# GYNECOLOGIC PATHOLOGY: EVOLVING CONCEPTS, CLASSICS, CAVEATS

## A LIVE ACTION BROADCAST FROM THE USCAP INTERACTIVE CENTER


PRESENTED BY

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# Case 1:

53-year-old with a large cervical mass.

**Evolving Concept: International Endocervical Adenocarcinoma Criteria and Classification**

# International Endocervical Adenocarcinoma Criteria and Classification

- Classifies endocervical adenocarcinomas into 2 groups based on their HPV status
- Refines criteria for subclassification/histotyping within each of the 2 groups

| Classification of endocervical adenocarcinomas based on WHO 2014 criteria: distribution of histotypes | |
|---|---|
| ENDOMETRIOID | 41% |
| MUCINOUS CARCINOMA | 26% |
| GASTRIC | 9.2% |
| INTESTINAL | 3.4% |
| MUCINOUS NOS | 13% |
| SIGNET RING | 0.2% |
| USUAL | 12 |
| ADENOSQUAMOUS | 11% |
| CLEAR CELL | 2.9% |
| VILLOGLANDULAR | 2.6% |
| SEROUS | 2.2% |
| ADENOCARCINOMA, NOS | 1.7% |
| MESONEPHRIC | 0.2% |

ECA tumor types, IECC classifications

| IECC (%)** N=371 | |
|---|---|
| USUAL | 74 |
| USUAL-TYPE | 73 |
| VILLOGLANDULAR | 0.8 |
| GASTRIC(MUCINOUS NHPVA) | 10 |
| MUCINOUS HPVA | 8.6 |
| INTESTINAL | 3.0 |
| MUCINOUS NOS | 3.0 |
| iSMILE | 2.4 |
| SIGNET RING | 0.3 |
| CLEAR CELL | 3.0 |
| ADENOCARCINOMA, NOS | 2.4 |
| ENDOMETRIOID | 1.1 |
| SEROUS | 0.5 |
| MESONEPHRIC | 0.3 |

**Table 1.** Endocervical adenocarcinoma classification by World Health Organisation 2014 compared to International Endocervical Criteria and Classification (IECC)

| WHO 2014 | IECC 2018 | |
|---|---|---|
| Usual type | HPV-associated (HPVA) | Non-HPV-associated (NHPVA) |
| Mucinous carcinoma, NOS | Usual type | Gastric type |
| Gastric type | Villoglandular | Clear cell |
| Intestinal type | Mucinous, NOS | Mesonephric |
| Signet ring cell | Mucinous, intestinal | Endometrioid |
| Villoglandular | Invasive stratified mucin-producing | |
| Endometrioid | Micropapillary | |
| Clear cell | 'Serous'-like | |
| Serous | | |
| Mesonephric | | |

Stolnicu S et al. Am J Surg Pathol 2018;42:214-226
Park KJ. Histopathology. 2020 Jan;76(1):112-127

# International Endocervical Adenocarcinoma Criteria and Classification (IECC 2017)

| | HPV-associated | Non-HPV associated |
|---|---|---|
| **Proportions** | 80% | 20% |
| **Most common histotype** | Usual-type (72-74%) | Gastric type (71%) |
| **Patient age** | Younger (median 42 yrs) | Median age 55 years |
| **Tumor size** | Smaller (median 21 mm) | Median 38 mm |
| **Stage distribution** | Mostly stage I | 50% stage II or more |
| **LVSI** | Less frequent | More frequent |
| **Recurrences** | Less frequent | More frequent |
| **Lymph node involvement** | Less frequent | More frequent |
| **Mutational burden** | Comparatively lesser | Comparatively higher *(TP53, CDKN2A, STK11, ATM,* and *NTRK3* more common in gastric-type than HPVA) |

Stolnicu S et al. Am J Surg Pathol. 2019 Apr;43(4):466-474; Stolnicu S, et al. Am J Surg Pathol 2018;42:214-226.;
Hodgson A et al. J Clin Pathol. 2019 May;72(5):347-353; Hodgson A, et al. Int J Gynecol Pathol. 2019

# Prognostic differences between HPVA and NHPVA: Not a simple story

- Univariate analysis: HPVAs have superior OS, DFS and PFS compared to NHPVAs.
- Multivariate analysis: HPV status was nearly statistically significantly associated with OS (HR=0.14 [0.02–0.99], p=0.06) and DSS (HR=0.15 [0.02–1.06], p=0.06), with HPVAs having better outcomes
- Survival did not differ between HPVAs and NHPVAs in patients who underwent surgery alone, but HPVAs had better outcomes in patients treated with a combination of surgery and adjuvant therapy.
- HPVAs with pelvic recurrence had a better OS, DFS and PFS than NHPVAs with pelvic recurrence, but no differences were observed in the setting of distant recurrence
- For NHPVA (but NOT HPVAs), patient age, stage and tumor size were significantly associated with overall survival

Stolnicu S et al. Am J Surg Pathol. 2019 Apr;43(4):466-474

# Case 2:
39-year-old diagnosed with adenocarcinoma in situ on a biopsy; recently underwent a resection.

**Evolving Concept: Silva Pattern System in Endocervical Adenocarcinoma**

# Silva pattern system in endocervical adenocarcinoma: risk stratification system for node metastases and patient outcomes based on pattern of invasion

| Pattern A | Pattern B | Pattern C |
|---|---|---|
| Well-demarcated glands with rounded contours, usually forming groups<br><br>No destructive stromal invasion<br><br>No single cells or cell detachment<br><br>No lymphovascular invasion<br><br>Complex intraglandular growth acceptable (cribriform, papillae)<br><br>Lack of solid growth (well-moderately differentiated) | Localized (limited, early) destructive stromal invasion arising from pattern A glands (well-demarcated glands)<br><br>Individual or small groups of tumor cells, separated from pattern A-type glands, frequently in desmoplastic or inflamed stroma<br><br>Single, multiple, or linear foci at base of tumor<br><br>Lymphovascular invasion (present/absent)<br><br>Lack of solid growth (well-moderately differentiated) | Diffuse destructive stromal invasion, characterized by:<br><br>Diffusely infiltrative glands, with associated extensive desmoplastic response<br><br>Glands often angulated or with canalicular pattern, with interspersed open glands<br><br>Confluent growth filling a 4x field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes<br><br>Solid, poorly differentiated component (architecturally high grade); nuclear grade is disregarded<br><br>Lymphovascular invasion (present/absent) |

*Adapted from Roma AA, et al. Am J Surg Pathol. 2015 May;39(5):667–72.*

# Silva pattern system in endocervical adenocarcinoma: risk stratification system for node metastases and patient outcomes based on pattern of invasion

| | Pattern A | Pattern B | Pattern C |
|---|---|---|---|
| Percentage of cases | 21% | 26% | 54% |
| Stage I | 100% | 100% | 83% |
| Lymph node metastases | 0% | 4.4%<br>(all also had LVSI) | 23.8% |
| Recurrences | 0% | 1.2% | 21.5% |
| DOD | 0% | 0% | 9.5% |

*Roma AA, et al. Gynecol Oncol. 2016 Apr; 141(1): 36–42.*

# Silva pattern system in endocervical adenocarcinoma: risk stratification system for node metastases and patient outcomes based on pattern of invasion

- Risk of recurrences and lymph node mets increase with increasing FIGO stage
  - Node mets: IA1 (4%); IA2 (3.8%); IB1(7.8%); IB2 (29.4%)
  - Recurrences: IA1 (0%); IA2(0%); IB1(9.5%); IB2 (23%)
- However, no recurrences for Silva pattern A cases even when FIGO stage IB; node mets and recurrences restricted to patterns B and C, suggesting that the patterns are better predictors of outcomes at least in early stages
- Diagnostic reproducibility: moderate to good (K=0.488-0.65; C>A>B; reproducibility is poor when the decision point is AIS vs Pattern A)
- Concordance in pattern assignment between cone/LEEP and resection (92.8%) is excellent; less so between biopsy and resection (37.5%)
- Pattern C can be further substratified into prognostically “good” and “bad” subsets based on histologic features and LVI
- Patterns correspond with mutational patterns, with most actionable/driver-type mutations, being exclusive to pattern B or C (destructively invasive) subgroups
- Pattern A can theoretically still go to endometrium and ovary; patient outcomes unclear for these

*Roma AA, et al. Gynecol Oncol. 2016 Apr; 141(1): 36–42; Rutgers JKL et al. Mod Pathol. 2016 Sep;29(9):1083-94; Parra-Herran C, et al. Mod Pathol 2016;29; 879–892; Alvarado-Cabrero I, et al. Int J Gynecol Pathol. 2017Sep;36(5):476-485; Roma AA et al. Am J Surg Pathol. 2017 Sep;41(9):1205-1211.; Djordjevic B. et al. Int J Gynecol Pathol. 2016 Sep;35(5):456-66*

# Case 3:
56-year-old with endometrial carcinoma.

**Evolving concept: ”new” entity**

# Mesonephric-like carcinoma

- "new" entity recognized in WHO 5th Ed (2020): "**Mesonephric-like adenocarcinoma** is an adenocarcinoma resembling mesonephric differentiation"
- Most authors define it as did Pors et al "tumors exhibiting the classic morphologic features of mesonephric carcinoma, but occurring outside of the cervix and without convincing mesonephric remnants"
- Represents 1% of endometrial carcinomas
- Compared to low grade endometrial carcinomas, mesonephric-like carcinomas are larger, present at advanced stage, more frequently show LVSI; patients are possibly younger

McFarland et al. Histopathology. 2016 Jun;68(7):1013-20
Pors et al. Am J Surg Pathol . 2018 Dec;42(12):1596-1606
Kolin et al. Am J Surg Pathol. 2019 Mar;43(3):389-398
Euscher et al. Am J Surg Pathol. 2020 Apr;44(4):429-443

# Mesonephric-like carcinoma

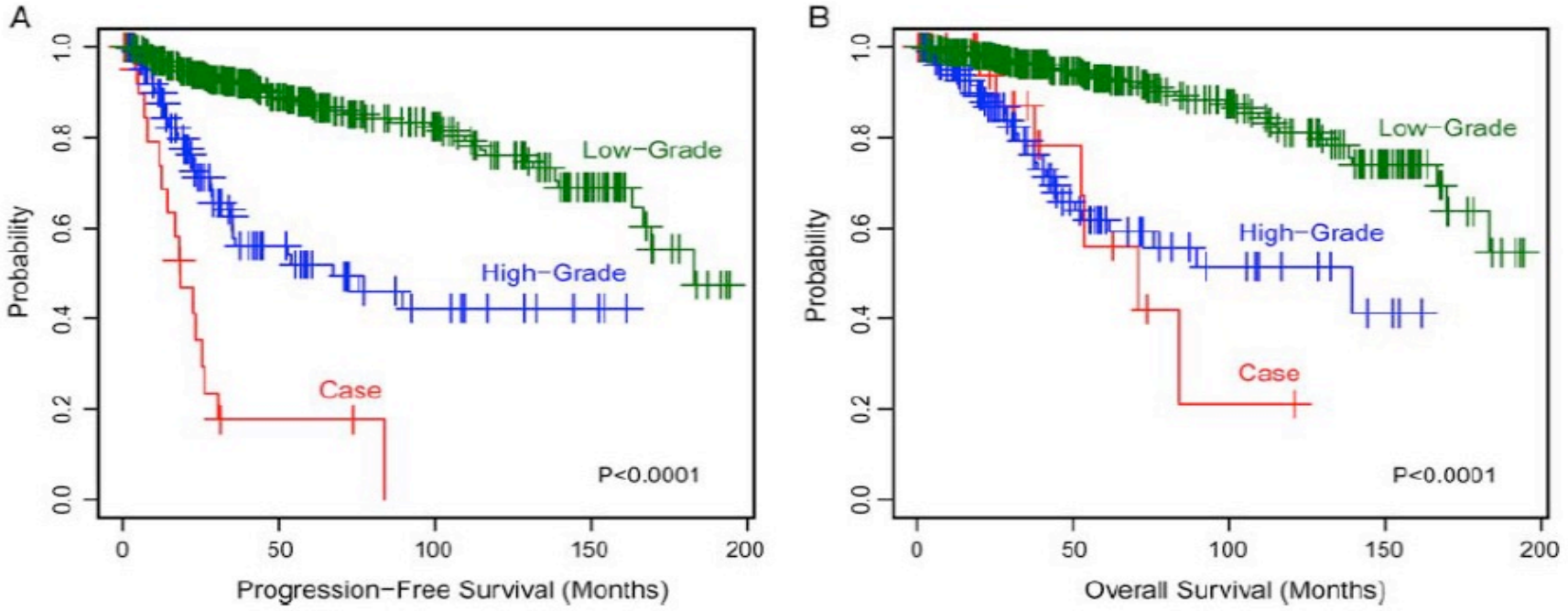
- Architecture: frequently multipatterned, but 2 predominate: ductal/glandular (91%); tubular (83%); papillary (57%); solid (65%); cords/trabeculae (30%); glomeruloid (22%); retiform (17%); sieve-like (9%)
- Cytology:
  - nuclear features similar to those of papillary thyroid carcinoma at least focally: nuclear overlap, nuclear grooves and open to vesicular chromatin
  - Mostly mild to moderate pleomorphism; continuous severe pleomorphism would be uncharacteristic.
- Distinctive immunoprofile: usually positive for PAX8, **GATA-3**, CD10 (luminal), **TTF-1**, and negative for **ER** and **PR**
- Recurrent KRAS mutations (>80%). *ARID1A* and *TP53* wild type. *KRAS* along with *PIK3CA, PTEN* and/or *CTNNB1* mutations in a subset

McFarland et al. Histopathology. 2016 Jun;68(7):1013-20
Pors et al. Am J Surg Pathol . 2018 Dec;42(12):1596-1606
Kolin et al. Am J Surg Pathol. 2019 Mar;43(3):389-398
Mirkovic et al. Am J Surg Pathol . 2018 Feb;42(2):227-233
Euscher et al. Am J Surg Pathol. 2020 Apr;44(4):429-443

# Mesonephric-like Carcinoma of the Endometrium

## *A Subset of Endometrial Carcinoma With an Aggressive Behavior*

*Elizabeth D. Euscher, MD,* Roland Bassett,† Dzifa Y. Duose, PhD,* Chieh Lan,* Ignacio Wistuba, MD,* Lois Ramondetta, MD,‡ Preetha Ramalingam, MD,* and Anais Malpica, MD**




(*Am J Surg Pathol* 2020;44:429–443)

# Case 4:

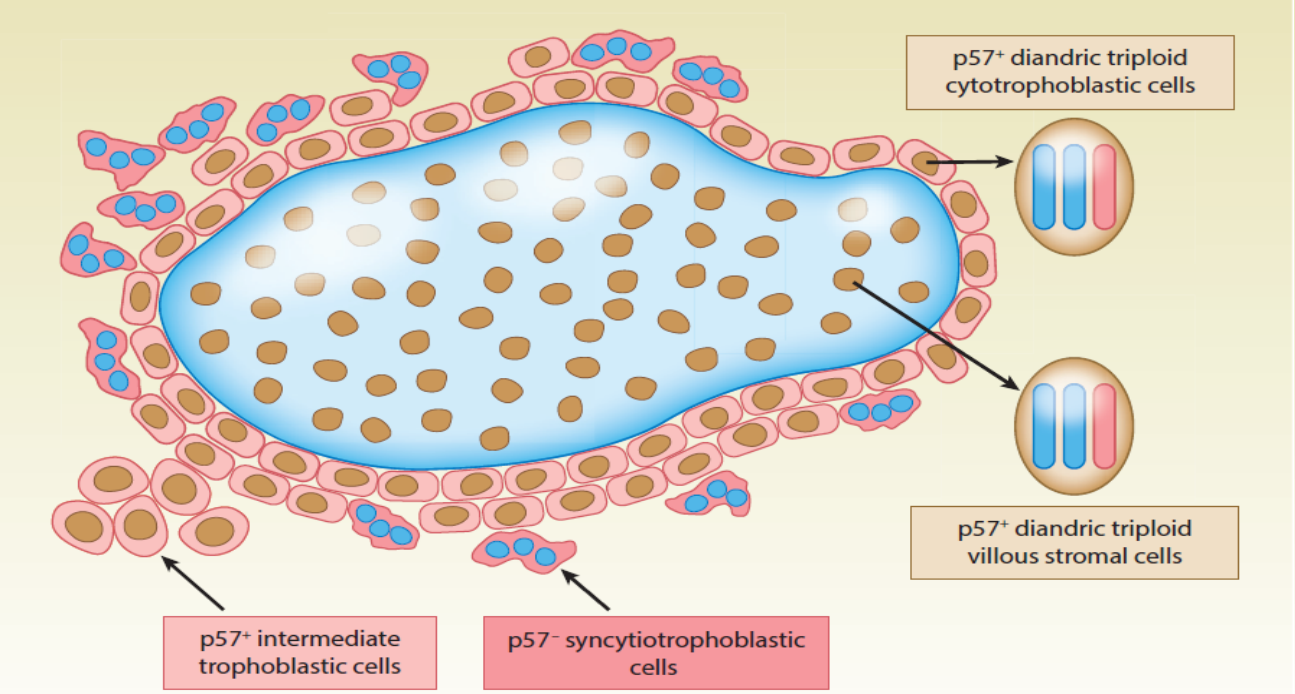
36-year-old, EGA 13 weeks 2 days; POC specimen after abnormal ultrasound.

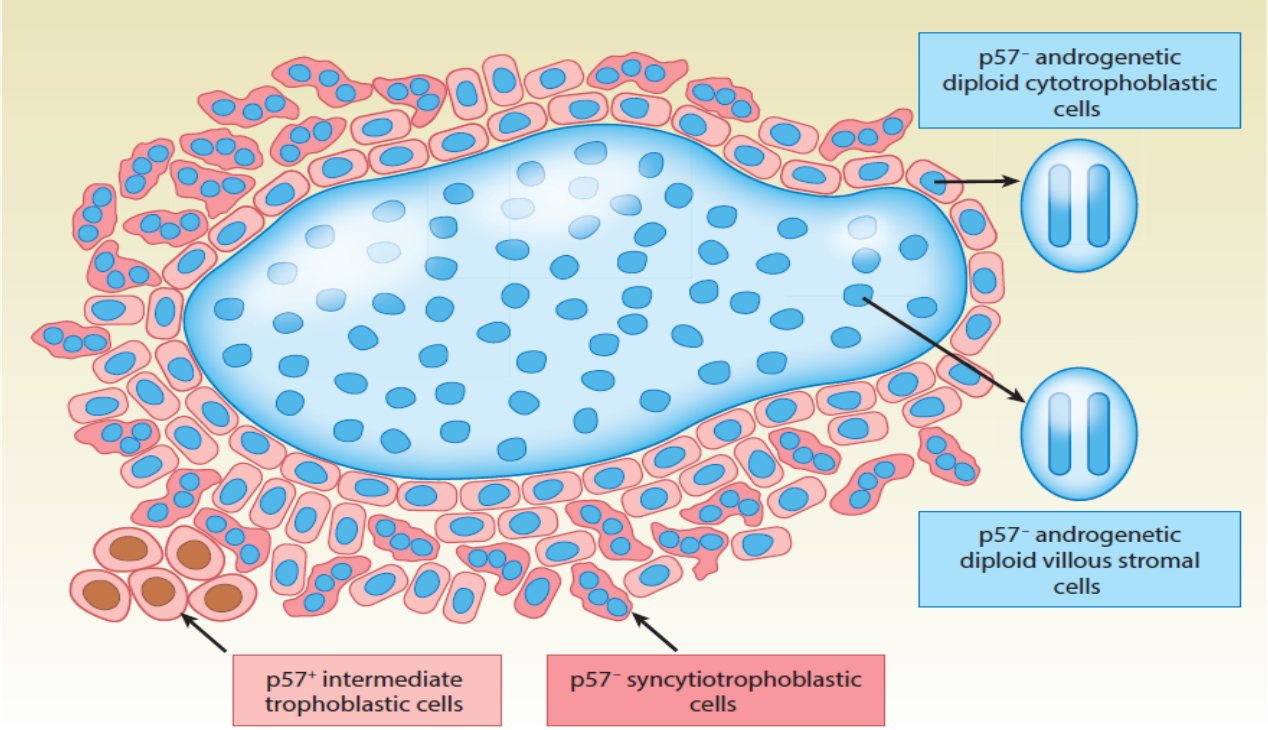
**Evolving Concept: Genotyping for classification of hydatidiform moles**

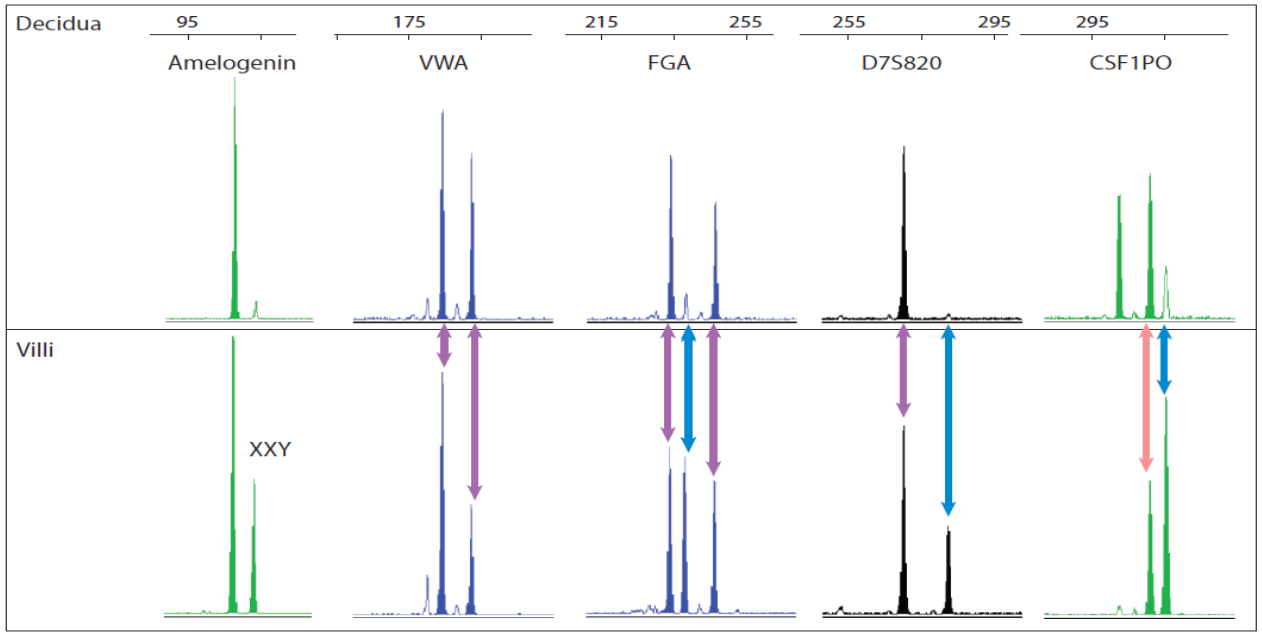
# The“possible mole”

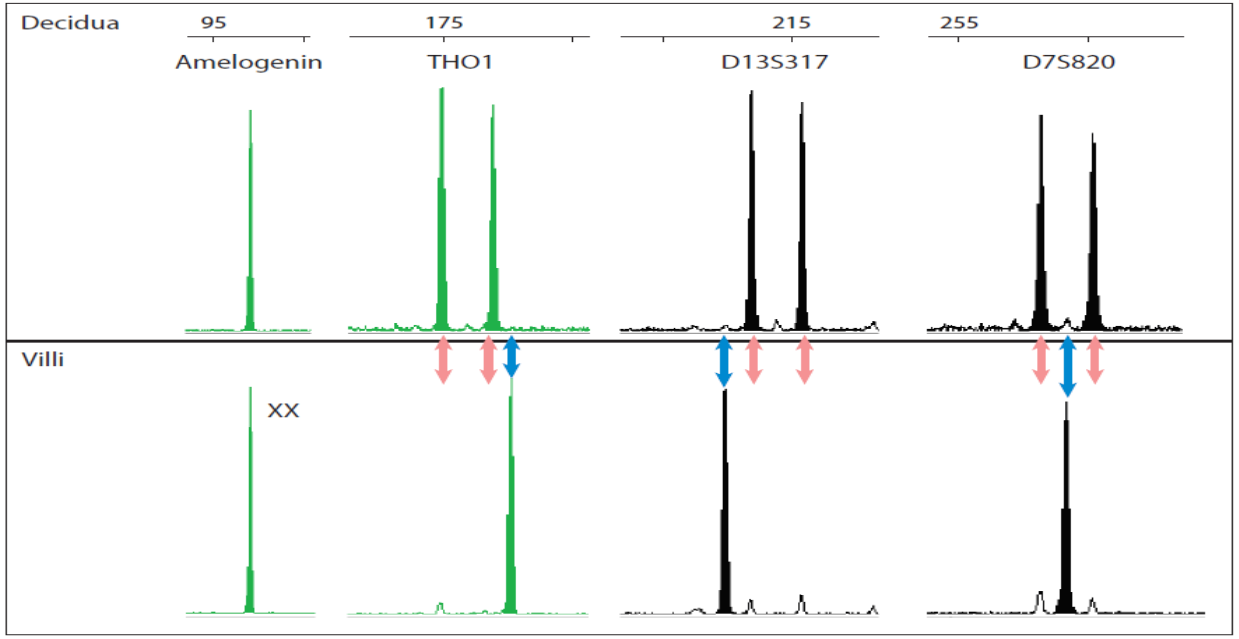
- Possible mole (frequency?; Pathology versus Clinical)
- Differential diagnosis
  - TRUE MOLAR GESTATIONS
    - Complete hydatidiform mole, including early forms
    - Partial hydatidiform mole
    - Invasive mole
  - NON-MOLAR GESTATIONS
    - Hydropic abortus or abortus with trophoblastic hyperplasia
    - Abnormal villous morphology related to chromosomal disorders, digynic monoandric tripoid gestations, etc
  - ANDROGENETIC/BIPARENTAL MOSAIC CONCEPTION
    - Early forms of placental mesenchymal dysplasia (non-molar)
    - Androgenetic/biparental mosaic conceptions with a molar component
- p57 IHC: Interpreted as: “**Negative**” [0-10% of cytotrophoblastic and villous stromal cells staining], “**Positive**” [≥50% of same cells staining], “**Discordant**” [cytotrophoblasts/stromal cells show different staining patterns], “**Divergent**” [morphologicaly distinct villous populations showing different staining patterns]
- Possible moles classified by morphology and p57 IHC only: **20% to 30% of cases will be misclassified**

Ronnett BM. Arch Pathol Lab Med. 2018
Vang RS et al. Am J Surg Pathol. 2012 Mar;36(3):443-53

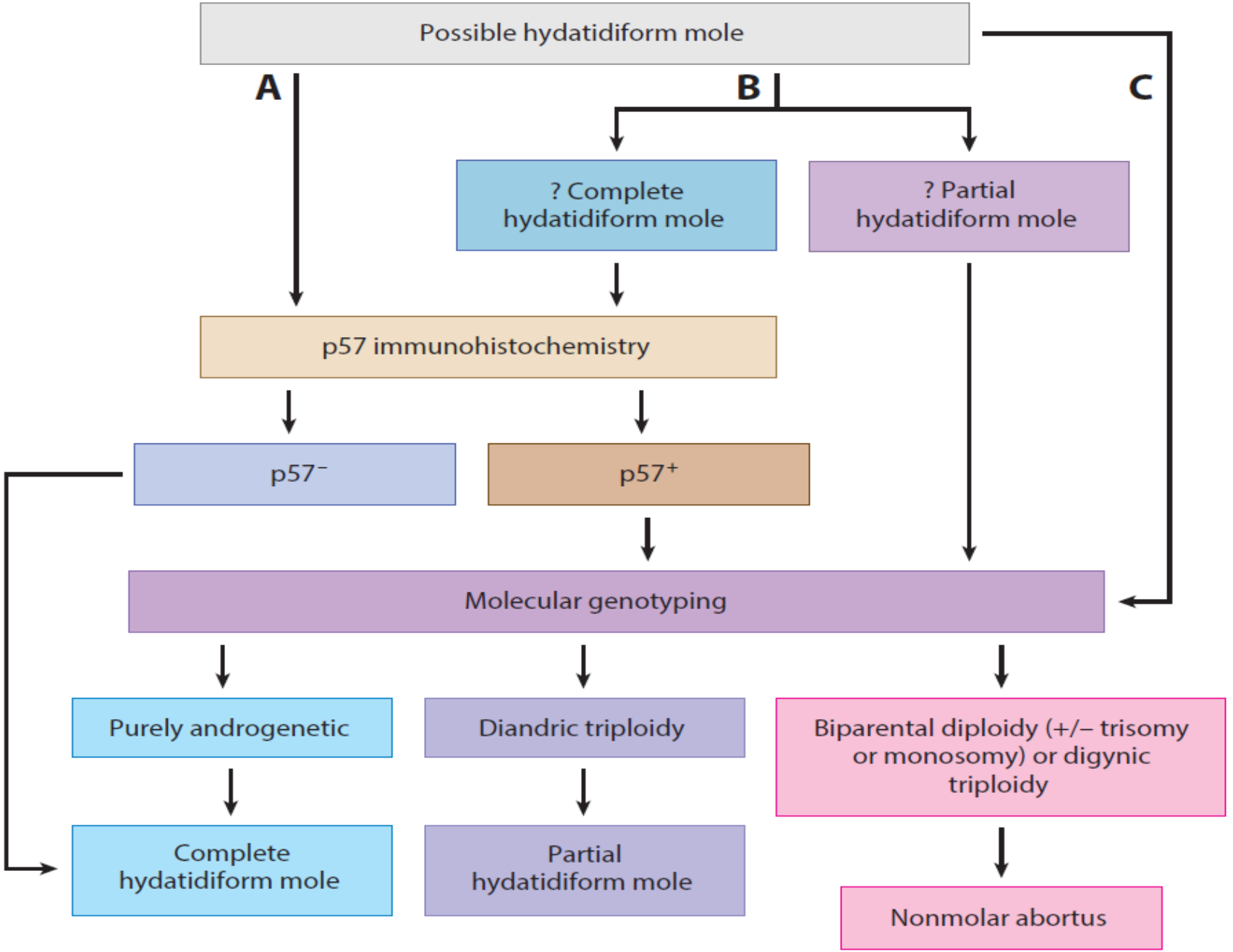



Hui P, et al. Annu Rev Pathol. 2017 Jan 24;12:449-485.




Hui P, et al. Annu Rev Pathol. 2017 Jan 24;12:449-485.

# Case 5:

62-year-old diagnosed with advanced stage high grade serous carcinoma of tubo-ovarian origin; s/p several cycles of platinum-based neoadjuvant chemotherapy. Now undergoing interval debulking surgery.

**Evolving Concept: Chemotherapy Response Score**

# CRS score: a required data element in the CAP synoptic report; recommended system by ICCR

| |
|---|
| **CRS 1: No or minimal tumor response**<br>**Mainly viable tumor with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration** |
| **CRS 2: Appreciable tumor response amidst viable tumor, both readily identifiable and tumor regularly distributed**<br>**Ranging from multifocal or diffuse regression associated fibro-inflammatory changes, with viable tumor in sheets, streaks, or nodules, to extensive regression associated fibro-inflammatory changes with multifocal residual tumor which is easily identifiable** |
| **CRS3: Complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm in maximum size. Mainly regression-associated fibro-inflammatory changes or, in rare cases, no/very little residual tumor in complete absence of any inflammatory response; advisable to record whether "no residual tumor" or "microscopic residual tumor present"** |

Regression associated fibro-inflammatory changes: fibrosis associated with macrophages, including foam cells, mixed inflammatory cells and psammoma bodies; to be distinguished from tumor-related inflammation or desmoplasia.

Bohm S, Faruqi A, Said I, et al. J Clin Oncol. 2015;33(22):2457-2463.

# Chemotherapy Response Score (CRS)

- Introduced by Bohm S/Singh N et al in 2015, the chemotherapy response score (CRS) stratifies patients into complete/near-complete (CRS3), partial (CRS2), and no/minimal (CRS1) response after NACT.
- In their seminal paper, the CRS system applied to omental samples showed high reproducibility (kappa, 0.67) and predicted PFS (CRS 1 and 2 v 3). CRS 3 also predicted sensitivity to first-line platinum therapy; less reproducibility and prognostic stratification if assessed in adnexa

Bohm S, Faruqi A, Said I, et al. J Clin Oncol. 2015;33(22):2457-2463.

# Chemotherapy Response Score (CRS)

## Meta-analysis, 877 patients

- CRS is significantly associated with PFS and OS in multivariate models adjusting for age and stage and debulking status (CRS 1/2 vs 3)
- CRS 1 and CRS 2 show no significant differences in OS and PFS
- Most of the patients who will not relapse at five years show CRS3
- Patients with BRCA1/2 mutations are more likely to have a CRS3 compared to those who are BRCA1/2 wild type, validating BRCA1/2 as predictor of platinum sensitivity
- Within CRS3, “no residual disease in omentum” shows better PFS and OS than “residual microscopic disease in omentum”
- CRS3 does NOT mean PCR ***for the patient***: 66% will still show disease elsewhere

Cohen PA et at. Gynecol Oncol. 2020 May;157(2):558-559

# Case 6:

46-year-old with a unilateral, 8 cm ovarian mass discovered during the work up of her presenting chief complaint: menorrhagia.

**Evolving Concept: *FOXL2* mutation testing**

# *FOXL2*-Mutation in Cases Diagnosed as AGCT

| Reference | Morphology-diagnosis of AGCT | Number with *FOXL2* mutation (402C-->G (C134W) | Percent of *FOXL2* wild-type cases reclassified after review |
|---|---|---|---|
| Monechy et al (J Natl Cancer Inst. 2016 Jun 13;108(11). | 336 | 256 (76%) | 79% |
| Komoss et al (Histopathology. 2014;64:380-8.) | 46 | 40 (87%) | 87% |
| Shah et al (N Engl J Med. 2009 Jun 25;360(26):2719-29) | 89 | 86 (97%) | |
| Buza et al (Int J Gynecol Pathol. 2017 Jul 11.) | 35 | 31 (89%) | |
| Jamieson et al. (Mod Pathol. 2010;23:1477-85) | 56 | 52 (93%) | 75% |
| Zannoni et al (Oncol Lett. 2016;12:1159-1163) | 37 | 33 (89.2) | |
| Oseto et al (J Obstet Gynaecol Res 2014 May;40(5):1197-204.) | 44 | 27 (61.4%) | |

*AGCT: adult granulosa cell tumor

# Specificity of *FOXL2* mutations for AGCT

- **Potentially positive SCST**: 3% of juvenile granulosa cell tumors, 1.6% of conventional fibromas, 10-20% of thecomas, 13% of sertoli-leydig cell tumors, 50% of granulosa theca cell tumors, and 8% of gynandroblastomas.
- **Negative SCSTs**: Sertoli cell tumours, sex cord tumors with annular tubules (SCTATs), or gynandroblastomas, cellular fibromas, sclerosing stromal tumors, microcystic stromal tumors, steroid cell tumors
- **Negative non-SCSTs:** Müllerian carcinomas; carcinomas from pancreas, prostate, and thyroid, bladder, breast, colon, stomach, head and neck, kidney, liver, lung; ovarian germ cell tumors, melanomas, or sarcomas

Kim et al. Histopathology 2010; 56;408–410; Shah SP, et al. N. Engl. J. Med. 2009; 360;2719–2729; Al-Agha OM, et al. Am. J. Surg. Pathol. 2011; 35; 484–494.; Buza N et al. . Int. J. Gynecol. Pathol. 2018; 37;305–315; Goulvent T, et al. Histopathology 2016; 68; 279–285; Jamieson S, et al. Mod. Pathol. 2010; 23; 1477–1485; Kim et al. J. Pathol. 2010; D'Angelo E, et al. Mod. Pathol.2011; 24; 1360–1367; Oseto et al. J. Obstet. Gynaecol. Res. 2014; 40; 1197–1204.221; Karnezis AN, et al. Am. J. Surg. Pathol. 2019; 43; 628–638; Nolan A, et al.. Int. J. Gynecol. Pathol. 2017; 36; 568–574; Wang Y, et al. Histopathology 2018; 73;306–313; Conlon N et al. Mod. Pathol. 2015; 28; 1603–1612; Schrader et al. PLoS ONE 2009; 4; e7988.

# Potential uses of *FOXL2* mutational analysis (not to be deployed for pathologically classic AGCT cases).

- AGCT with diffuse or spindled areas versus cellular fibroma or thecoma.
- AGCT (luteinized) or with “thecoma-like areas” versus thecoma.
- AGCT versus juvenile granulosa cell tumor.
- AGCT with an abundance of fibromatous/thecomatous stroma versus fibroma with minor sex cord elements.
- Classification of an otherwise unclassified sex cord stromal tumor.

# THANK YOU!