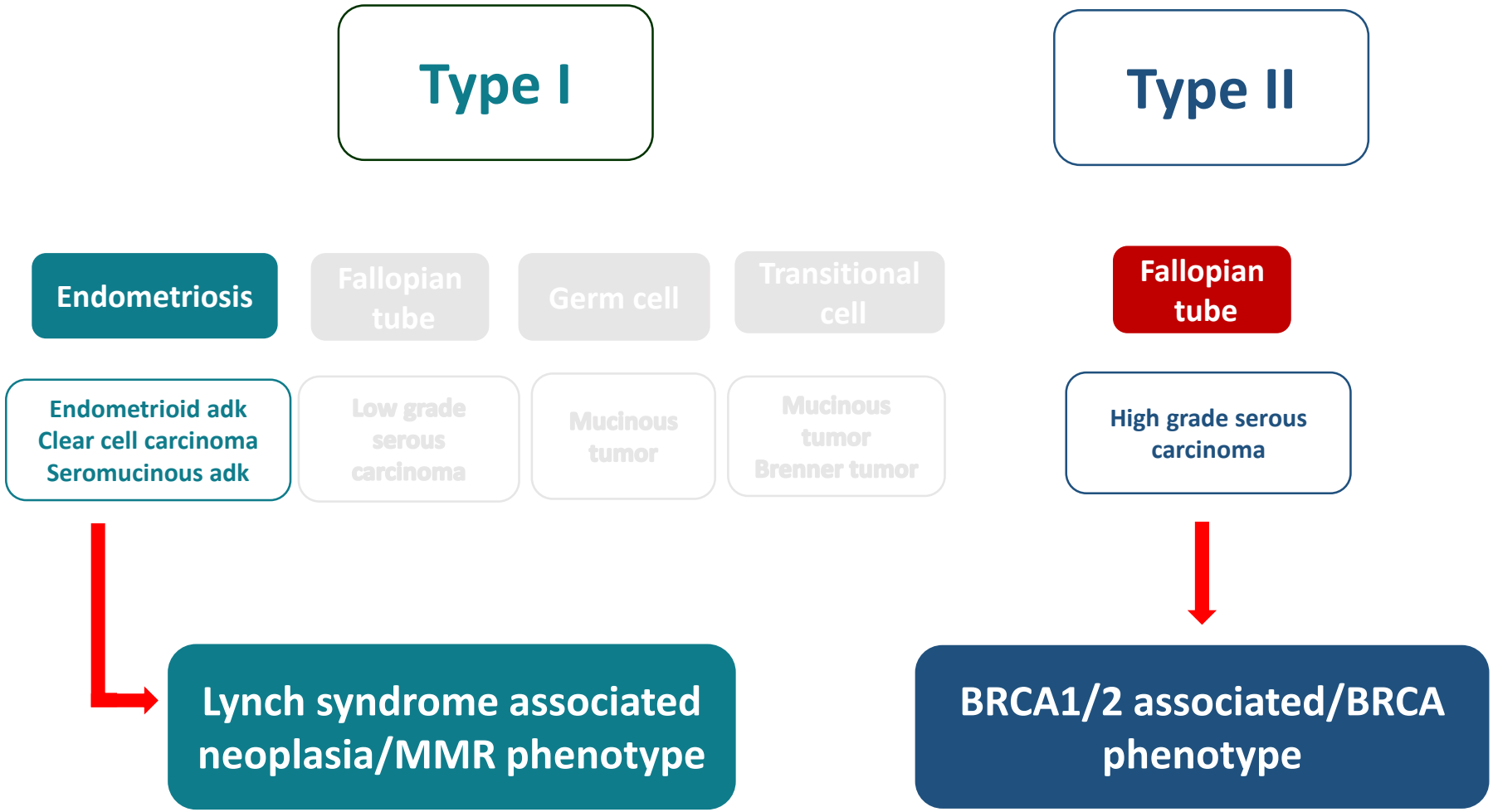
Robert J. Kurman and Ie-Ming Shih

The American Journal of Pathology, Vol. 186, No. 4, April 2016

The dualistic model of ovarian carcinoma



The dualistic model of ovarian carcinoma

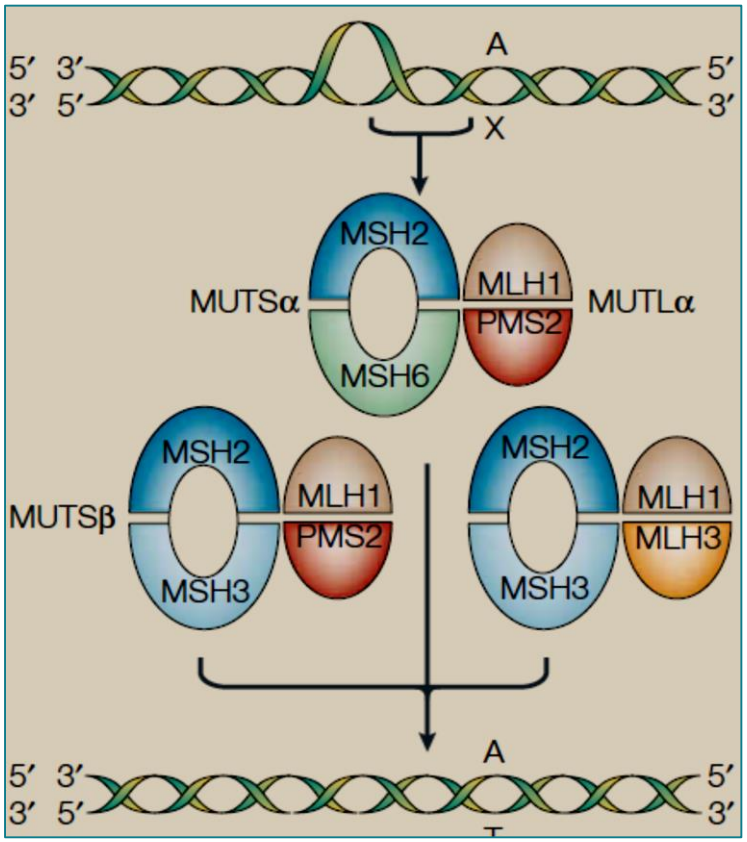


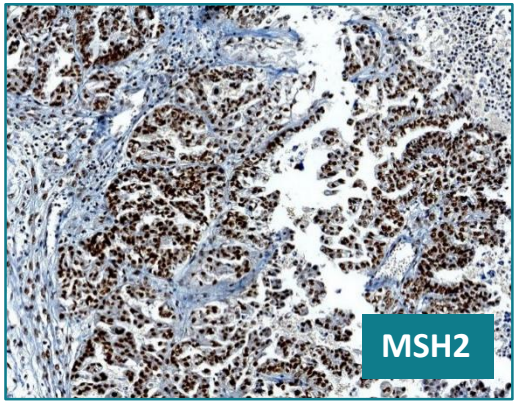
Lynch Syndrome (LS)/Heredetary Nonpolyposis Colorectal Carcinoma (HNPCC)

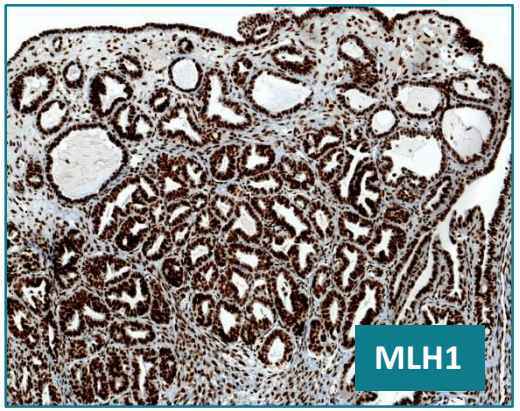
Autosomal dominant cancer syndrome caused by inactivating germline mutation in the DNA mismatch repair (MMR) genes

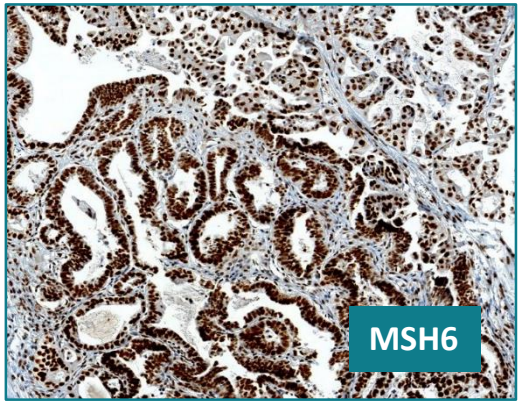
MISMATCH REPAIR

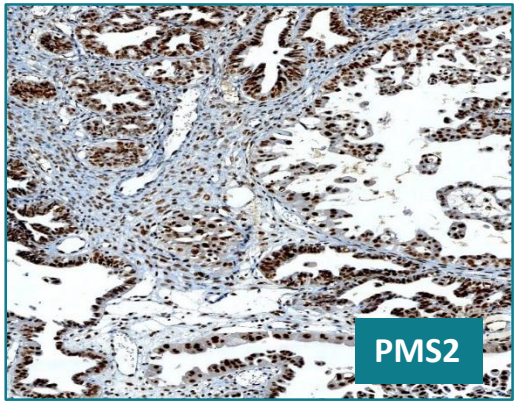
Biochemical process dedicated primarily to the excision of nucleotides that are incorrectly paired during DNA replication











Lynch Syndrome (LS)/Heredetary Nonpolyposis Colorectal Carcinoma (HNPCC)

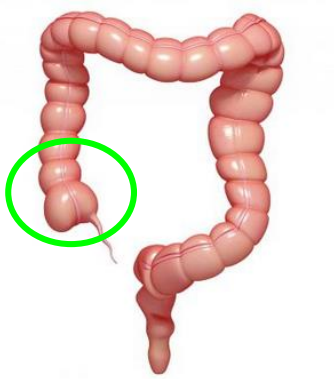
1. LS has traditionally been approached as a colorectal carcinoma-dominant syndrome

2. Women with LS are at equal/higher risk for development of gynecologic cancer when compared with their risk of colon cancer

3. 10% to 15% of hereditary ovarian cancers are part of LS

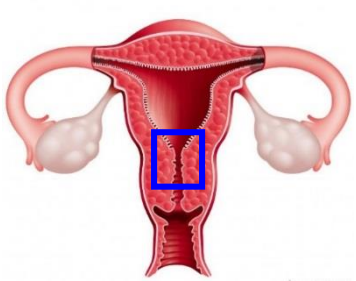
Is there any morphological aspect related to MISMATCH REPAIR deficiency?

Colorectal adenocarcinoma



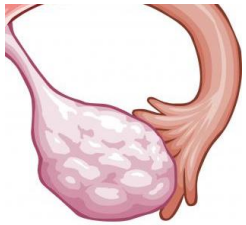
Right colon
High grade histology (colloid carcinoma)
Intratumoral and peritumoral (Crohn-like) inflammatory infiltration

Endometrial adenocarcinoma



Isthmus
High grade histology
Syncronous CCC
Intratumoral and peritumoral (Crohn-like) inflammatory infiltration

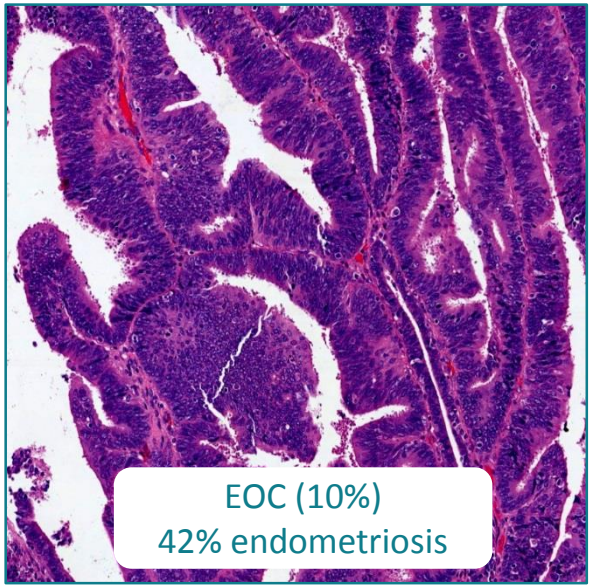
Ovarian carcinoma



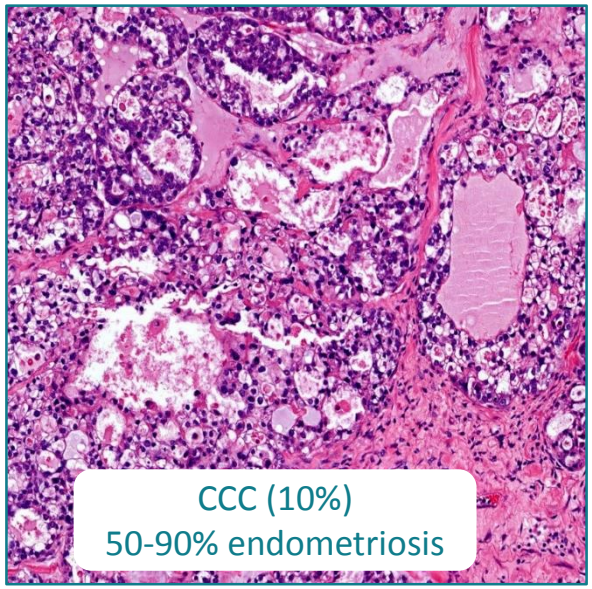
Endometrioid and clear cells histology
No intratumoral and peritumoral (Crohn-like) inflammatory infiltration

(*Am J Surg Pathol* 2014;38:1173–1181)

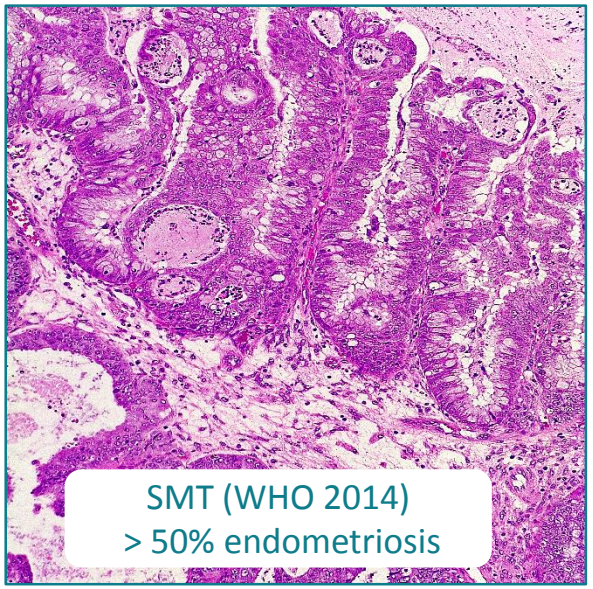
Lynch syndrome OC tumour subtypes commonly associated with endometriosis



10% MMR defects, pts< 50 yrs



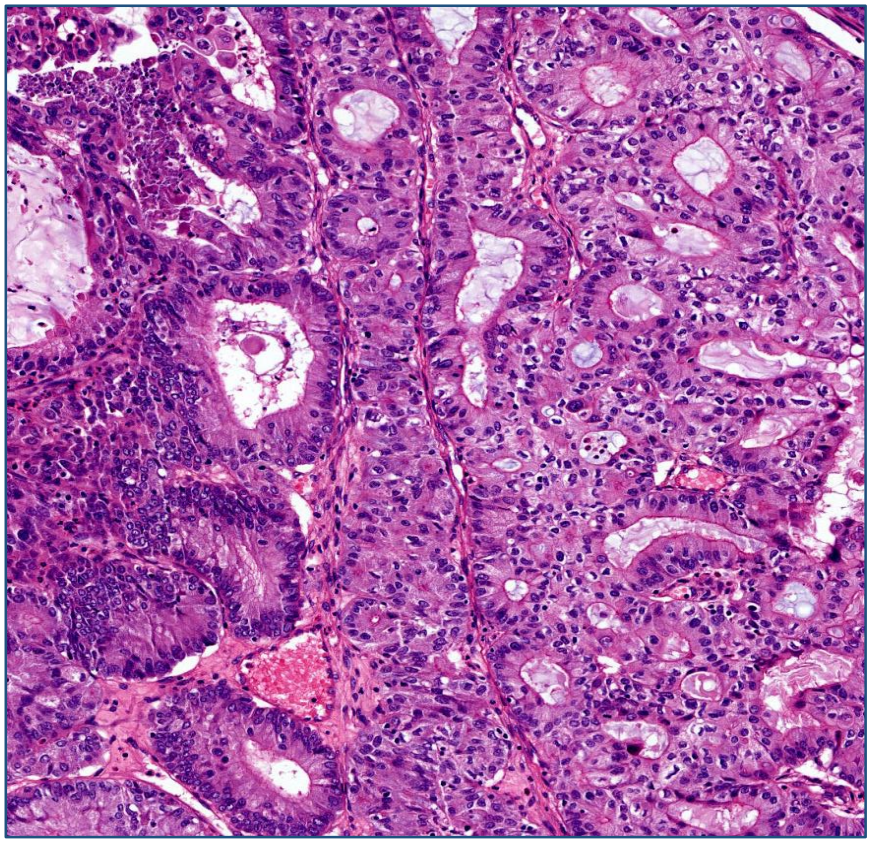
14-17% MMR defects,pts< 50 yrs

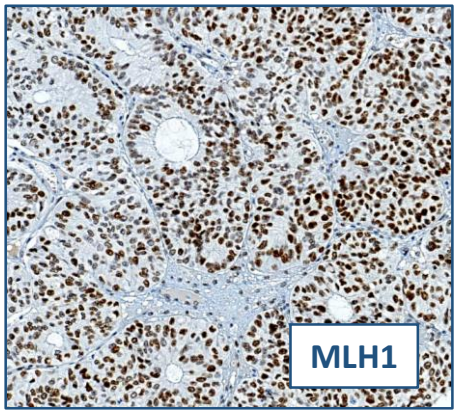


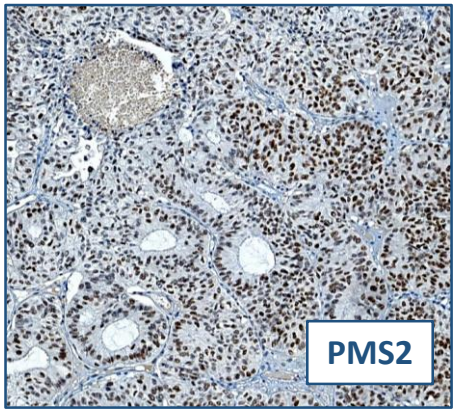
MMR defects ?

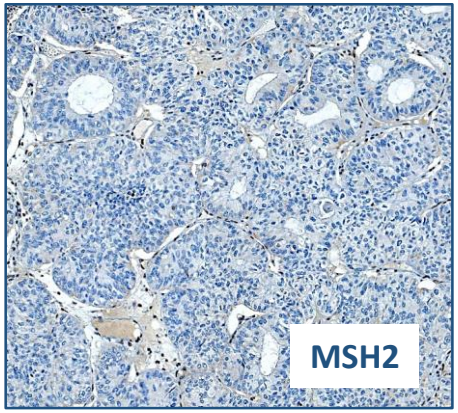
MMR-ICH testing raccomanded for EOC and CCC

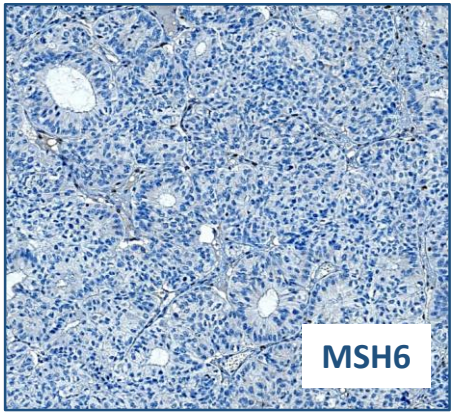
Endometrioid Ovarian Cancer with MMR defects



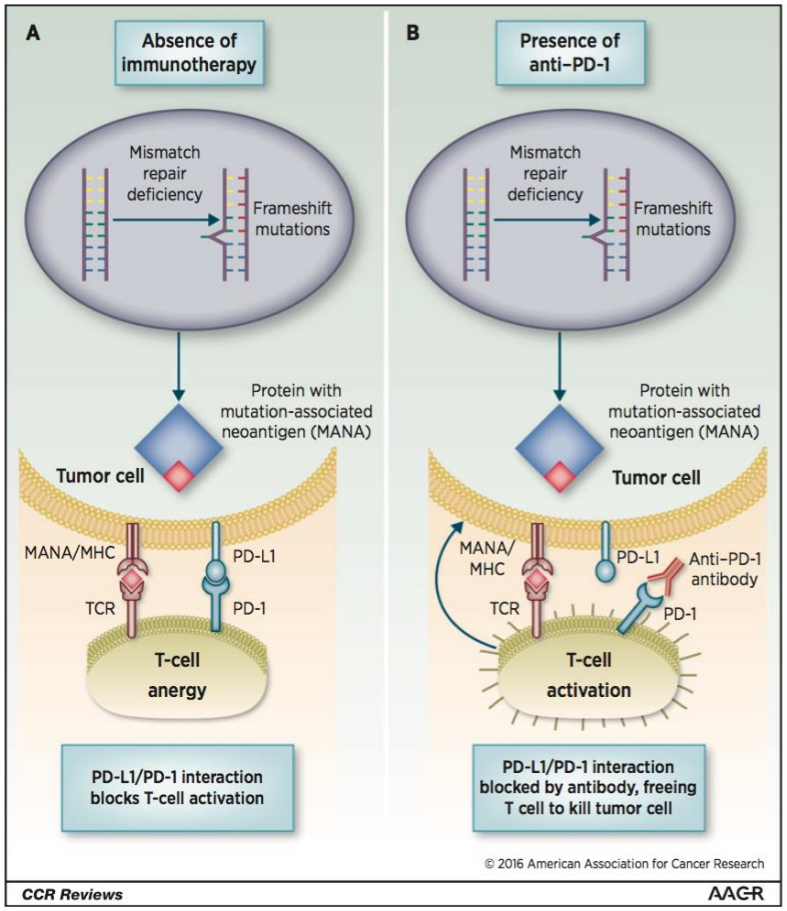








Ovarian Cancer with MMR defects and Checkpoint blockade Immunotherapy



PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

N ENGL J MED 372;26 NEJM.ORG JUNE 25, 2015

Review

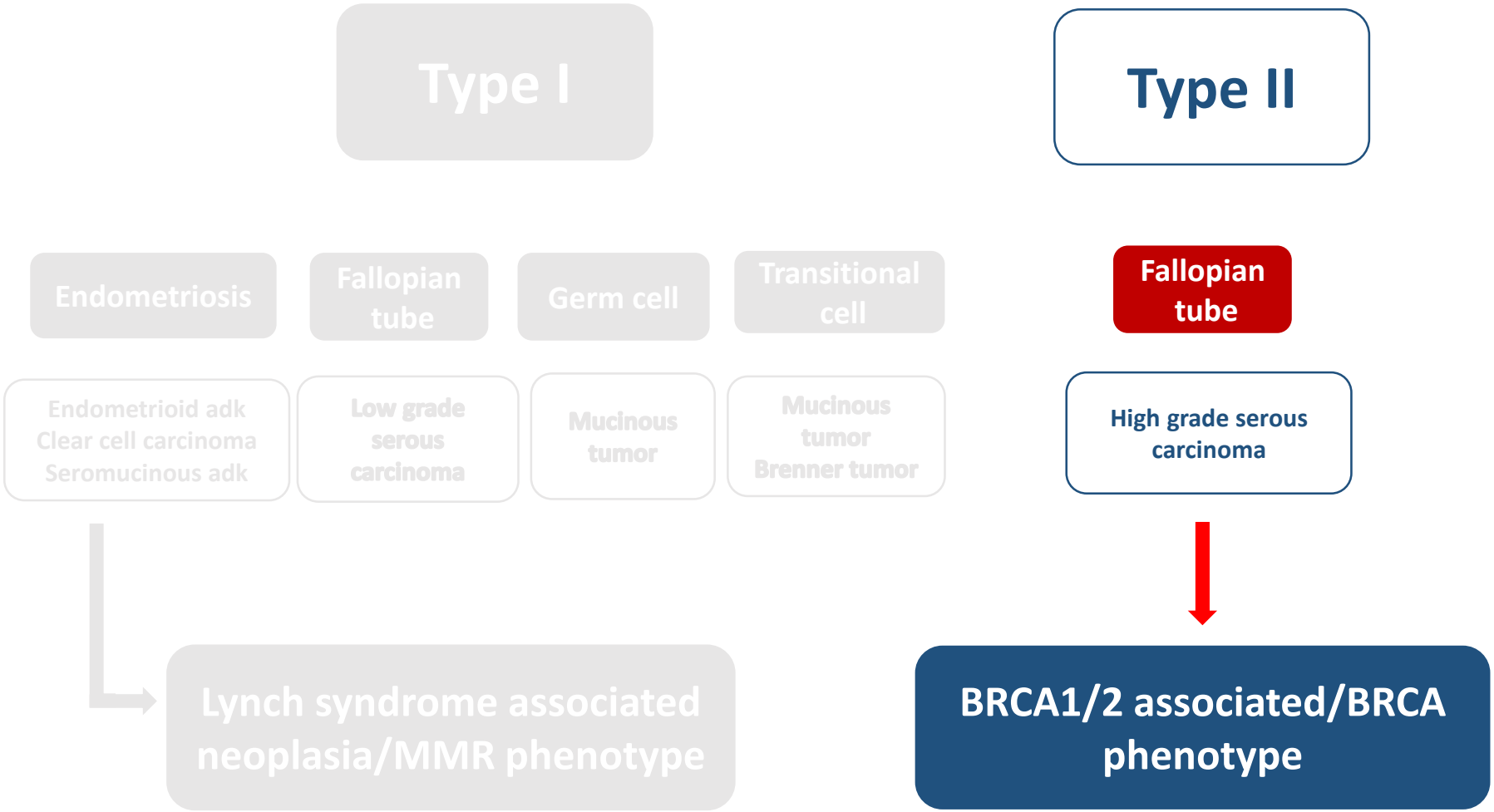
Clinical Cancer Research

Microsatellite Instability as a Biomarker for PD-1 Blockade

Jonathan C. Dudley[1], Ming-Tseh Lin[2], Dung T. Le[3], and James R. Eshleman[2,3]

MSI tumors expressing neopeptides constitute good targets for immunotherapy

The dualistic model of ovarian carcinoma



BRCA1/2 associated/BRCA phenotype

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OPINION

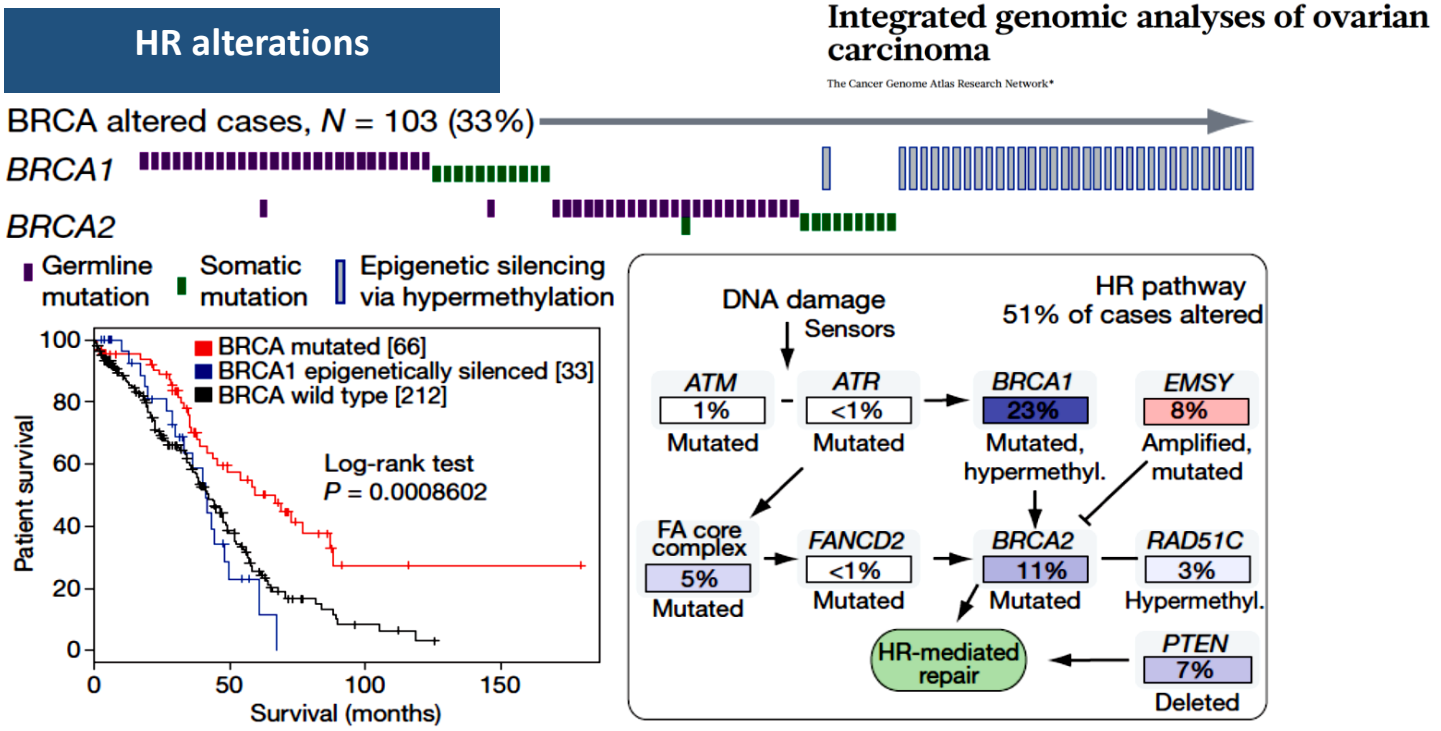
BRCAness revisited

Christopher J. Lord and Alan Ashworth

The phenotype that some sporadic tumours share with familiar-BRCA cancers related to response to platinum and PARP-inhibitor therapy

BRCAness is a phenocopy of BRCA1 or BRCA2 mutation; it describes a situation in which an HHR defect exists in a tumour in the absence of a germline BRCA1 or BRCA2 mutation.

BRCA1/2 associated/BRCA phenotype



Genes in the homolologous recombination (HR) pathway are altered in up to 51% of cases

20% BRCA1/2 germline or somatic mutation

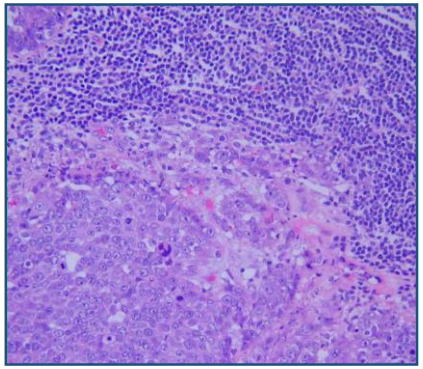
11% BRCA1 promoter methylation

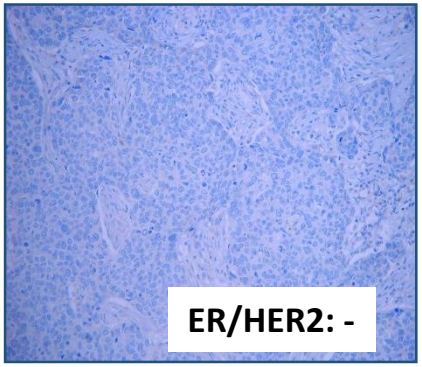
20% EMSY, PTEN or mutation in the Fanconi Anaemia genes

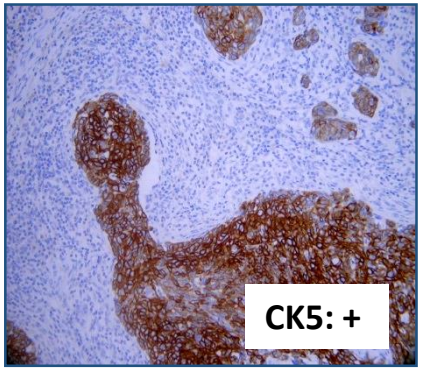
Is there any morphological aspect related to BRCAness phenotype?

Breast carcinoma

Triple negative/basal-like
High grade carcinoma
Inflammation
Pushing margins



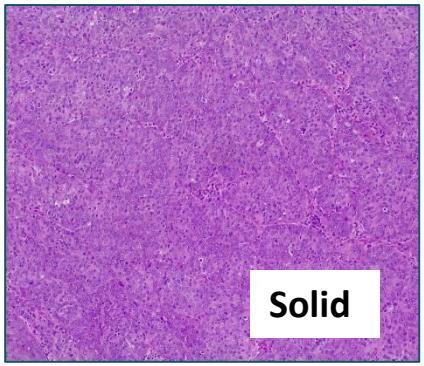


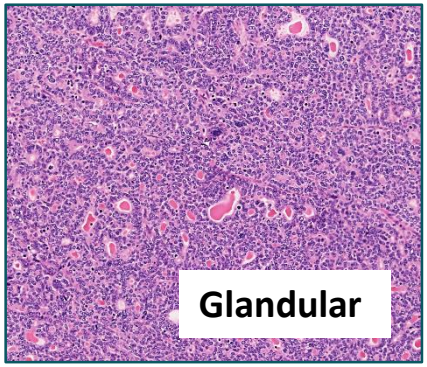


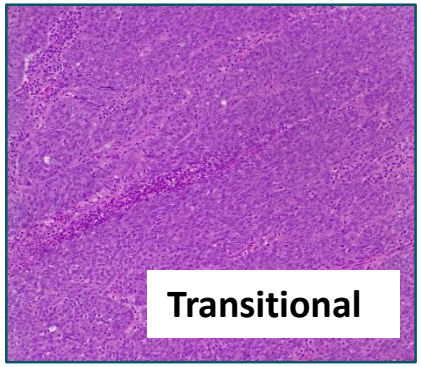
Courtesy of G.Bogina

Ovarian carcinoma

HG Serous Carcinoma with
Solid-pseudoEndometrioid-
Transitional morphology (SET)



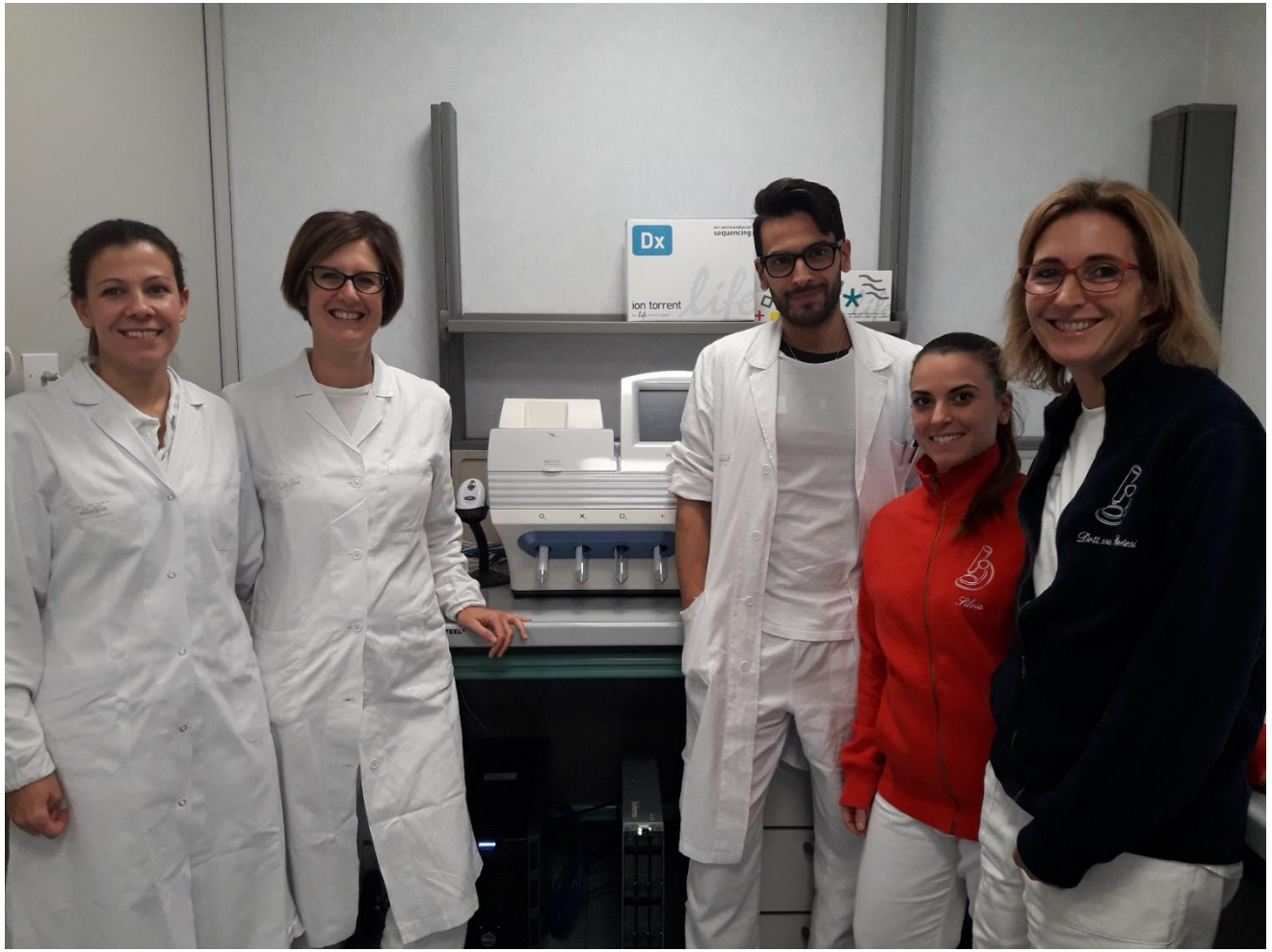




SUMMARY

- **Ovarian carcinomas are etherogeneous**
- **The study of rare Syndromes (LS/BRCA1-2) highligthed some morphological clues to drive the molecular characterization in sporadic carcinoma**
- **Type 1-MMR defects and Type 2-BRCAness subtypes constitute good targets for immunotherapy and platinum/PARP-inhibitor therapy**

Laboratorio Biologia Molecolare



Dott.ssa Laura Bortesi
Dott.ssa Anna Pesci

Biologo Giulio Settanni

Tec. LB Sara Lonardi
Tec. LB Silvia Sandrini