Gestational Trophoblastic Disease - Frontiers in Precision Medicine

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Disclosure of Relevant Financial Relationships

Dr. Pei Hui has the following disclosures that are unrelated to this presentation

AstraZeneca, Precision Medicine Pathologist Steering Committee (2023)
Verastem Oncology, Commercial Oncological Pathology Advisory Board (2024)

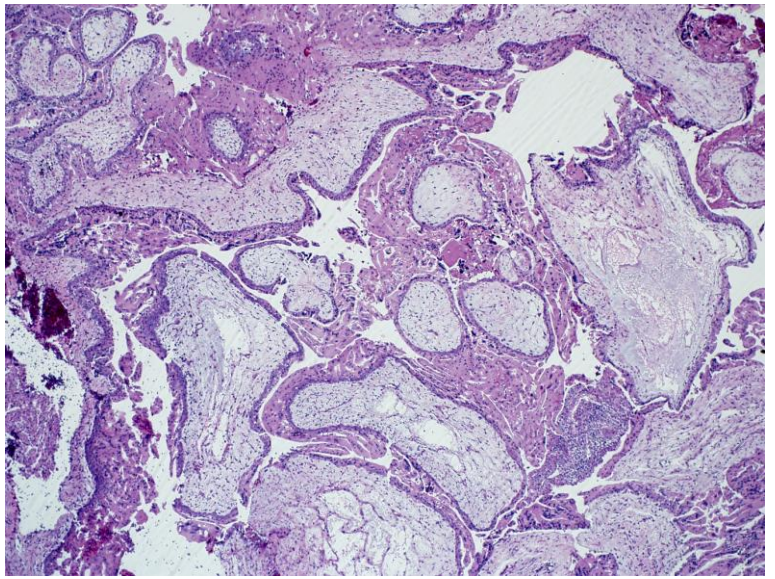
Proliferative Disorders of Trophoblasts

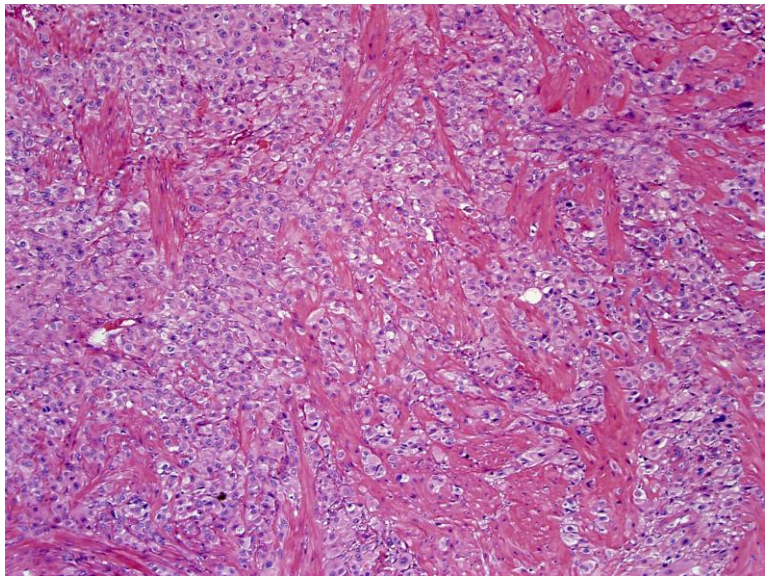
Hyperplastic Proliferation

Complete Hydatidiform Mole (CHM)
Partial Hydatidiform Mole (PHM)
Invasive Hydatidiform Mole

Neoplastic Proliferation

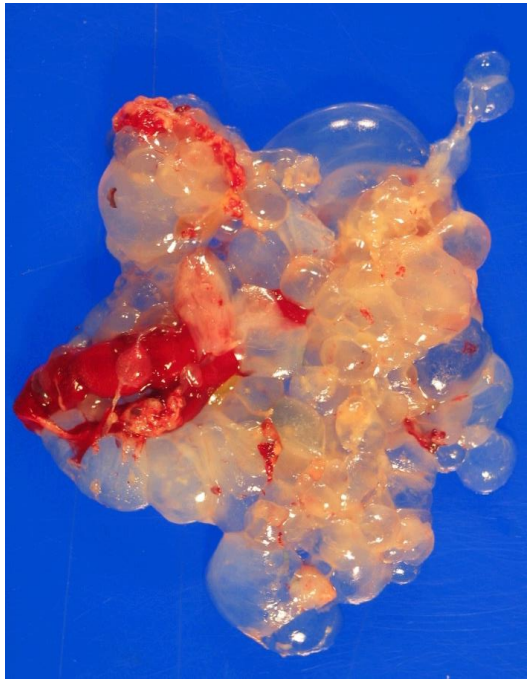
Gestational choriocarcinoma (CC)
Placental site trophoblastic tumor (PSTT)
Epithelioid Trophoblastic Tumor (ETT)

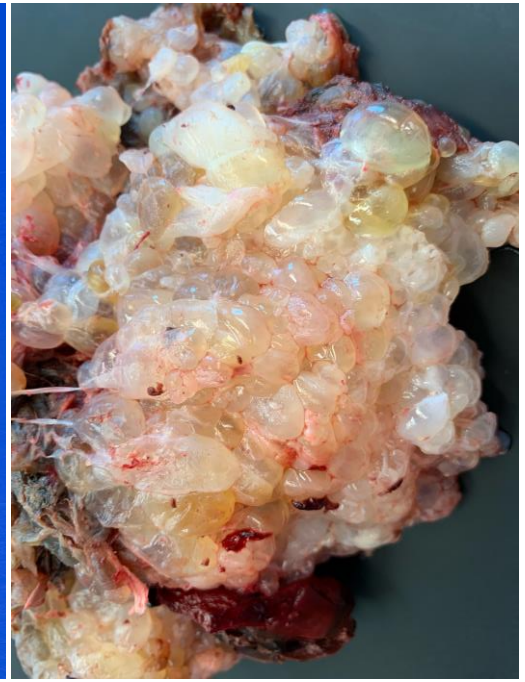


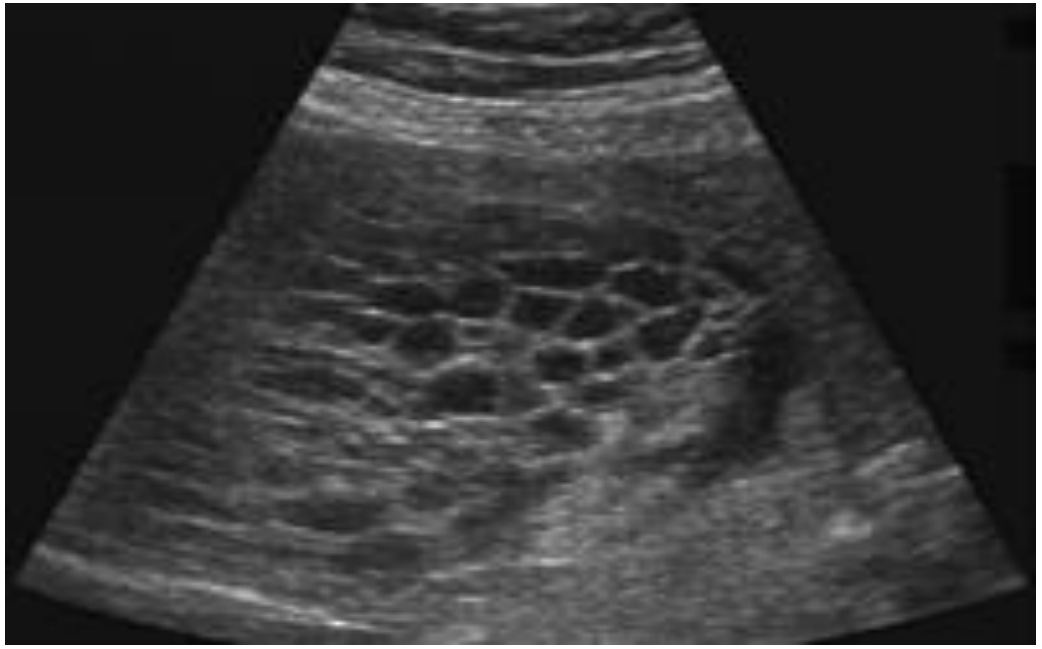


Diagnostic Challenges

Complete Hydatidiform Mole







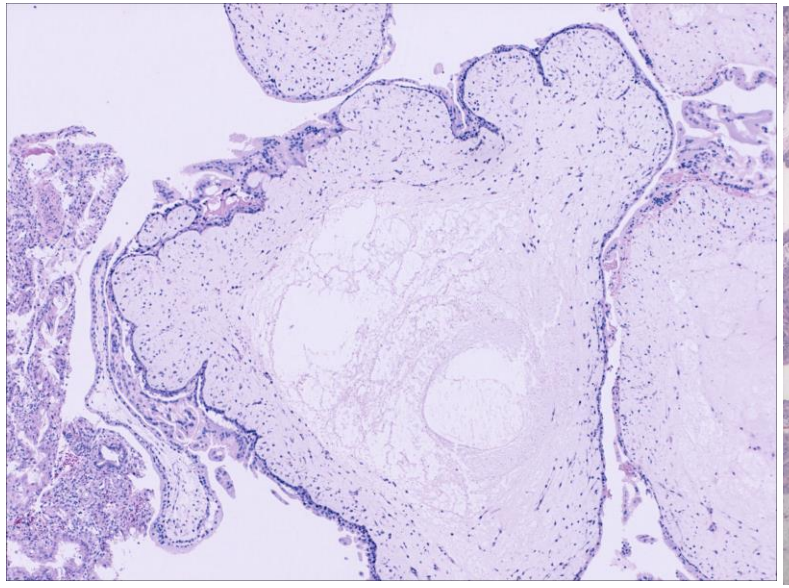
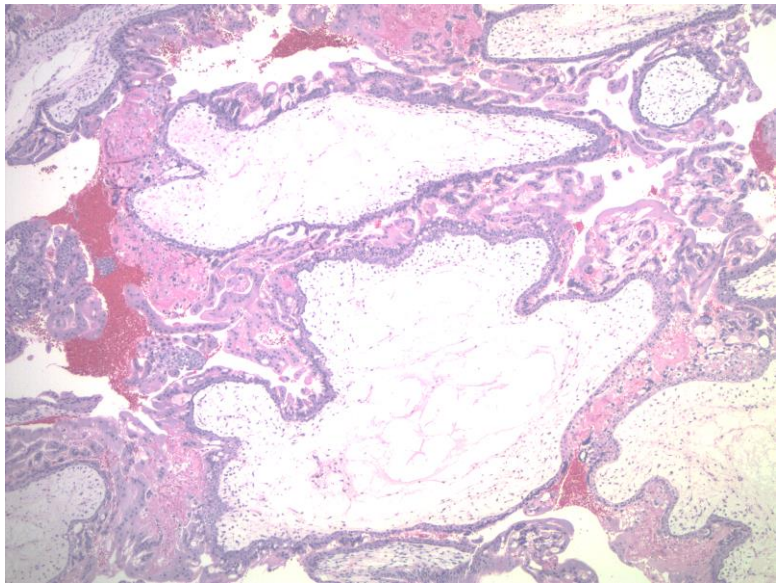
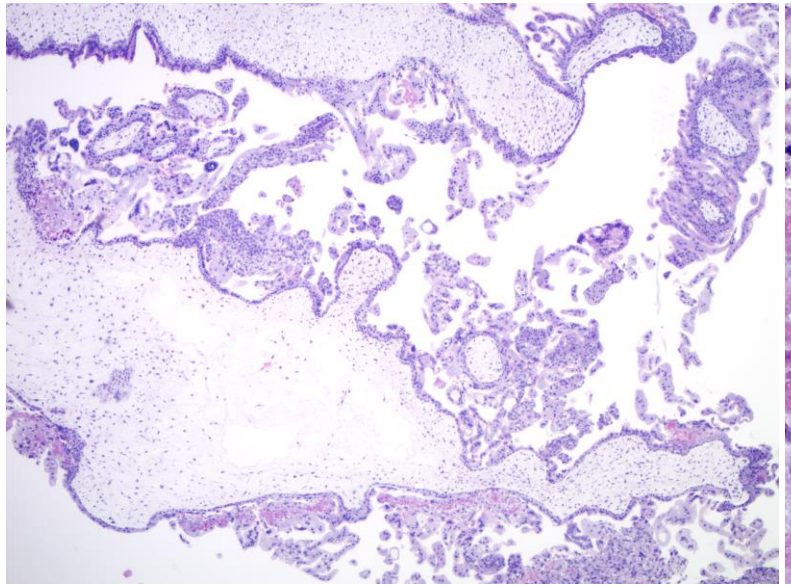
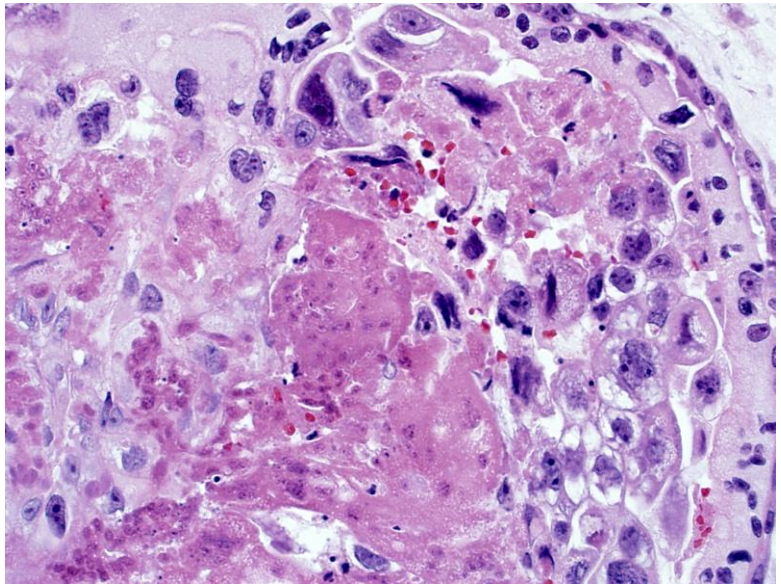
Well Developed CHM

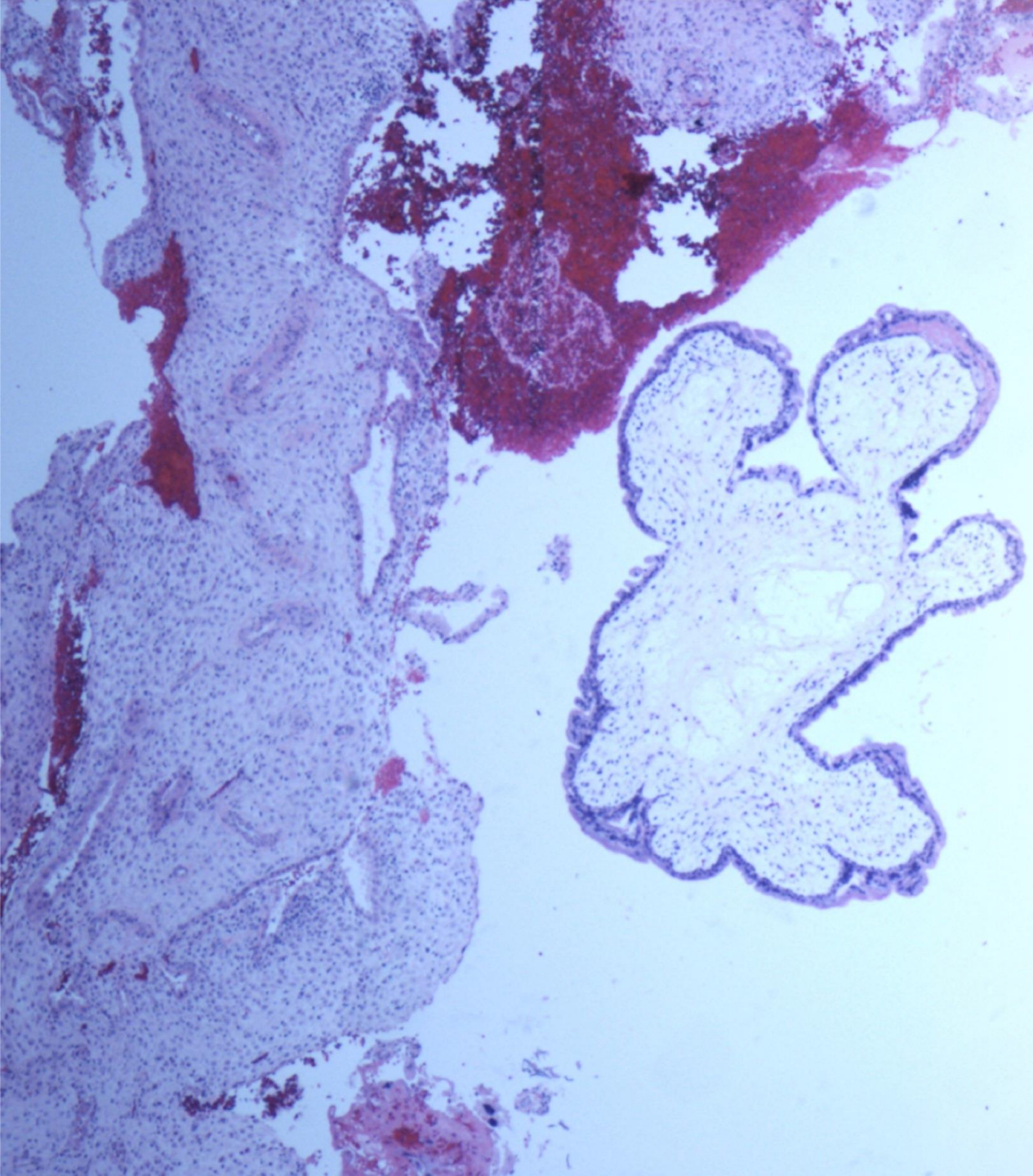
- Vaginal bleeding during 2nd trimester
- Excessive uterine size
- Markedly elevated serum hCG (hyperemesis)
- Toxemia, hyperthyroidism
- “Snowstorm” appearance on U/S

Elsayes K M et al. Radiographics 2009; 29:1371-1391.

Complete Mole

- Villous Hydrops, Cistern Formation
- Atypical Trophoblast Hyperplasia

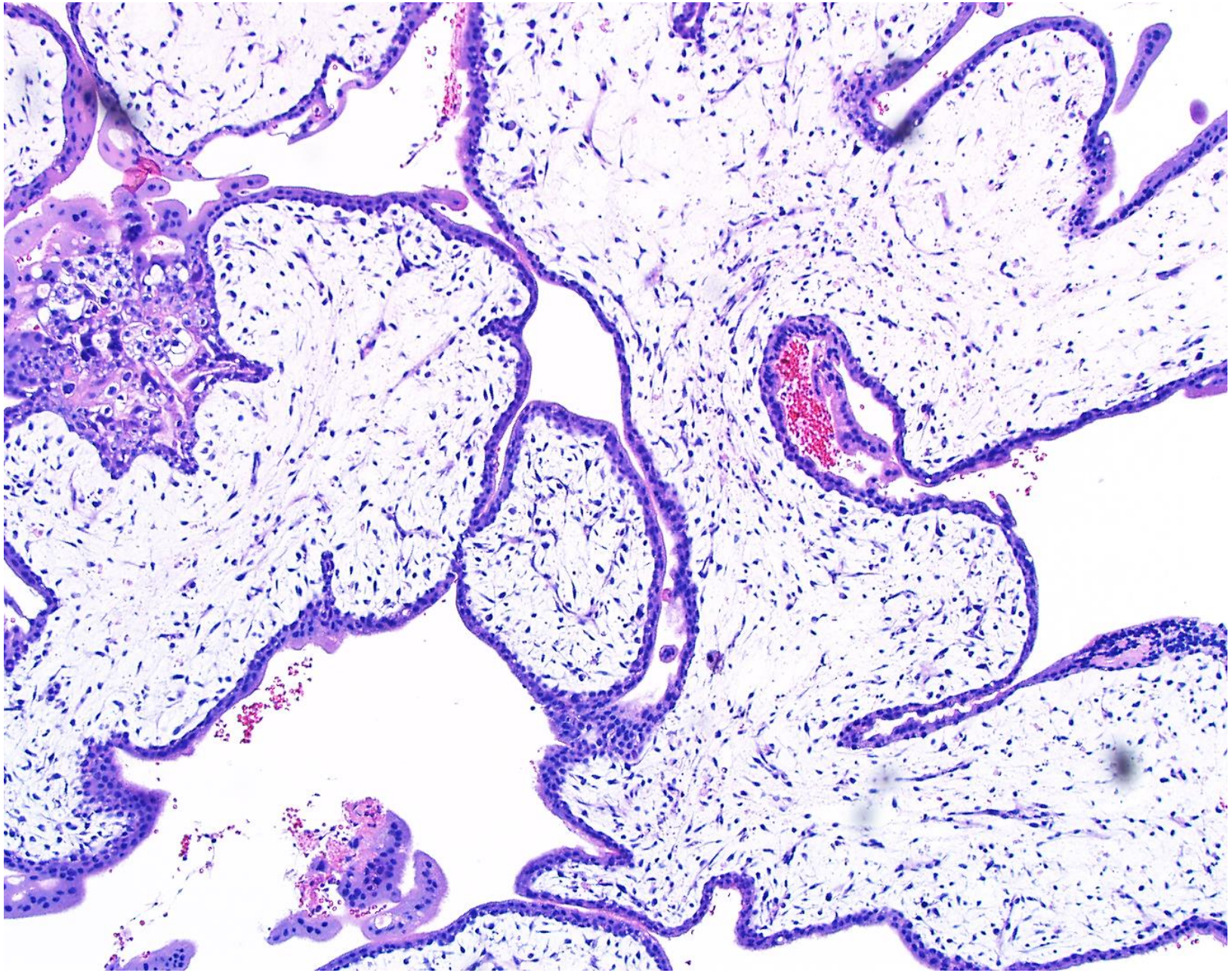


Very Early Complete Mole (VECHM)

- Polypoid chorionic villi
- Cellular myxoid villous
- Prominent karyorrhexis in the villous stroma
- No or focal trophoblastic hyperplasia

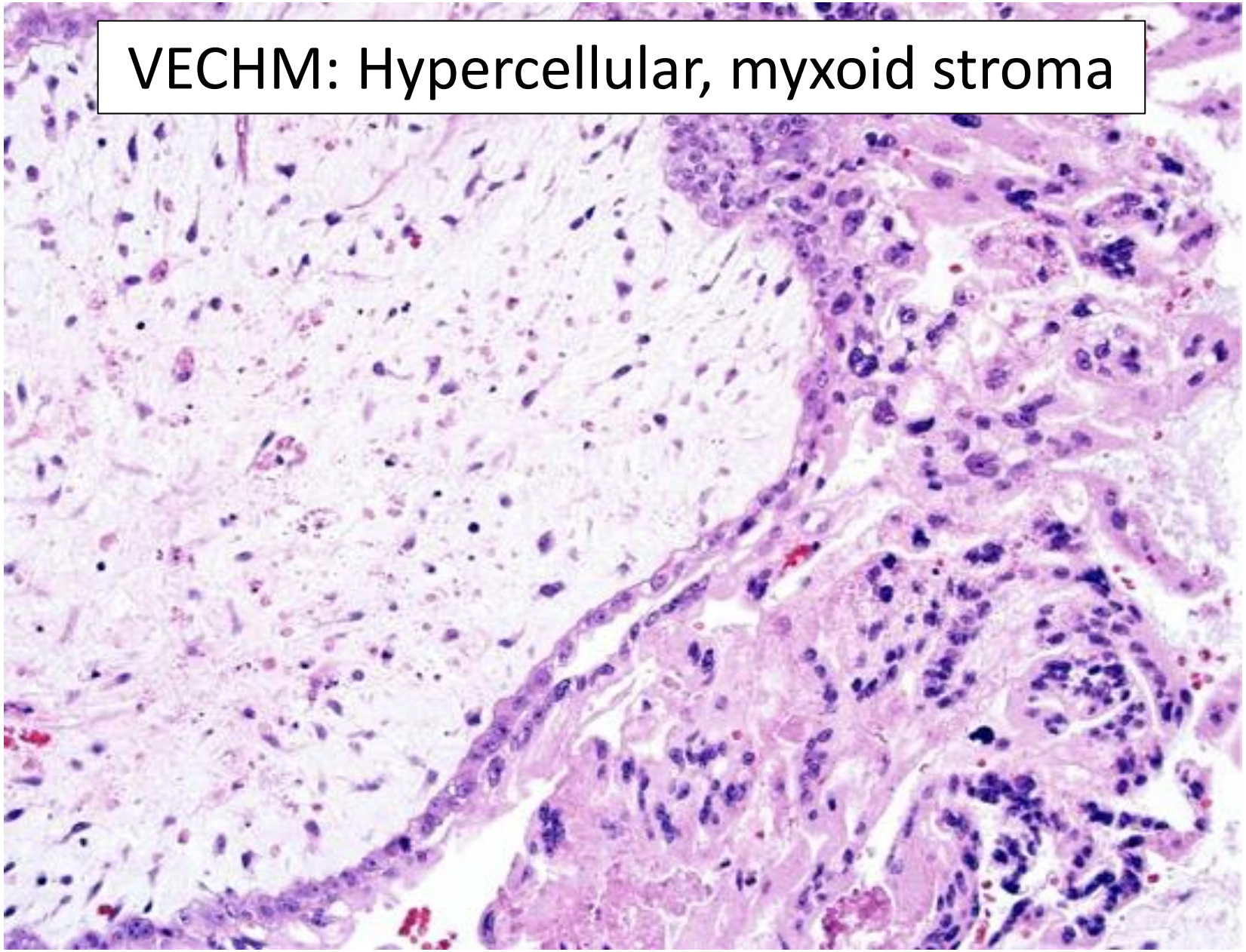
Very early CHM

- Bulbous, polypoid villi
- Cellular myxoid stroma
- Prominent karyorrhexis
- Trophoblast hyperplasia

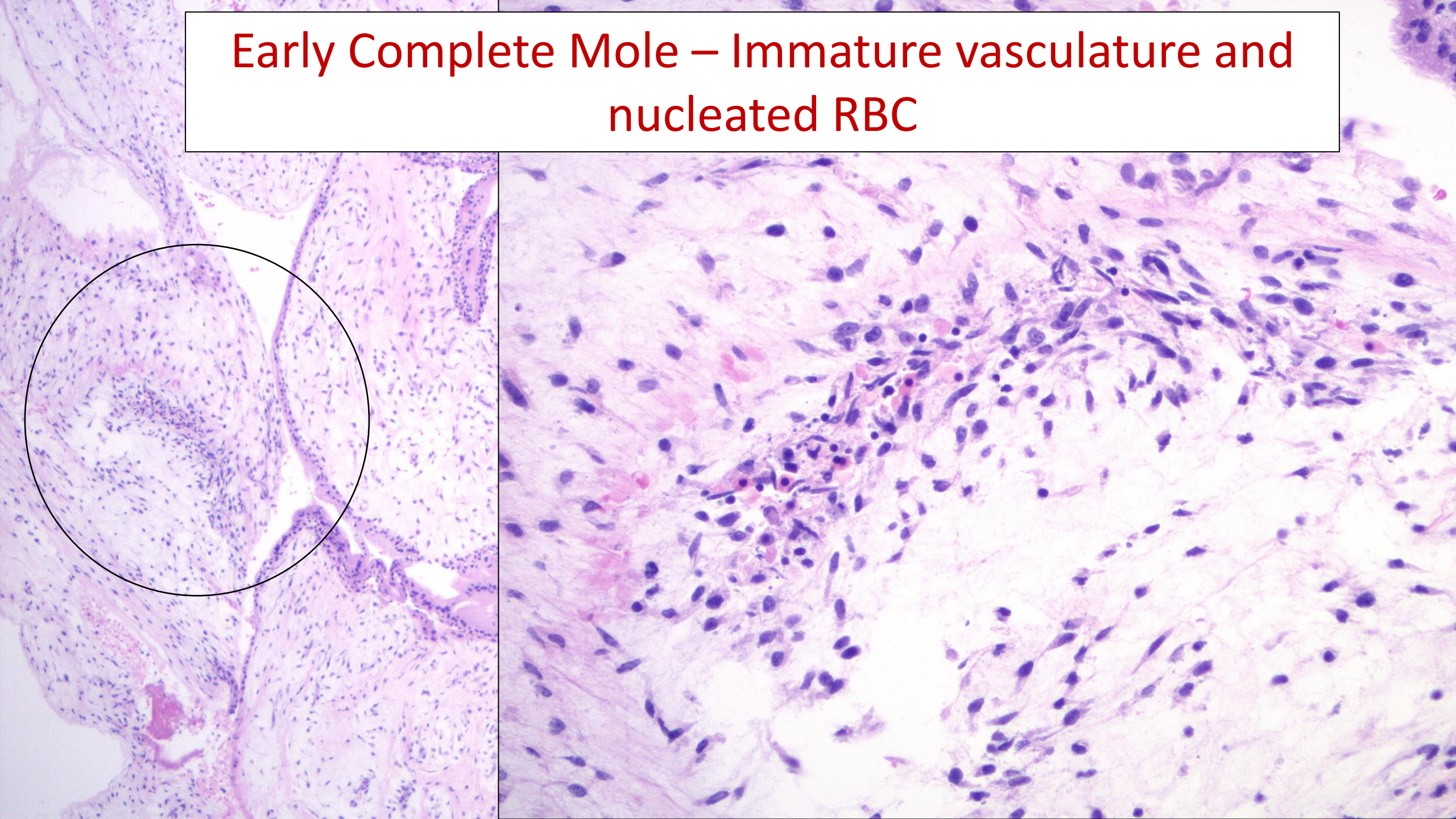


Very early CHM

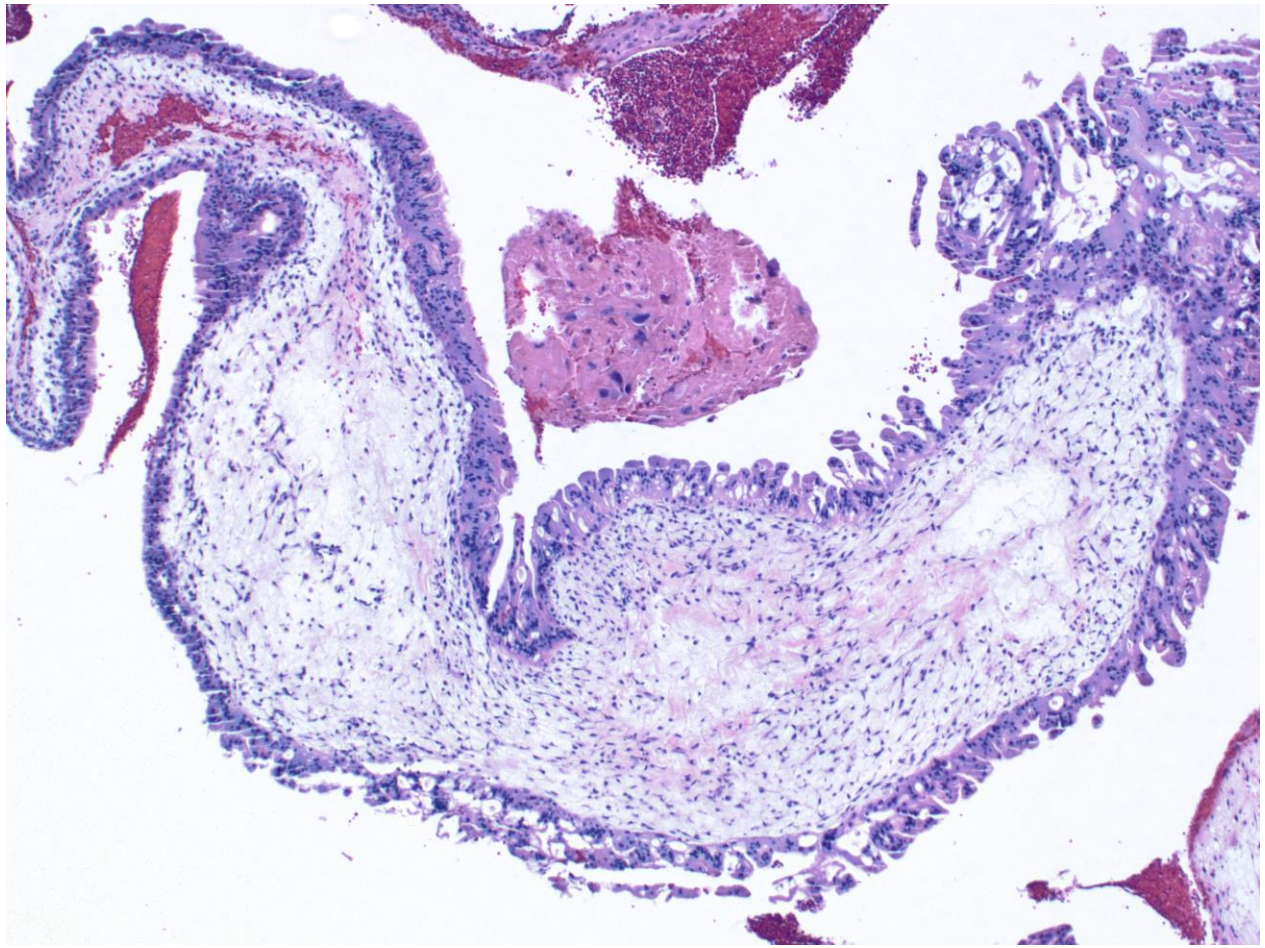
- Bulbous, polypoid villi
- Cellular myxoid stroma
- Prominent karyorrhexis
- Trophoblast hyperplasia

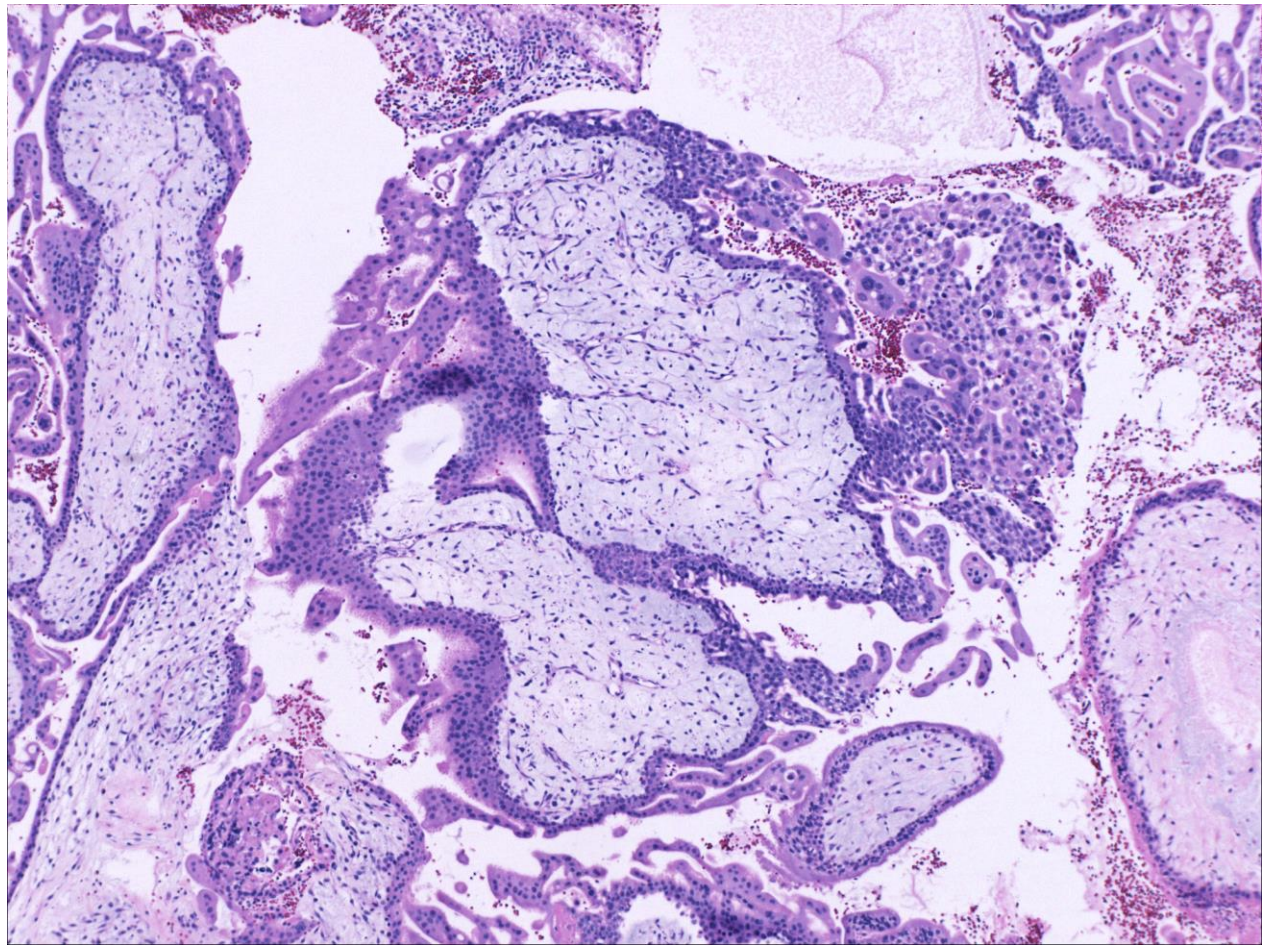


Early Complete Mole – Immature vasculature and nucleated RBC



Abnormal Villous Trophoblastic Proliferation





P57 IHC

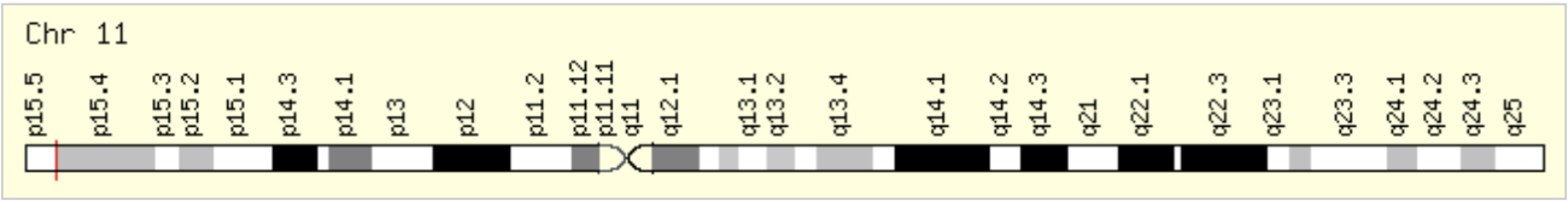
Cyclin-dependent kinase inhibitor protein

Encoded on 11p15.5

Paternally imprinted – expressed only from the maternal allele

Cytogenetic band: 11p15.4 by HGNC 11p15.4 by Entrez Gene 11p15.4 by Ensembl

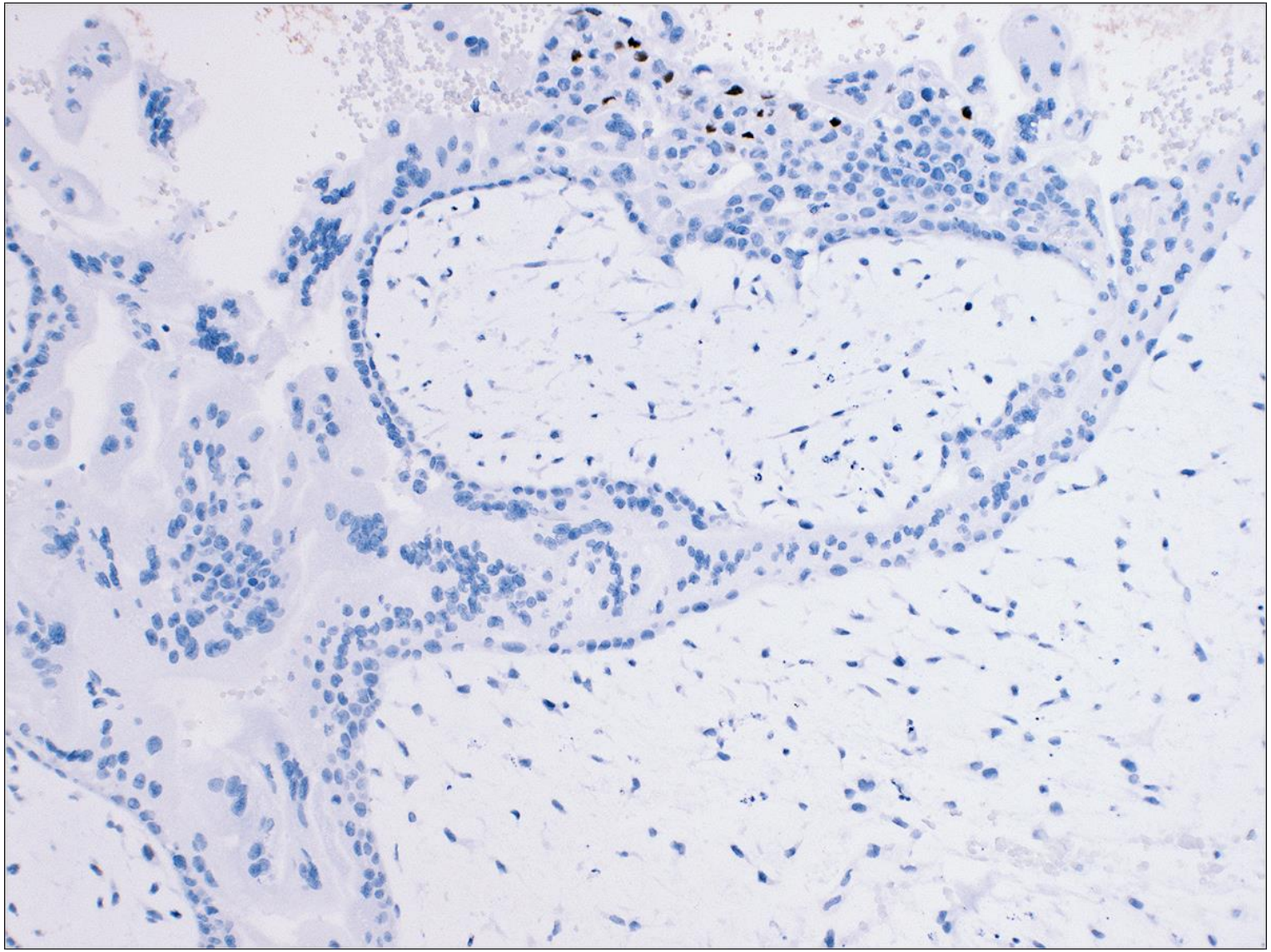
CDKN1C Gene in genomic location: bands according to Ensembl, locations according to GeneLoc (and/or Entrez Gene and/or Ensembl if different)



www.genecards.org

CHM

p57 - Absent in villous stroma and cytotrophoblast (<10%)



P57 IHC Interpretation Pitfalls

- Divergent p57 expression (Twin gestations, mosaicism/chimerism)
- Discordant p57 expression between villous cytotrophoblast and villous stroma
- CHM with retained p57
- P57 loss in gestations other than CHM

Divergent P57 Expression

Twin Gestation

Complete Hydatidiform Mole and Coexisting Fetus With Gastroschisis: A Case Report Highlighting the Importance of Diagnostic Genotyping

Austin McHenry[1], Urania Magriples[2], Pei Hui[1], and Raffaella Morotti[1]

Pediatric and Developmental Pathology
2021, Vol. 24(6) 575–580

DOI: 10.1177/10935266211024823
journals.sagepub.com/home/pdp
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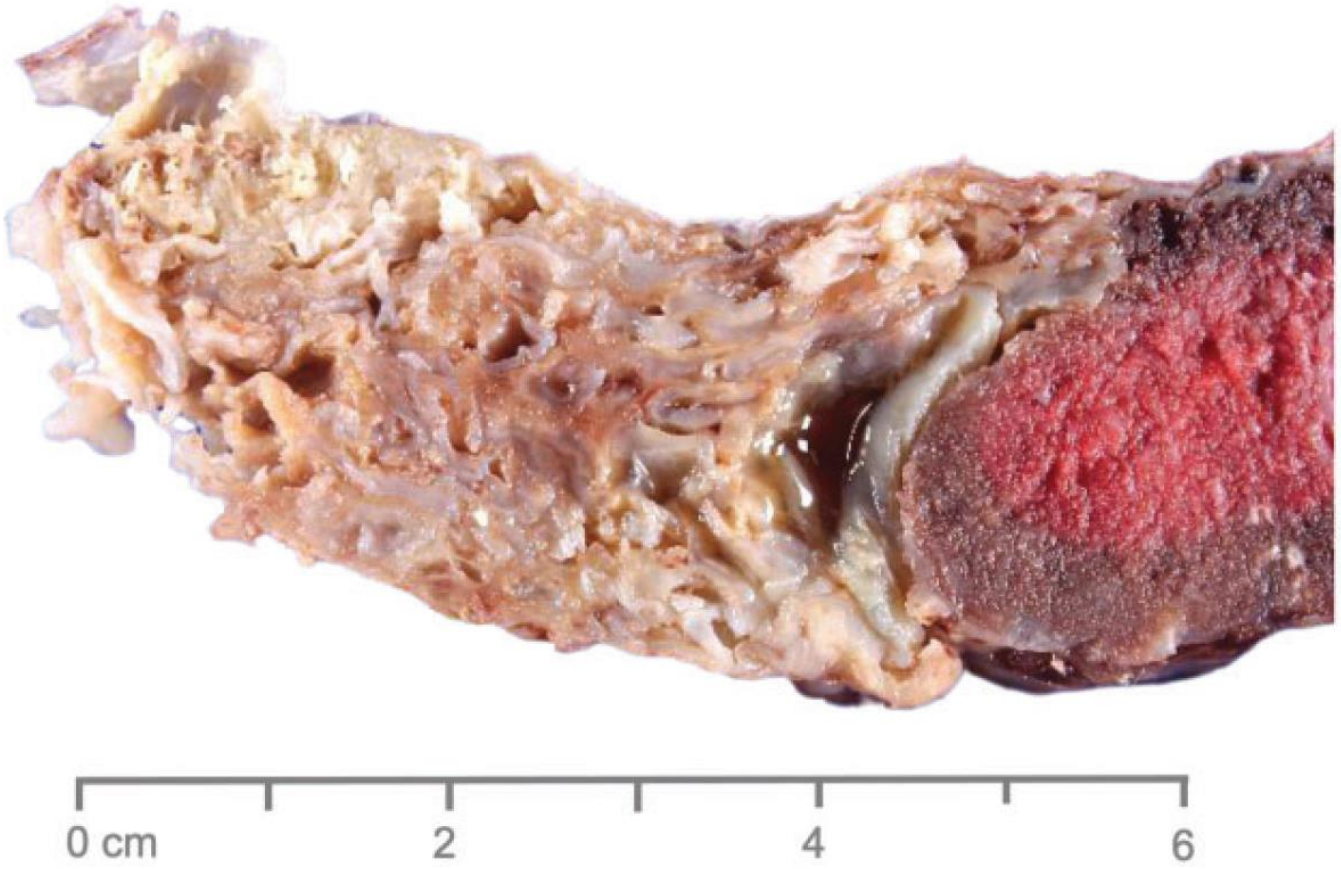
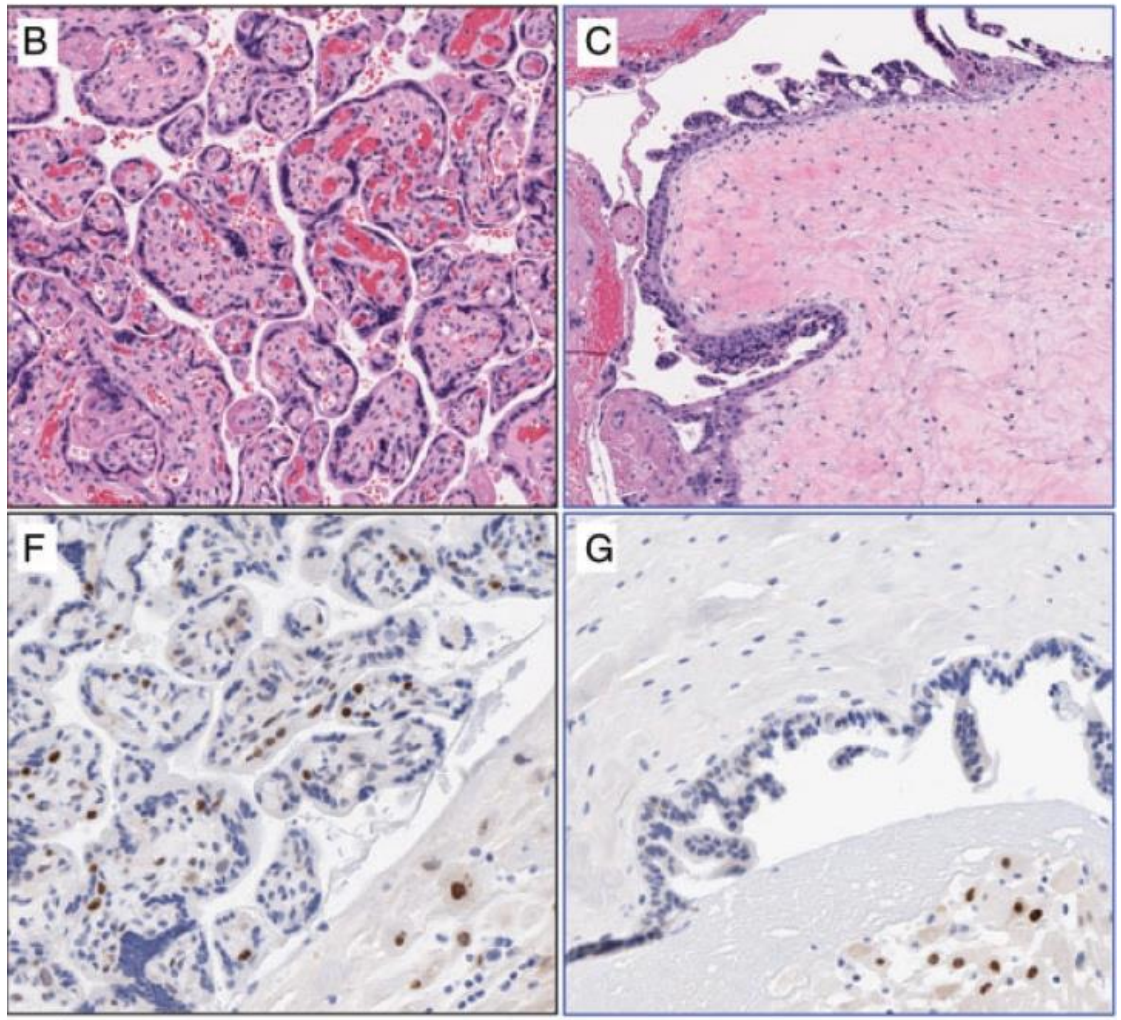
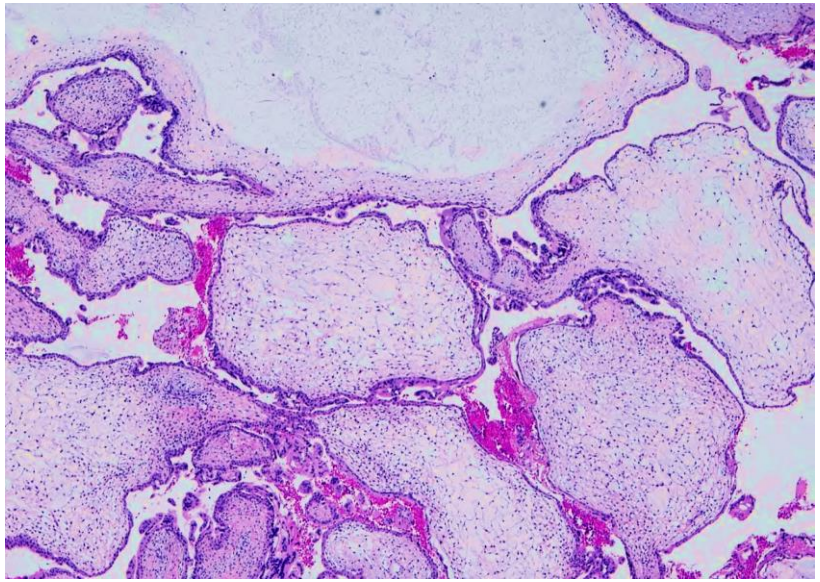
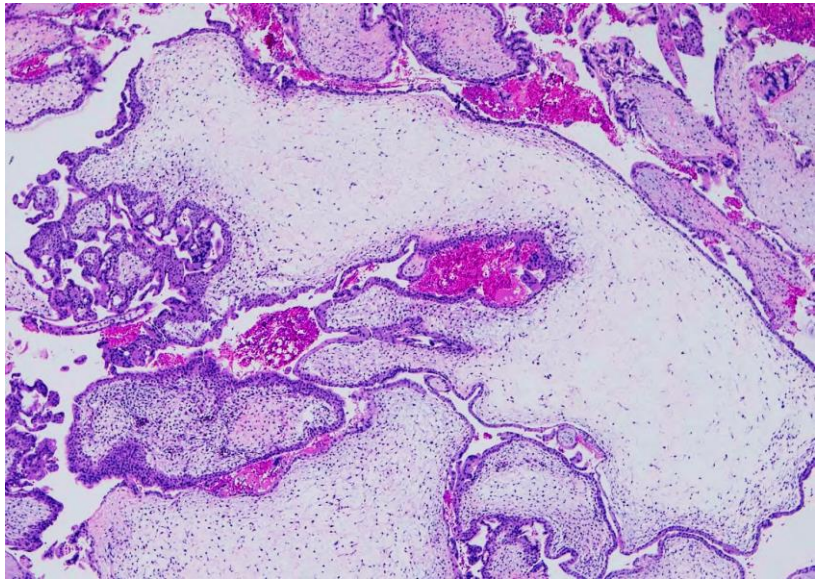
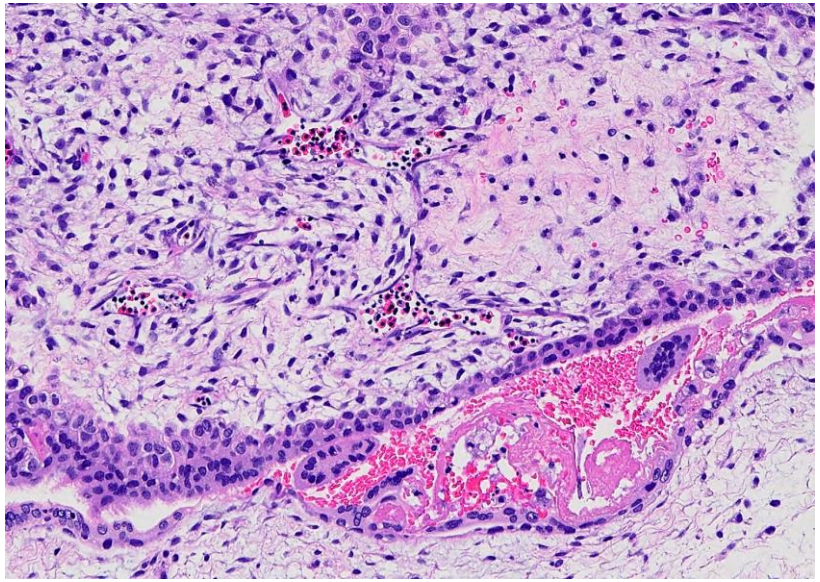


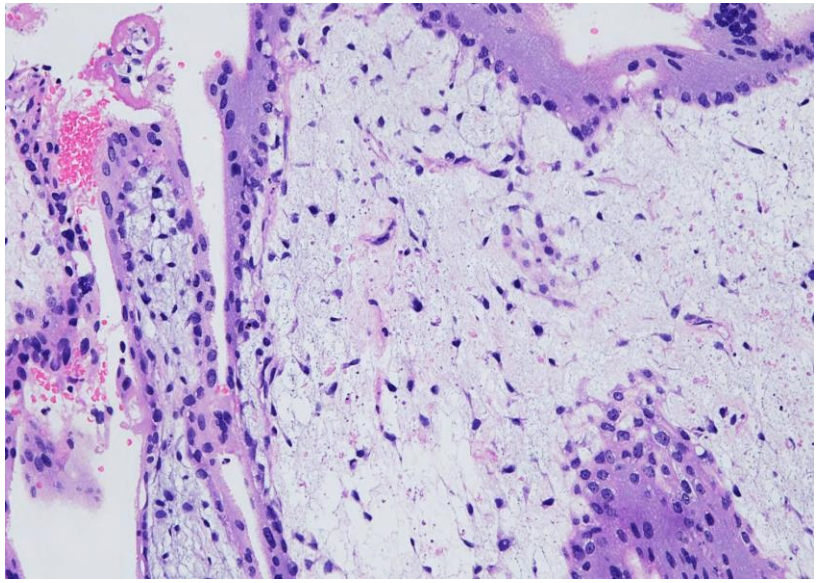


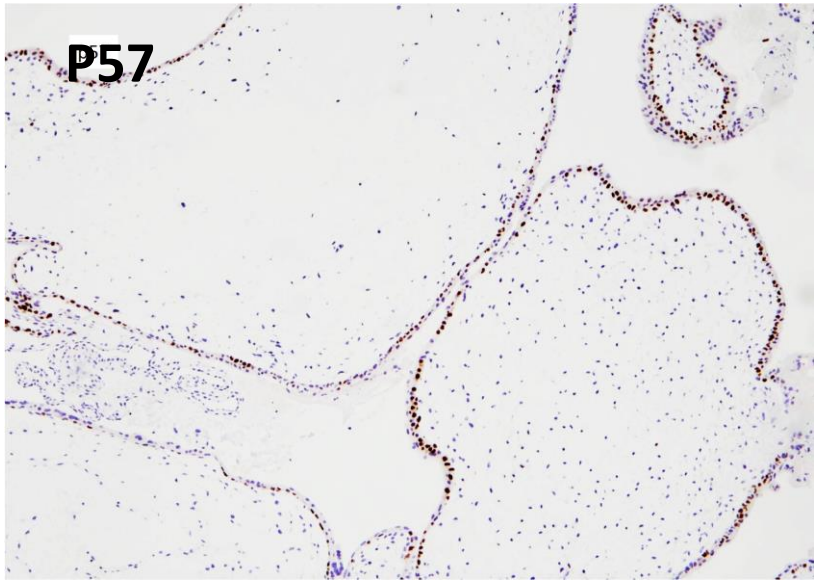
Discordant P57 Expression - Androgenetic/ Biparental mosaic/Chimeric Gestations

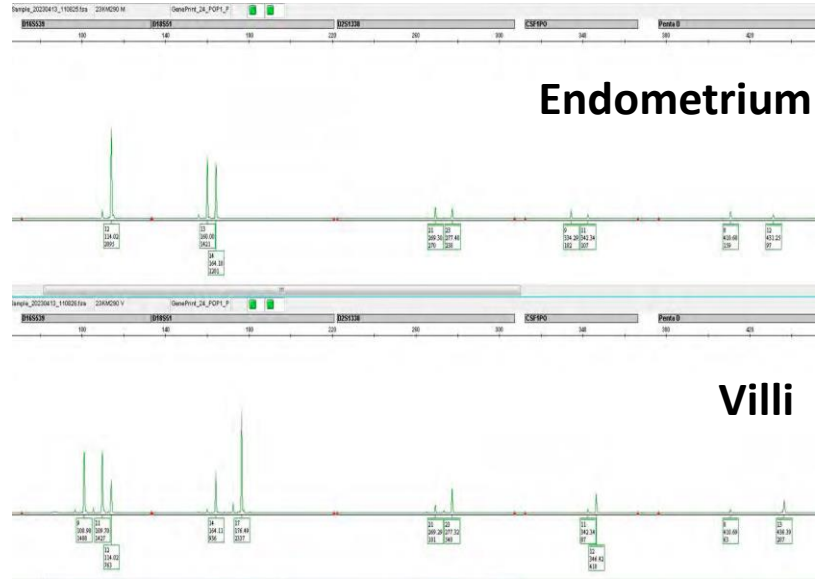












Y-GTD Case of November 2023

Modern Pathology (2004) 17, 1155–1160

www.modernpathology.org

Complete hydatidiform mole retaining a chromosome 11 of maternal origin: molecular genetic analysis of a case

Rosemary A Fisher[1], Marisa R Nucci[2], Harshwardhan M Thaker[3], Stanislawa Weremowicz[2], David R Genest[2] and Diego H Castrillon[2,*]

Complete Hydatidiform Mole With Retained Maternal Chromosomes 6 and 11

Thomas G. McConnell, MD, Alexis Norris-Kirby, BS,* Jill M. Hagenkord, MD,† Brigitte M. Ronnett, MD,*‡ and Kathleen M. Murphy, PhD**

(*Am J Surg Pathol* 2009;33:1409–1415)

Diandric Triploid Hydatidiform Mole With Loss of Maternal Chromosome 11

Cheryl DeScipio, PhD,† Lisa Haley, MS,* Katie Beierl, BS,* Ashwini P. Pandit, MBBS,‡§ Kathleen M. Murphy, PhD,* and Brigitte M. Ronnett, MD*†*

(*Am J Surg Pathol* 2011;35:1586–1591)

Loss of p57 Expression in Conceptions Other Than Complete Hydatidiform Mole

A Case Series With Emphasis on the Etiology, Genetics, and Clinical Significance

Deyin Xing, MD, PhD,†‡ Karin Miller, MD,* Katie Beierl, MS,* and Brigitte M. Ronnett, MD*†*

(*Am J Surg Pathol* 2022;46:18–32)

Modern Pathology (2019) 32:1180–1188
https://doi.org/10.1038/s41379-019-0266-0

USCAP

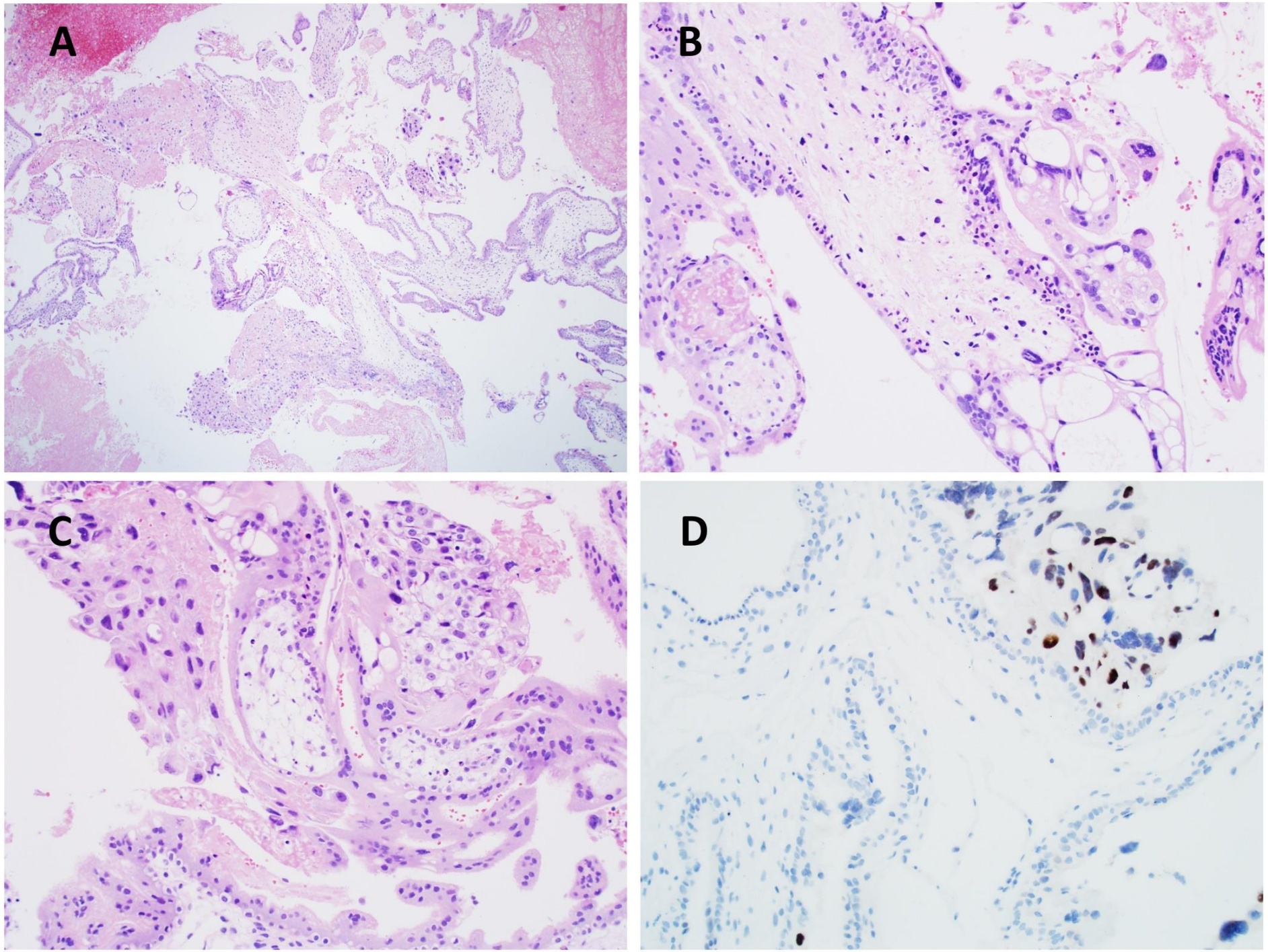
ARTICLE

Check for updates

Paternal uniparental isodisomy of tyrosine hydroxylase locus at chromosome 11p15.4: spectrum of phenotypical presentations simulating hydatidiform moles

Natalia Buza[1] · Stephanie M. McGregor[2] · Lisa Barroilhet[3] · Xingzheng Zheng[4] · Pei Hui[1]

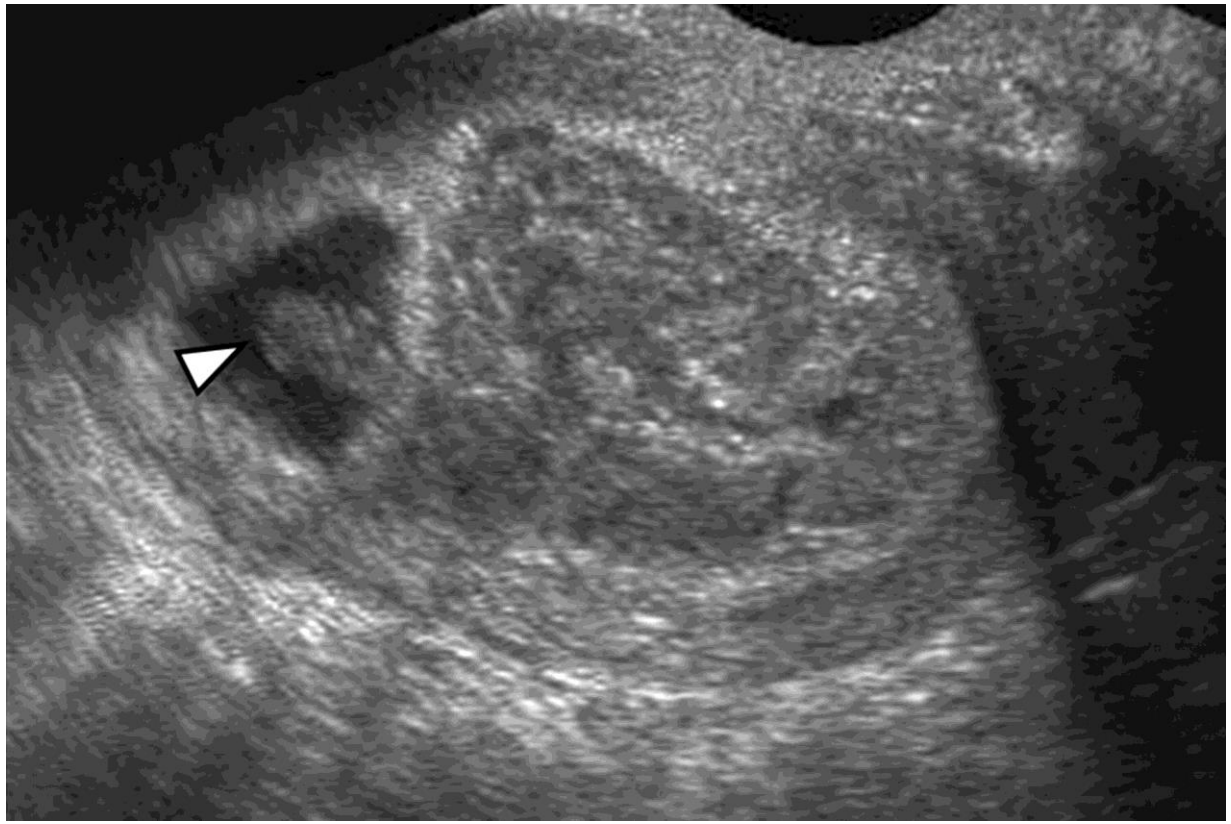
Paternal uniparental disomy (UPD) of chromosome 11

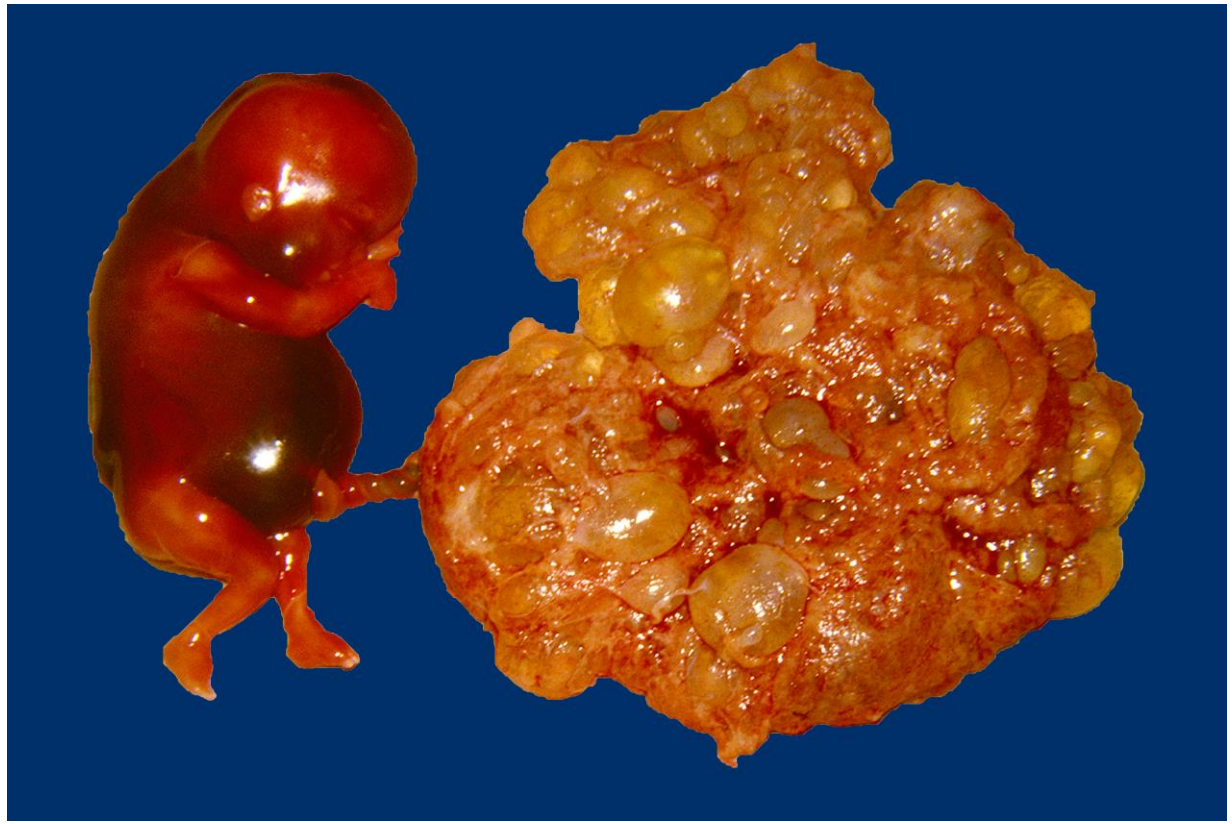


Buza et al., Mod Pathol 2019

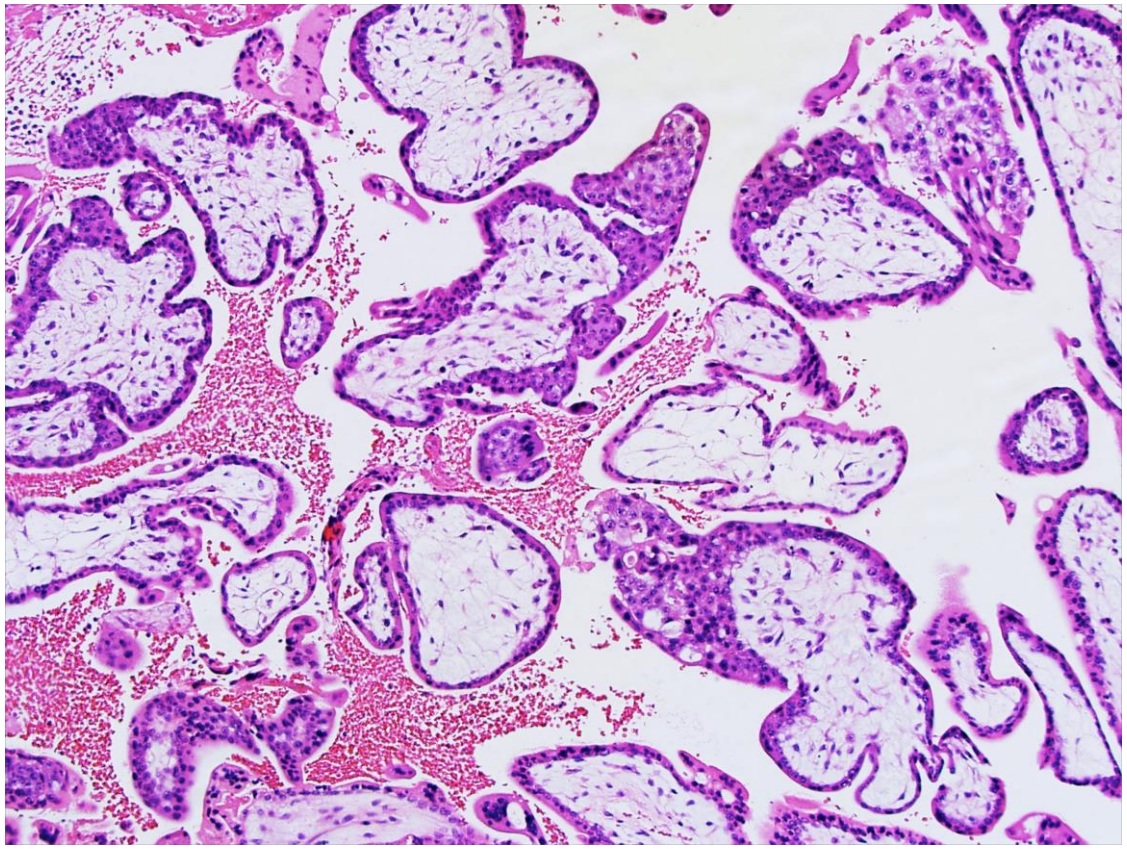
Partial Hydatidiform Mole

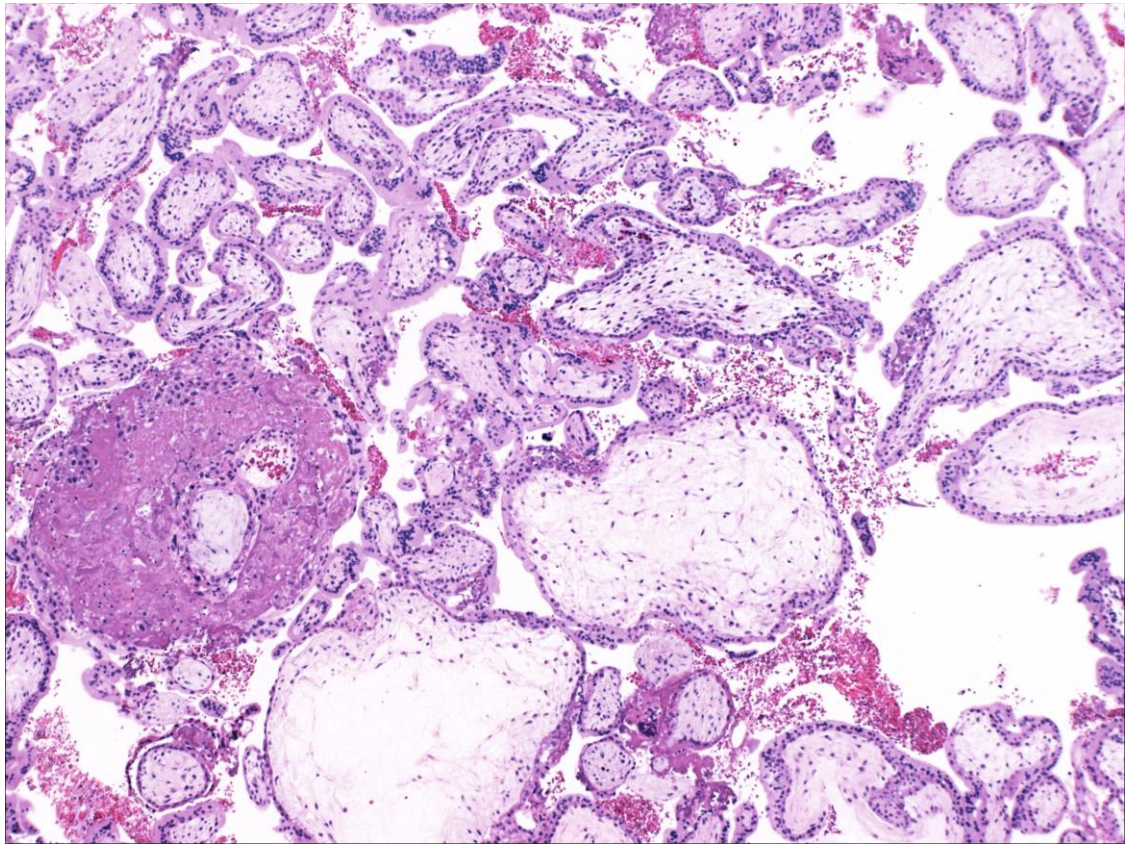
Partial Hydatidiform Mole (PHM)





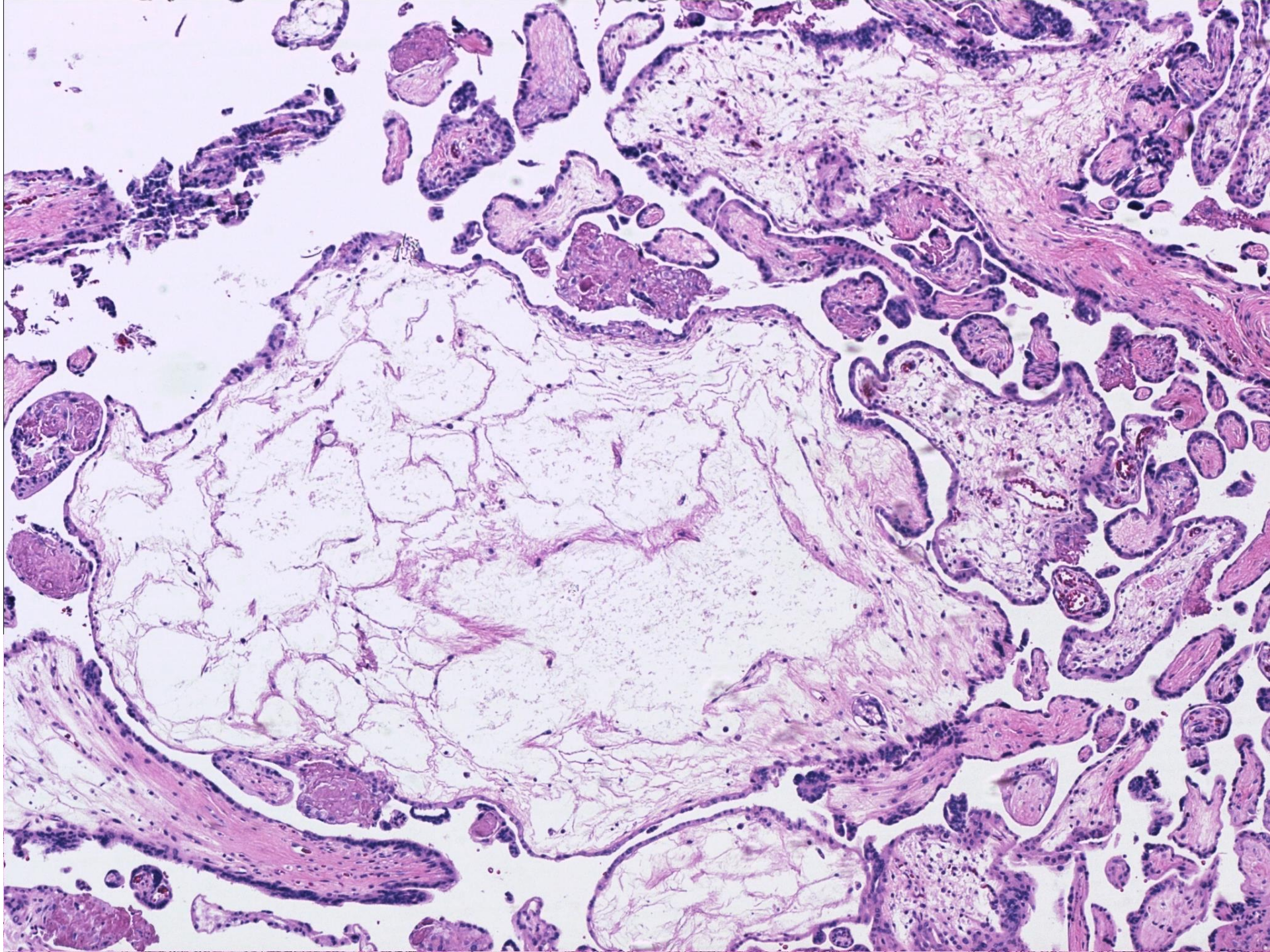
Partial Hydatidiform Mole (PHM) – Now also evacuated in first trimester





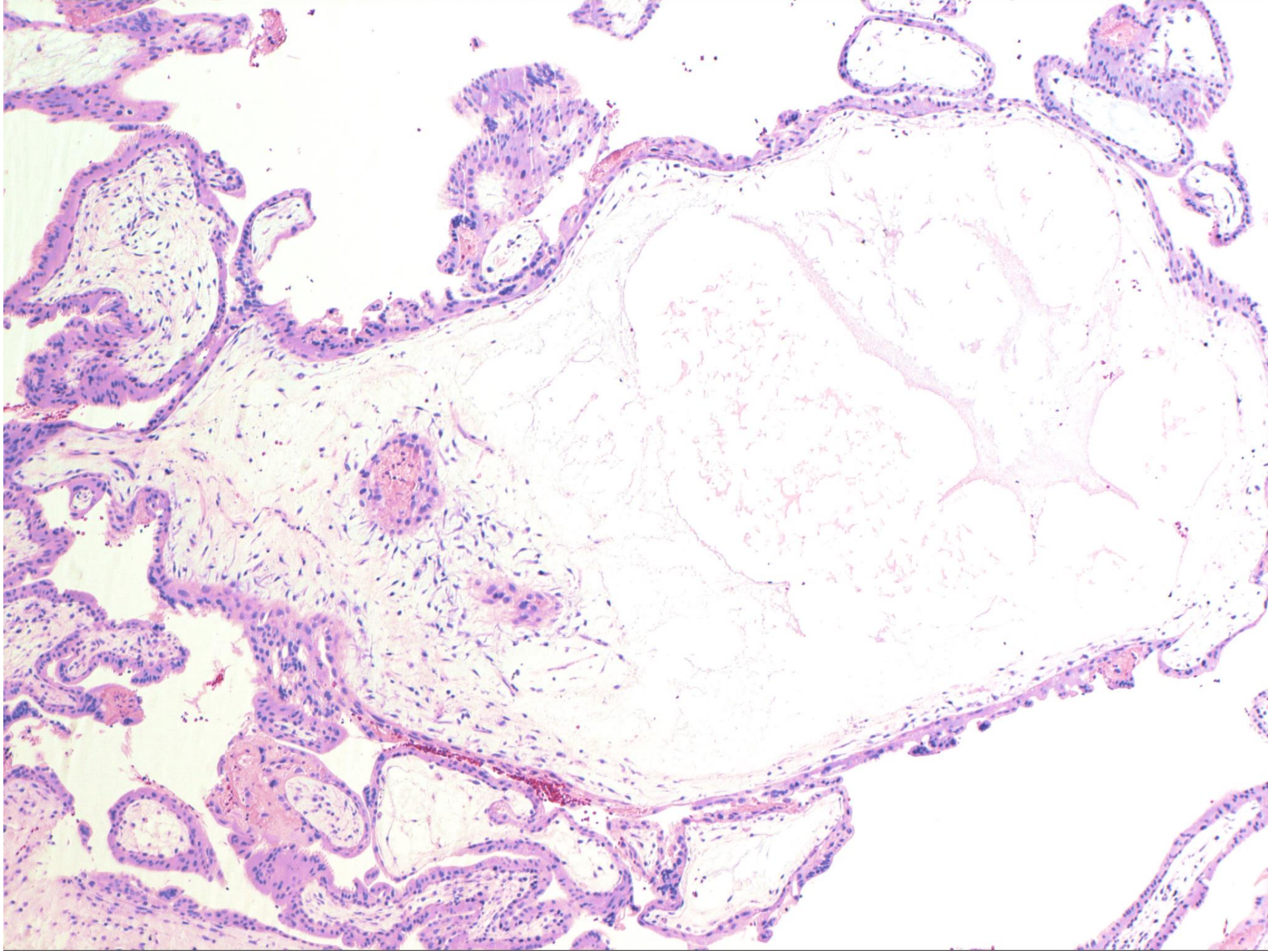
PHM –

Two Villous Populations



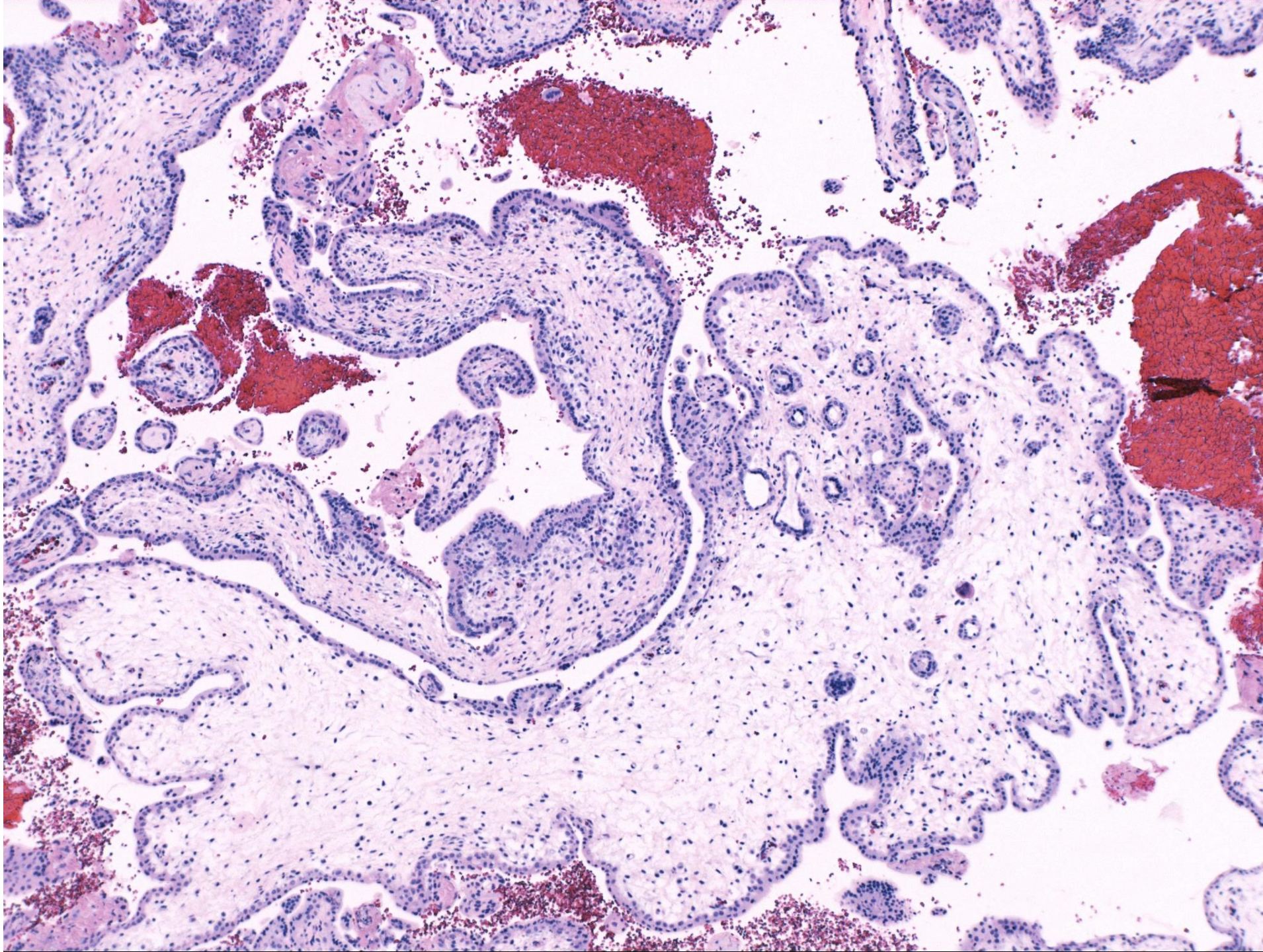
PHM –

Villous Hydrops and cisterns



PHM

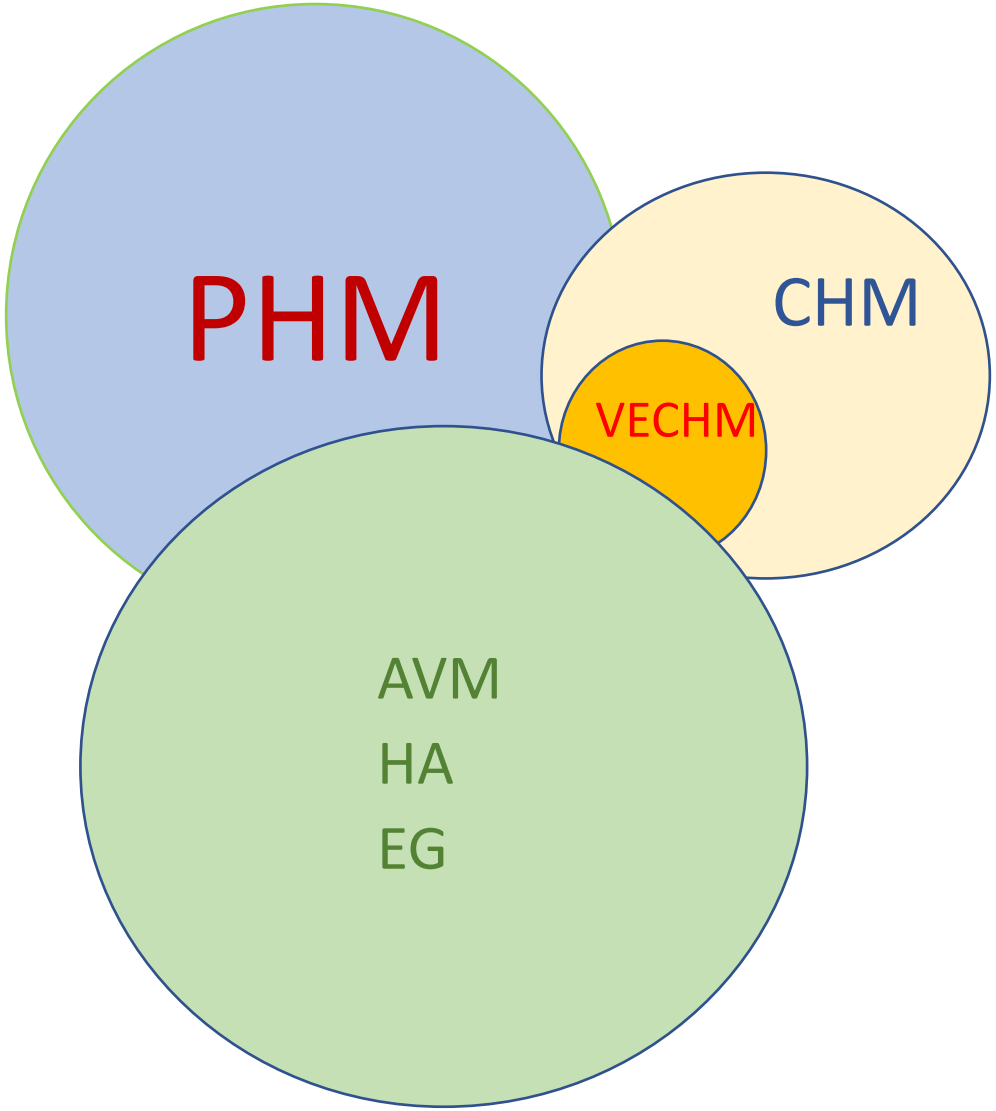
- Irregular Villous Contours
- Scalloping
- Trophoblastic pseudo-inclusions



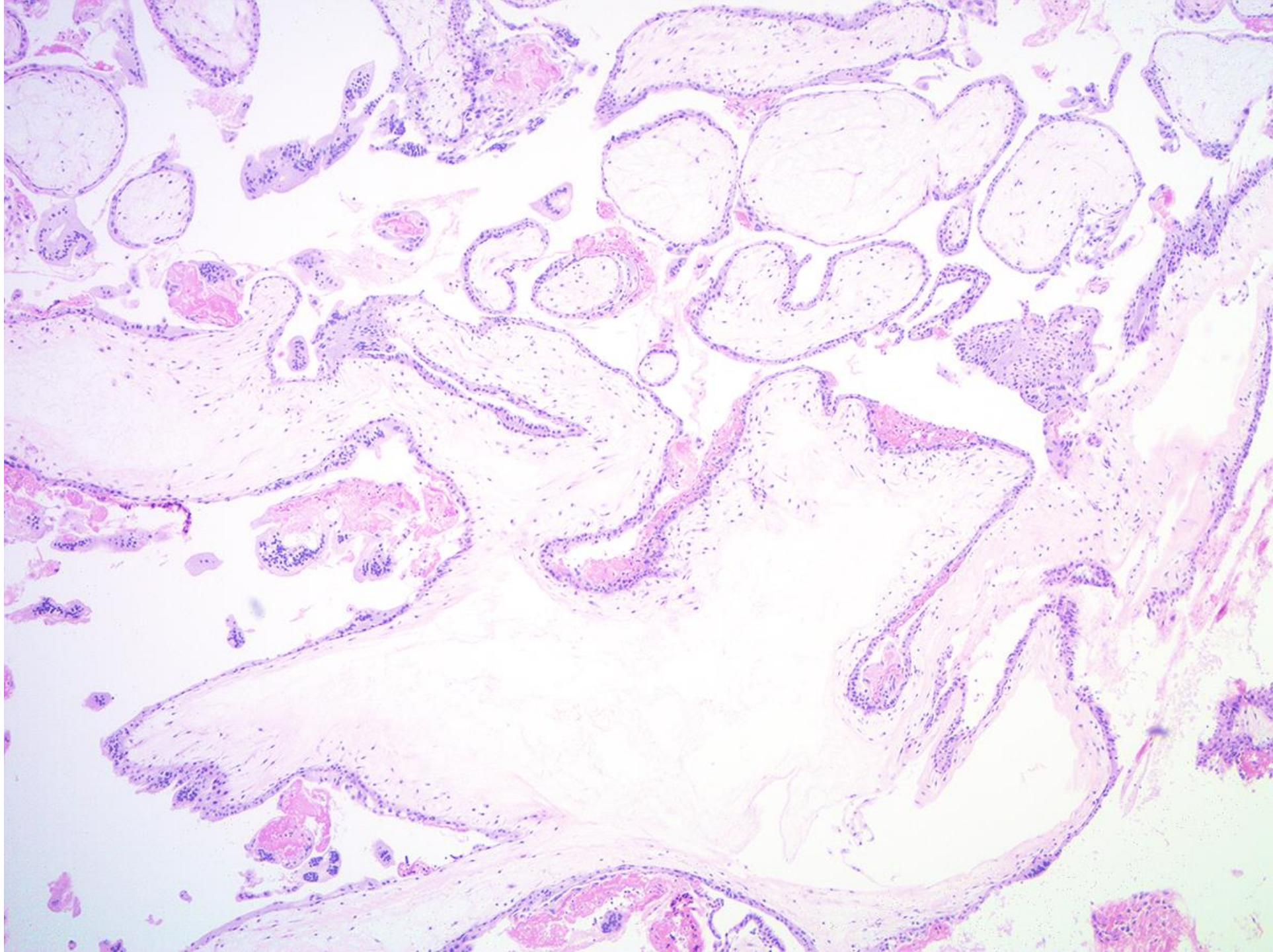
Hydatidiform moles

Differential diagnosis

- PHM: Partial mole
- CHM: Complete mole
- VECHM: Very early complete mole
- AVM: Abnormal villous morphology
- HA: Hydropic (non-molar) abortion
- EG: Early (non-molar) gestation

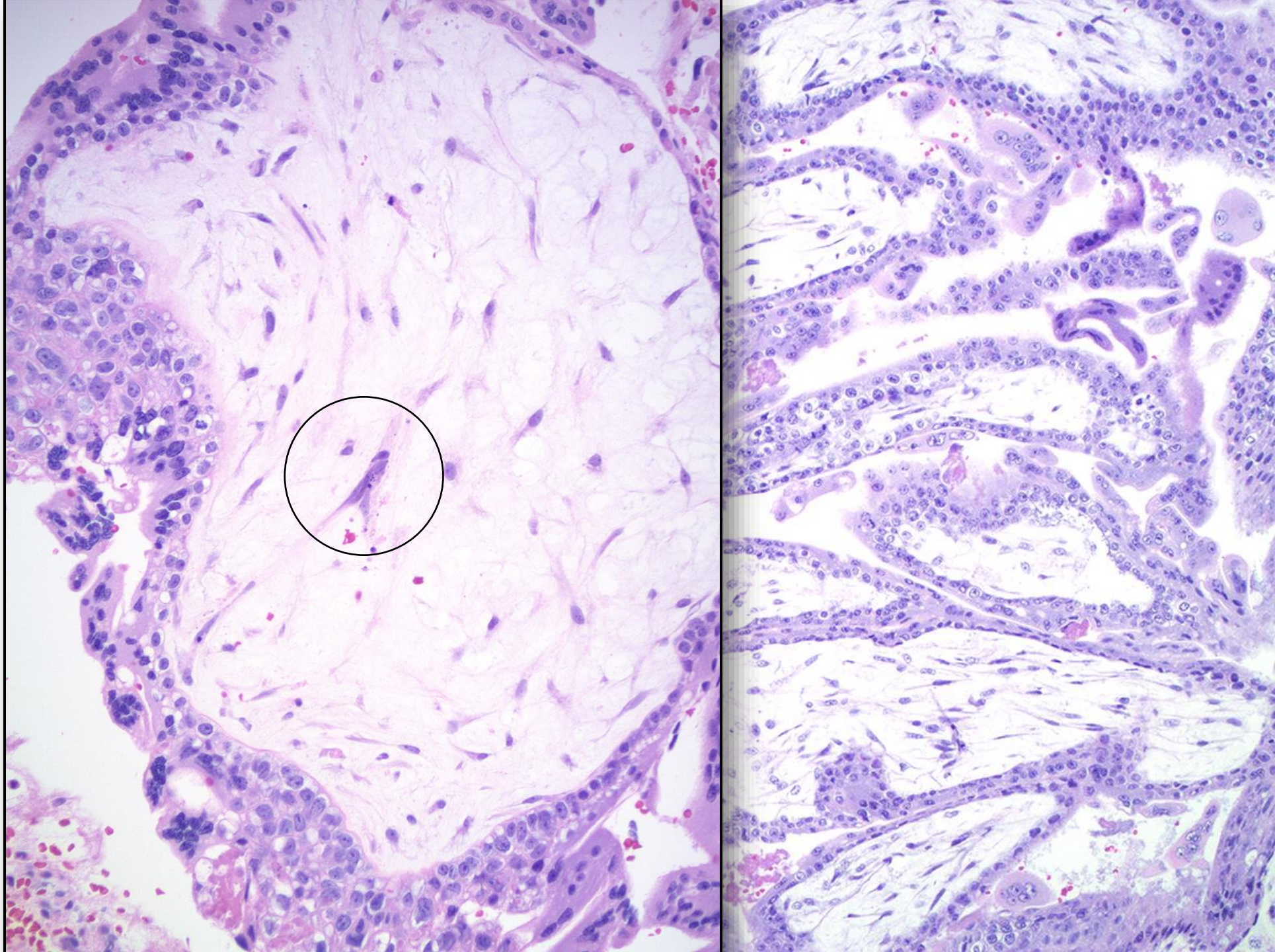


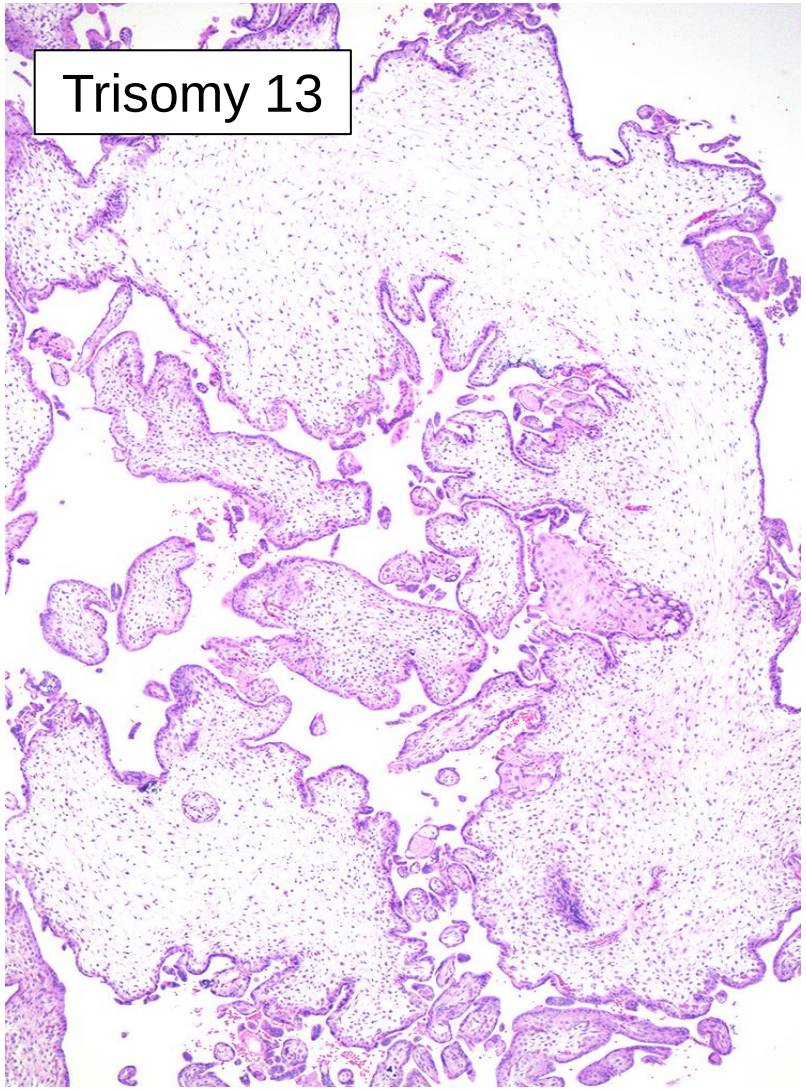
Hydropic non-molar diploid abortion

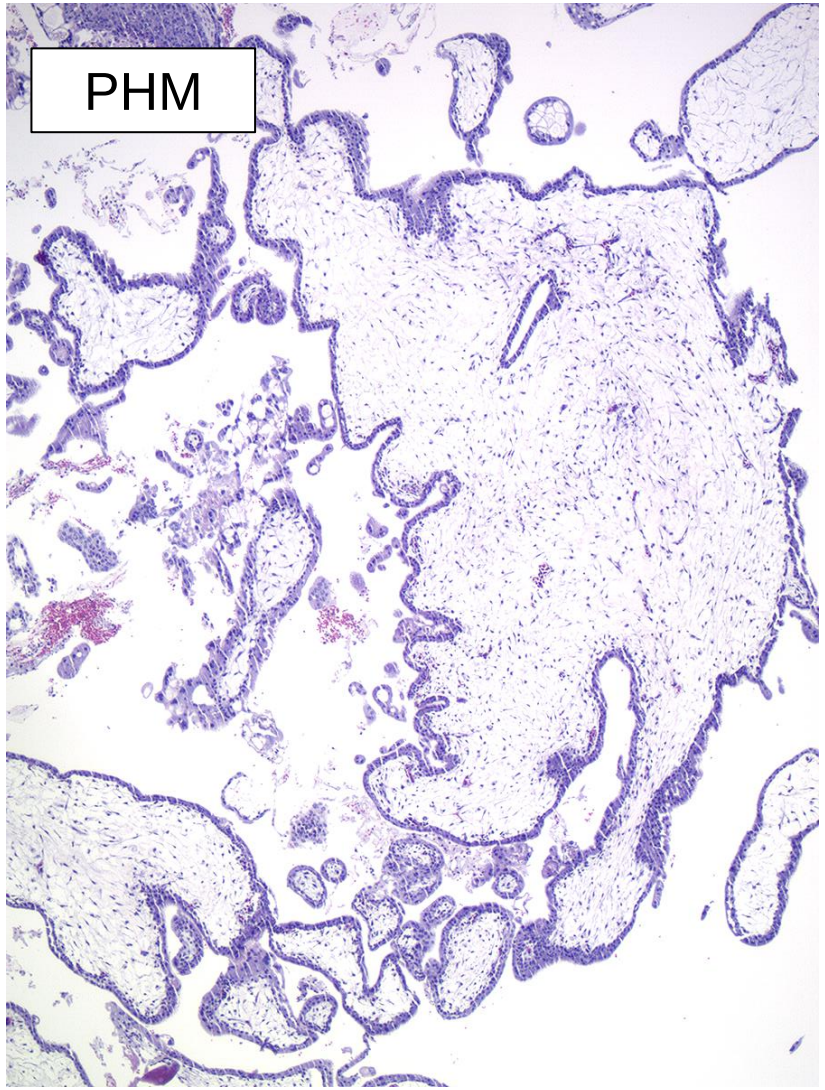


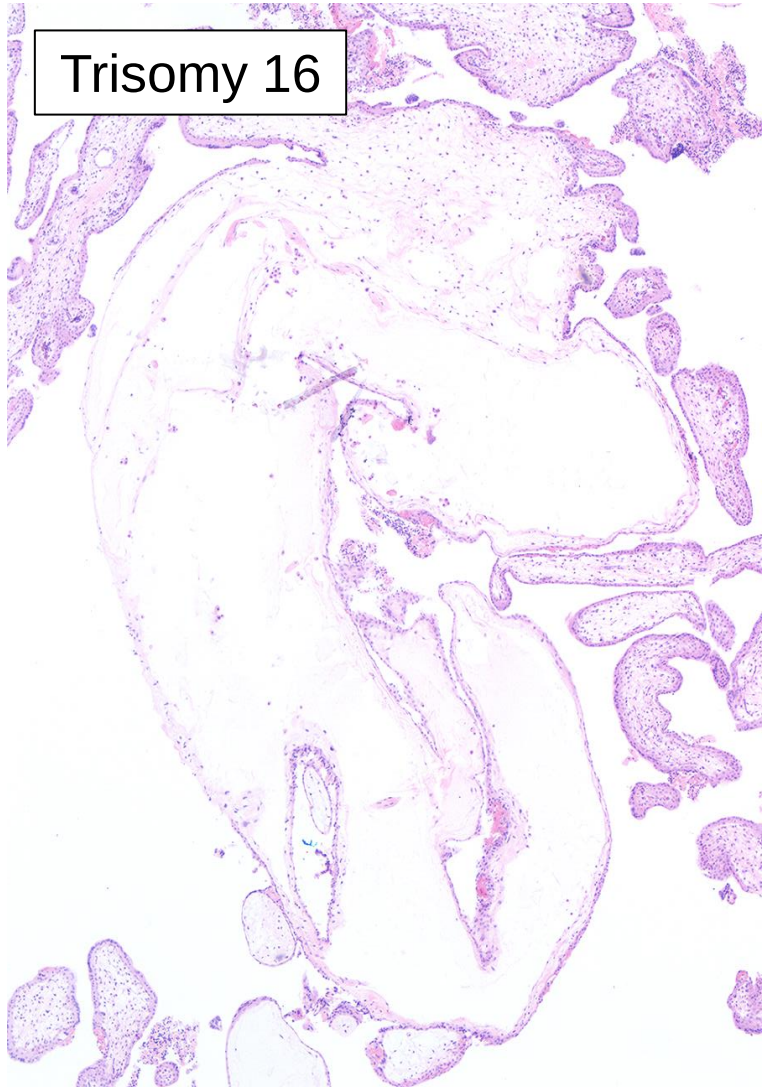
Early Non-molar Gestation

~ 6 weeks GA

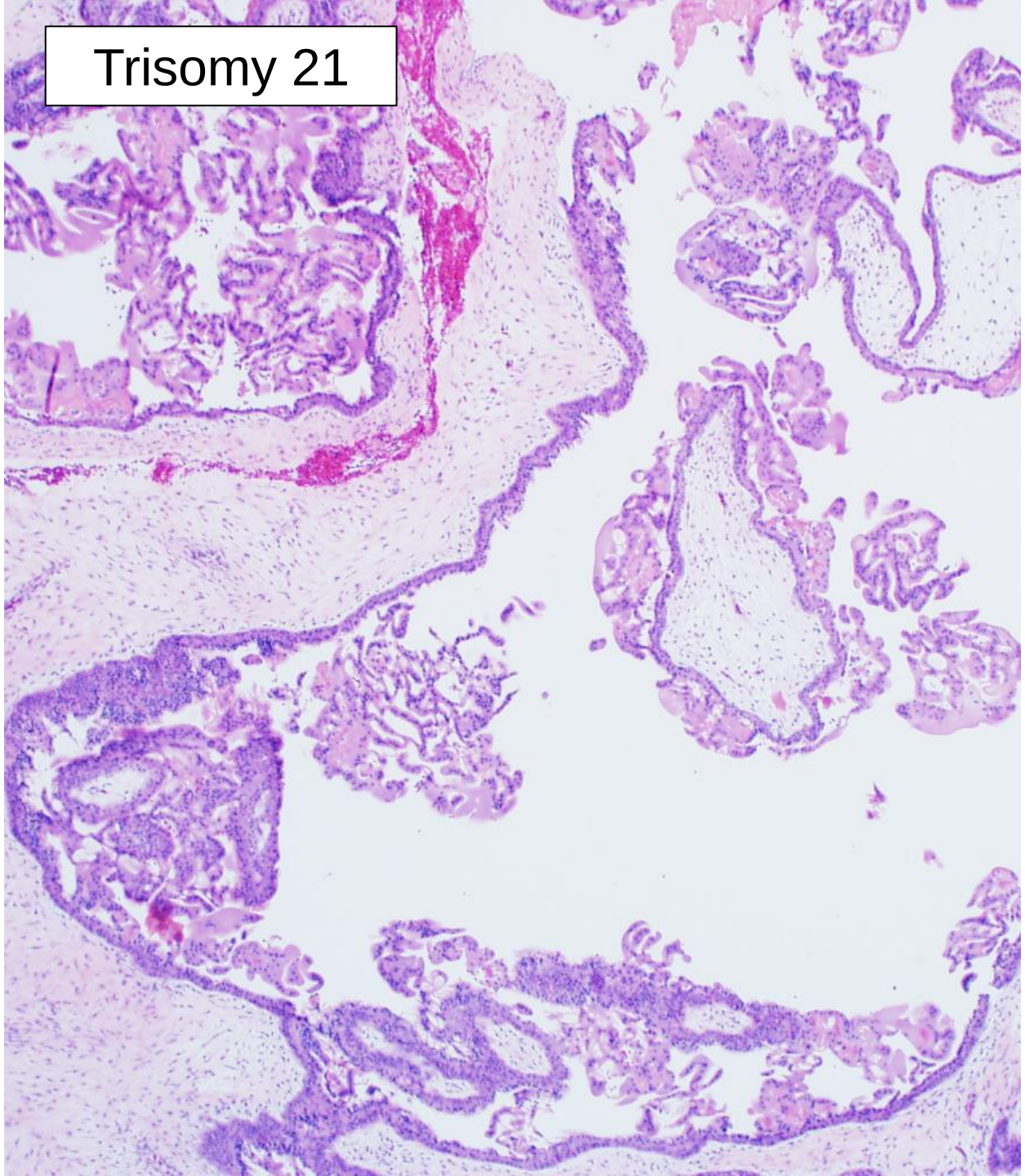


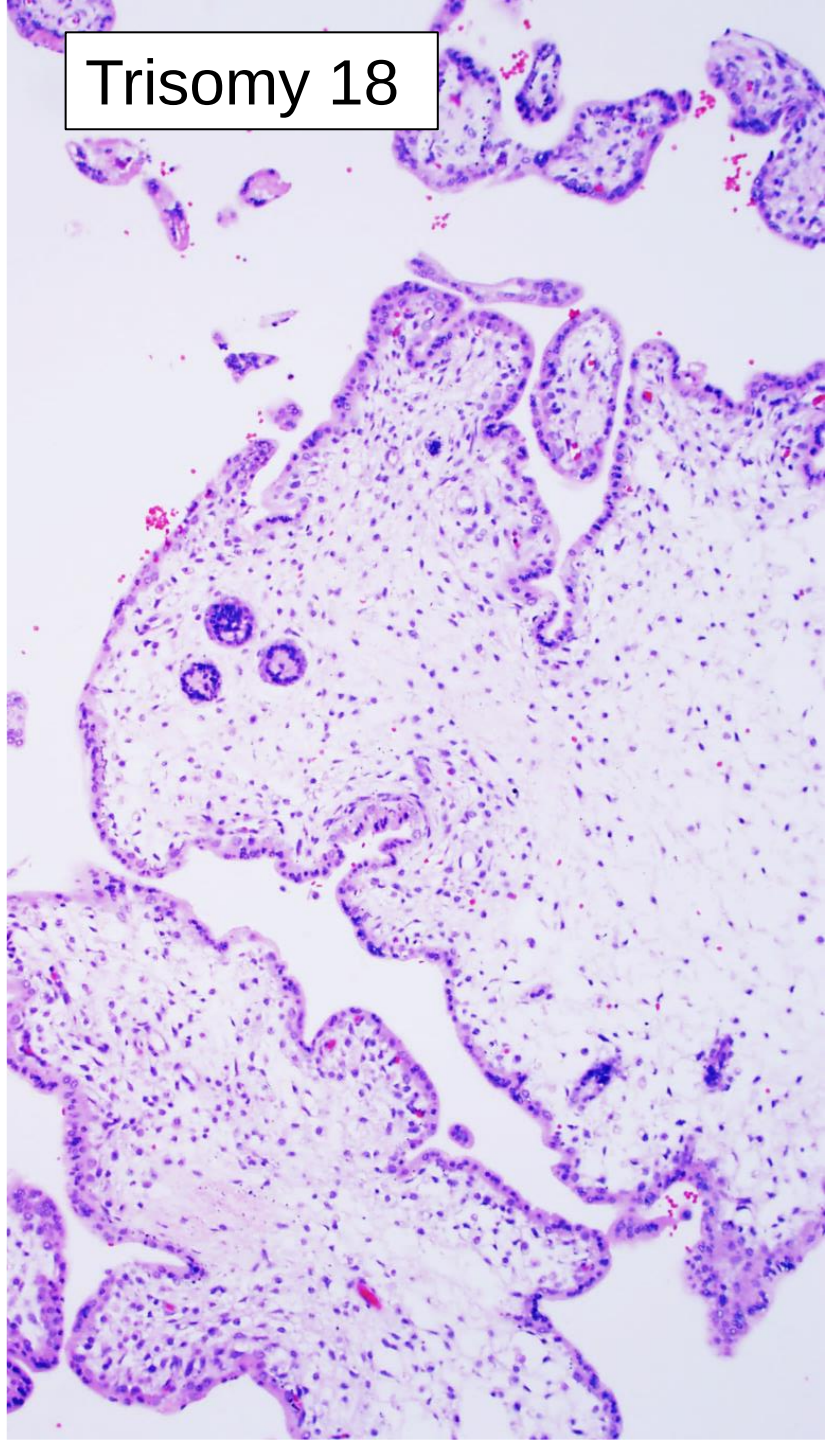

Trisomy 13


PHM


Trisomy 16

Chromosomal trisomies

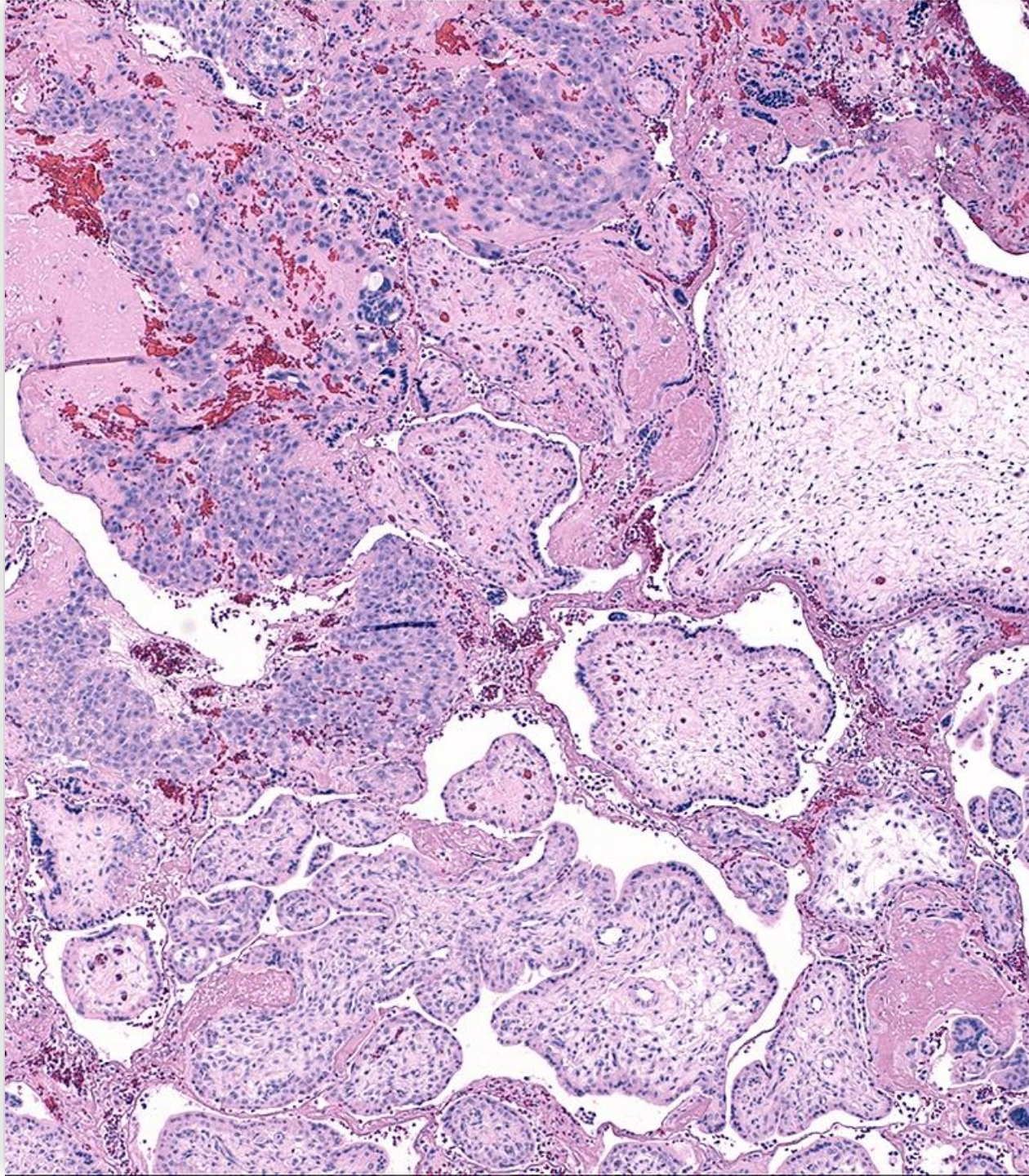




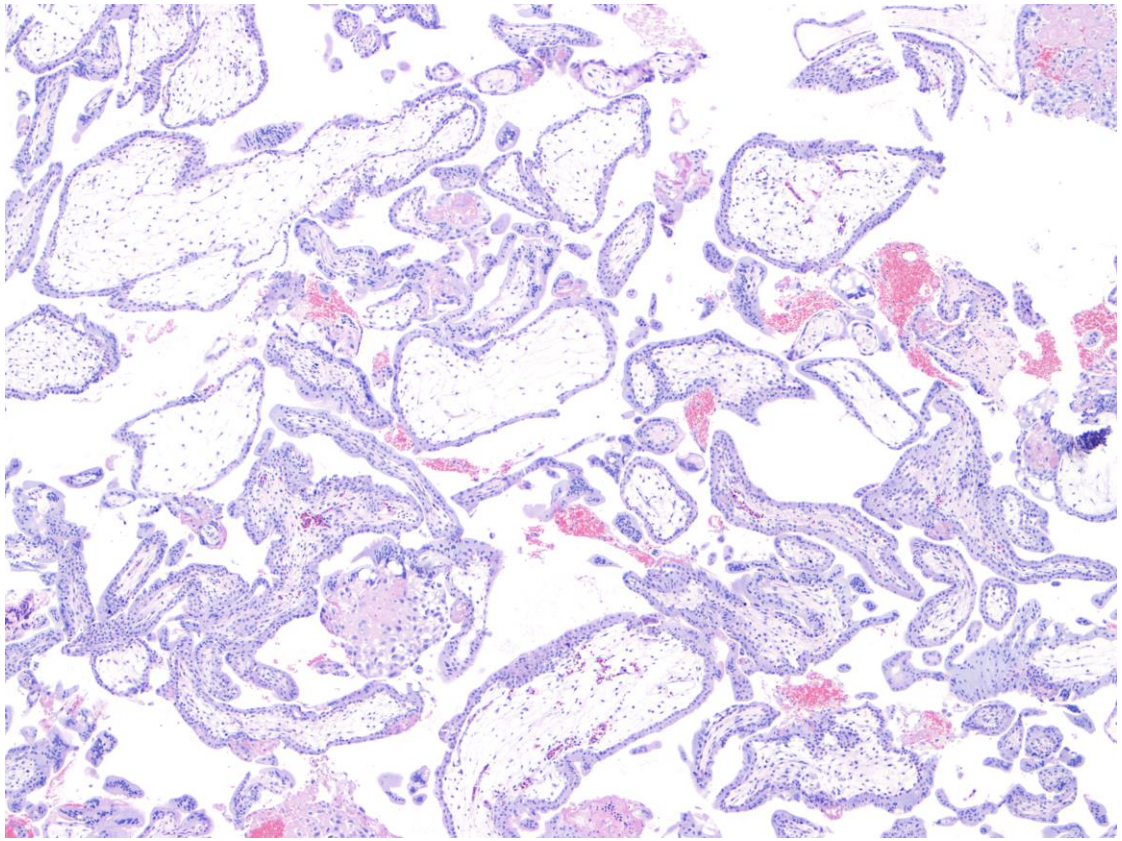
Placental Mesenchymal Dysplasia

Pathogenesis:

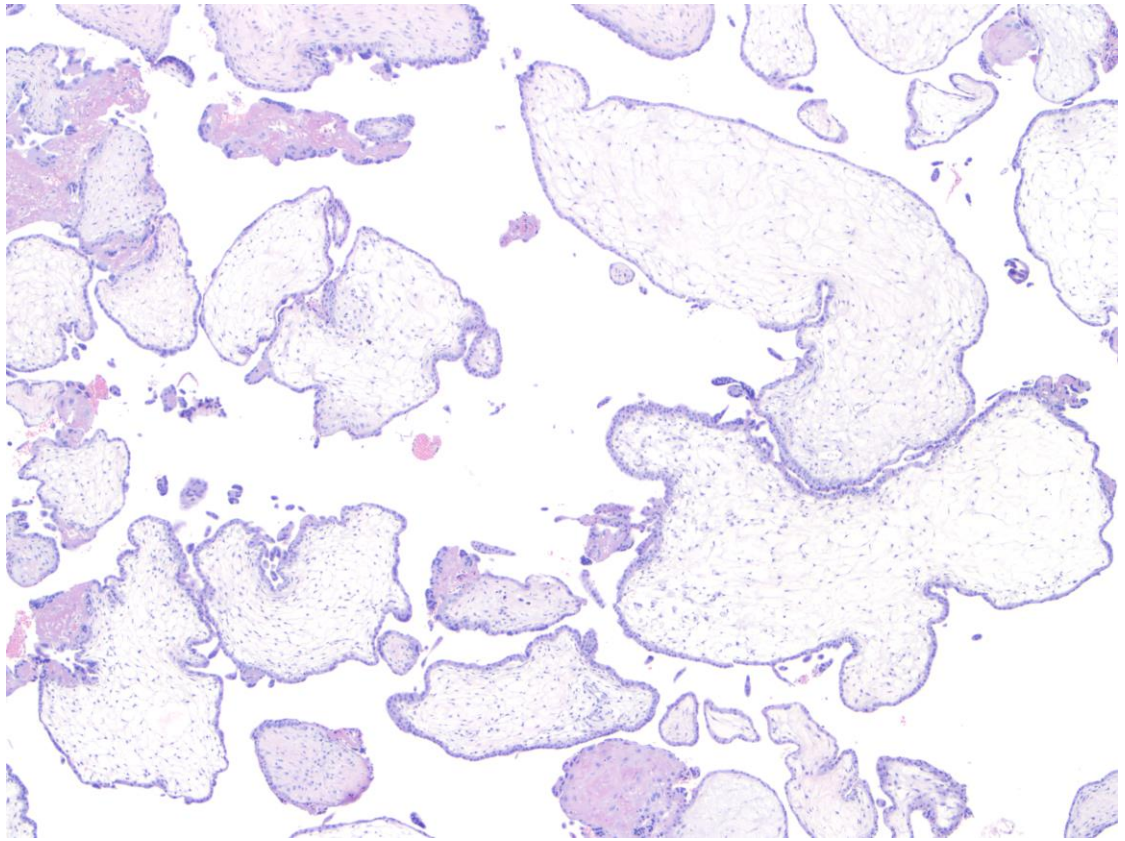
- androgenetic/ biparental mosaicism/ chimerism
- isolated alterations of the BWS imprinting centers on chromosome 11p15.5 (e.g. paternal uniparental disomy)
- mosaic disruption of the maternal GRB10 allele
- other sporadic chromosomal abnormalities



Dispermic Partial Mole



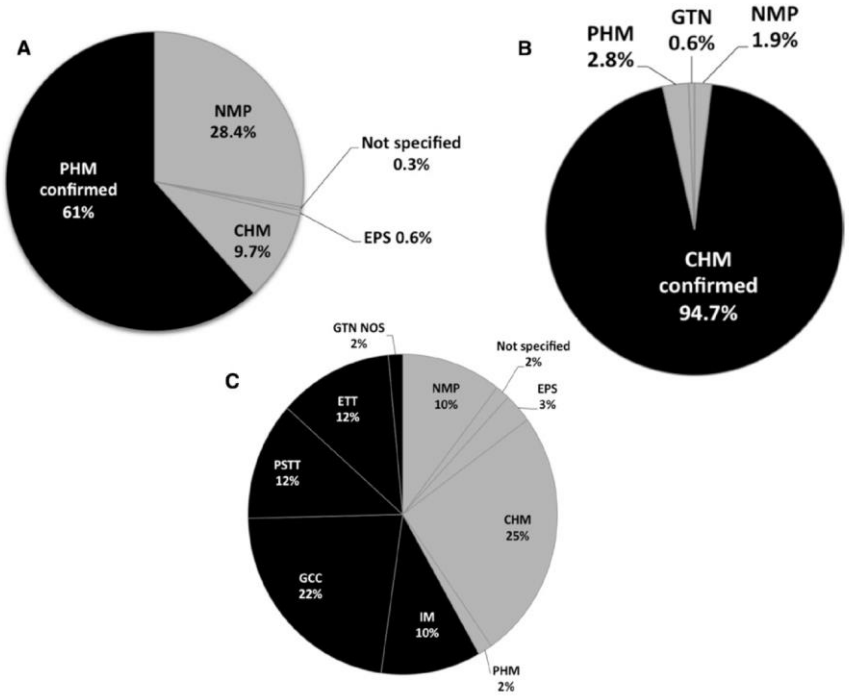
Dispermic Partial Mole



Minimal histological abnormalities of PHM

2022 Belgium Study - Only 61% PHMs were confirmed by Central Review

Initial diagnoses / Experts' review	NMP	Not specified	Mole NOS	EPS	PSN	APSN	CHM	PHM	IM	GCC	PSTT	ETT	GTN NOS	Total (initial diagnoses)
NMP	26	0	0	1	0	0	3	6	0	1	0	1	0	38
Not specified	21	2	0	2	1	0	6	7	0	2	1	1	0	43
Mole NOS	28	0	0	0	0	0	32	16	0	1	0	0	0	77
EPS	3	0	0	6	0	0	0	0	0	0	0	1	0	10
PSN	1	0	0	0	0	1	0	0	0	0	0	0	0	2
APSN	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CHM	6	0	0	0	0	0	303	9	1	1	0	0	0	320
PHM	88	1	0	2	0	0	30	189	0	0	0	0	0	310
IM	1	0	0	0	0	0	5	0	6	0	0	0	0	12
GCC	3	1	0	0	0	0	8	0	1	14	2	0	1	30
PSTT	1	0	0	2	0	0	3	0	0	0	6	0	0	12
ETT	0	0	0	0	0	0	0	1	0	0	0	8	0	9
GTN NOS	2	0	0	0	0	0	1	0	0	1	0	0	0	4
Total (experts' diagnoses) :	180	4	0	13	1	1	391	228	8	20	9	11	1	867



Importance of pathological review of gestational trophoblastic diseases: results of the Belgian Gestational Trophoblastic Diseases Registry

S. Schoenen, K. Delbecque, A. S. Van Rompuy, E. Marbaix, J. C. Noel, P. Delvenne, et al.

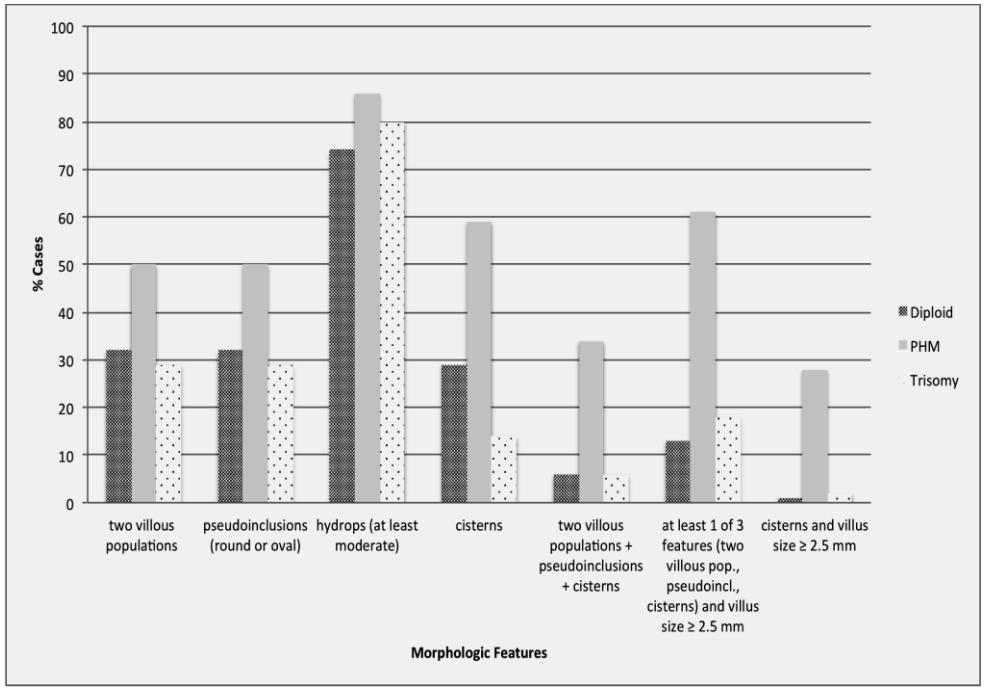
Int J Gynecol Cancer 2022

PHM vs Trisomy vs Non-molar diploid abortion

TABLE 2. *Morphologic parameters*

	PHM (n = 56)	Trisomy (n = 51)	Nonmolar diploid (n = 31)
Maximum size of chorionic villi: range (mean)	1–6 mm (3.2 mm)	0.9–4.5 mm (2.1 mm)	1–4 mm (2.0 mm)
2 villous populations	28 (50%)	15 (29.4%)	10 (32.2%)
Round or oval trophoblastic pseudoinclusions	28 (50%)	15 (29.4%)	10 (32.2%)
Villous hydrops (at least moderate)	48 (85.7%)	41 (80.4%)	23 (74.2%)
Cistern formation	33 (58.9%)	7 (13.7%)	9 (29.0%)
Trophoblastic hyperplasia (at least moderate)	10 (17.8%)	4 (7.8%)	2 (6.4%)
Single trophoblast inclusions	9 (16.1%)	12 (23.5%)	7 (22.5%)
Nucleated fetal red blood cells	38 (67.8%)	32 (62.7%)	20 (64.5%)
Syncytiotrophoblast knuckles	52 (92.8%)	51 (100%)	27 (87.1%)
Syncytiotrophoblast lacunae	53 (94.6%)	47 (92.2%)	27 (87.1%)
Irregular villous contour	52 (92.8%)	46 (90.2%)	22 (71.0%)

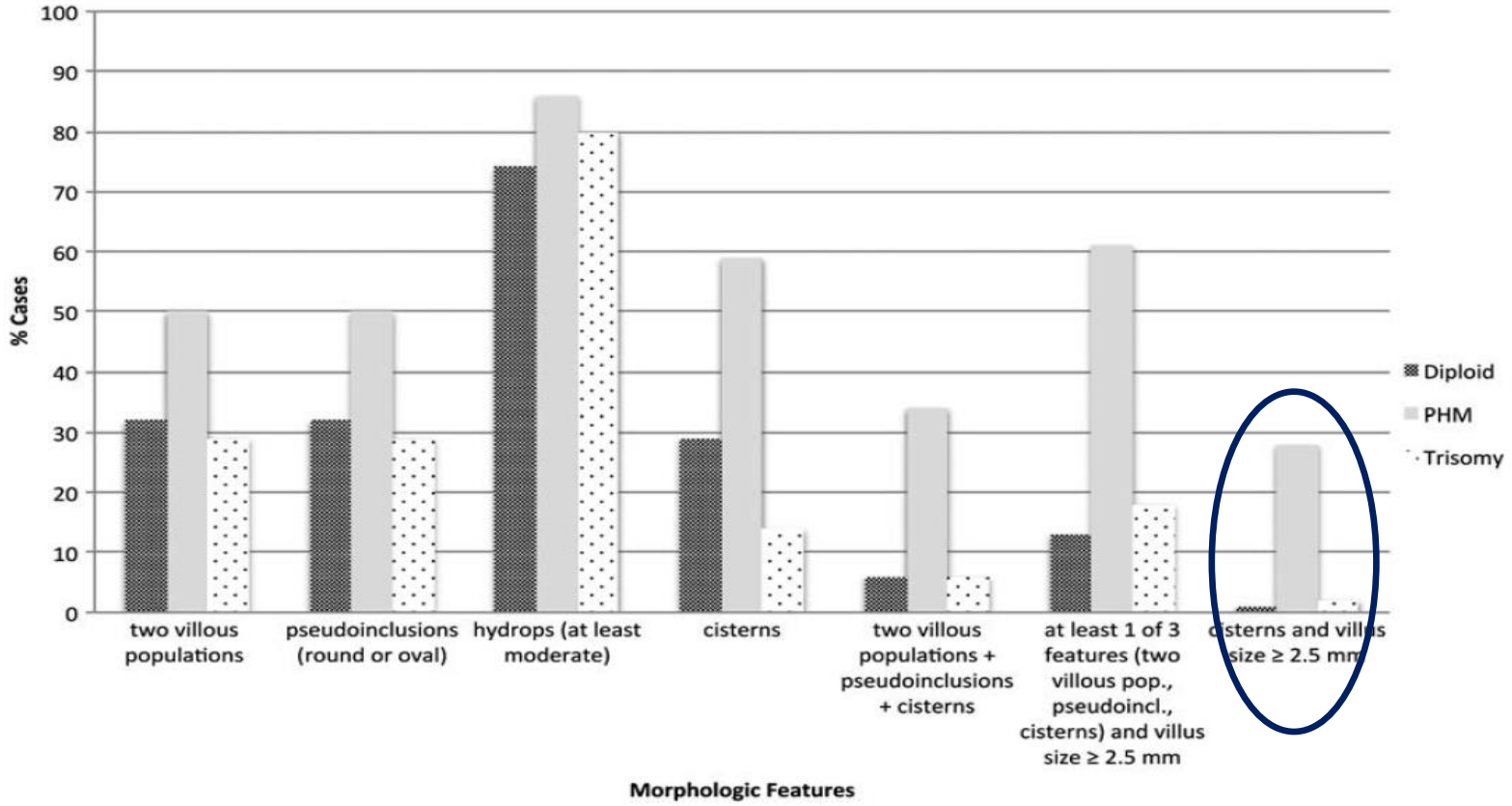
PHM indicates partial hydatidiform mole.



No single or combined histological parameters are specific for histologic diagnosis of PHM

Buza and Hui, Int J Gynecol Pathol 2013

If you only have HE slides …….



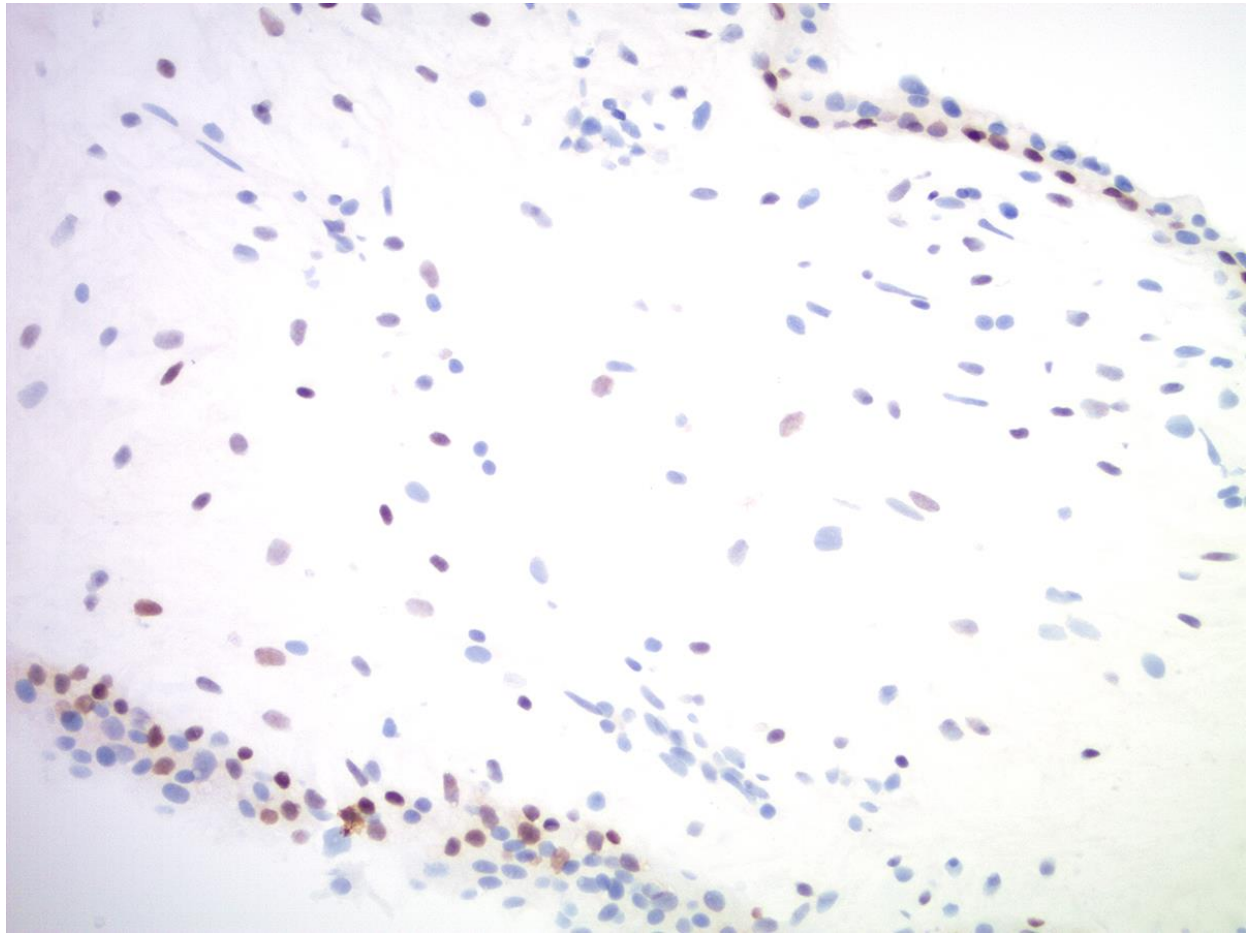
Buza and Hui, Int J Gynecol Pathol 2013

PHM: Villous size of 2.5 mm + cistern: 97% PPV but 32% sensitivity

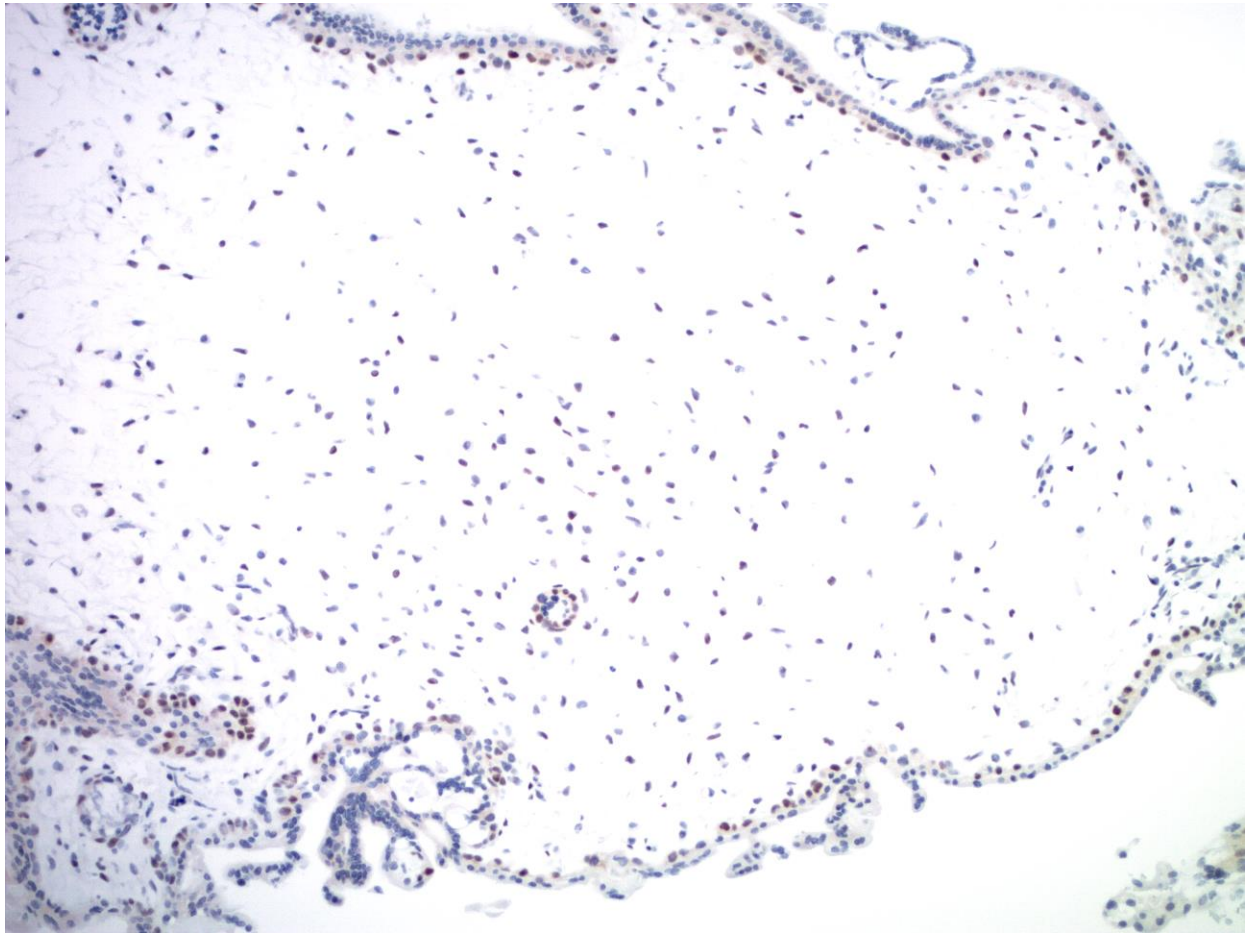
P57 Immunohistochemistry – Confirming CHM

- Normal expression in gestations containing maternal genetic material
    - PHM (Diandric triploidy)
    - Digynic triploidy
    - Non-molar hydropic abortions
    - Chromosomal trisomies

p57- Hydropic Abortion



p57- Partial Mole



STR Genotyping – Gold Standard

Comparison of allelic patterns between maternal decidua and villous tissue

Provides information about the exact parental genetic contribution

AmpFLSTR Identifiler™ (ABI)

LOCUS		SIZE (#ALLELE)
D2S1338	VIC	307-359(14)
TPOX (2p23-2per)	NED	222-250(8)
D3S1358	VIC	112-140(8)
FGA (4q28)	PET	215-355(28)
D5S818	PET	134-172(10)
CSF1PI (5q33.3-34)	FAM	304-341(10)
D7S820	FAM	255-291 (10)
D8S1179	FAM	120-170(12)
TH01(11p15.5)	VIC	169-202(10)
vWA (12p12-pter)	NED	145-207(14)
D13S317	VIC	217-245(8)
D16S539	VIC	253-293(9)
D18S51	NED	262-345(23)
D19S433	NED	102-195(15)
D21S11	FAM	185-240(24)
Amelogenin	PET	107/113(X/Y)

Simple multiplex PCR assay

Short amplicons: 100-360 bp

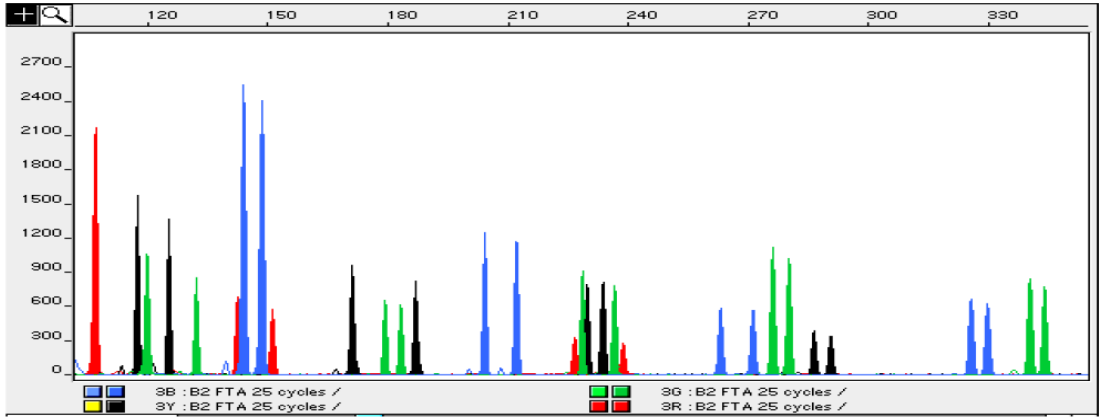
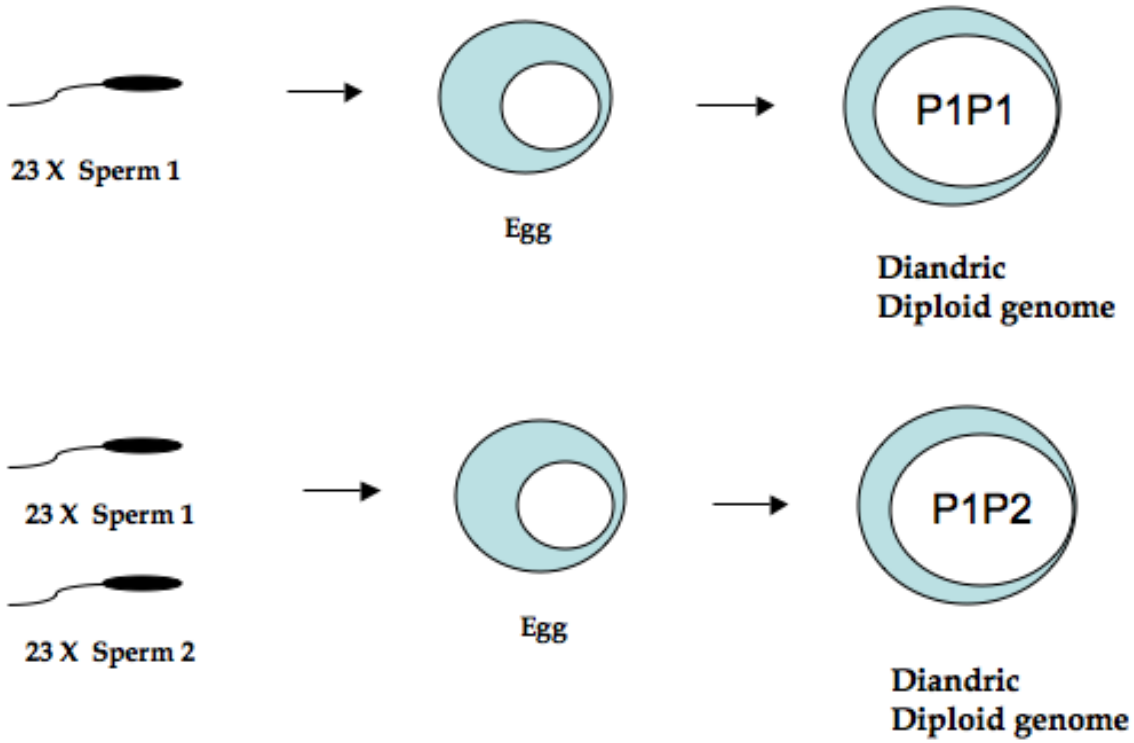


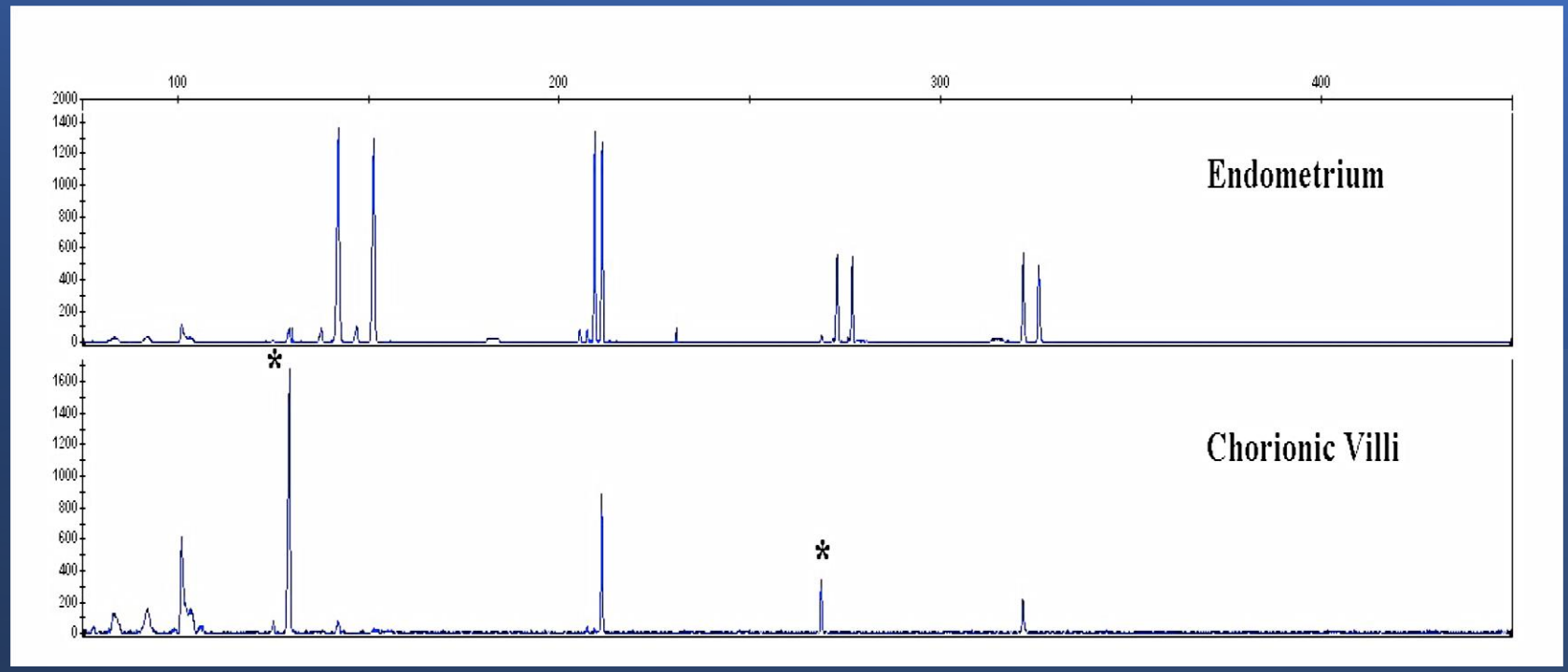
Figure 2-1 AmpFℓSTR Identifiler kit results from a 1.2-mm FTA bloodstain punch (25 cycle amplification), analyzed on the ABI PRISM 310 Genetic Analyzer

Sporadic CHM – Genetic Basis

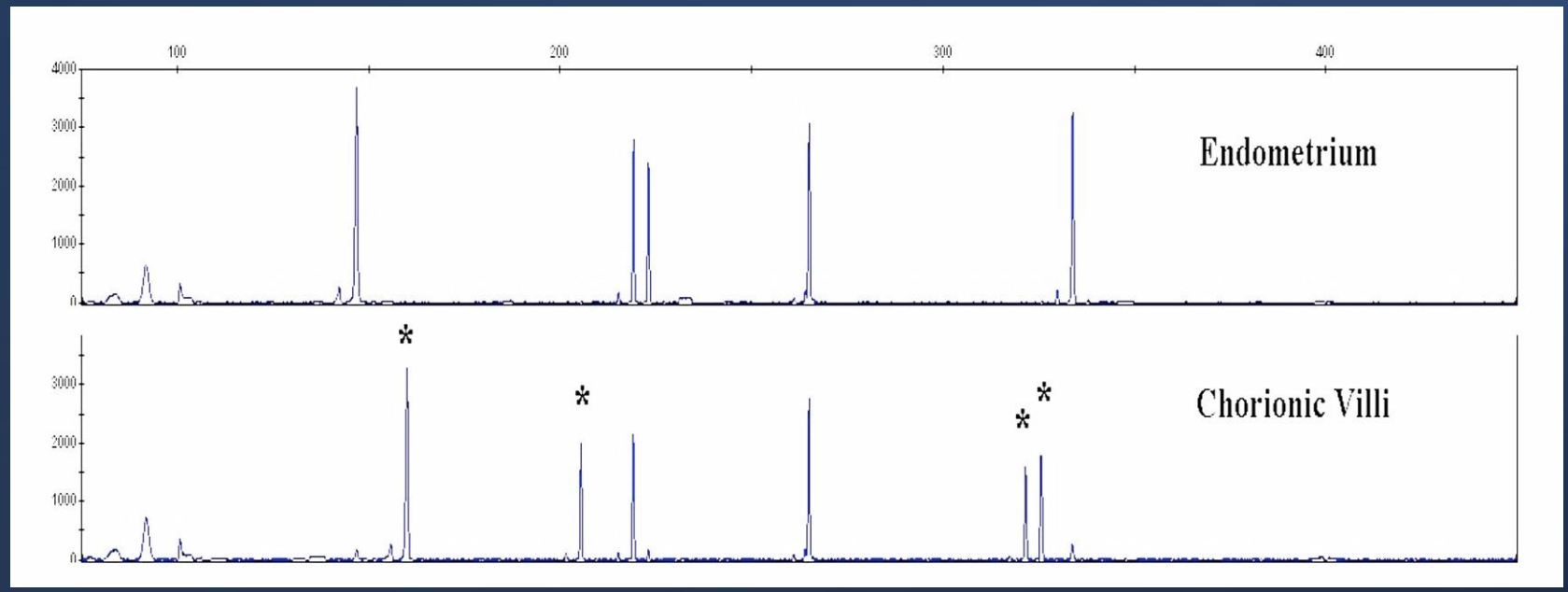


Monospermic
(Homozygous) – 90%

Dispermic
(Heterozygous) – 10%



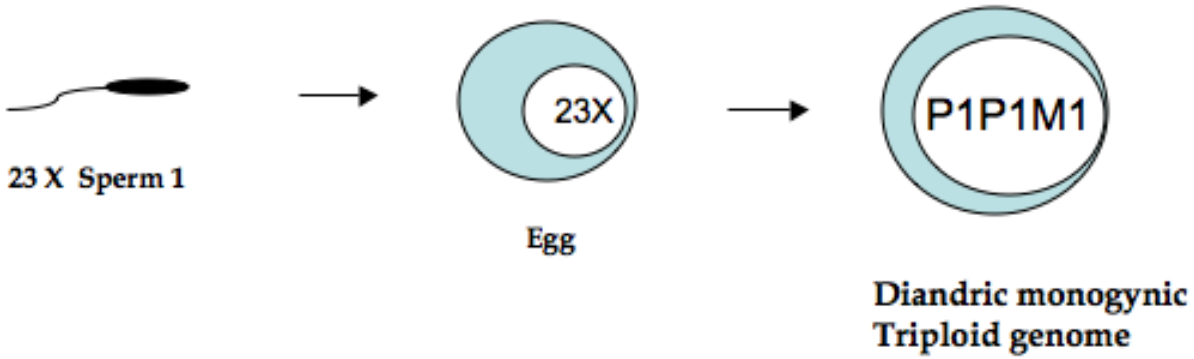
Monospermic (Homozygous) CHM



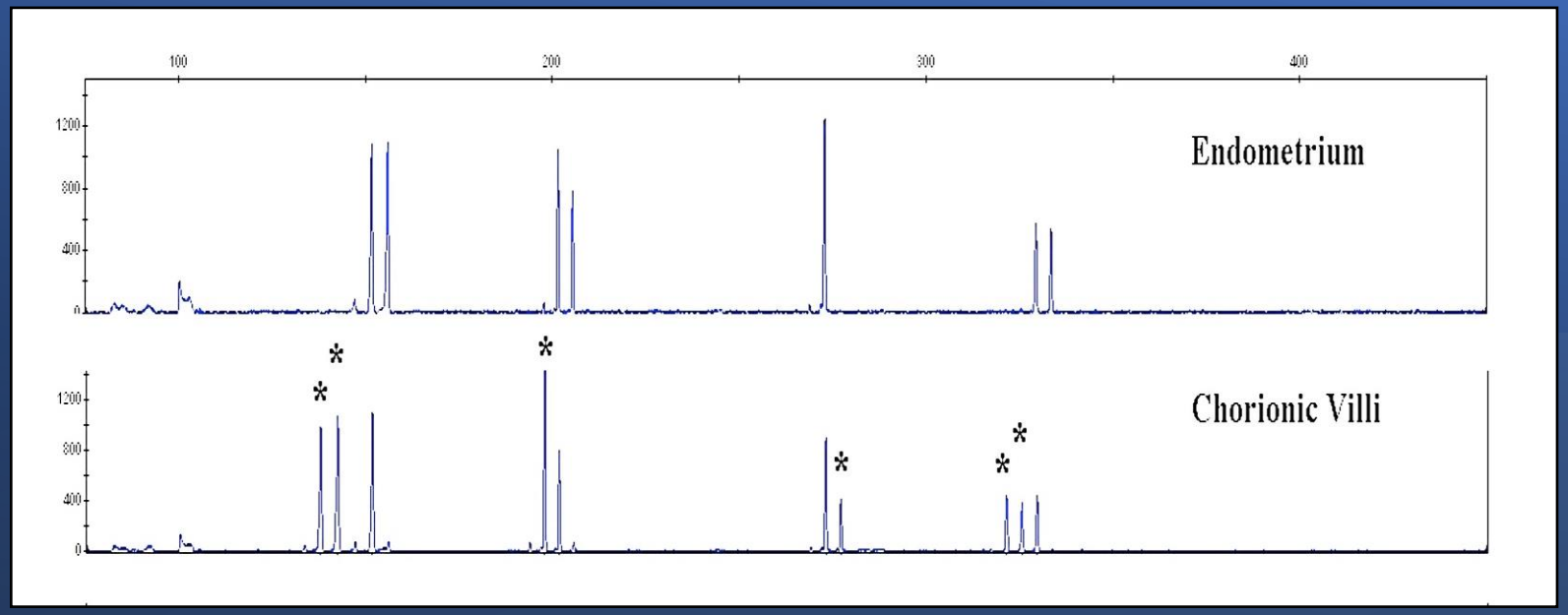
Dispermic (Heterozygous) CHM

Sporadic PHM – Genetic Basis

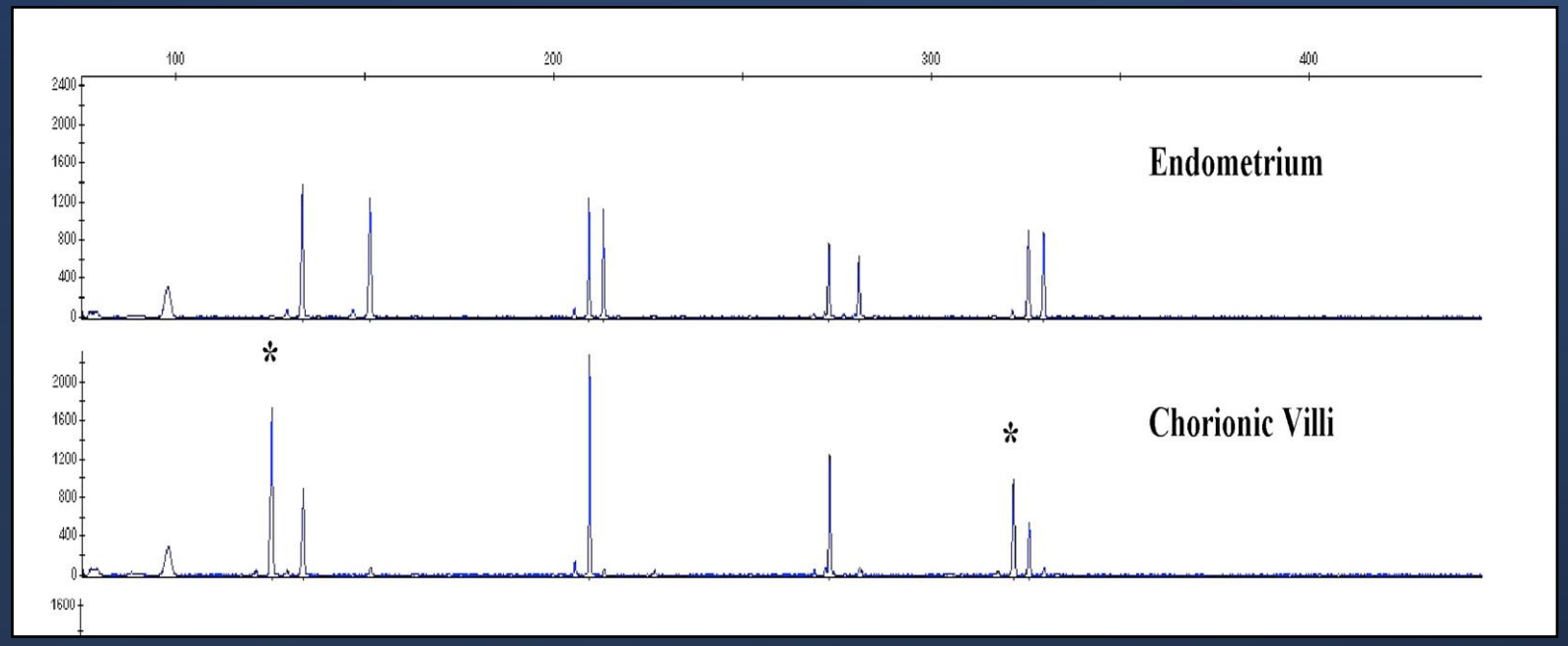
Dispermic
(Heterozygous) > 95%



Monospermic
(Homozygous) < 5%



Dispermic PHM



Monospermic PHM

ORIGINAL ARTICLE

Genotypic Analysis of Hydatidiform Mole: An Accurate and Practical Method of Diagnosis

Carlo Bifulco, MD, Chaline Johnson, Liming Hao, MD, Husnain Kermalli, Susan Bell, and Pei Hui, PhD, MD

American Journal of Surgical Pathology, 32:445-451,2008

Precise DNA Genotyping Diagnosis of Hydatidiform Mole

Fredilyn Lipata, Vinita Parkash, Monica Talmor, Susan Bell, Suping Chen, Vesna Maric, and Pei Hui

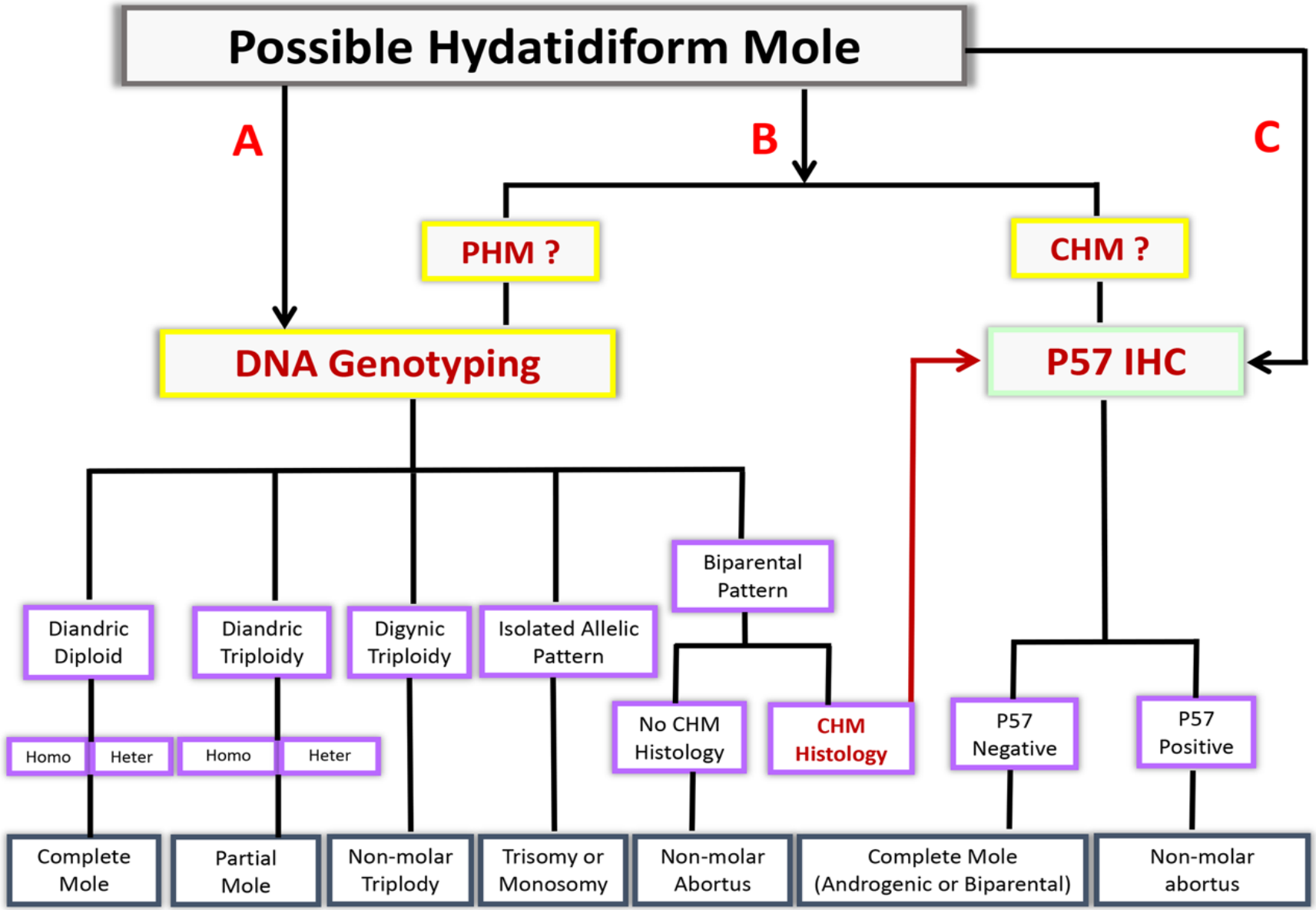
OBJECTIVE: To estimate whether tissue DNA genotyping is effective for the confirmation and subclassification of hydatidiform moles.

METHODS: Consecutive cases of products of concep-

CONCLUSION: Tissue DNA genotyping is a practical and highly accurate method for the confirmation and subclassification of hydatidiform moles.

(Obstet Gynecol 2010;115:1–1)

Obstetrics and Gynecology,115:784-794, 2010

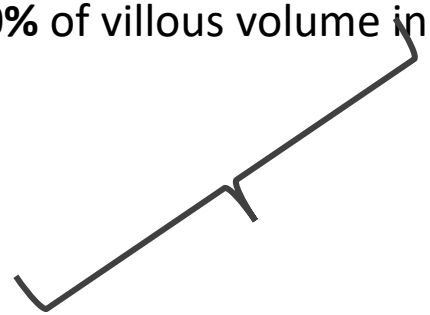


Buza and Hui, Mod Pathology, 2021,34:1658-1672

PHM in first trimester POC – When do you trigger STR Genotyping?

Up to 56% of genetic PHM lacks characteristic histological features:

- Two villous populations: hydropic enlarged & fibrotic small
- At least moderate hydrop or Cistern formation (hydropic cavity ≥ **50%** of villous volume in terminal villi)
- Villous size ≥ **2.5** mm
- Pseudoinclusions



Trigger STR genotyping

Buza and Hui: Int J Gyn Path 2013, 32:307-315

Special Diagnostic Considerations

- Post-molar Gestational Trophoblastic Neoplasia (GTN)
- Triploid Digynic Non-molar Gestation
- Recurrent Biparental Hydatidiform Moles

Post-molar GTN

Risk of persistent GTD (invasive or metastatic mole):	
~15-20% after CHM (similar for VECM and FBCHM)	~0.5-5% after PHM

Risk of choriocarcinoma:	
~2-3% after CHM (Heterozygous/dispermic CHM may have a higher risk)	~0.1% after PHM (3/2000)

Hydatidiform Moles – Patient Management

- Follow-up with serial hCG levels
  - Weekly until non-detectable for 3 weeks
  - Then monthly until non-detectable for 6 months
- Contraception is advised during hCG monitoring
- Significant consequences of both under- and overdiagnosis

Post-molar GTN

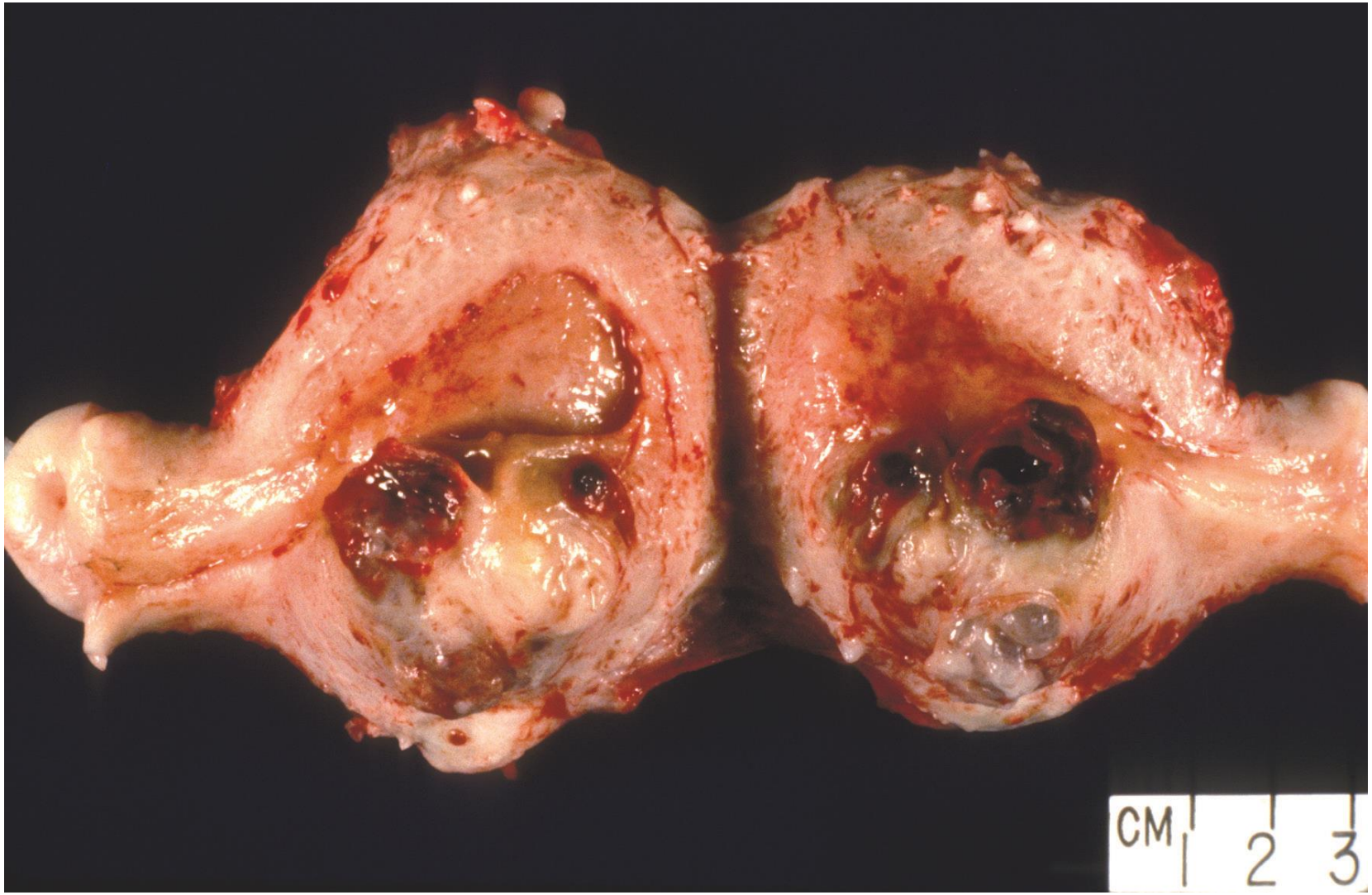
- Clinical Diagnosis – plateauing or rising serum hCG during surveillance
- Histologic confirmation – typicaly not available
- Risk unchanged by gestational age or degree of morphologic abnormalities (VECHM)

Invasive Hydatidiform Mole

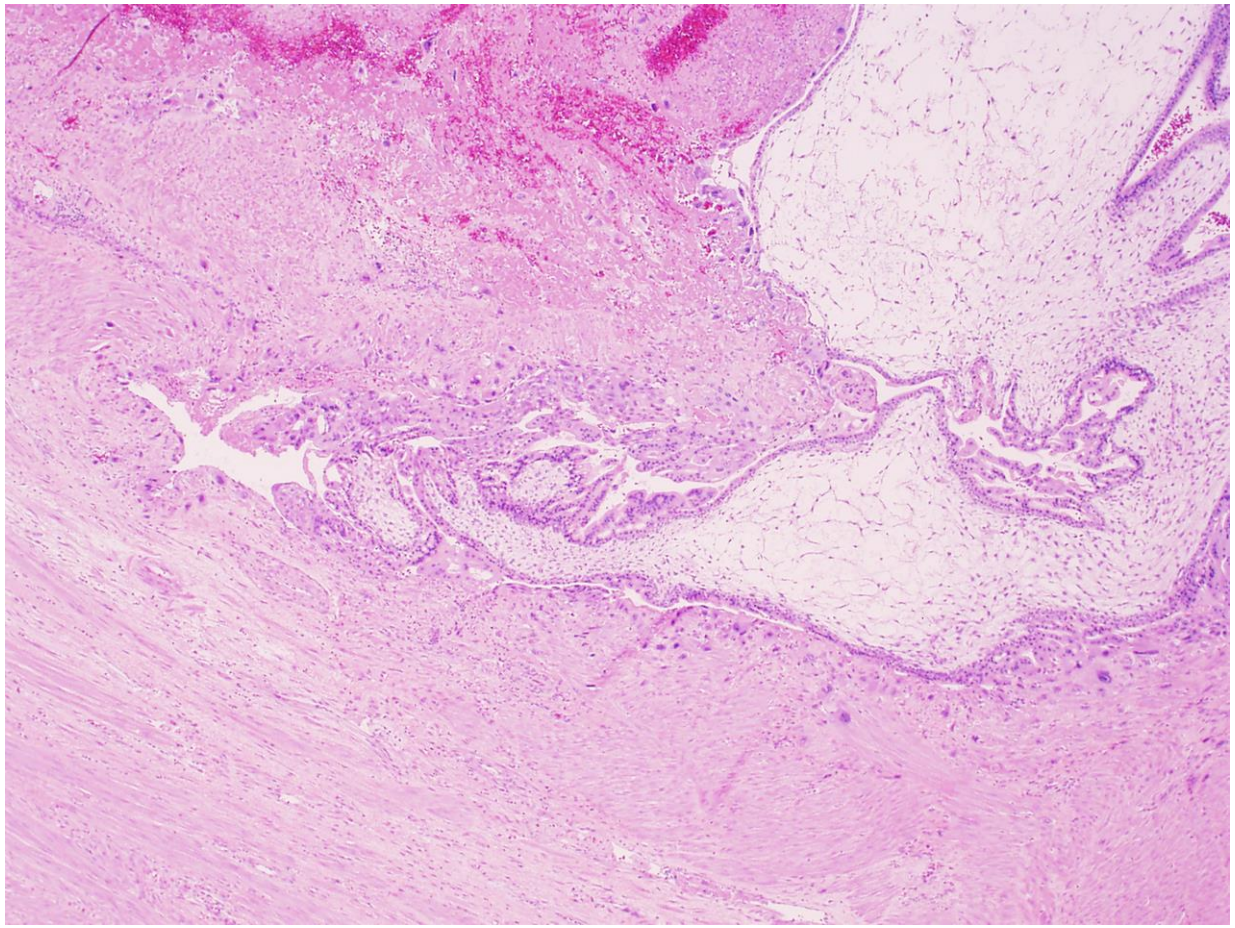
Invasive Hydatidiform Mole

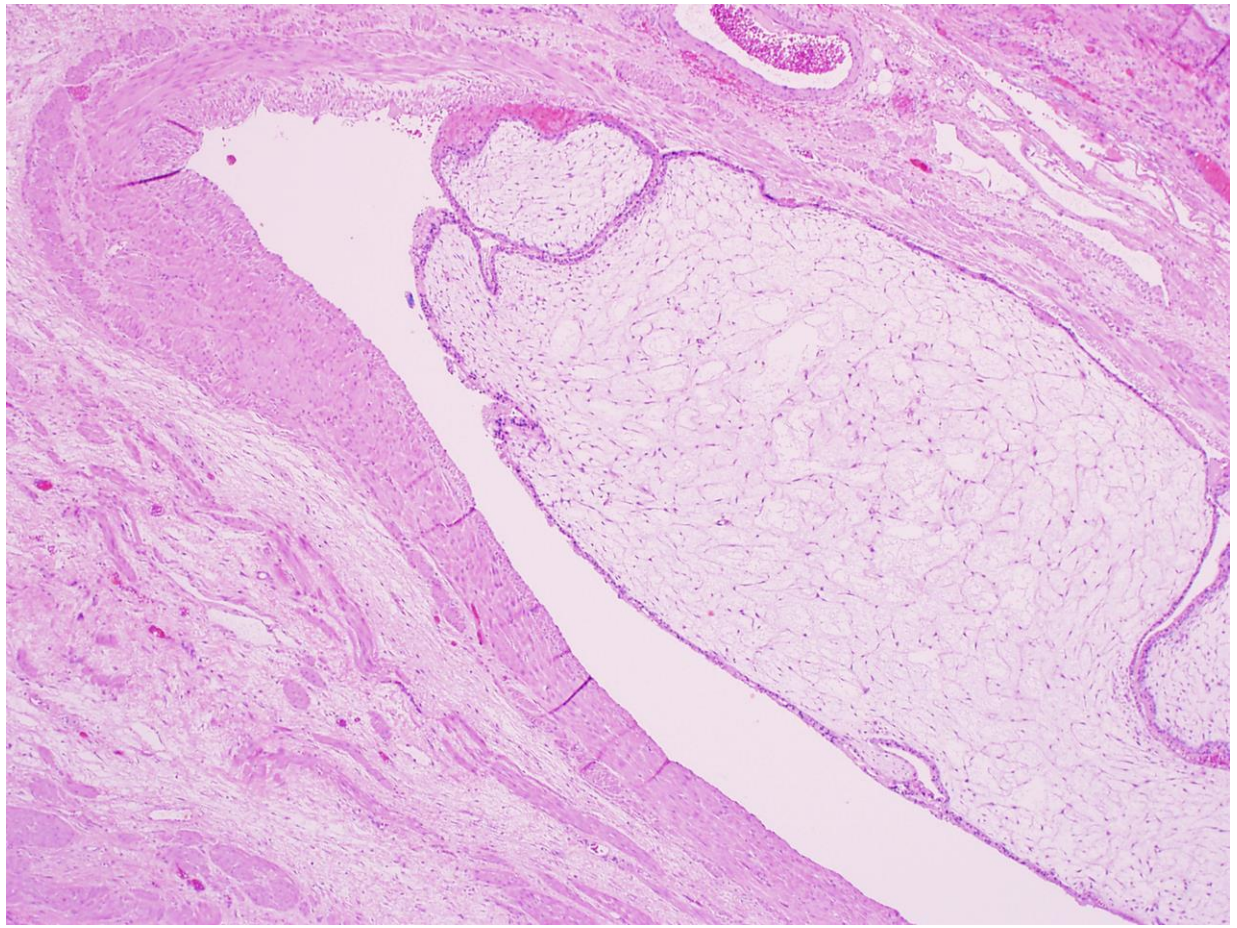
- Most often complete mole
- Invasion of molar villi into the myometrium or lymphovascular spaces
- Like other GTD/ persistent GTD – very responsive to chemotherapy, typically no tissue diagnosis required

Invasive Complete Mole

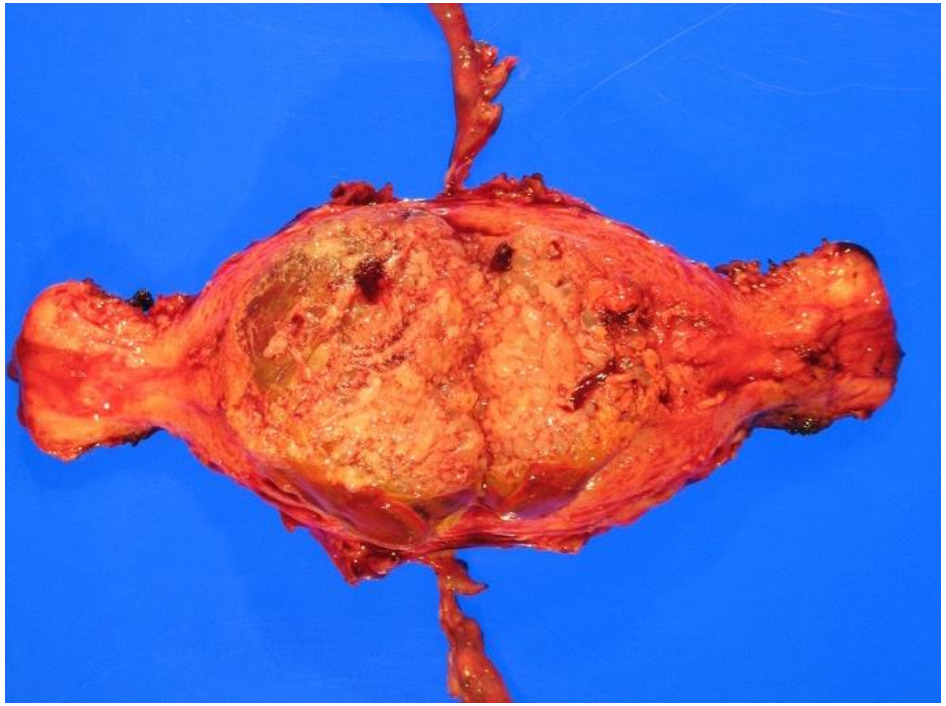


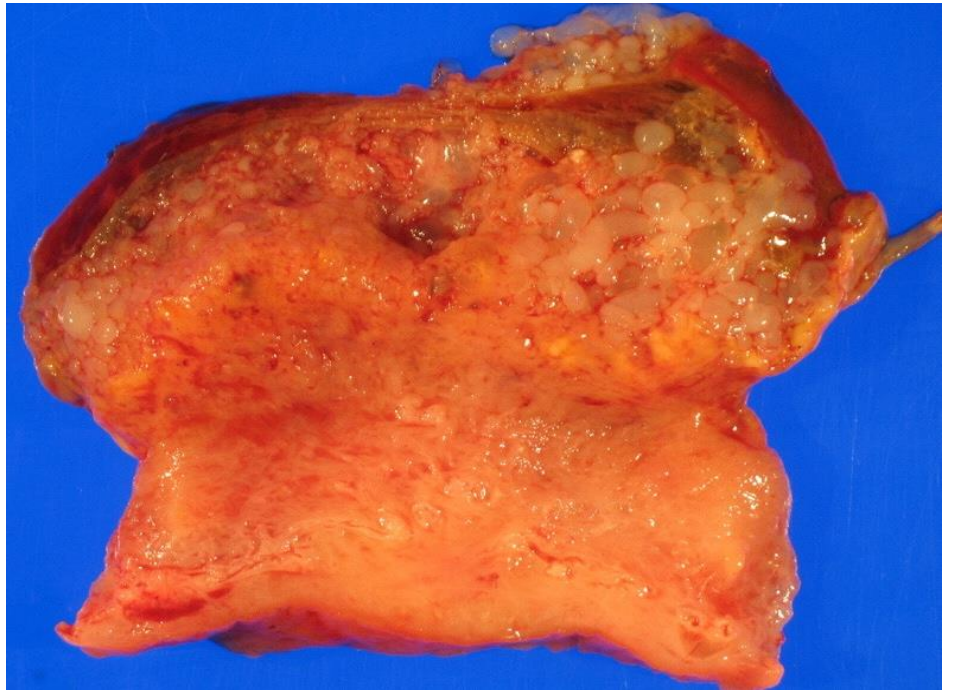
Invasive Complete Mole

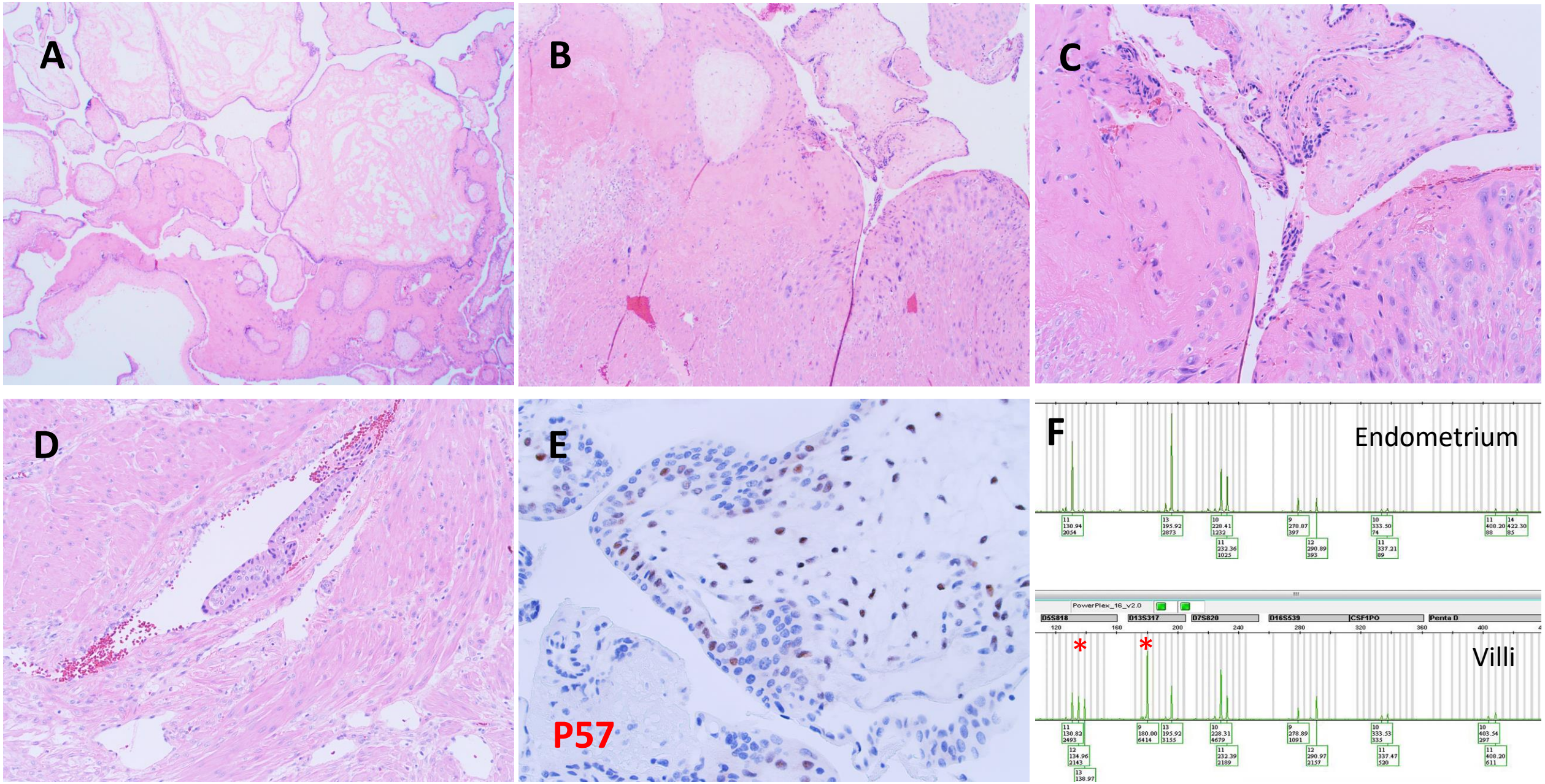




Invasive Partial Mole






A
B
C
D
E
P57
F
Endometrium
PowerPlex_16_v2.0
D5S818
D13S317
D7S820
D16S539
CSF1PO
Penta D
Villi

0.1% PHM progress to choriocarcinoma

Three gestational choriocarcinomas directly arising from their corresponding partial moles (STR genotyping and flow cytometry) among 3,000 PHM

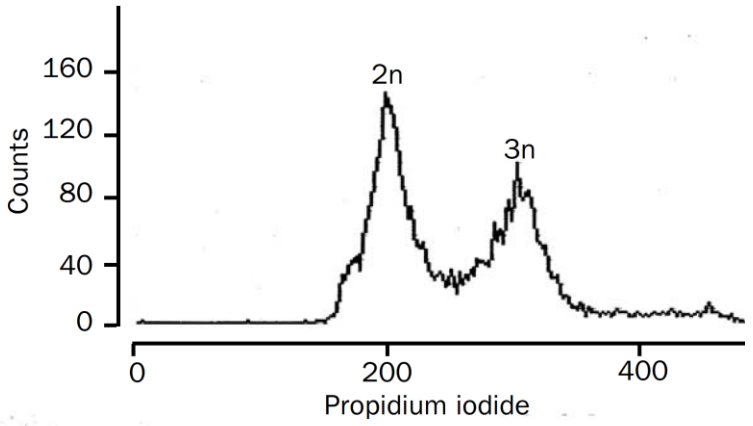


Figure 2: **Flow cytometry analysis (patient 1)**

Patient number	Microsatellite	Patient	PM	Tumour	Partner
1	VWA	a–b	b-c–d	b-c–d	c-d
1	D16S516	a–b	b-c–d	b-c–d	c-d
1	D20S186	a–b	b-c–d	b-c–d	c-d
2	D10S179	a–b	a–b-c	a–b-c	NA
2	D18S535	a	a–b-c	a–b-c	NA
3	D2S1391	a–b	a-c–d	a-c–d	c-d
3	D20S481	a–b	b-c–d	b-c–d	c-d

The letters a, b, c, and d are used to differentiate between different alleles and do not represent specific polymorphisms. NA=not available.

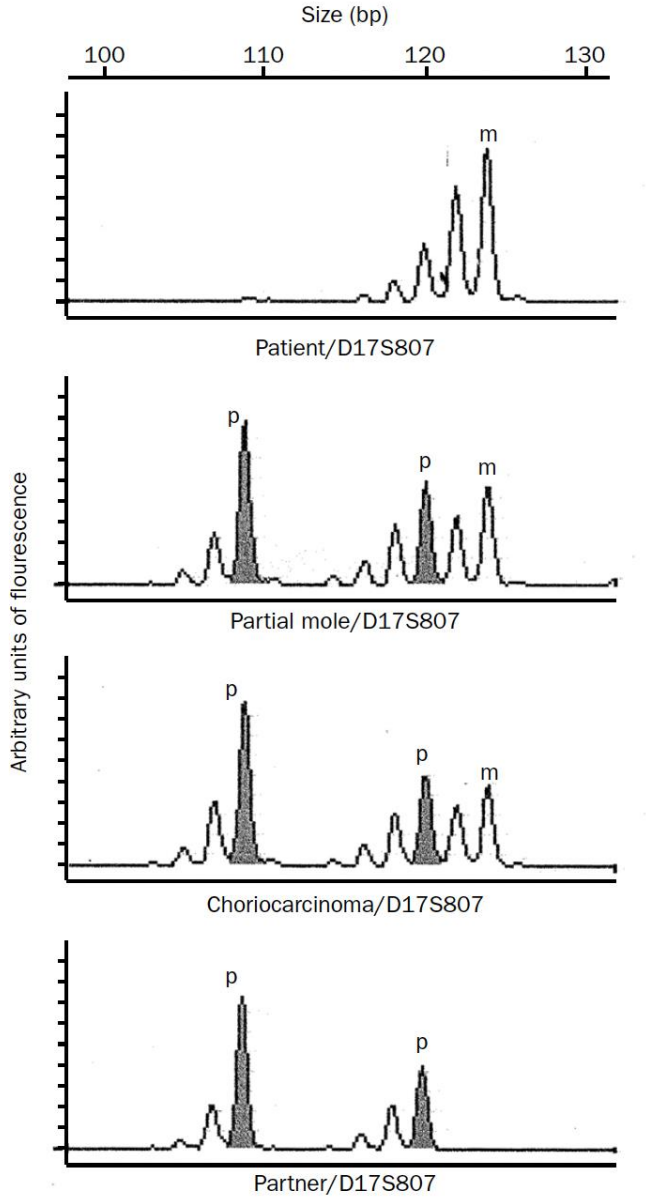
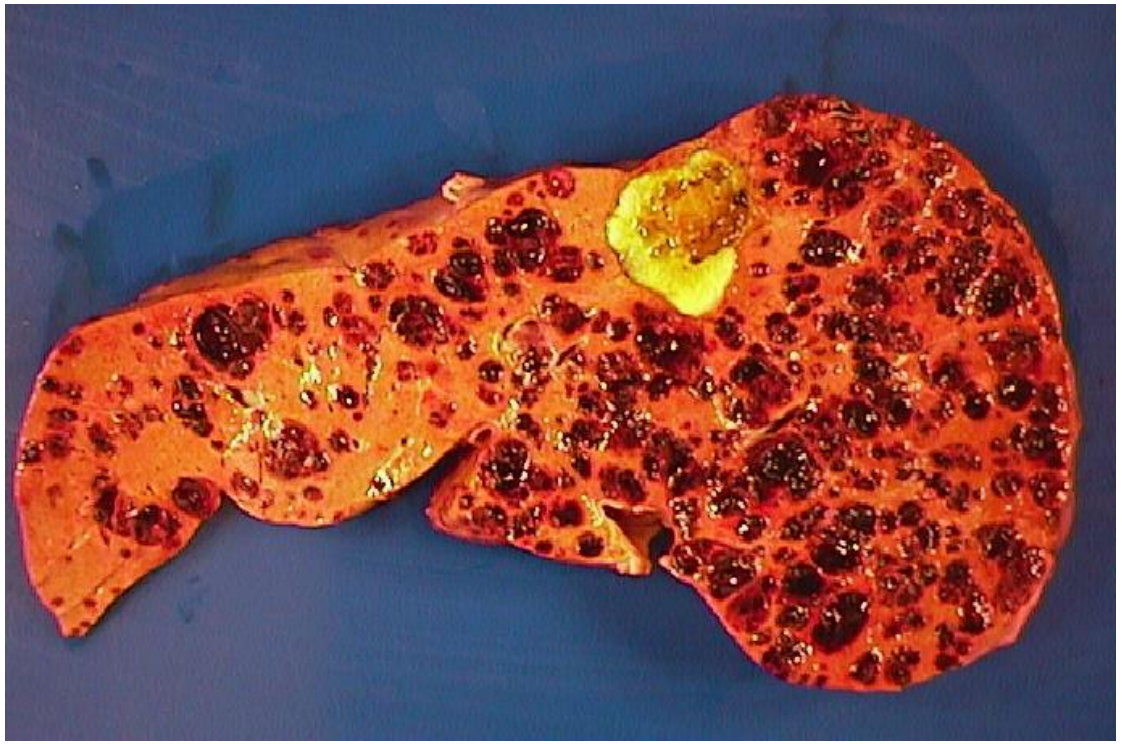


Figure 4: **Genetic analysis**
Fluorescently labelled microsatelites are displayed as characteristic electropherogram peaks after capillary gel electrophoresis. M=maternally derived alleles. P=paternally derived alleles.

Seckl MJ, et al: Choriocarcinoma and Partial Hydatidiform Moles. Lancet. 2000;356:36-39.

While gestational choriocarcinomas can be treated very successfully by chemotherapy, rare patients may die of high stage tumor/high risk scores at presentation primarily due to a delayed diagnosis - unnoticed preceding hydatidiform mole



Seckl MJ, et al: Choriocarcinoma and Partial Hydatidiform Moles. Lancet. 2000;356:36-39.

Special Diagnostic Considerations

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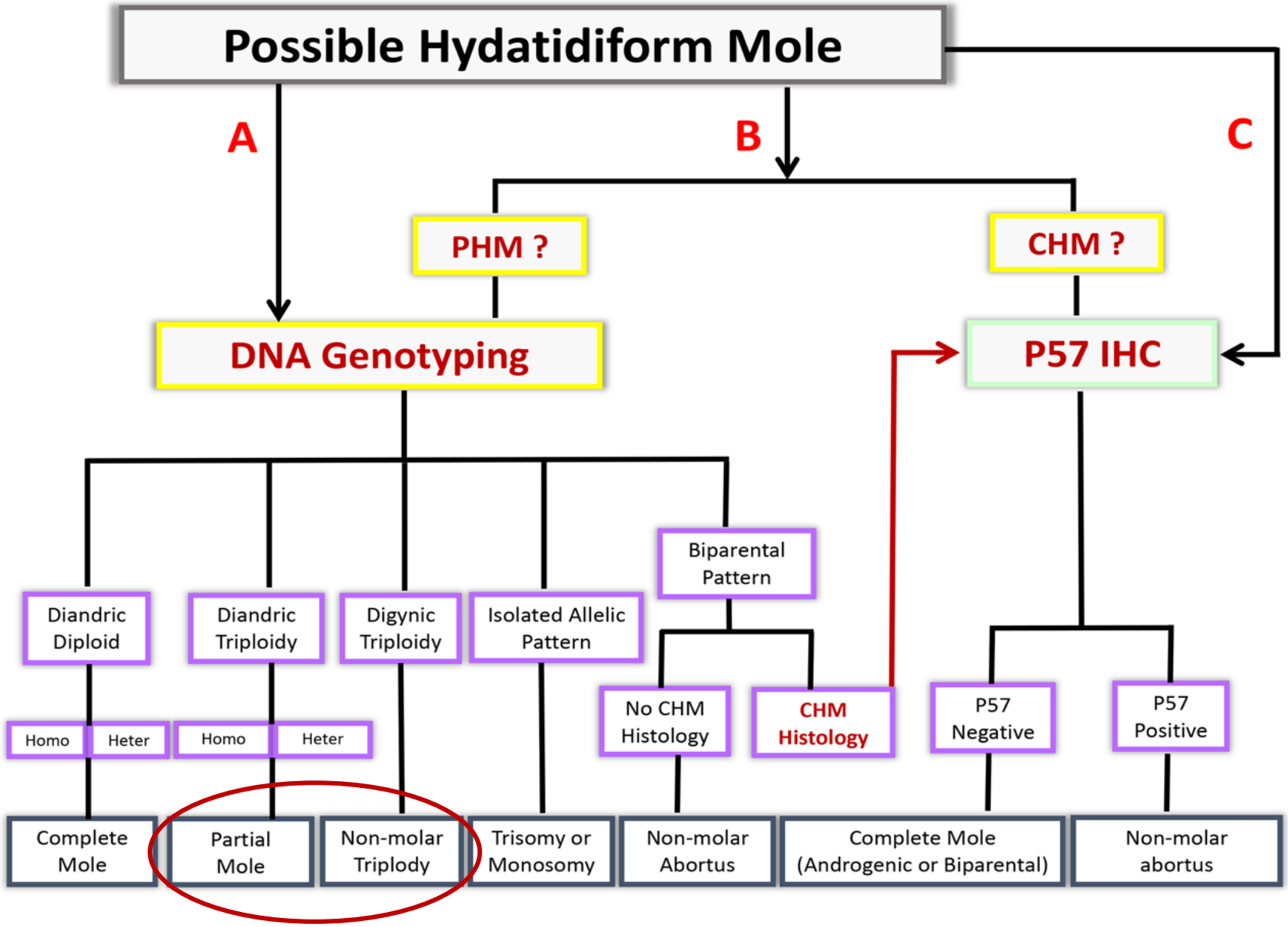
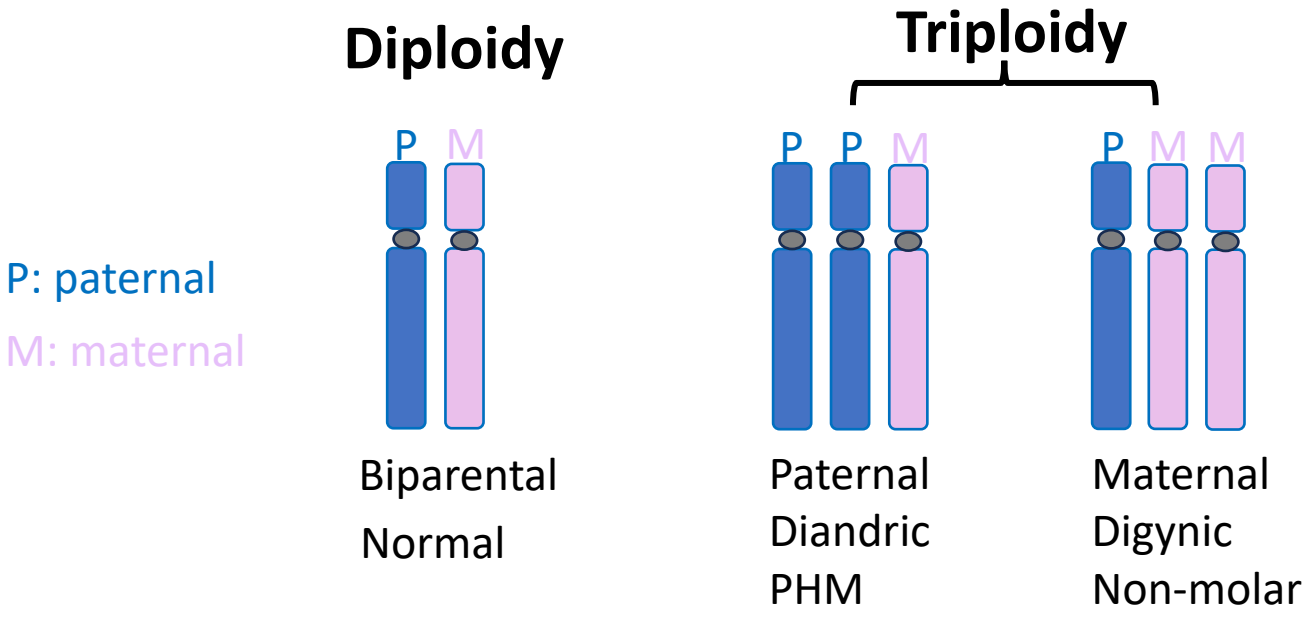


Center for The Precision Medicine of Trophoblastic Disease

Buza and Hui, Mod Pathology, 2021,34:1658-1672

Triploid Gestations

- Triploidy is one of the most common chromosomal aberrations among human conceptions (2-3%)
- 5% of spontaneous abortions are triploids →
  - 35-50% digynic, ~65% diandric, depending on the gestational age



Jacobs et al. Ann Jum Genet, 1982;45:223; Redline et al. Hum Path. 1998, 28:505; Zaragoza et al. Am J Hum Gen 2000,66:1807; Genest, 2000. Int J Gyneco Pathol, 2001, 20:315; Han et al. Am J Surg Pathol, 2020; 44:849.

Table 2 Distribution of diandric and digynic triploid pregnancies depending on gestational age

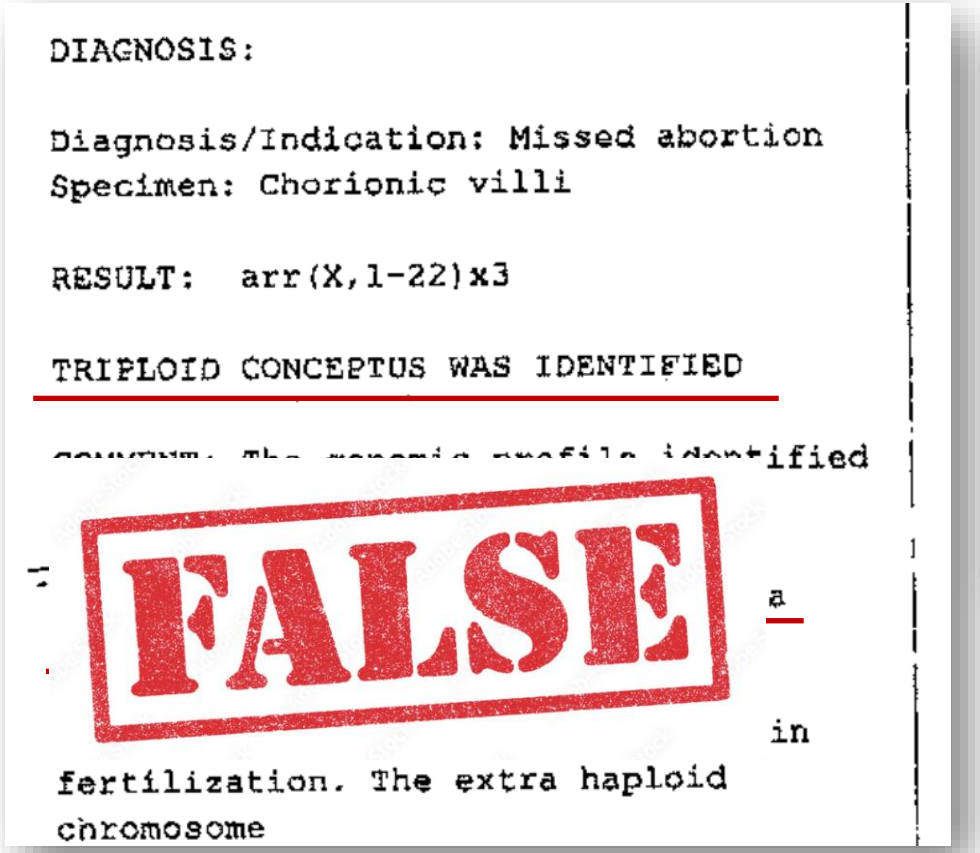
Gestational age (gw)	Parental origin of triploidy		All *n*
	Diandric *n* (%)	Digynic *n* (%)	
<11	20 (46.5%)	23 (53.5%)	43
11–14	18 (64.3%)	10 (35.7%)	28
>14	10 (27.8%)	26 (72.2%)	36

107 triploids by STR genotyping:

- 55% digynic and 46% diandric

Massalska D, et al. J Assist Reprod Genet. 2021, 38(9):2391-2395

Can you make a diagnosis of PHM based on morphology and ploidy analysis?



DIAGNOSIS:

Diagnosis/Indication: Missed abortion
Specimen: Chorionic villi

RESULT: arr(X,1-22)x3

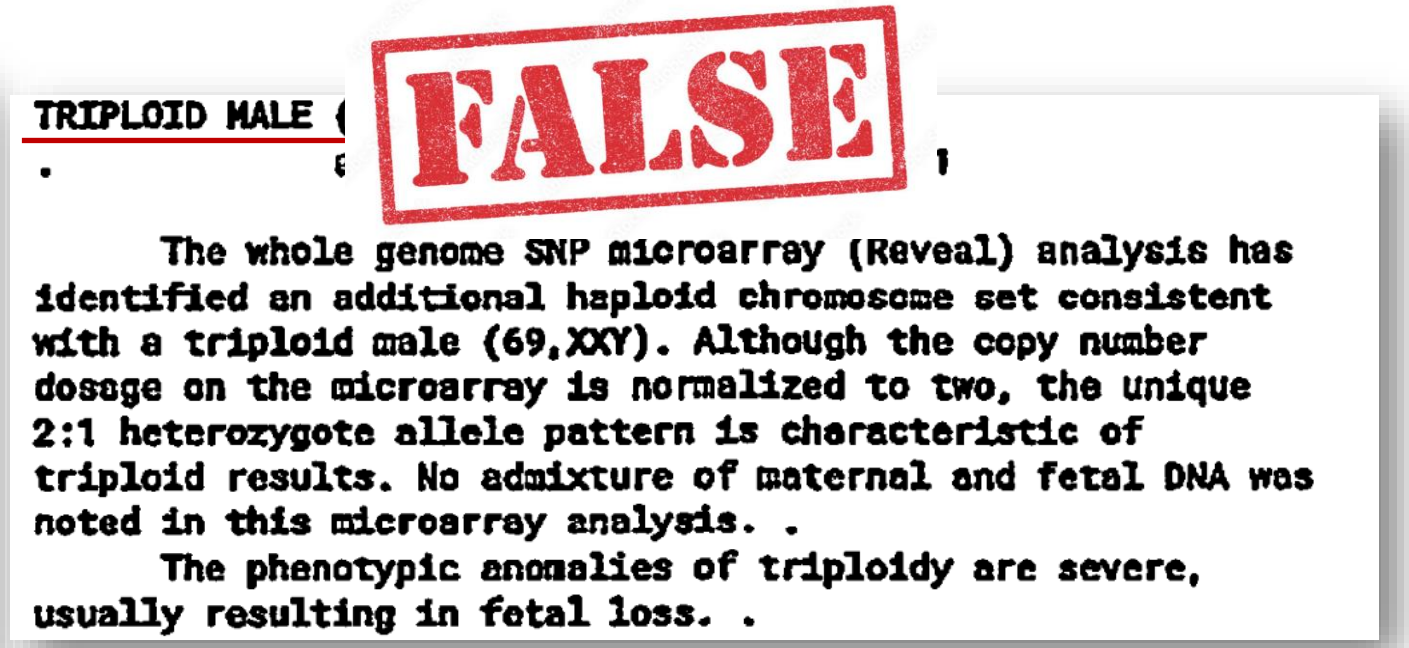
TRIPLOID CONCEPTUS WAS IDENTIFIED

FALSE

a

in

fertilization. The extra haploid
chromosome



TRIPLOID MALE

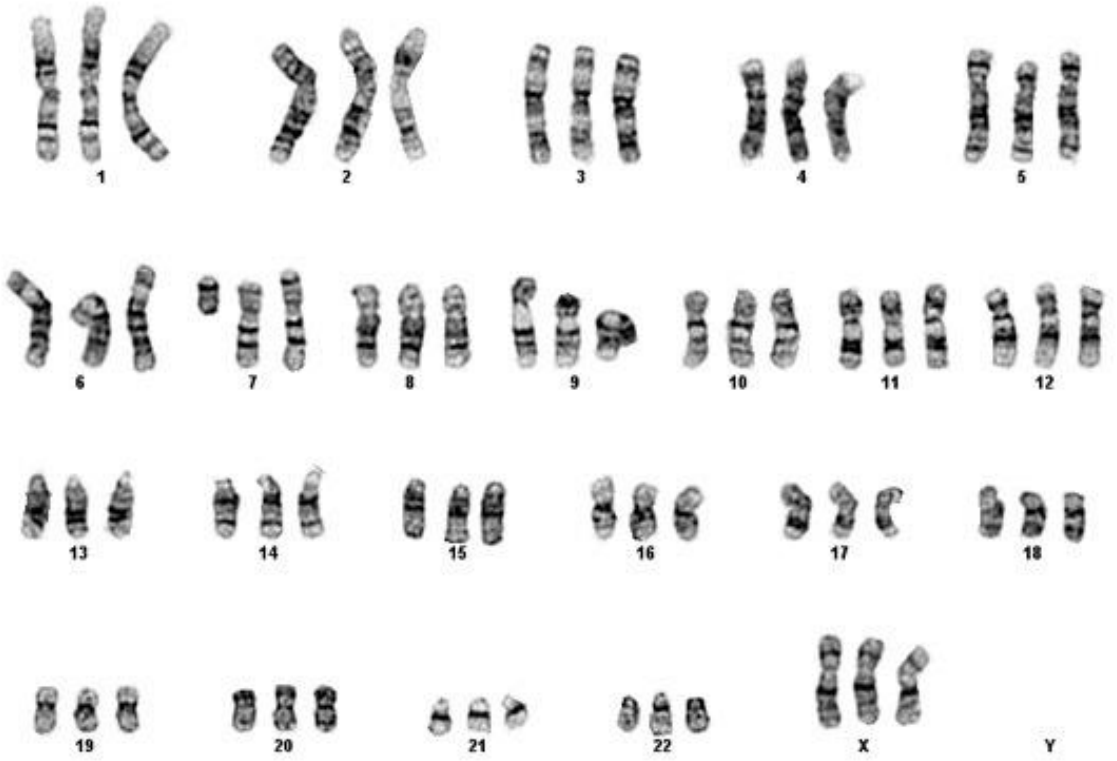
FALSE

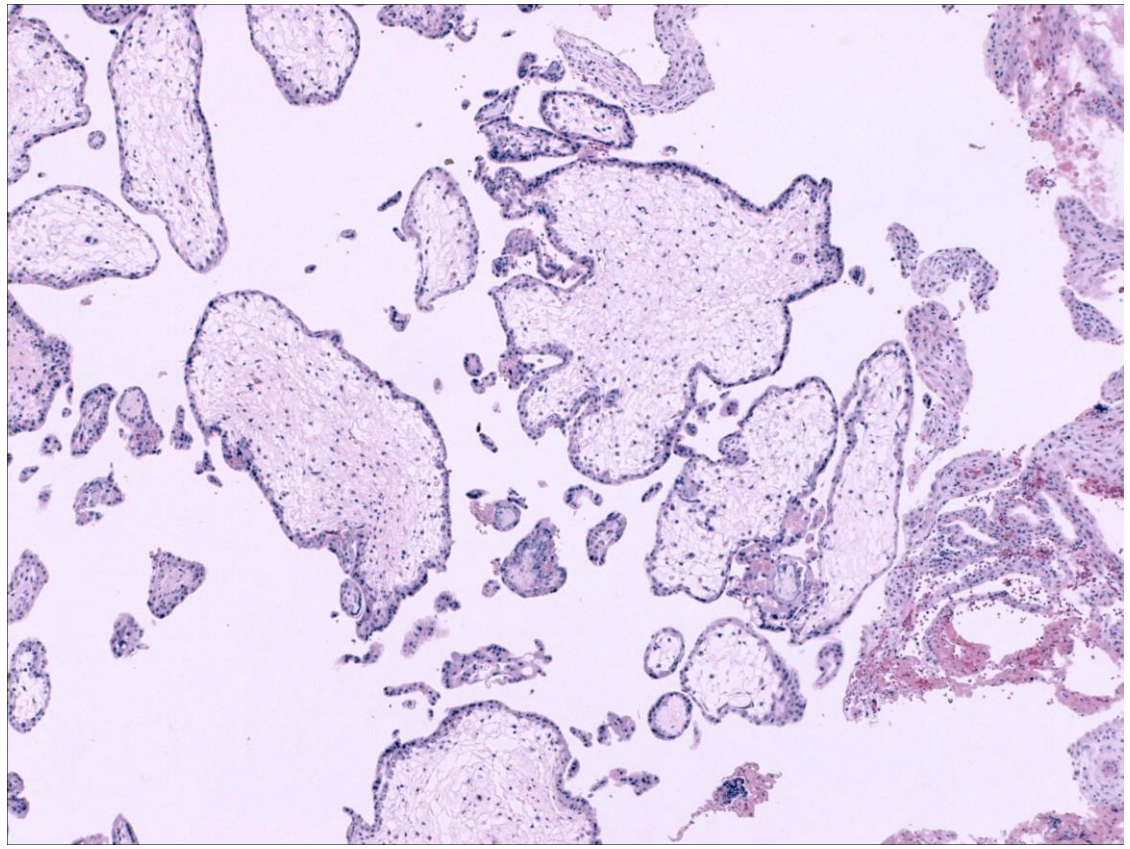
The whole genome SNP microarray (Reveal) analysis has identified an additional haploid chromosome set consistent with a triploid male (69,XXY). Although the copy number dosage on the microarray is normalized to two, the unique 2:1 heterozygote allele pattern is characteristic of triploid results. No admixture of maternal and fetal DNA was noted in this microarray analysis. .

The phenotypic anomalies of triploidy are severe, usually resulting in fetal loss. .

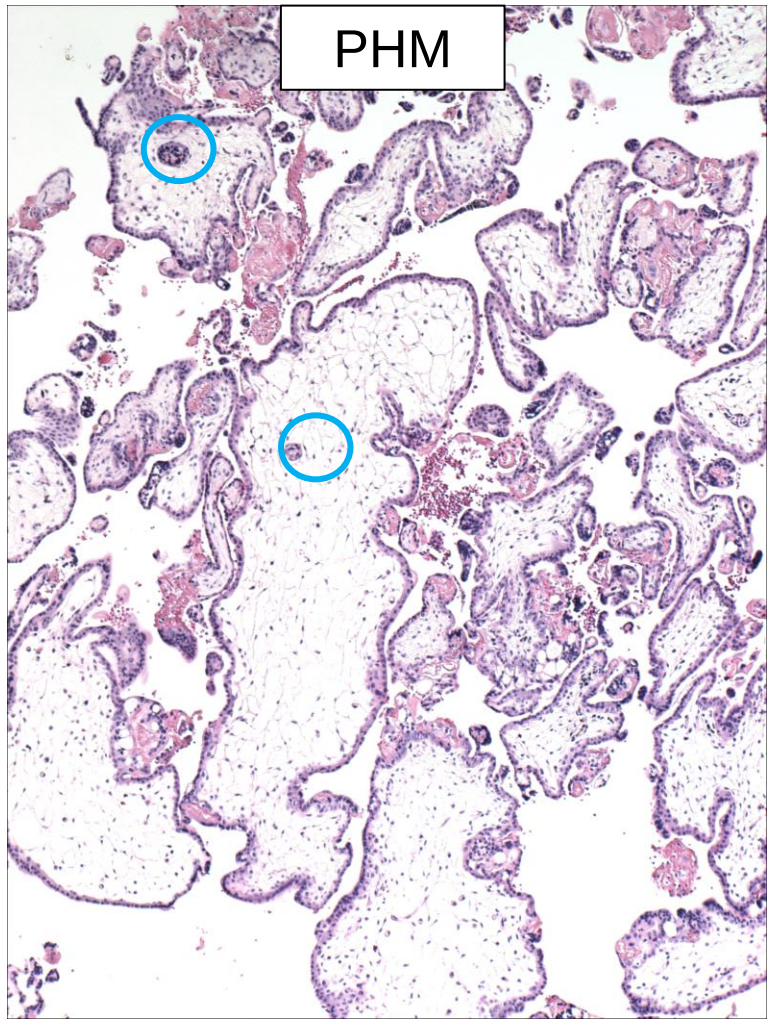
Triploidy ≠ Partial mole

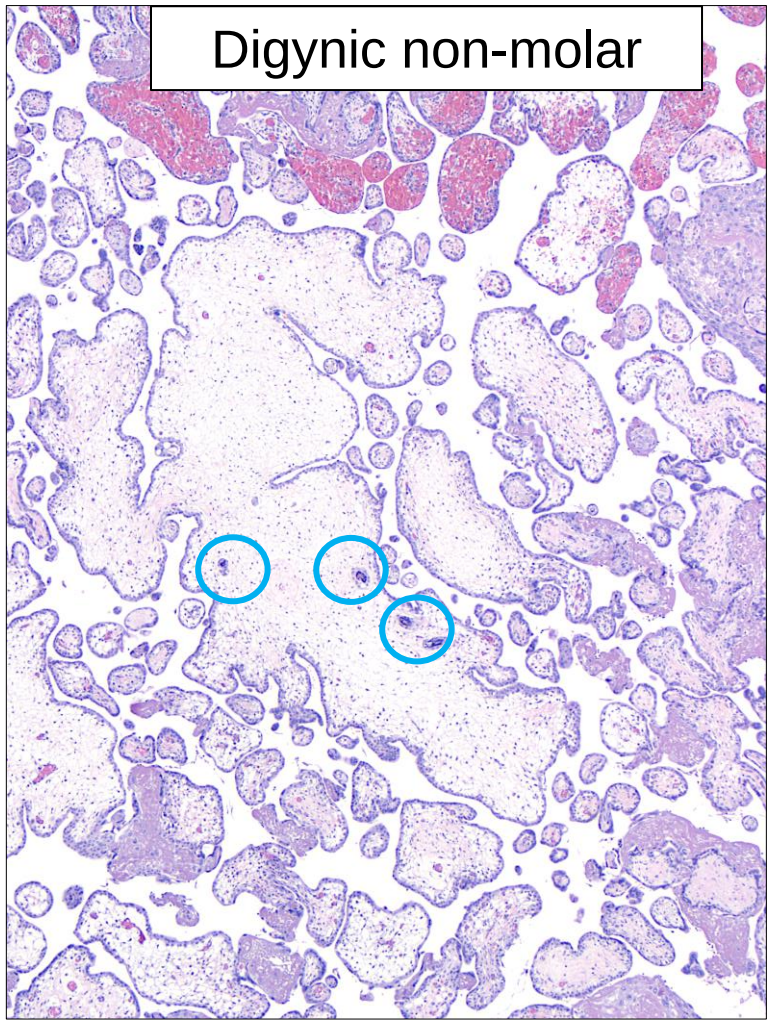
Triploidy ≠ Partial Mole

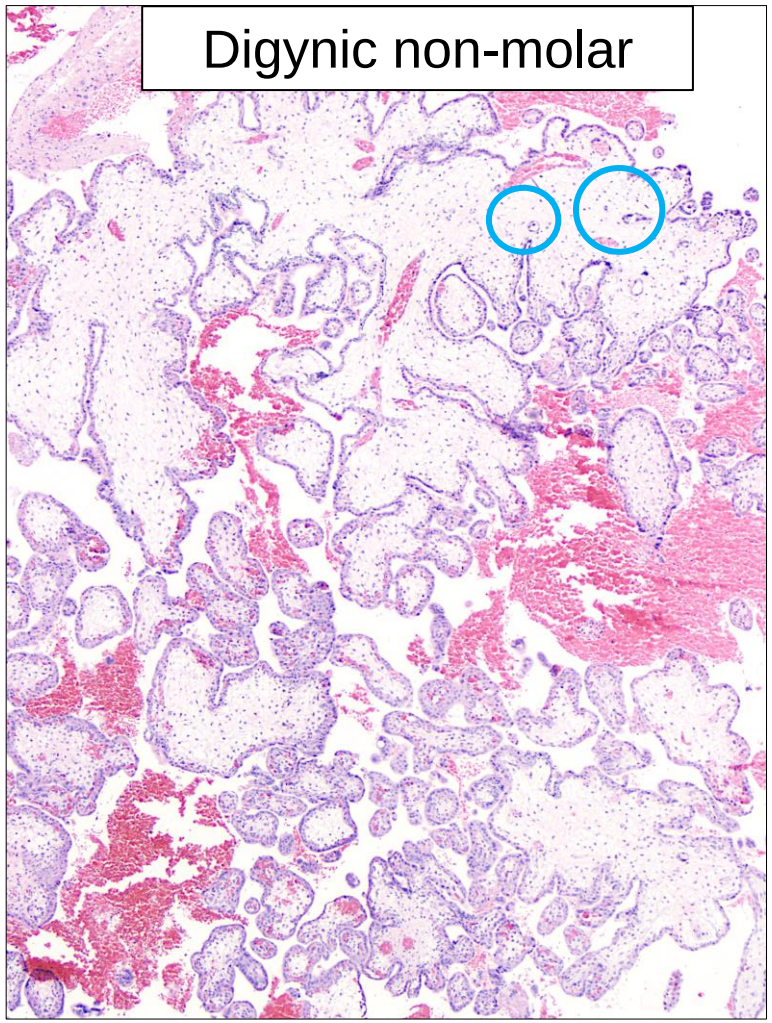




Triploid Gestations – PHM?







Pseudoinclusion: invagination of surface trophoblastic cells

Triploid POC: Genotyping – Phenotyping Correlation Study 2024

Table 1. Clinical features

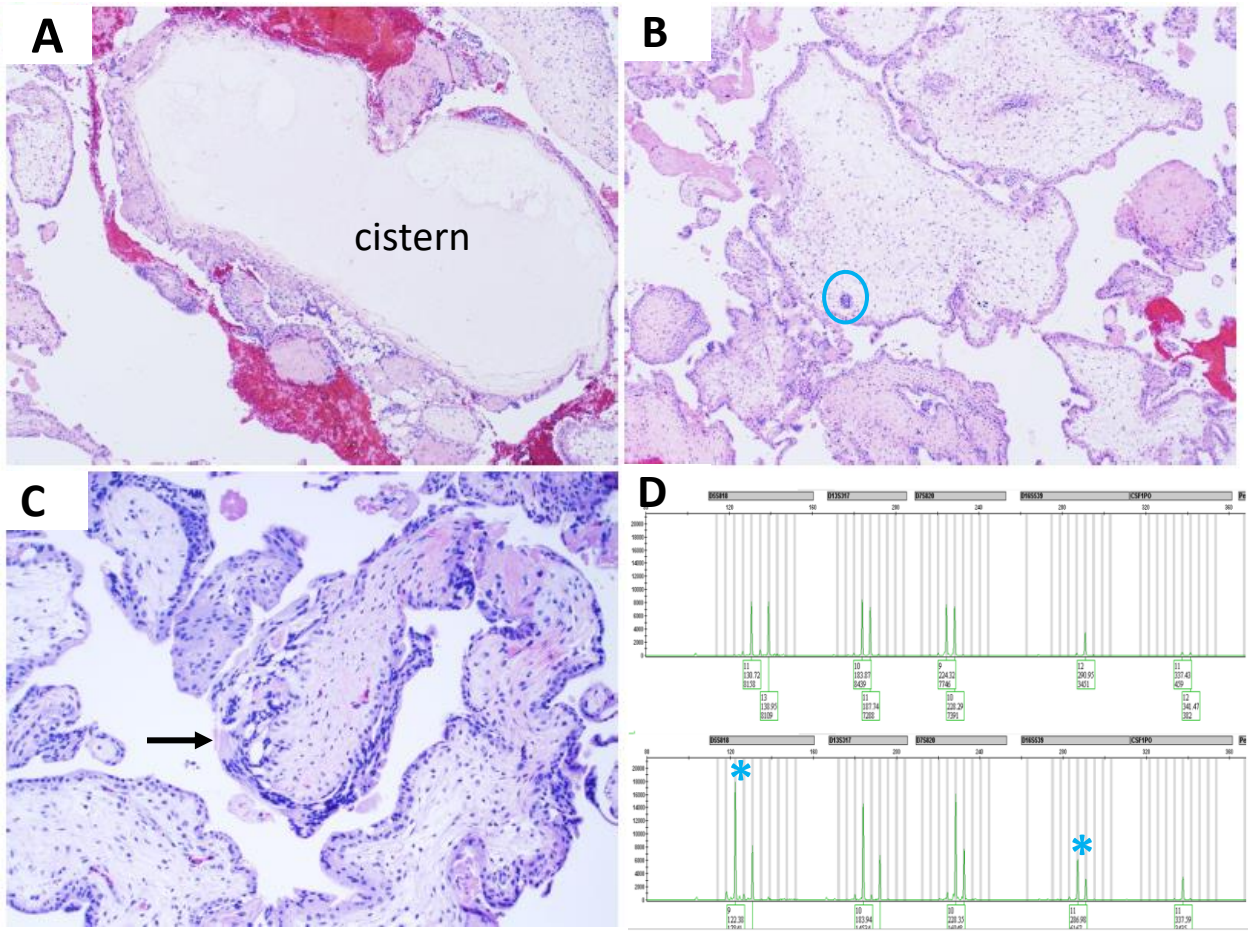
	PHM (n=19)	Digynic triploidy (n=16)
Maternal age (years, median)	19-40 (32)	25-43 (34)
Gestational age (wks)*	6-12 (11)	6-24 (11)
Clinical history		
Missed/incomplete abortion	17	14
IUFD	0	1
Suspicious for molar pregnancy	2	1

*Data on clinical gestational age was available in 35 cases. IUFD, intrauterine fetal demise; PHM, partial hydatidiform mole

Niu N, et al: 2024 USCAP Presentation

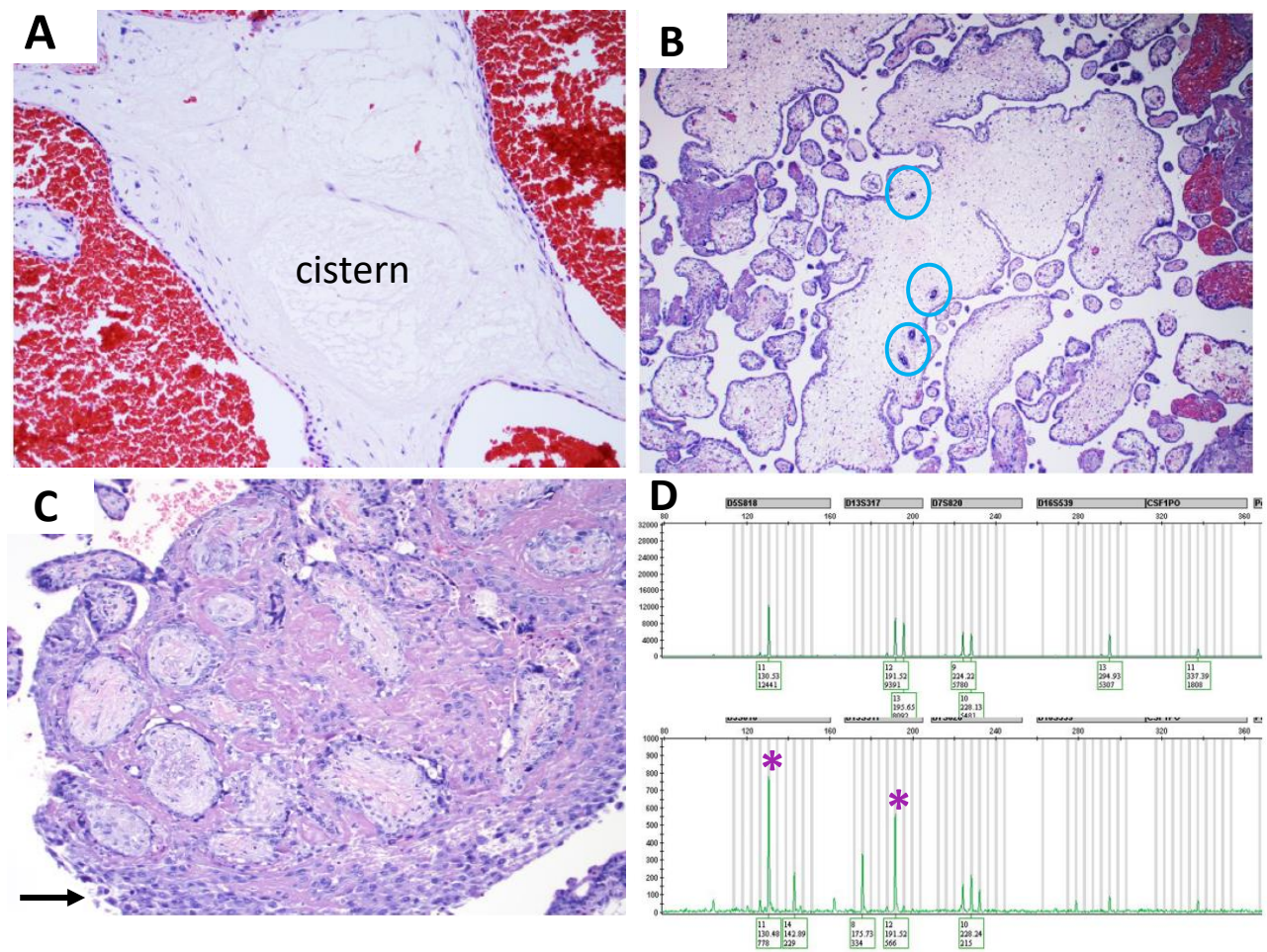
*

PMH



* Double paternal alleles

DTG



*Double maternal alleles

Cistern formation: hydropic cavity≥**50%** of villous volume in terminal villi

Pseudoinclusion: invagination of surface trophoblastic cells

Individual parameters

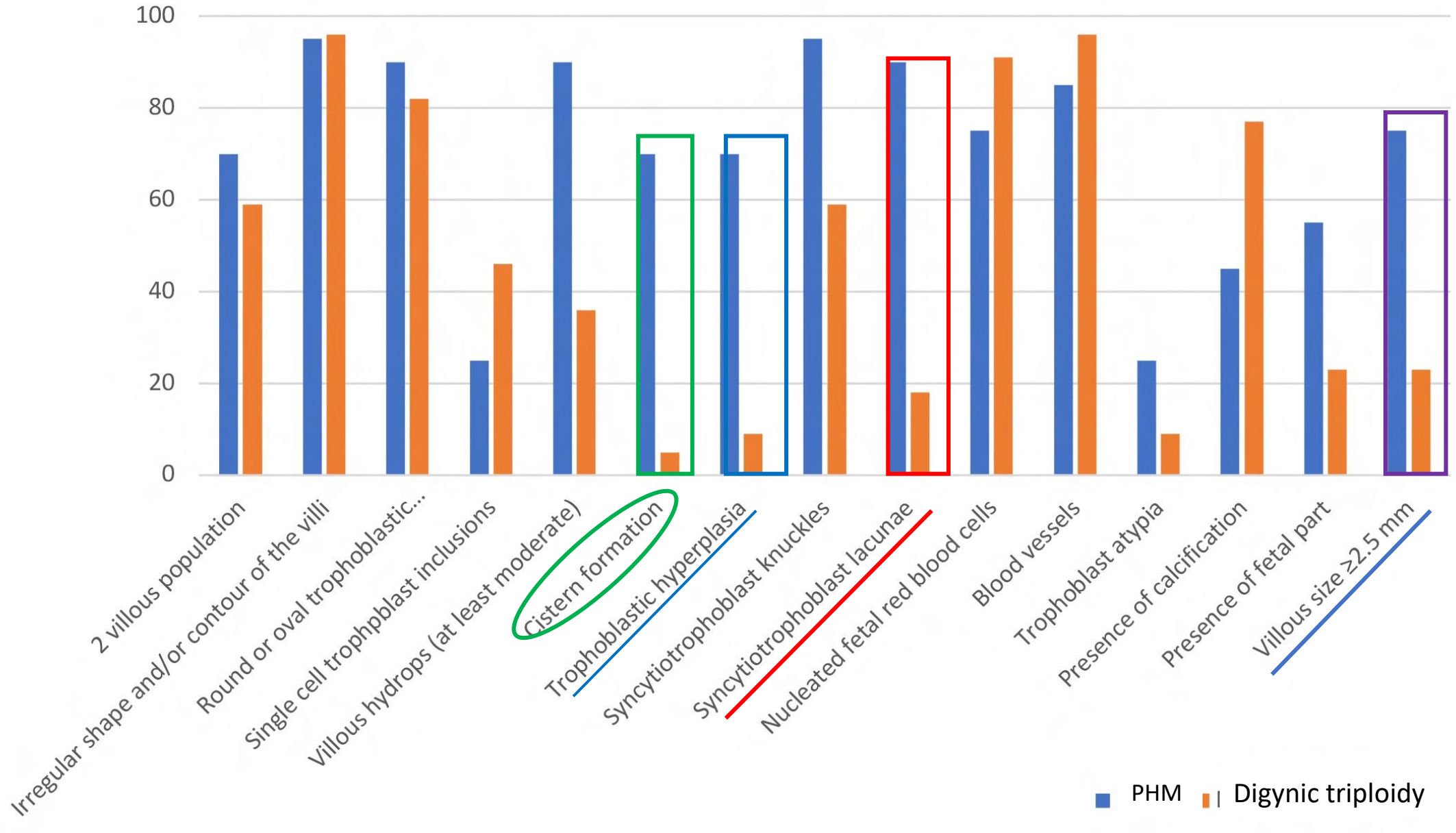
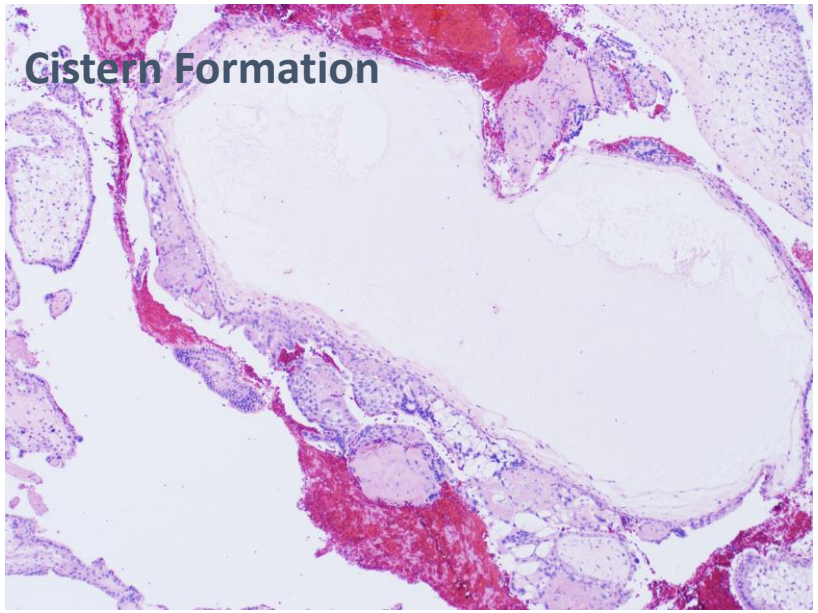


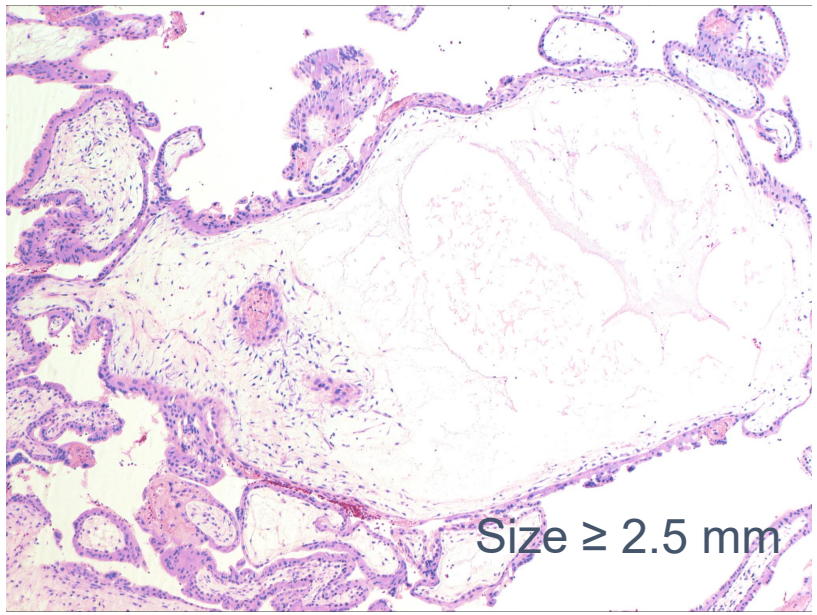
Table 2. Sensitivity, Specificity, and PPV of Pathological Parameters

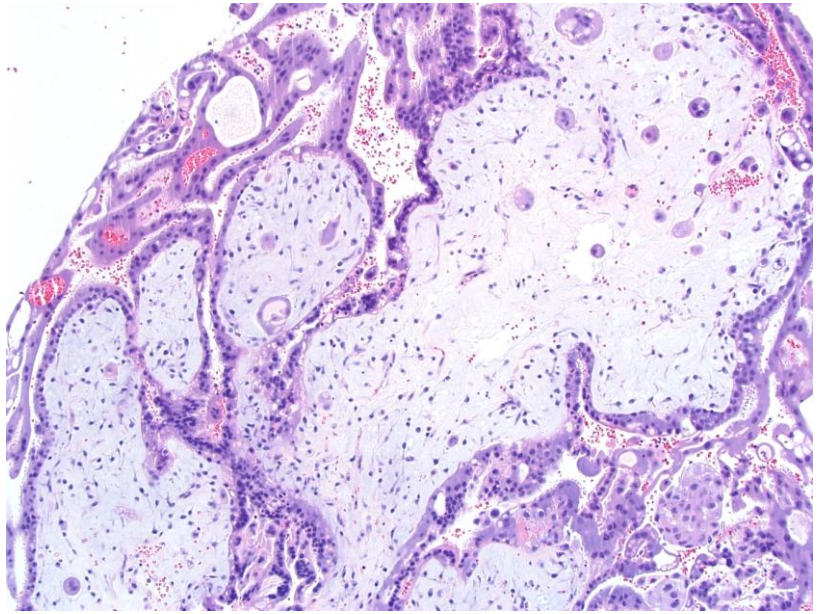
Histological Parameters (single or combined)		PHM (N=20)	DTG (N=22)	Sensitivity %	Specificity%	PPV%	P Value
Single parameters	Cistern formation	14	1	70	96	93	<0.0001
	Trophoblast hyperplasia	14	2	70	91	88	0.00005
	Syncytiotrophoblast lacunae	18	4	90	82	82	<0.00001
	Villous size ≥2.5 mm	15	5	75	77	75	0.00075
	Trophoblast atypia	5	2	25	91	71	0.167
	Villous hydrops (at least moderate)	18	8	90	64	69	0.0035
	Presence of fetal parts	11	5	55	77	69	0.0315
	Syncytiotrophoblast knuckles	19	13	95	41	59	0.0064
	Two villous populations	14	13	70	41	52	0.461
	Trophoblastic pseudo-inclusions	18	18	90	18	50	0.449
	Irregular villous shape and/or contour	19	21	95	4.5	48	0.945
	Blood vessels	17	21	85	4.5	45	0.249
	Nucleated fetal red blood cells	15	20	75	9	41	0.167
	Presence of calcifications	9	17	45	23	35	0.0315
	Single cell trophoblast inclusions	5	10	25	55	33	0.167
Combined parameters	Cistern + villous size ≥2.5 mm	12	0	60	100	100	
	Cistern +trophoblast hyperplasia	12	0	60	100	100	
	Cistern + Syncytiotrophoblast lacunae	13	0	65	100	100	
	Syncytiotrophoblast Lacunae + trophoblast hyperplasia	13	1	65	96	93	
	Villous size ≥2.5 mm +lacunae	18	2	90	91	90	
	Villous size ≥2.5 mm +trophoblast hyperplasia	10	2	50	91	83	

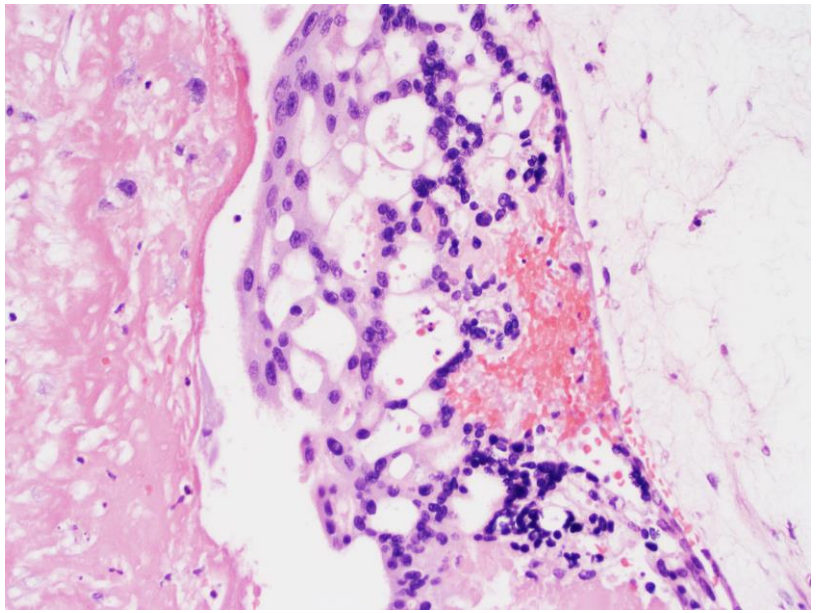
Triploid POC



- Cistern formation: 93.3% PPV/70% sensitivity for PHM
- Cistern formation: 100% PPV (60% Sensitivity) **IF**
  - size ≥ 2.5 mm
  - or trophoblastic hyperplasia
  - or syncytiotrophoblast lacunae







Diagnostic Summary of PHM

- **Only H.E.:** Villous size of >=2.5 mm plus cistern: 97% PPV but 32% sensitivity. All histological parameters are nonspecific. Rule out CHM.

- **H.E. and Triploidy**: If cistern formation PLUS villous size of >=2.5 mm plus, or trophoblastic hyperplasia, or syncytiotrophoblast lacunae: 100% PPV but 65% sensitivity. Otherwise, Dx as suspicious with recommendation of STR genotyping or clinical hCG follow-up with risk of overdiagnosis.

- **STR genotyping required for accurate diagnosis:** Simple PCR test with comparable cost to tissue ploidy analysis. Many labs have STR for other applications and are encouraged to validate for GTD diagnosis.

Special Diagnostic Considerations

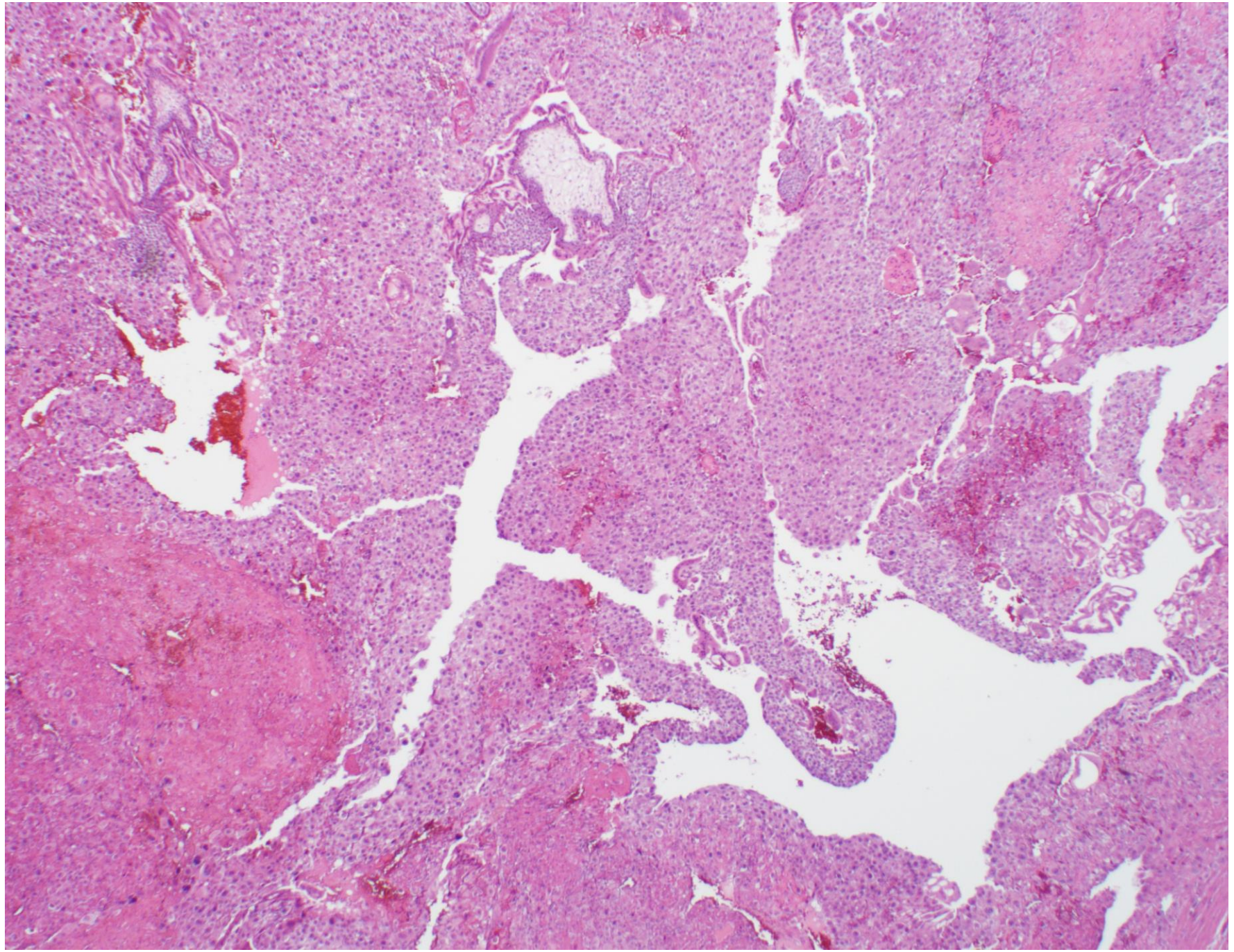
- Post-molar Gestational Trophoblastic Neoplasia (GTN)
- Triploid Digynic Non-molar Gestation
- Recurrent Biparental Hydatidiform Moles

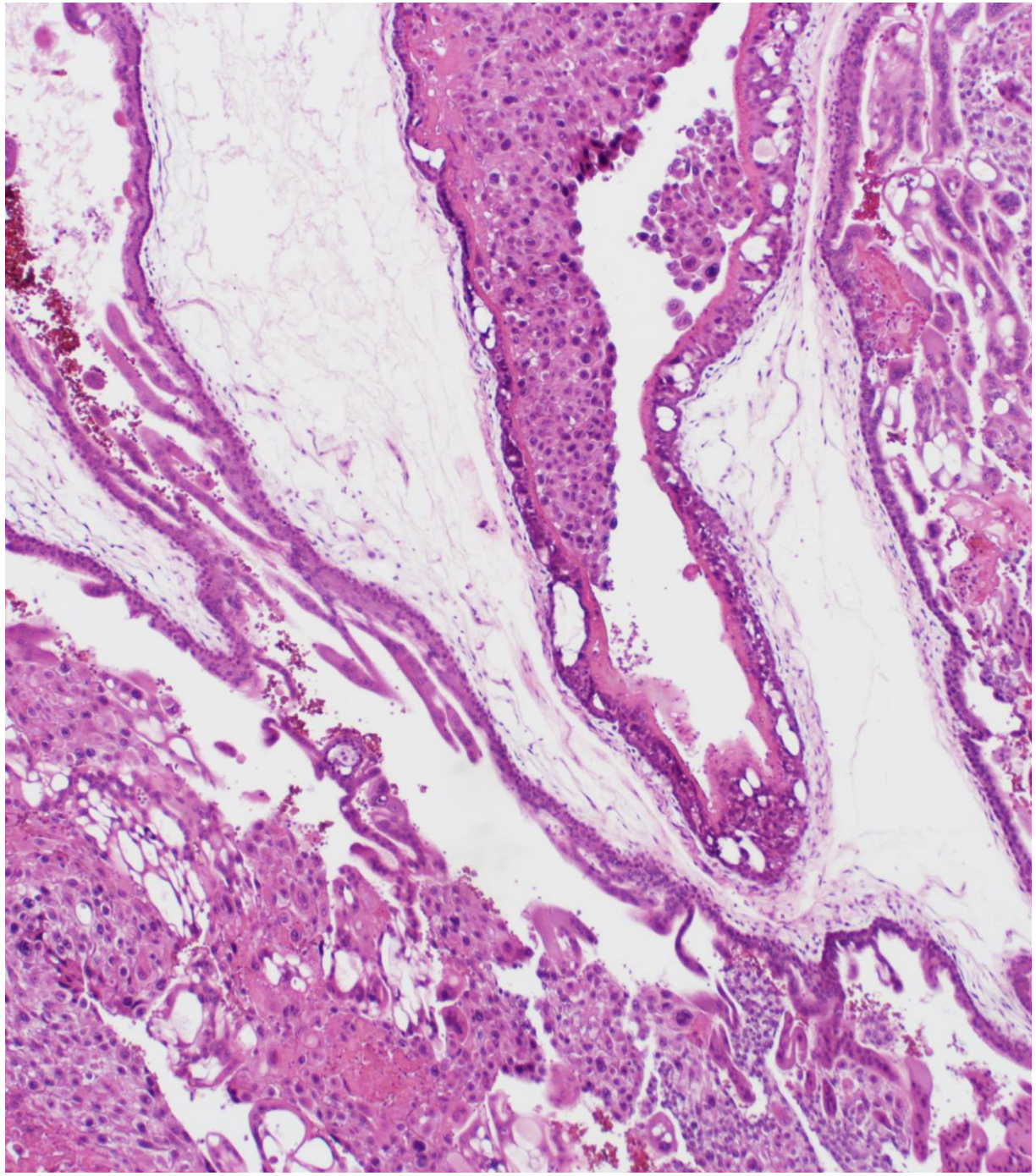
Y-GTD Center Case of 2024

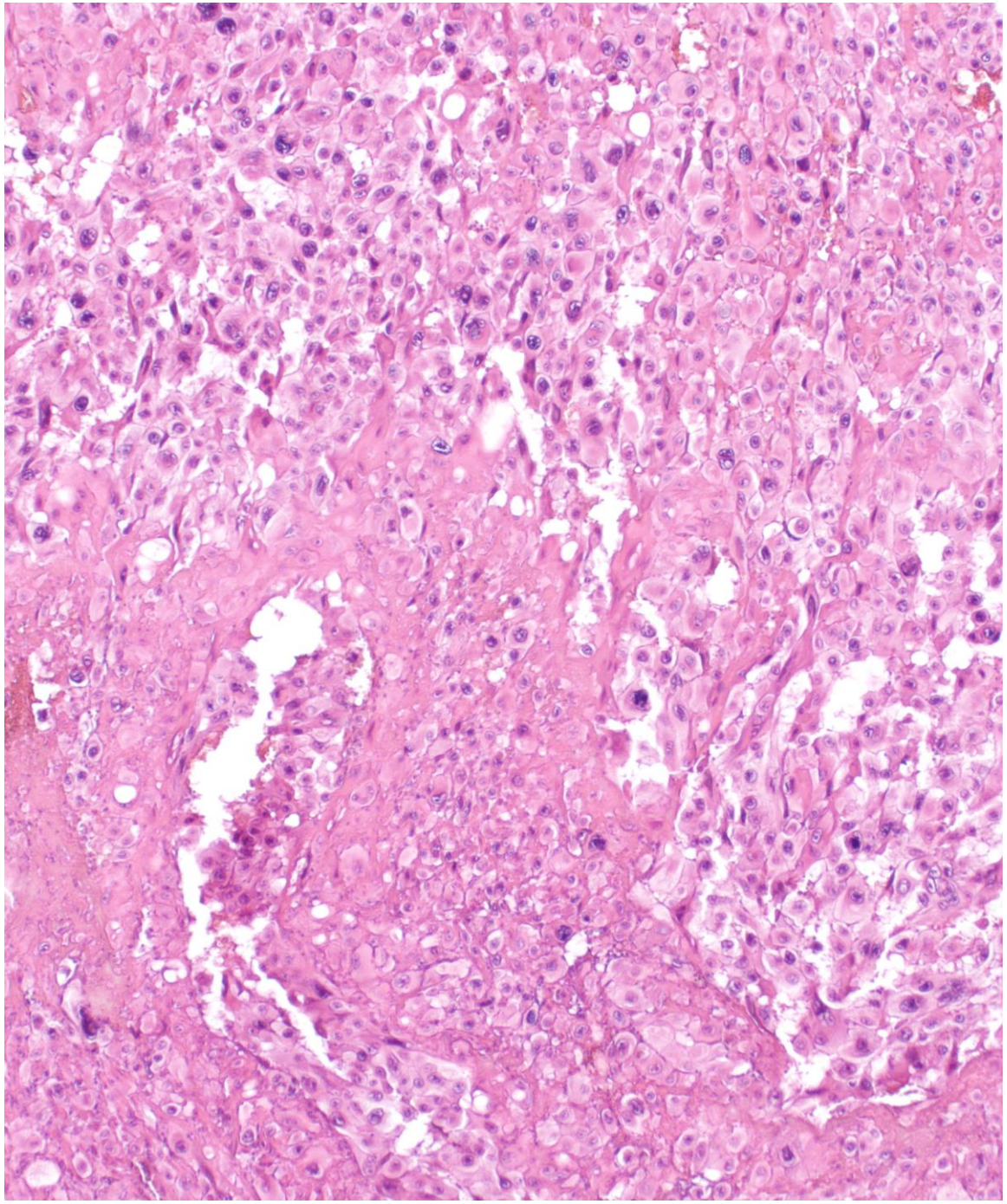
31-year-old patient presenting with abnormal gestation after multiple failed pregnancies; Abnormal high serum hCH; uterine mass lesion and multiple lung nodules. Undergoing hysterectomy.

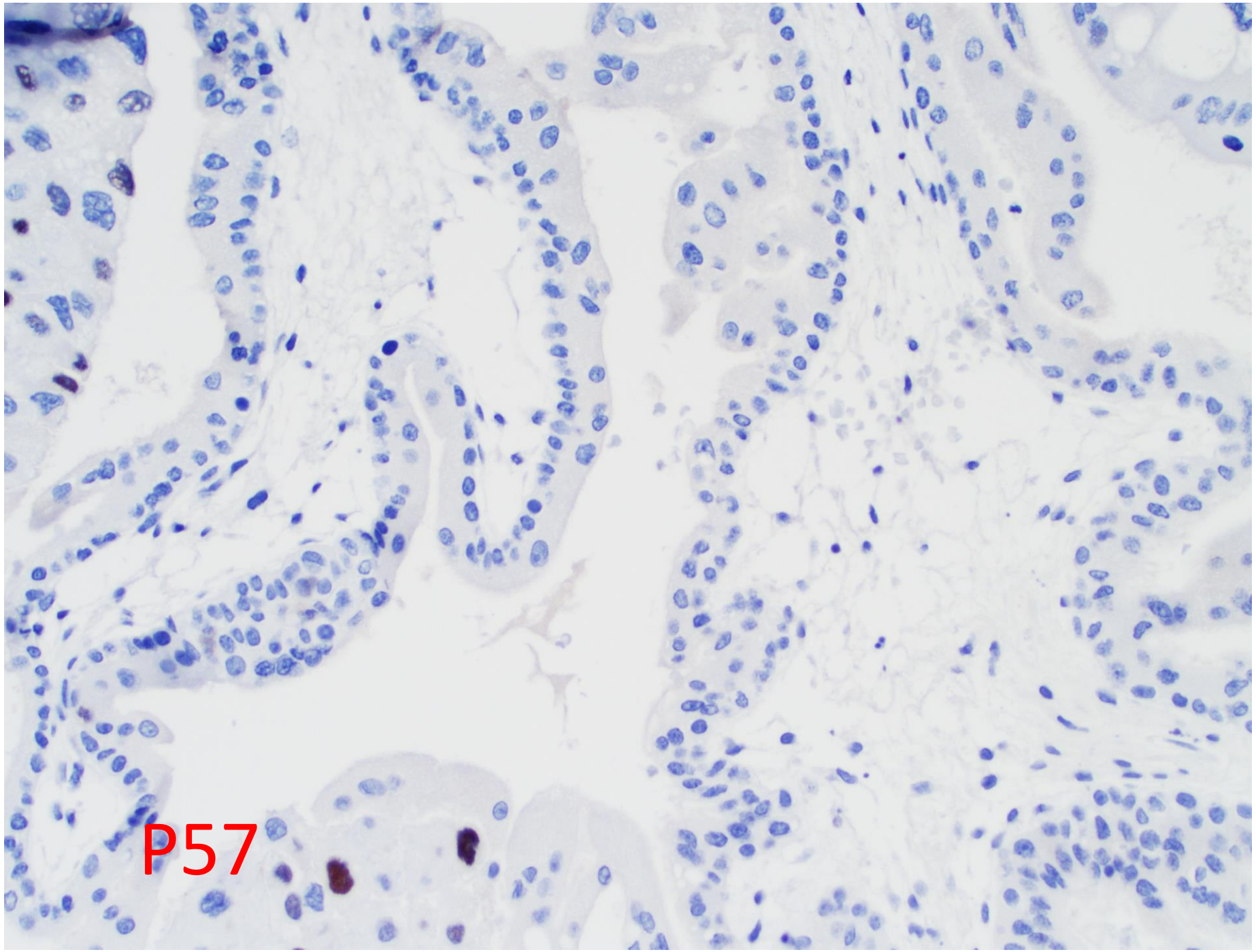
Contributed by Dr. Peter Chen

Invasive Myometrial Lesion

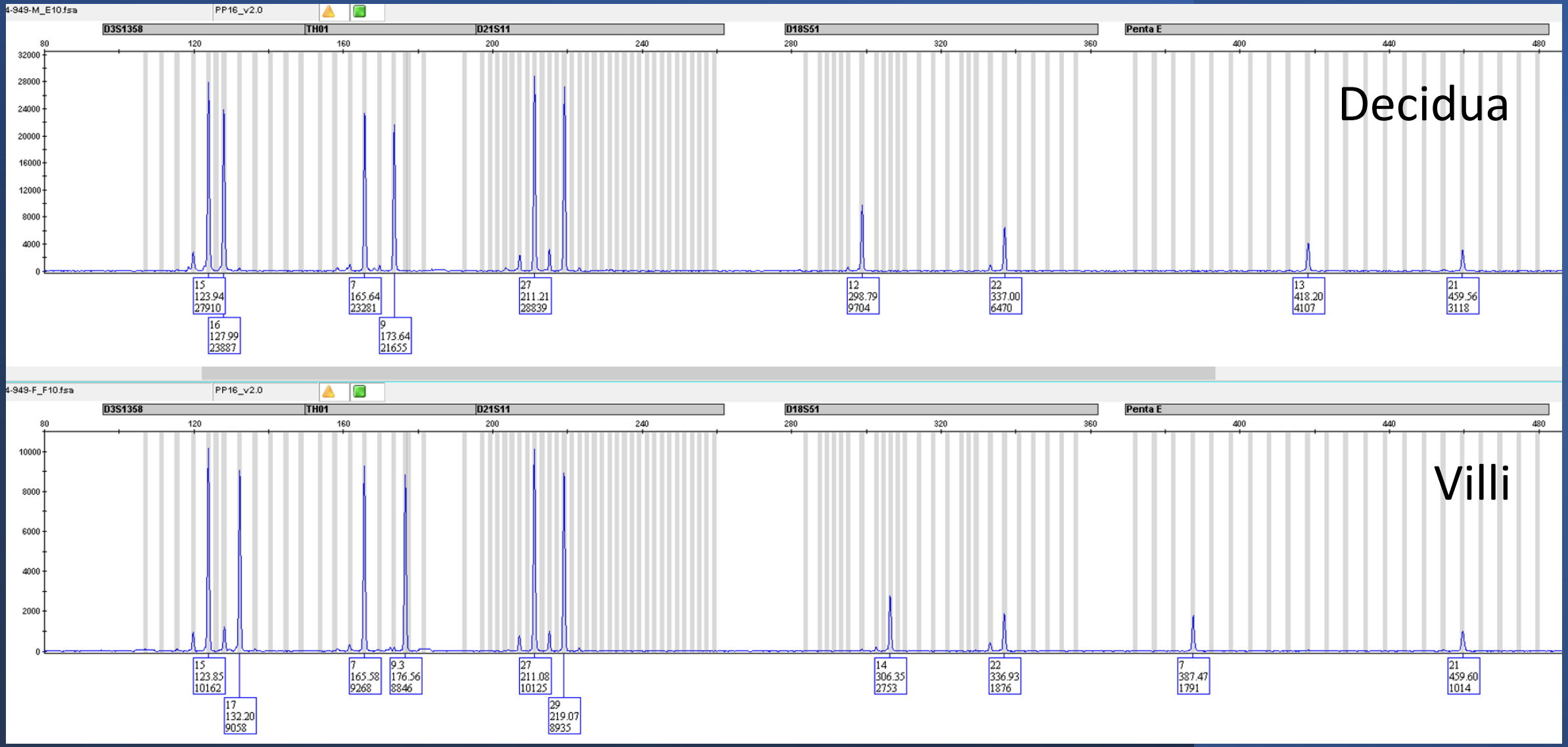







P57

Balanced Biparental Genotype

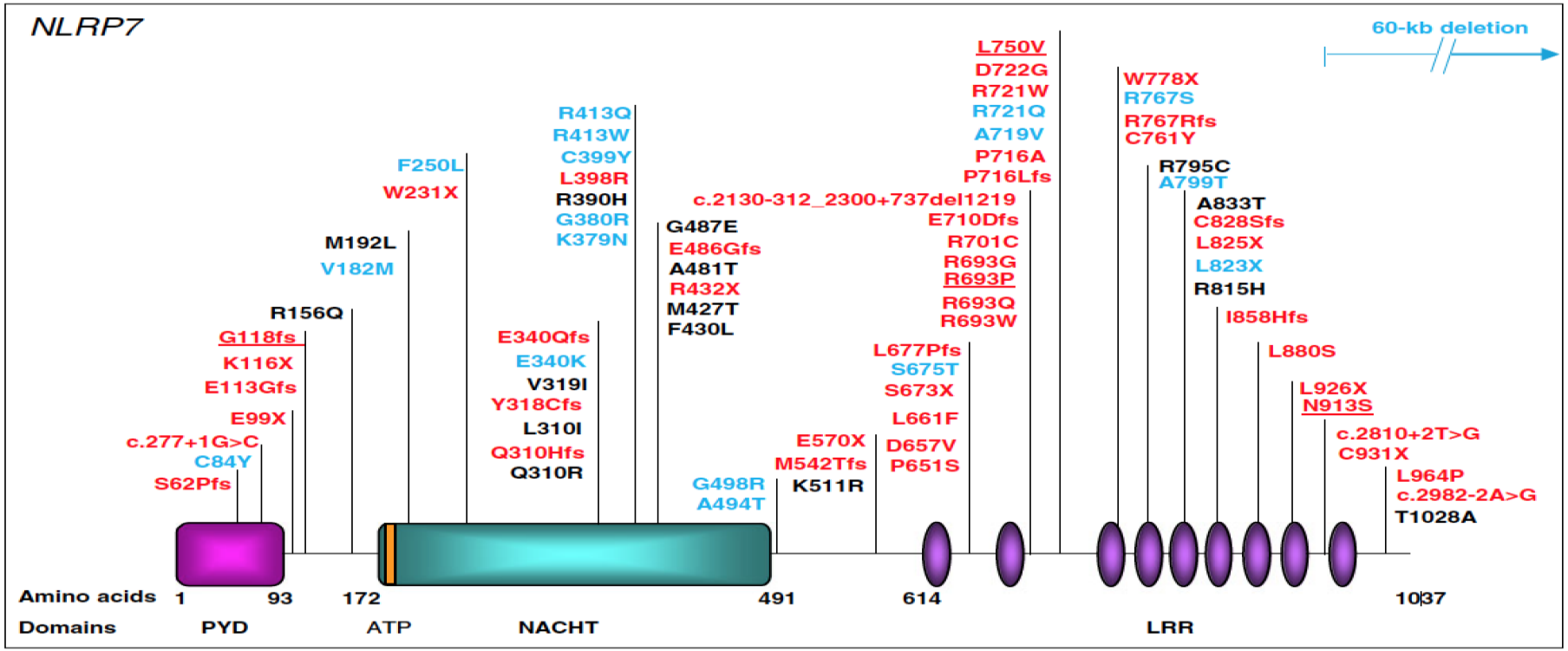


Hydatidiform Moles

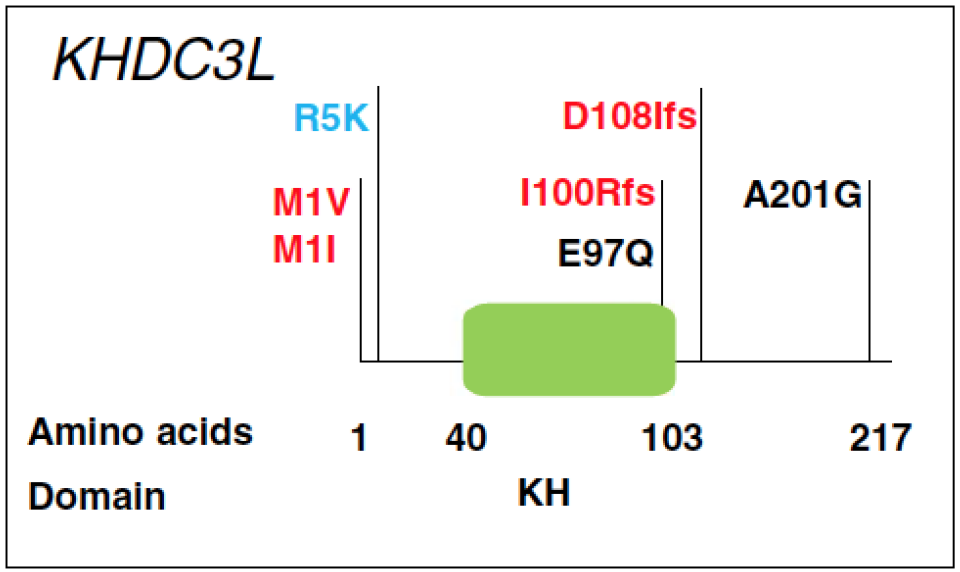
- Sporadic Hydatidiform Moles (>97%)
- Familial Biparental Hydatidiform Moles

Biparental Recurrent Hydatidiform Moles

Familial recurrent hydatidiform moles represent 0.6 to 2.6% of all hydatidiform moles, among which familial biparental CHM (FBCHM) is an exceptional condition. Initially reported 40 years ago as recurrent moles in multiple pregnancies of sisters in three unrelated families, close to 300 cases of FBCHM have since been reported to date.



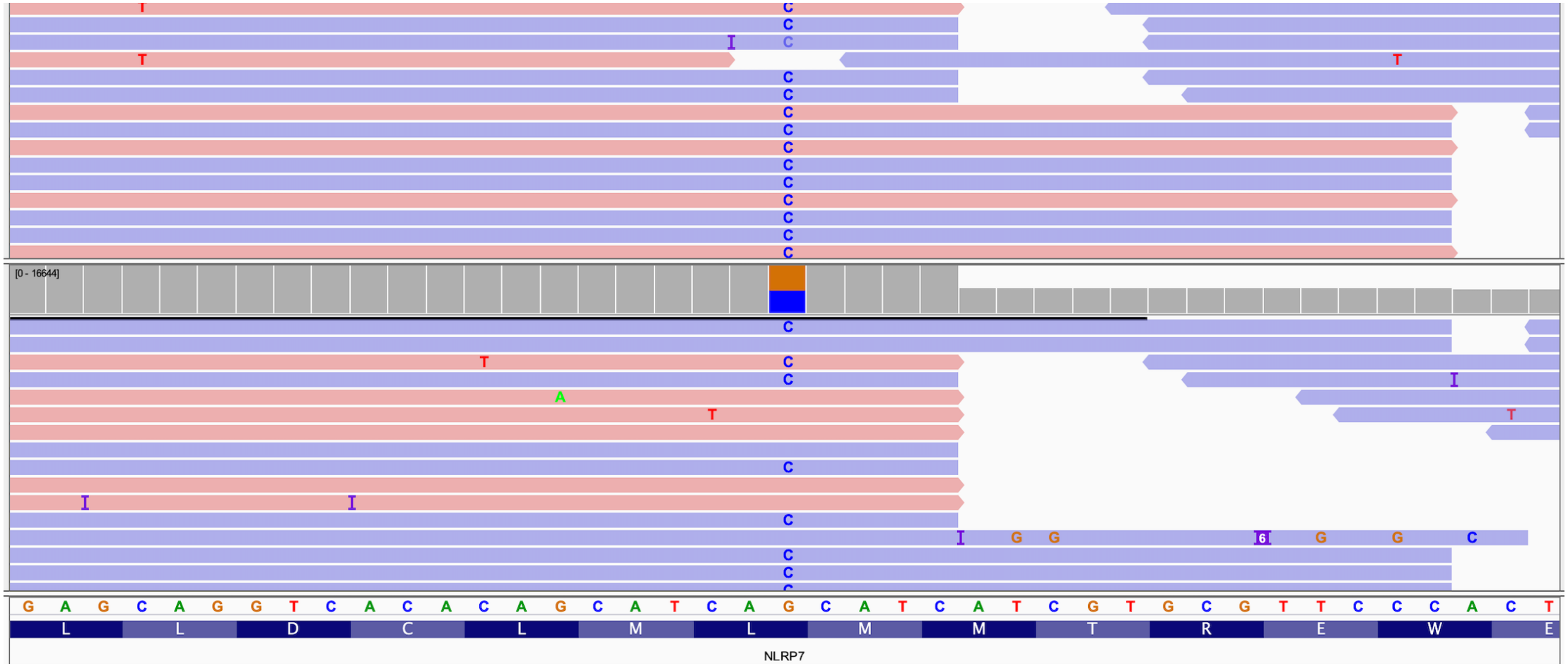
FBCHM

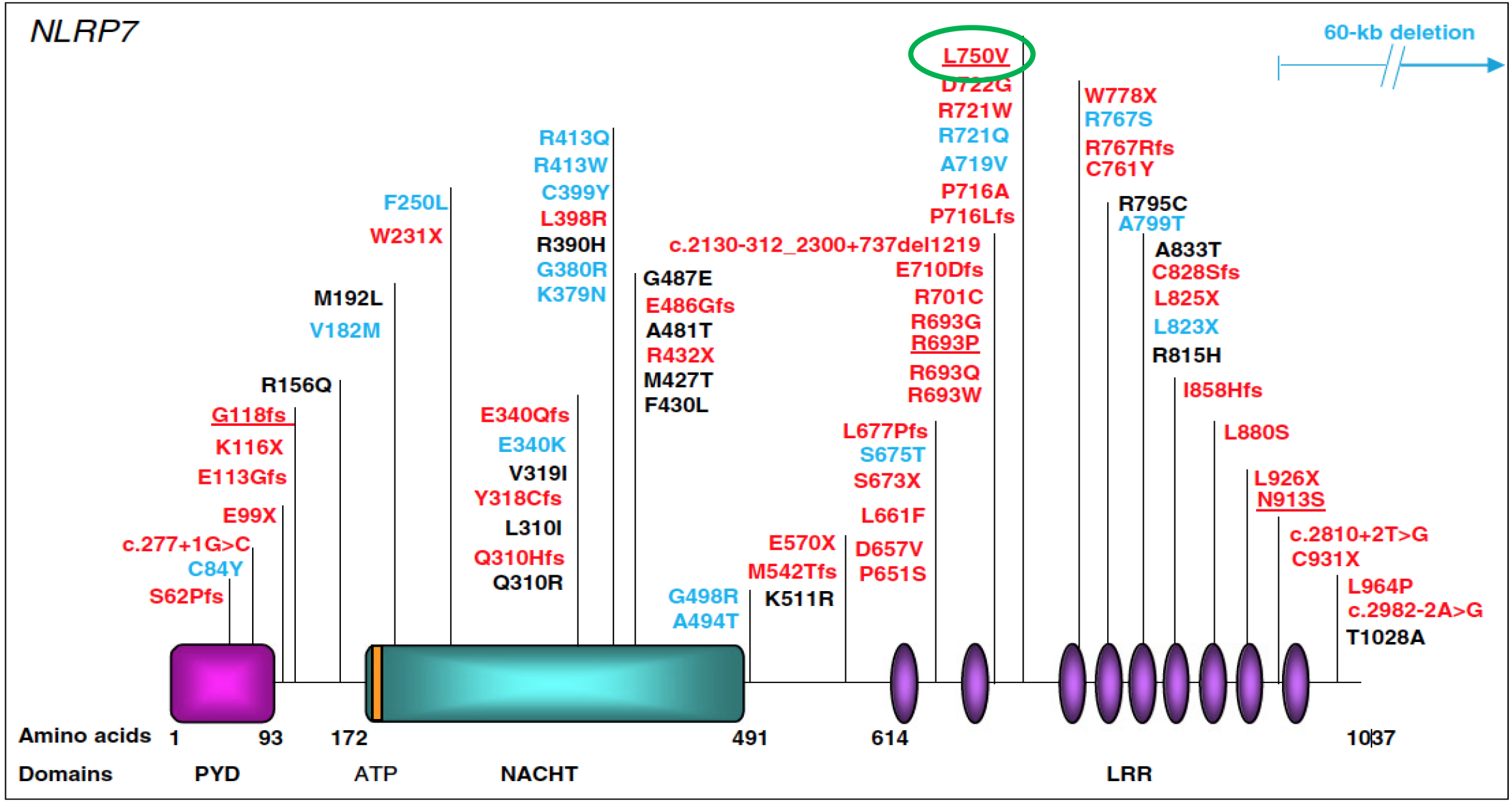


Homozygous or compound heterozygous mutations: 86 variants of *NLRP7* and 4 variants of *KHDC3L* in FBCHM patients.

Nguyen and Slim:Curr Obsete Gynecol Rep,2014.

Decidua: Homozygous p.Leu750Val
Molar villi: Heterozygous p.Leu750Val

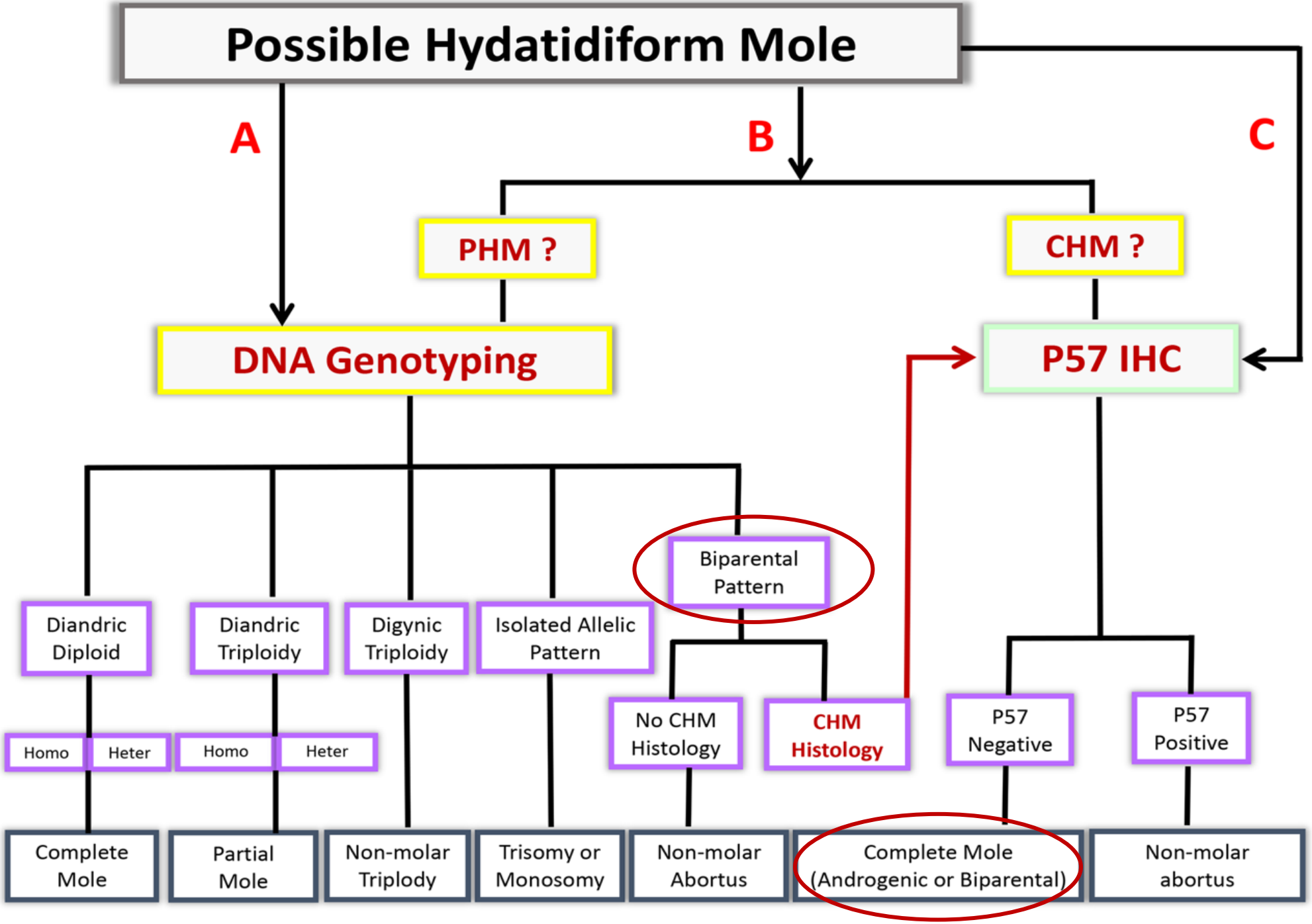



NLRP7
60-kb deletion
L750V
D722G
R721W
R721Q
A719V
P716A
P716Lfs
W778X
R767S
R767Rfs
C761Y
R795C
A799T
A833T
C828Sfs
L825X
L823X
R815H
I858Hfs
L880S
L926X
N913S
c.2810+2T>G
C931X
L964P
c.2982-2A>G
T1028A
R413Q
R413W
C399Y
L398R
R390H
G380R
K379N
F250L
W231X
M192L
V182M
R156Q
G118fs
K116X
E113Gfs
E99X
c.277+1G>C
C84Y
S62Pfs
G487E
E486Gfs
A481T
R432X
M427T
F430L
c.2130-312_2300+737del1219
E710Dfs
R701C
R693G
R693P
R693Q
R693W
E340Qfs
E340K
V319I
Y318Cfs
L310I
Q310Hfs
Q310R
L677Pfs
S675T
S673X
L661F
D657V
P651S
E570X
M542Tfs
K511R
G498R
A494T
Amino acids
1
93
172
491
614
1037
Domains
PYD
ATP
NACHT
LRR

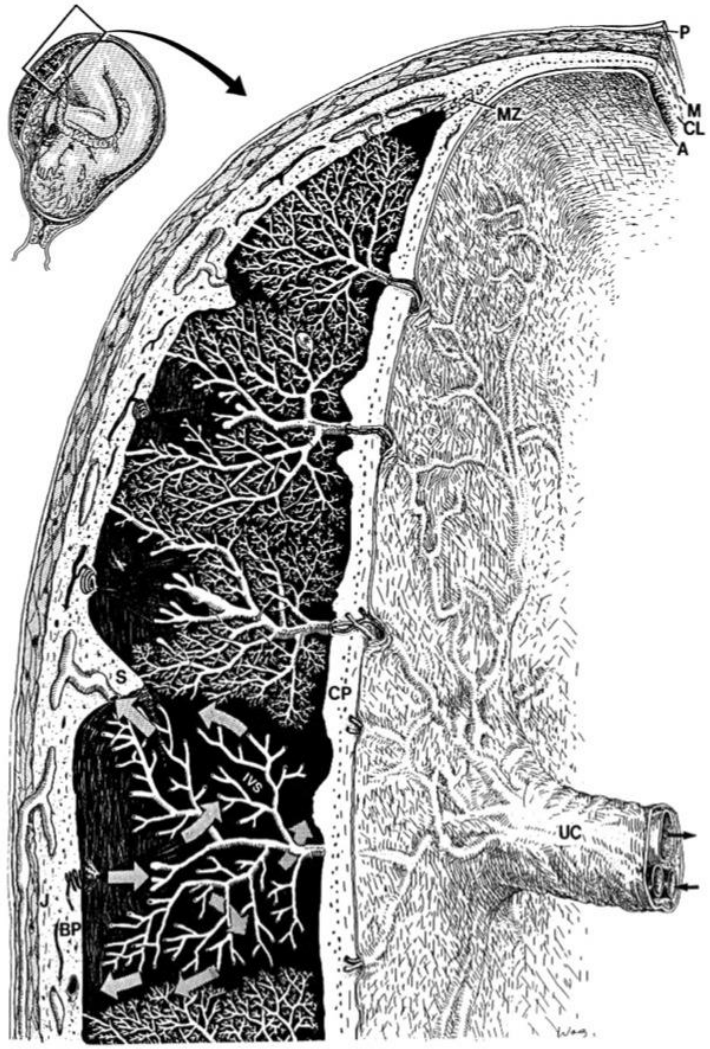
Case Summary: Invasive Biparenal CHM/GTN

- Hysterectomy: Invasive complete mole, abnormal P57 and exaggerated implantation site reaction
- History of multiple failed pregnancies
- GTN: high serum hCG and multiple lung nodules
- STR genotyping: balanced biparental profile
- NGS FBCHM Panel: homozygous germline mutation of *NLRP7*
- Treatment: GTN chemotherapy
- Implications: family mutation screening and fertility planning
- Prognosis: egg donor pregnancy

Contributed by Dr. Peter Chen


Possible Hydatidiform Mole
A
B
C
PHM ?
CHM ?
DNA Genotyping
P57 IHC
Biparental Pattern
Diandric Diploid
Diandric Triploidy
Digynic Triploidy
Isolated Allelic Pattern
No CHM Histology
CHM Histology
P57 Negative
P57 Positive
Homo
Heter
Homo
Heter
Complete Mole
Partial Mole
Non-molar Triplody
Trisomy or Monosomy
Non-molar Abortus
Complete Mole (Androgenic or Biparental)
Non-molar abortus

GTN - WHO Tumor Classification



Villous Trophoblast

- Hydatidiform Moles
  - Complete Hydatidiform Mole (CHM)
  - Partial Hydatidiform Mole (PHM)
  - Invasive Hydatidiform Mole
- Choriocarcinoma

Implantation Site Trophoblast

- Exaggerated Placental Site Reaction
- Placental Site Trophoblastic Tumor

Chorionic Trophoblast

- Placental Site Nodule/Atypical Placental Site Nodule
- Epithelioid Trophoblastic Tumor

- Mixed Trophoblastic Tumor

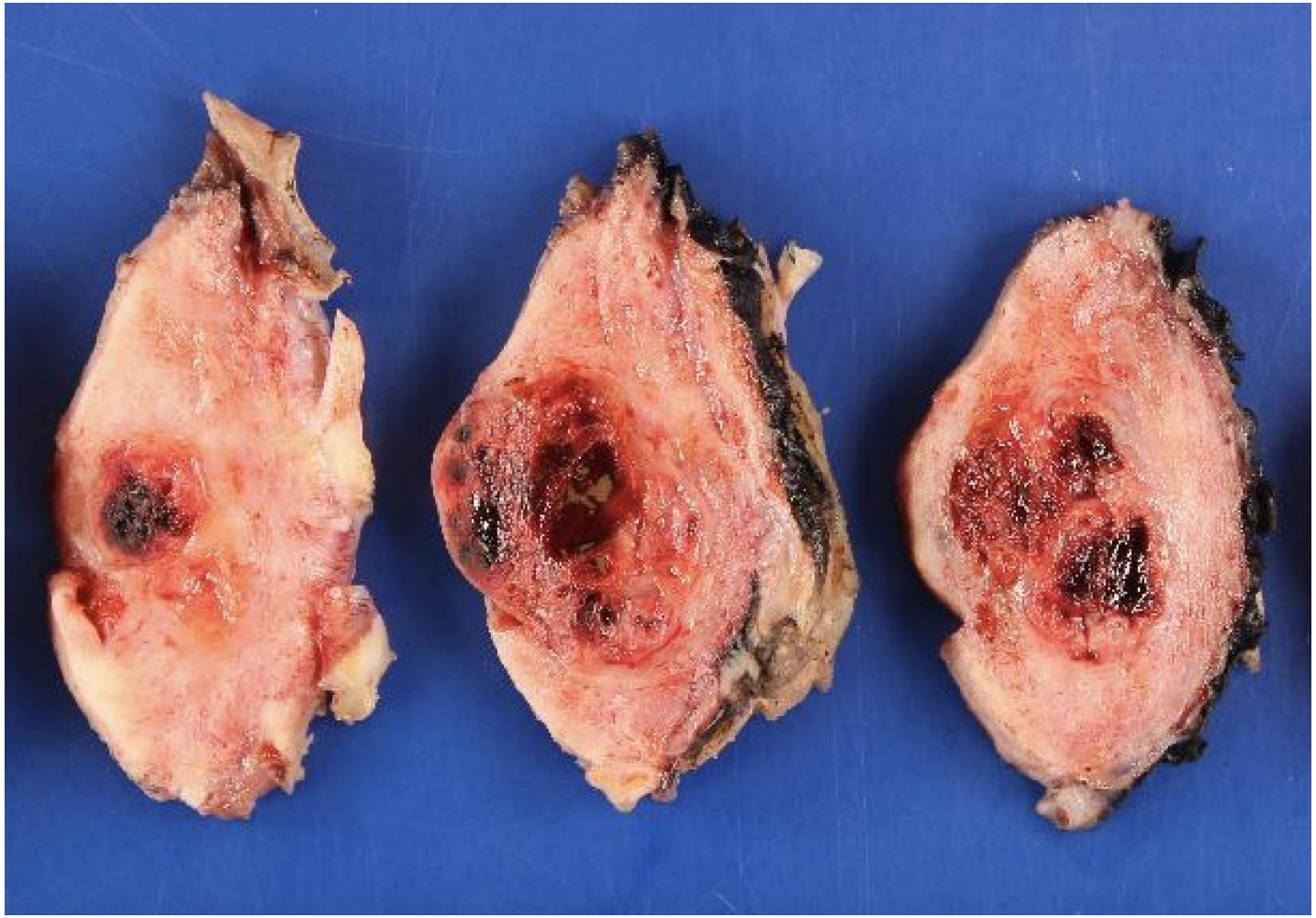
Clinical Significance

- Choriocarcinoma requires prompt diagnosis and chemotherapy
  - ~100% survival
  - Surgery only for uncontrollable bleeding and/or chemotherapy-resistant disease
- Epithelioid trophoblastic tumor and Placental Site Trophoblastic Tumor
  - Primarily surgical disease
  - 10-30 % mortality

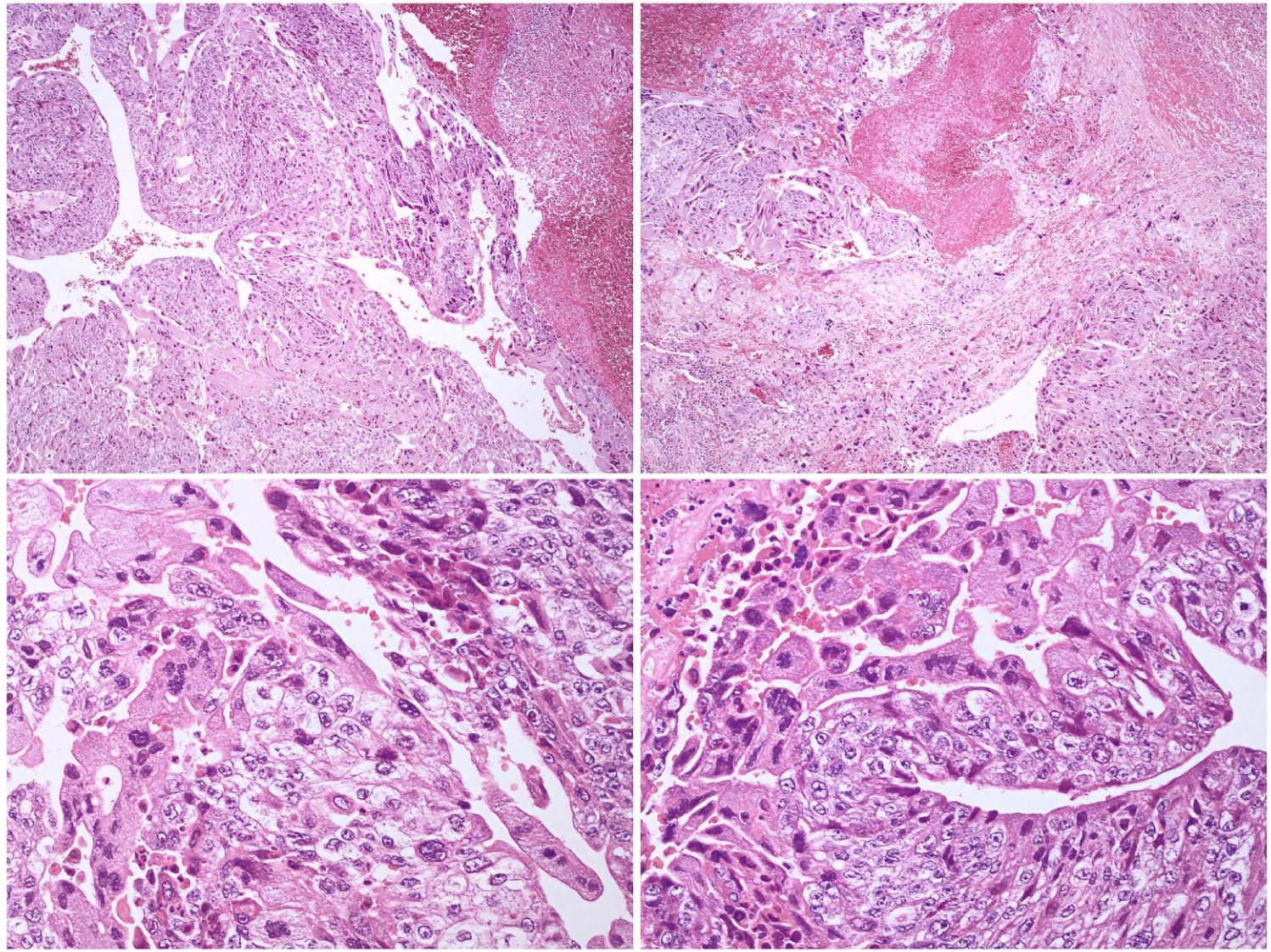
Gestational Choriocarcinoma

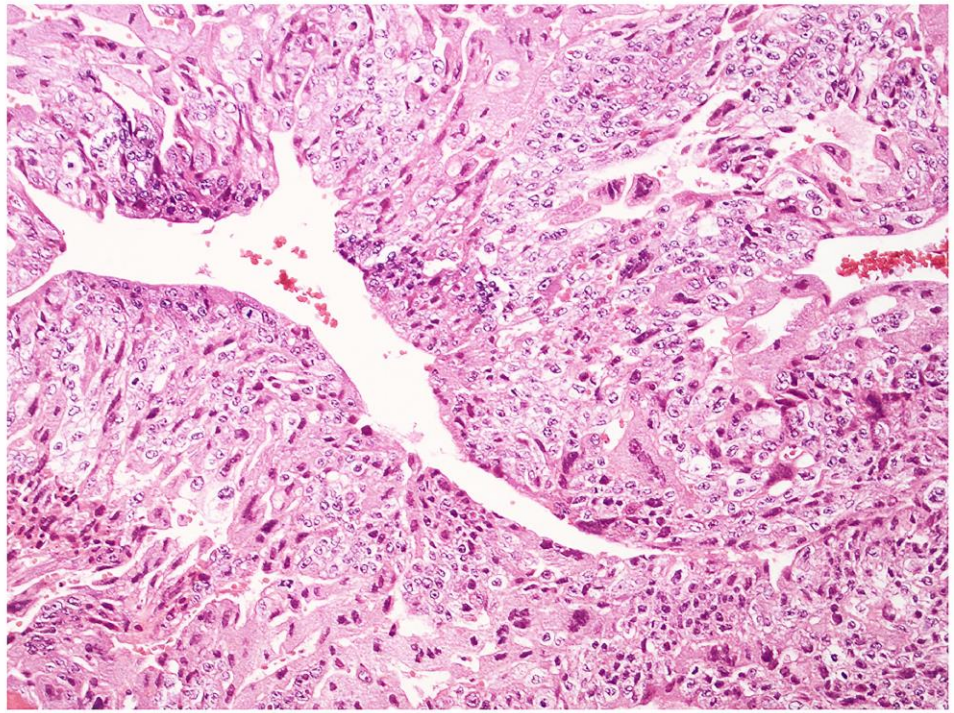
- The most common gestational trophoblastic tumor
- Vaginal bleeding or extrauterine hemorrhagic event
- Serum hCG over 10,000 mIU/ml
- Bulky uterine masses with extensive hemorrhage and necrosis

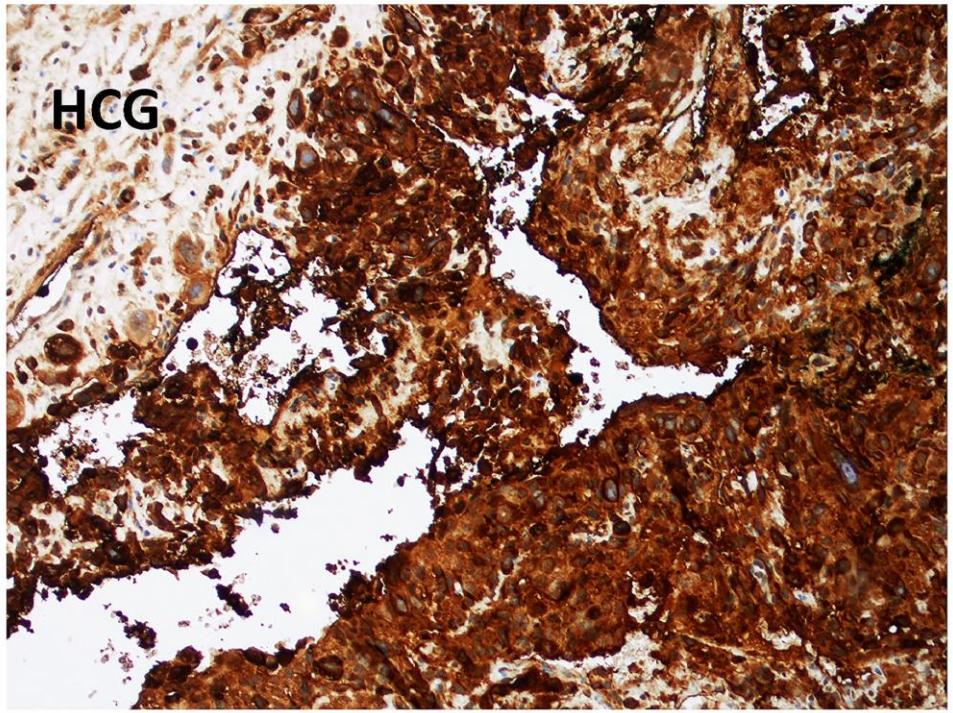
Gestational Choriocarcinoma

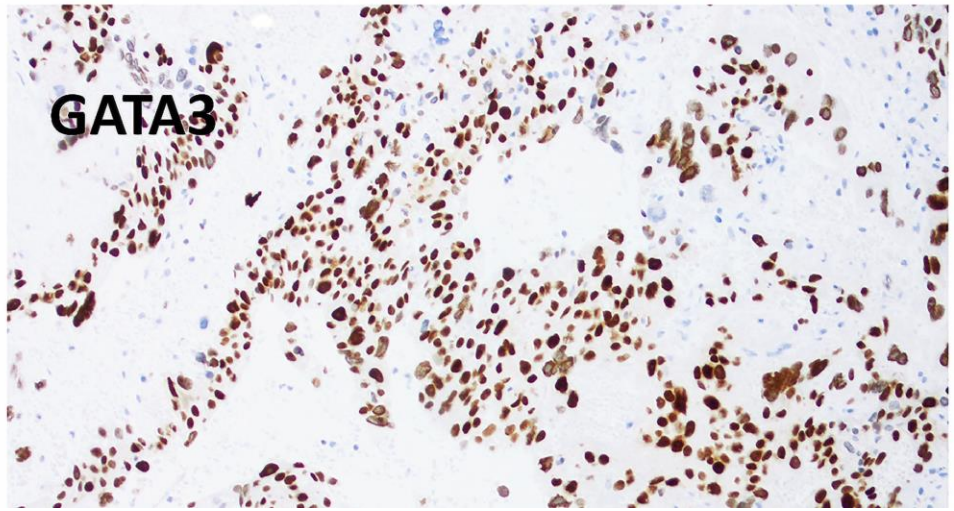


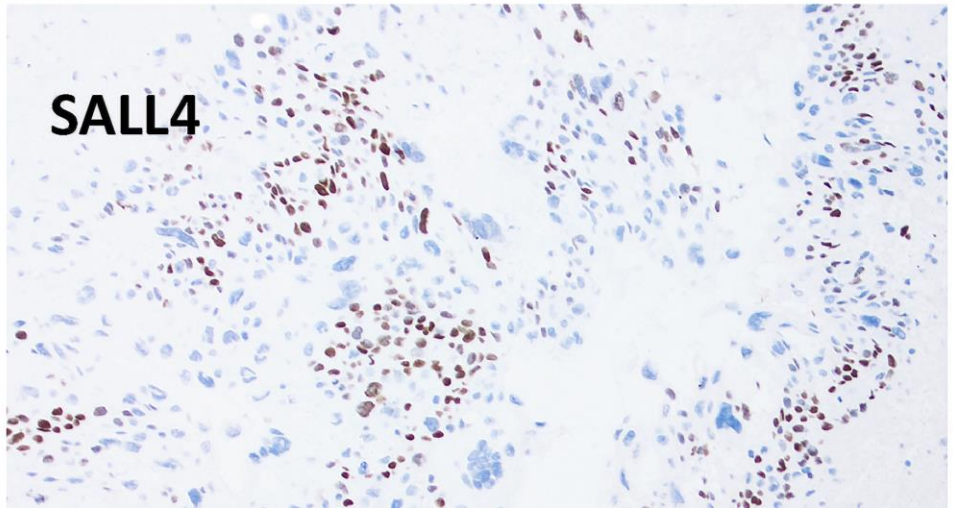
Gestational Choriocarcinoma






HCG


GATA3

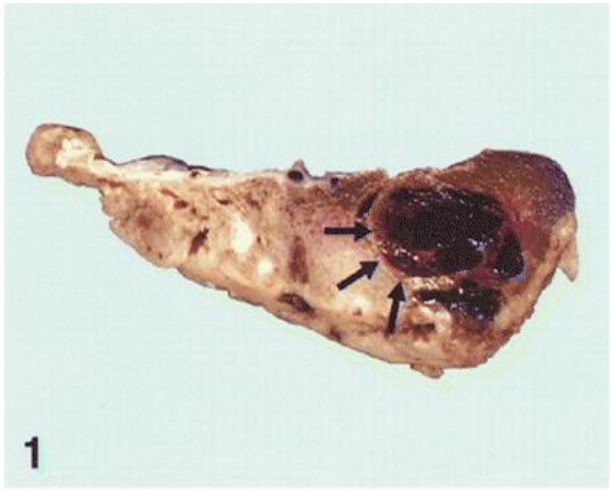

SALL4

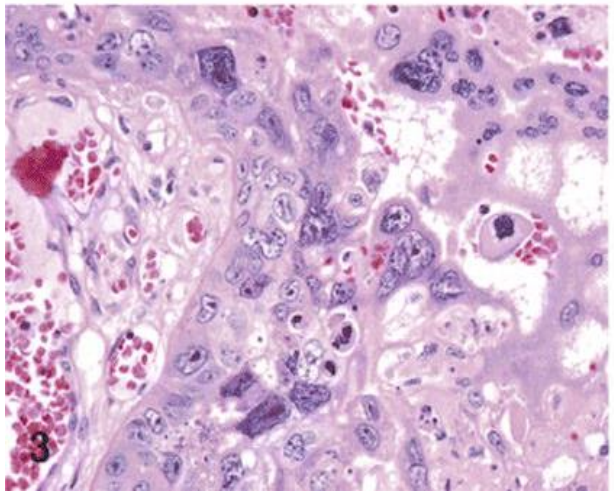
WHO Tumor Classification (2020)

Intraplacental choriocarcinoma: intraplacental aggregates of markedly atypical trophoblasts resembling choriocarcinoma

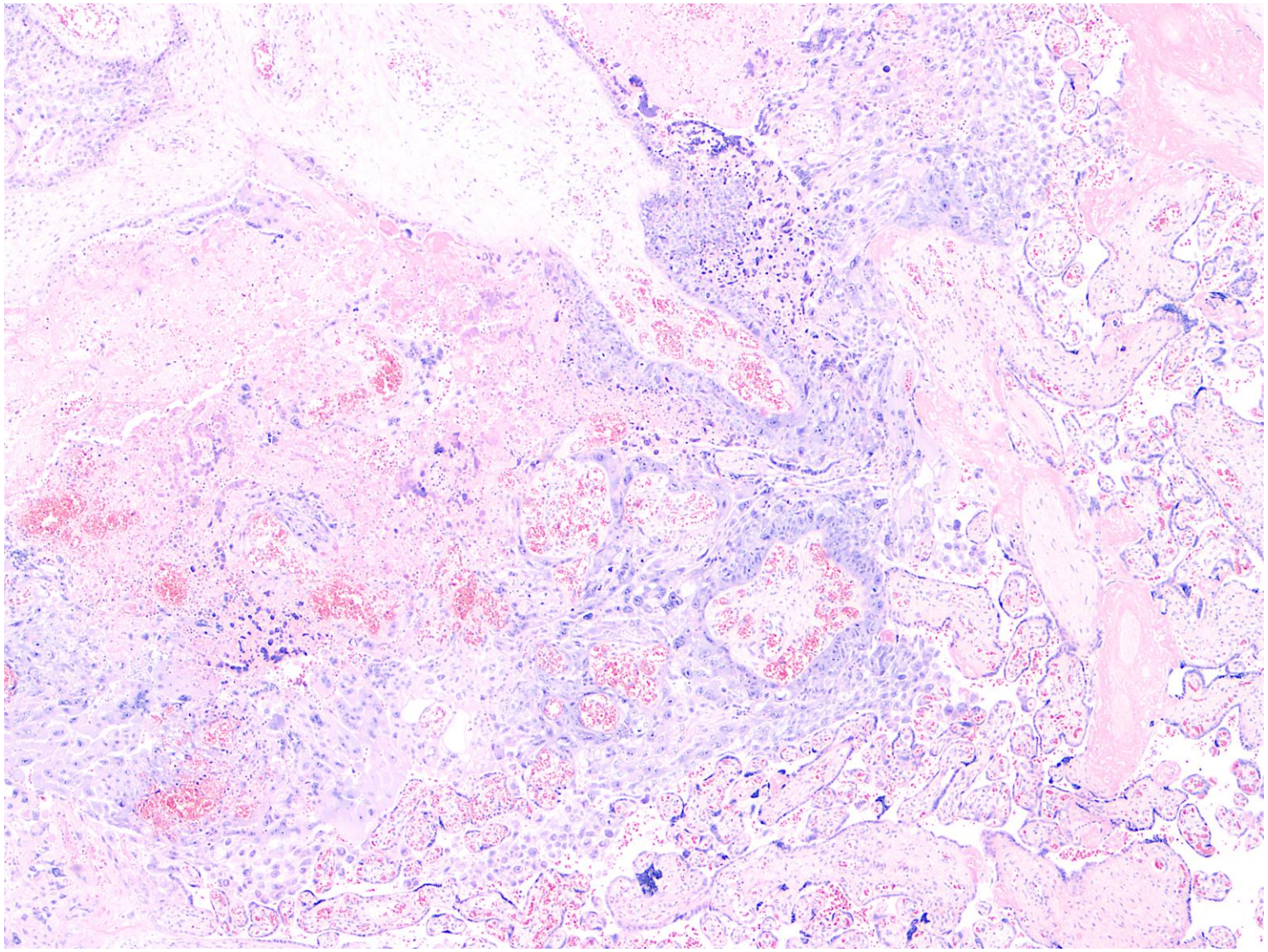
Intramolar choriocarcinoma: molar villi surrounded by markedly atypical trophoblasts resembling choriocarcinoma.

Intraplacental/ In-situ Choriocarcinoma



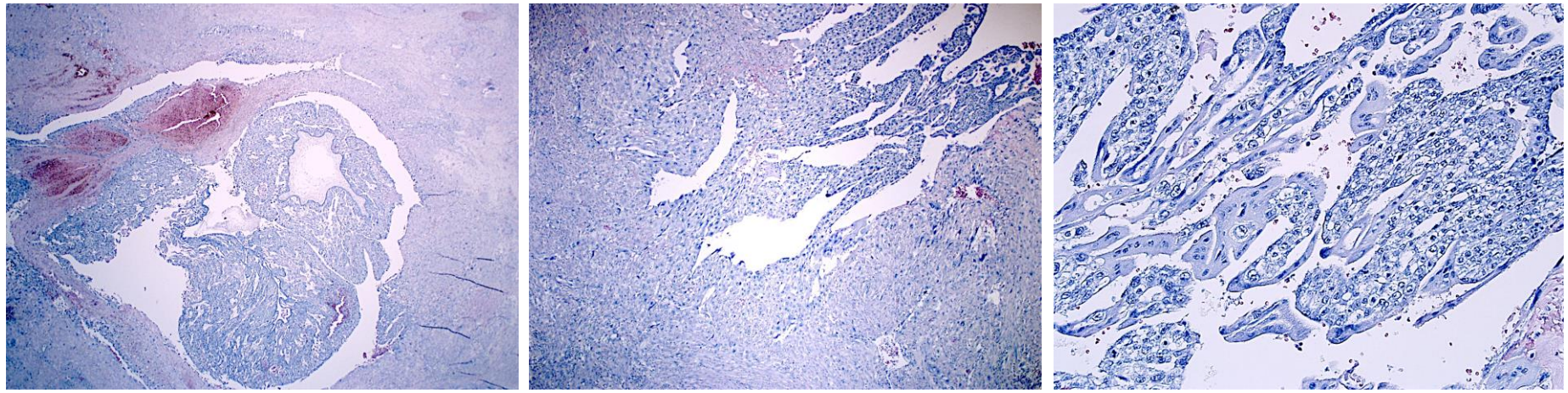


Black et al., Arch Pathol Lab Med 2003



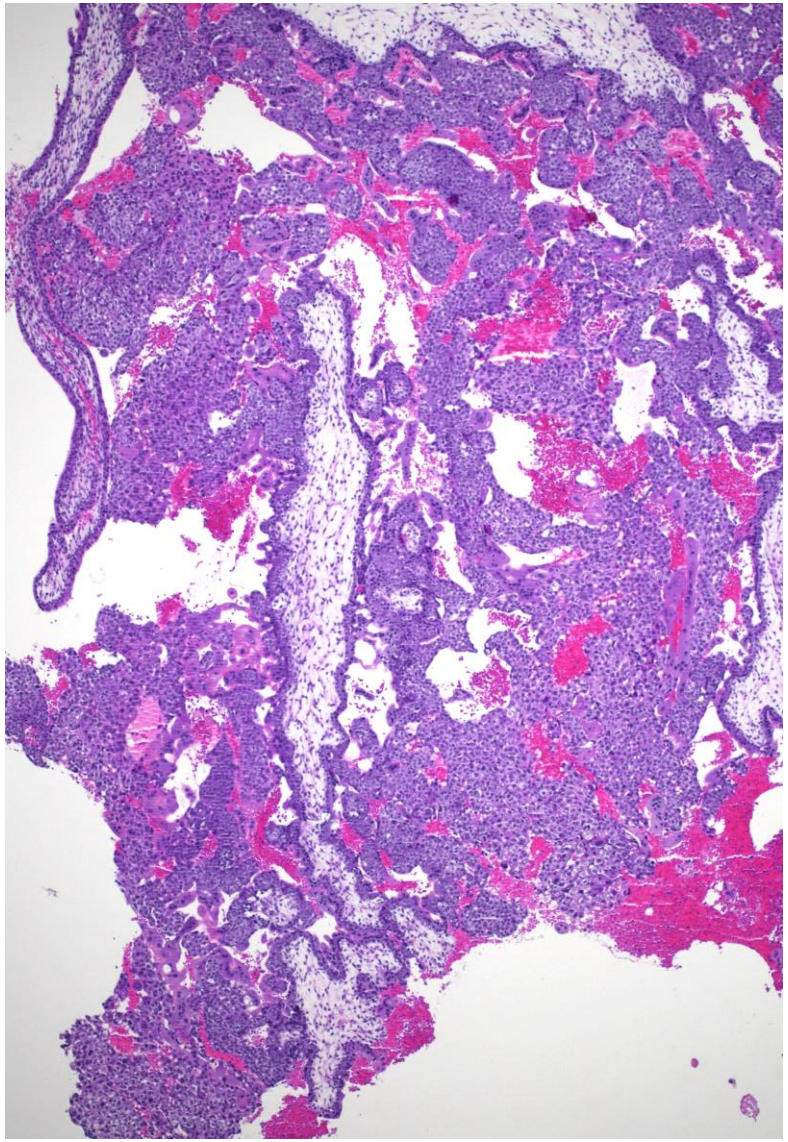
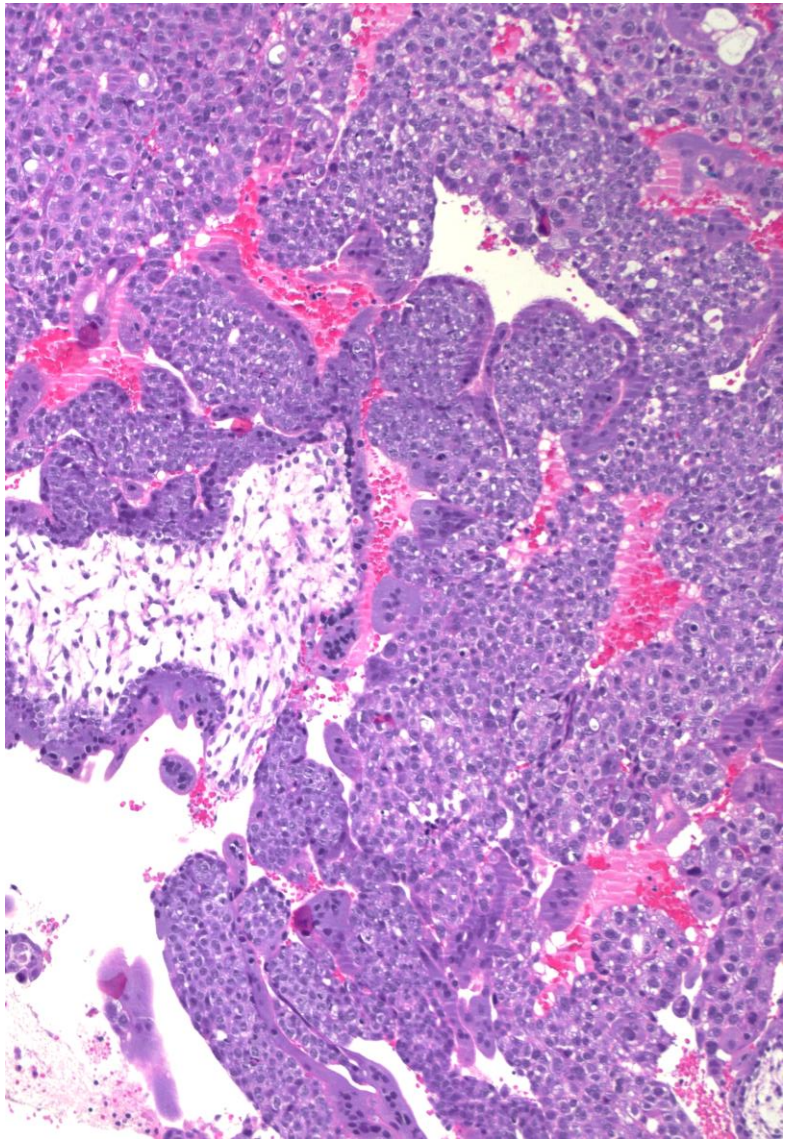
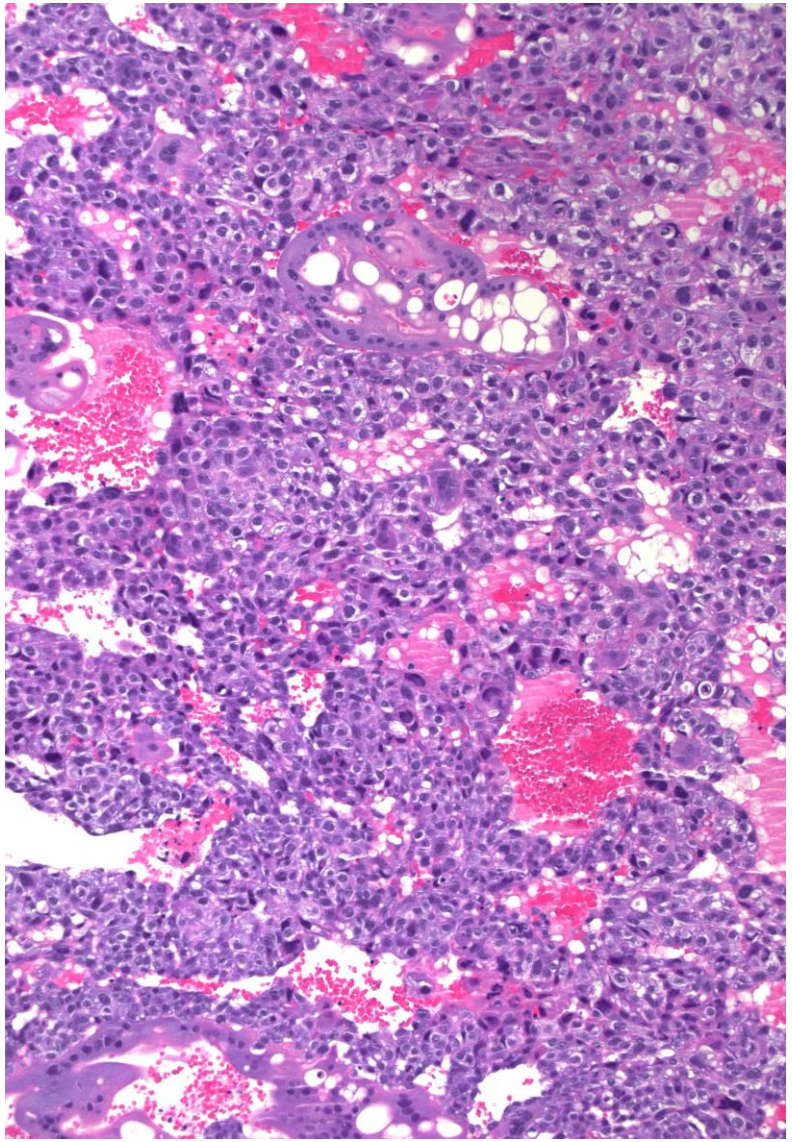
Intramolar Choriocarcinoma

Malignant transformation of trophoblast with histological features of conventional choriocarcinoma in association with villi of hydatidiform mole, complete or partial



Hui P. Arch Pathol Lab Med. 2019 Jan;143(1):65-74

Intramolar Choriocarcinoma in Complete Mole

Intramolar Choriocarcinoma

- Evolving entity
- No well-defined criteria
- Large solid haphazard biphasic proliferation, >50% Ki-67 labeling among mononuclear trophoblast and necrosis

Nowadays, these early forms of tumors are not encountered by pathologists and primary gestational choriocarcinomas are treated without a tissue diagnosis!

Gestational choriocarcinomas more often now present as extrauterine metastatic tumors, leading to major differential diagnoses.

Choriocarcinoma at Extrauterine Sites

Gestational choriocarcinoma: Trophoblast

- - From term placenta (50%)
- - From complete and partial mole (25%)
- - From missed abortion (25%)

Germ cell choriocarcinoma: Germ cell origin

- - Pure germ cell choriocarcinoma
- - Mixed germ cell tumor component

Somatic choriocarcinoma: Epithelial origin

- - Carcinoma with trophoblastic differentiation

Metastatic Gestational choriocarcinoma

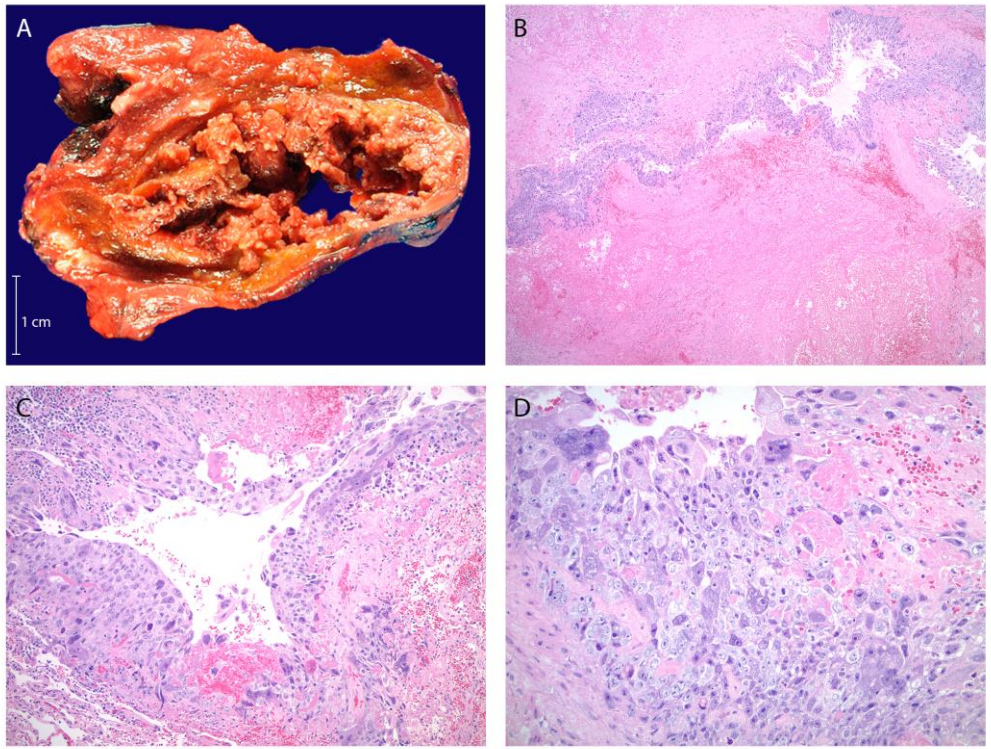
48-year-old G3P2: chest pain at emergency room

CT: right hemothorax and lung tumor

Term delivery 6 years ago with retained placenta.

Beta-hCG measurement was NOT considered preoperatively.

Lung wedge resection: 7 cm cystic hemorrhagic mass

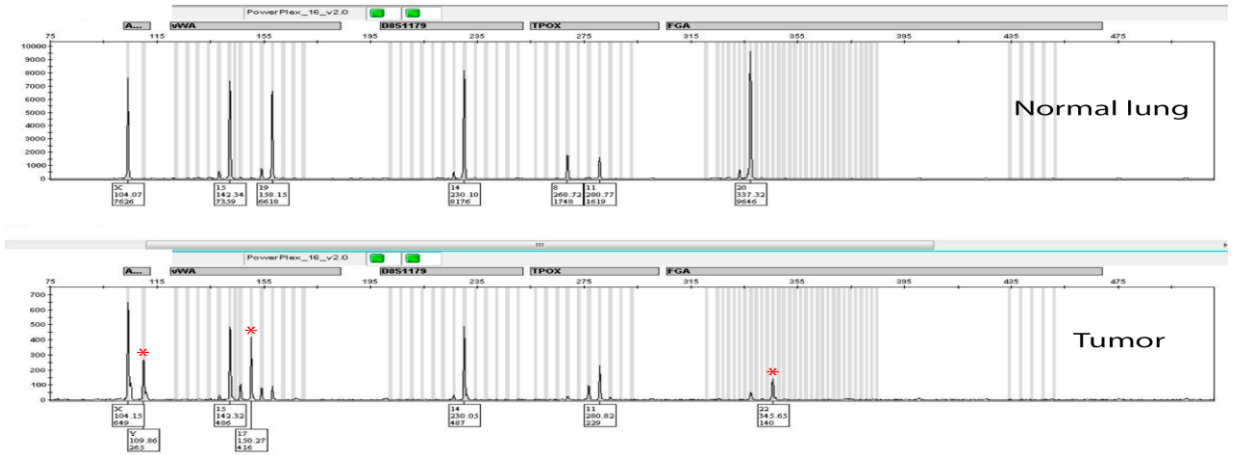


Initial pathology diagnosis: large cell carcinoma of lung (Positive for CK7, GATA3, and PAX8 but negative for p40, TTF-1, Napsin A, CK5-6, OCT4, ER and CDX2)

- Targeted next generation sequencing: no mutations
- ALK and ROS1 FISH: negative

GYN pathology consultation: rule out choriocarcinoma

Beta-hCG of 315 mIU/mL



AJCC: pT1 M1a, Stage III and FIGO risk score of 8

EMA-CO chemotherapy

Serum beta-hCG normalized after 2 cycles

Well without evidence of disease 4 months after

Buza, Bain, Hui: Mod Pathol. 2019;32:1271-1280.

Germ Cell Choriocarcinoma

22-year old G1P1: "right adnexal mass" at emergency room.

Term pregnancy with C-section one year ago

Last menstrual period (LMP) was 10 weeks prior

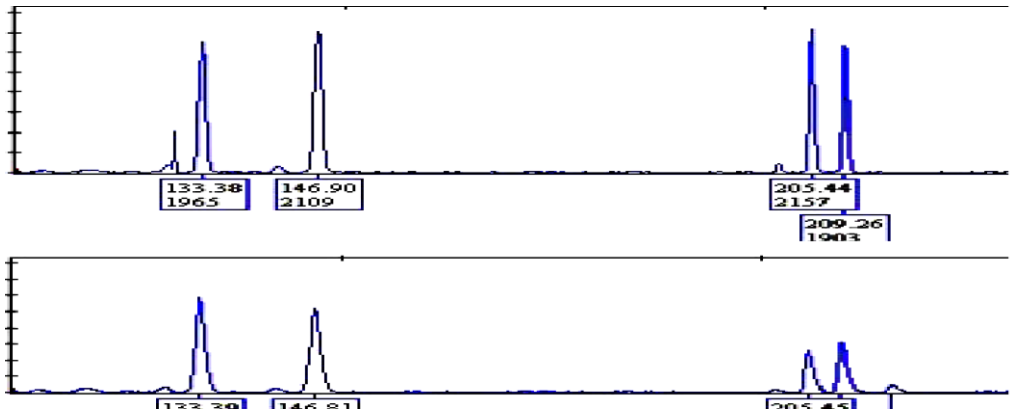
Serum β-hCG > 200,000 mIU/mL and normal AFP

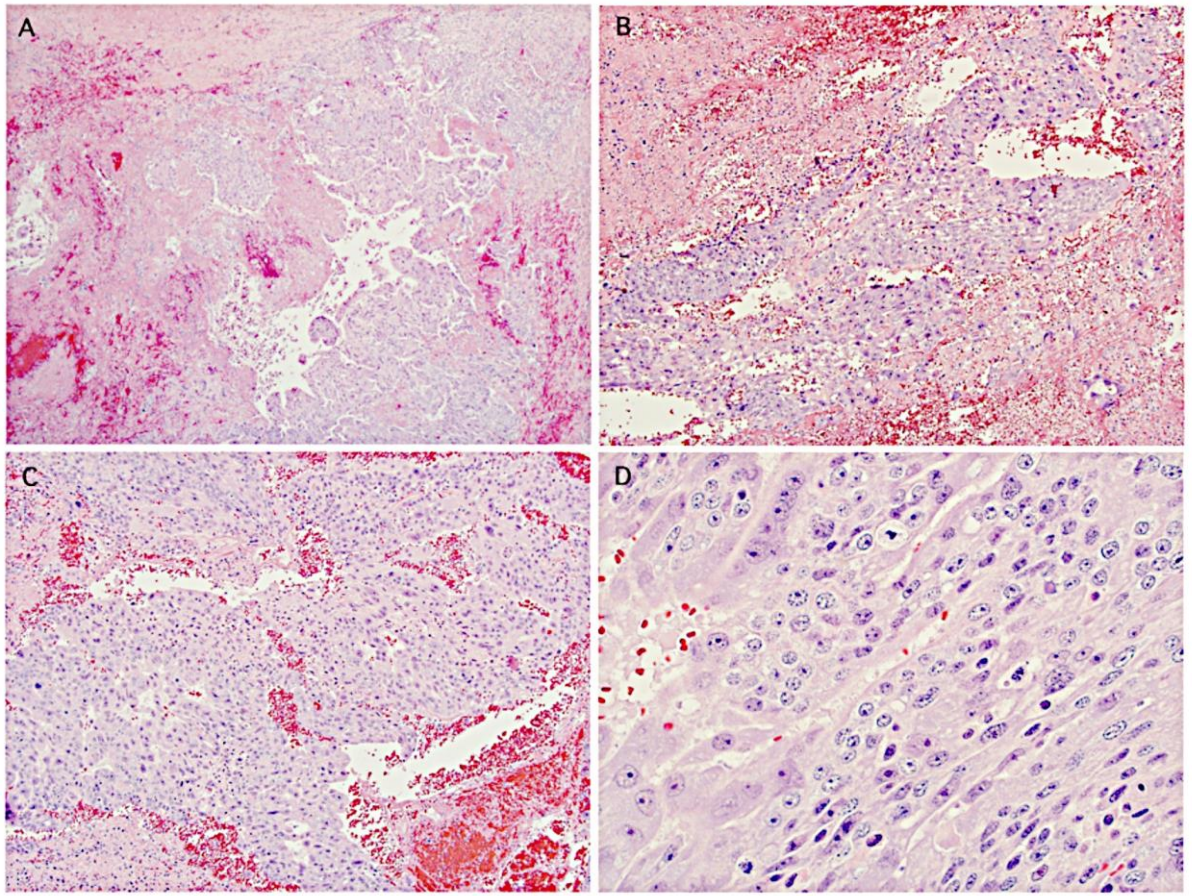
Pelvic examination: no intrauterine gestation

CT: 9.3 cm mass involving right ovary and broad ligament

Clinical diagnosis: "ruptured ectopic pregnancy"

Right salpingectomy with excision of the right broad ligament.





Buza, Hui: Int J Gyn Path 2014;33:507-10

Large cell carcinoma of lung with trophoblastic differentiation

41 year old G5P2: Heavy smoker with vaginal bleeding for 4 months

Positive urine pregnancy test but negative D/C

Last pregnancy: 6 years ago

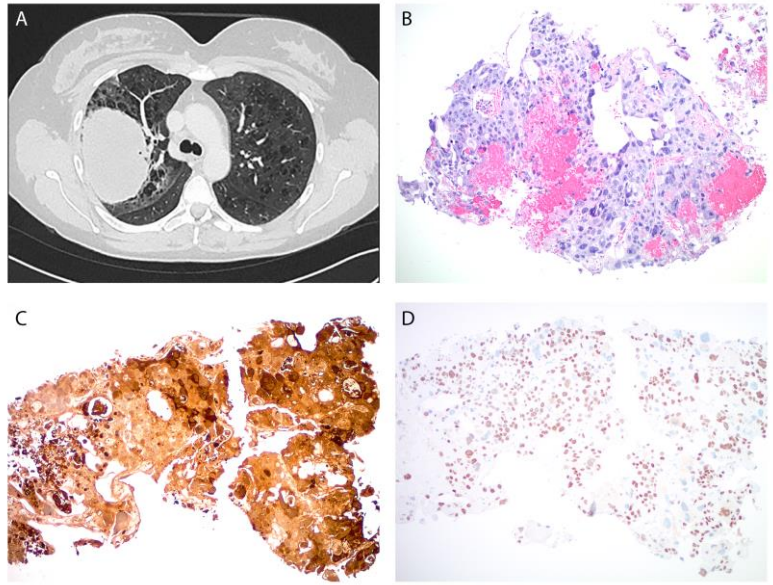
Clinical impression: ectopic pregnancy

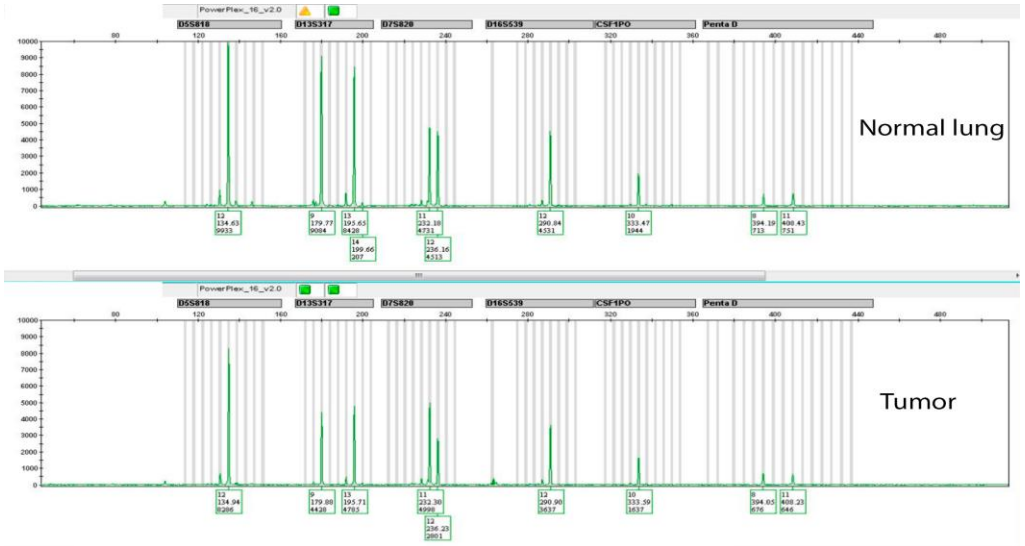
Treated with MTX but continued rising hCG

U/S: no adnexal mass or uterine lesion

CT scan: 9.7 cm lung mass

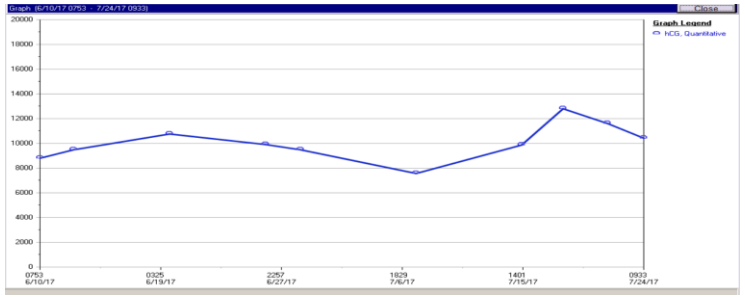
Rule out metastatic gestation choriocarcinoma





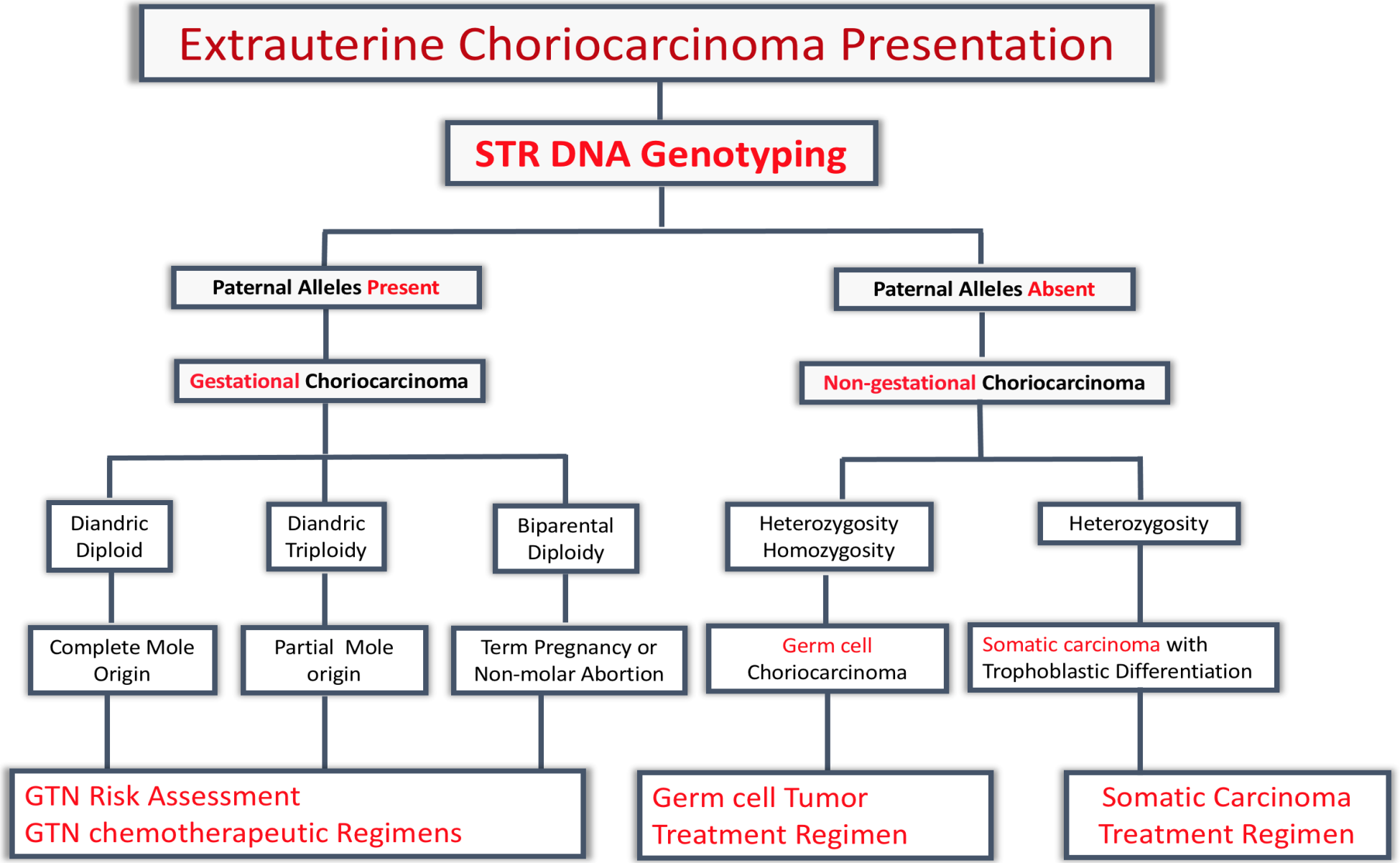
6 cycles of carboplatin, paclitaxel, followed by pembrolizumab

Patient died of the disease 15 months later



Buza, Bain, Huil: Mod Pathol. 2019;32:1271-1280.

Extrauterine Choriocarcinoma Presentation



- Non-gestational choriocarcinoma: According to FIGO, patients are treated with cisplatin based multi-agent chemotherapy regardless of the stage and risk factor scores.

- Gestational choriocarcinoma: rigorously evaluated by FIGO/WHO risk scoring scheme into low or high-risk groups for either single or multi-agent chemotherapy

FIGO/WHO Risk Factor	0	1	2	4
Age	< 40	> 40	-	-
Index pregnancy	**Mole**	**Abortion**	**Term**	
Interval from index pregnancy, months	**< 4**	**4-6**	**7-12**	**> 12**
Pretreatment hCG mIU/mL	$< 10^3$	$> 10^3$-10^4	$> 10^4$-10^5	$> 10^5$
Largest tumor size including uterus, cm	-	3-4	≥ 5	-
Site of metastases including uterus	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	-	1-4	5-8	> 8
Previous failed chemotherapy	-	-	Single drug	Two or more drugs

No Primary Tissue Diagnosis of GTN

Uncertain type of the index gestation (when multiple pregnancies)

Immediate prior pregnancy may not be the index/causative gestation

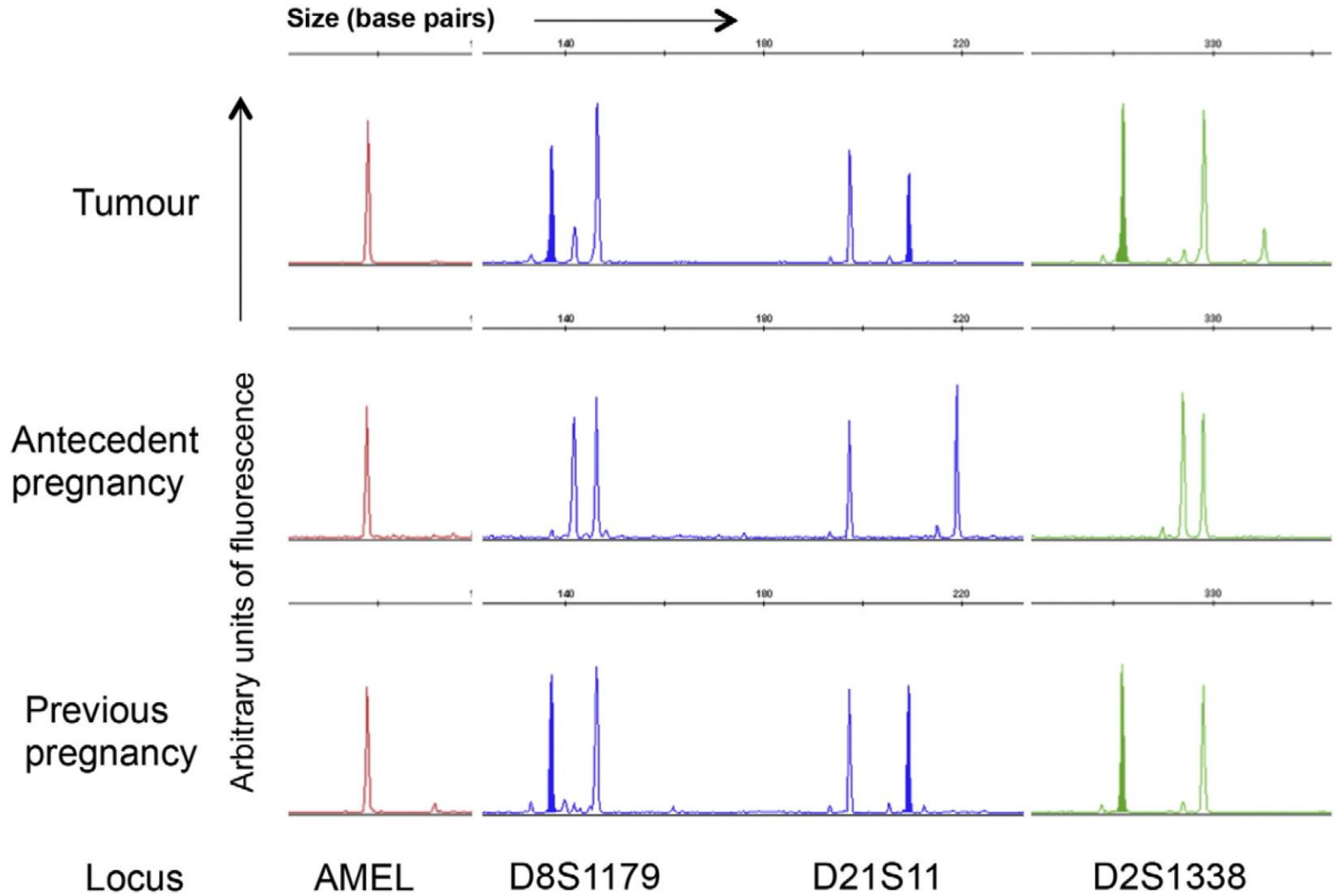


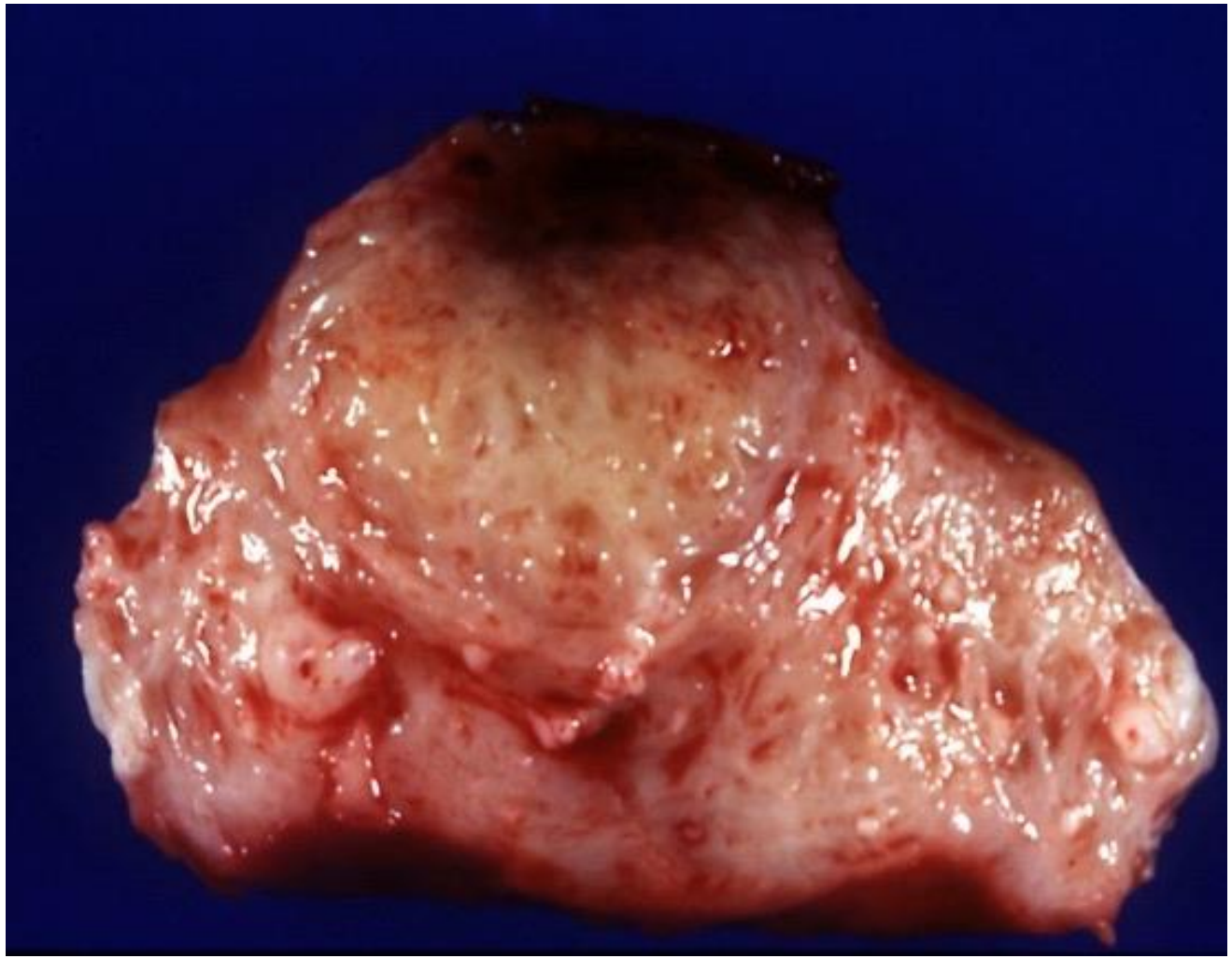
Fig. 4. Partial genotypes of tumour tissue in a case of PSTT/ETT following a female term birth. Both the tumour and antecedent pregnancy are female. However, genotyping of the tumour for STR loci D8S1179, D21S11 and D2S1338 (and others not shown) identified alleles in the tumour that were not present in DNA from the child of the antecedent pregnancy (solid peaks). Genotyping of the child from the previous pregnancy identified a genotype consistent with that in the tumour.

Zhao, et al. Gynecologic Oncology. 2016: 142:501-507

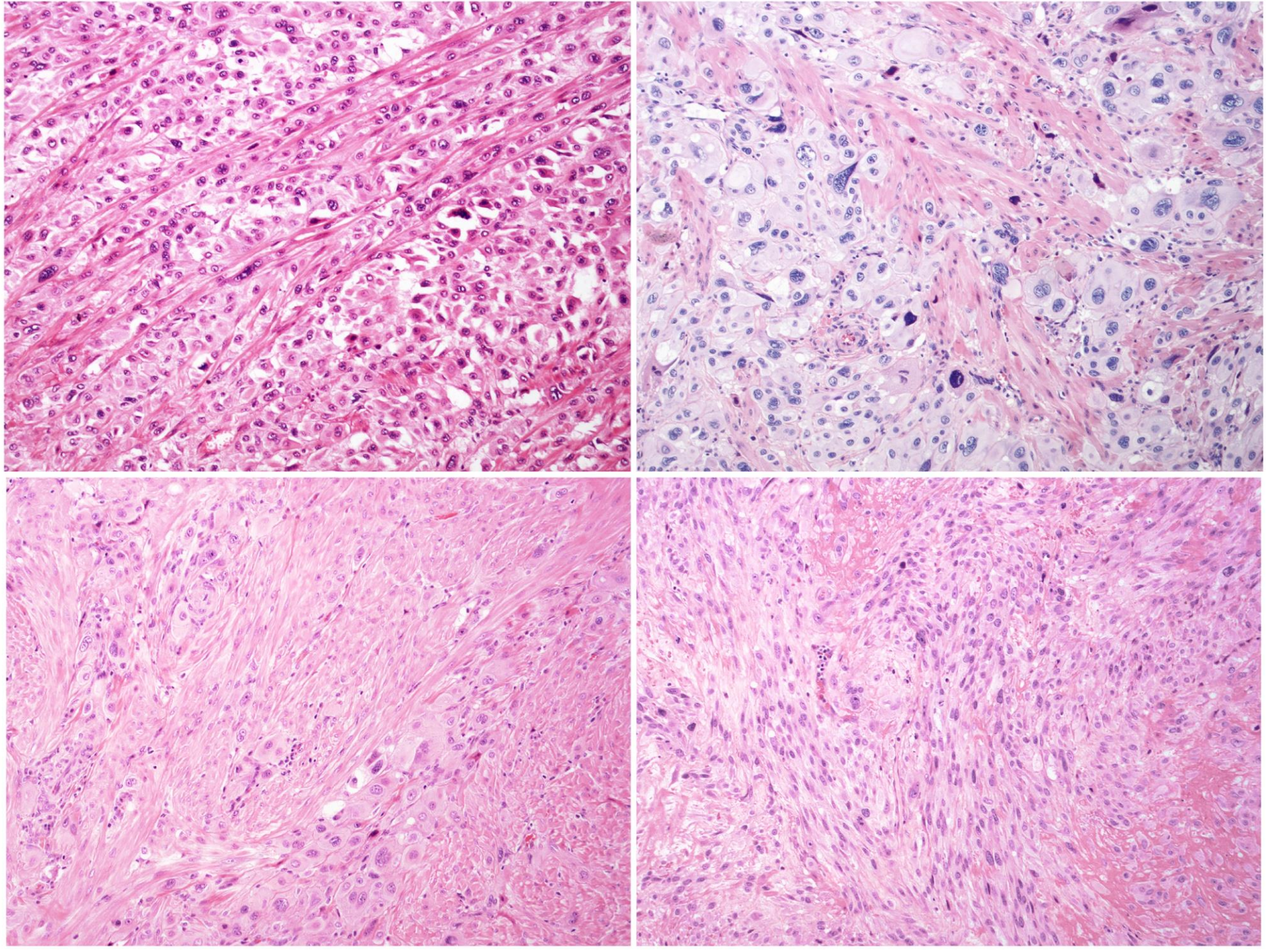
Placental Site Trophoblastic Tumor

Placental Site Trophoblastic Tumor (PSTT)

- Reproductive age
- Vaginal bleeding or amenorrhea
- 12-18 months after pregnancy (mostly term)
- HCG <1000 mIU/ml
- Recurrence rate: 25-30%



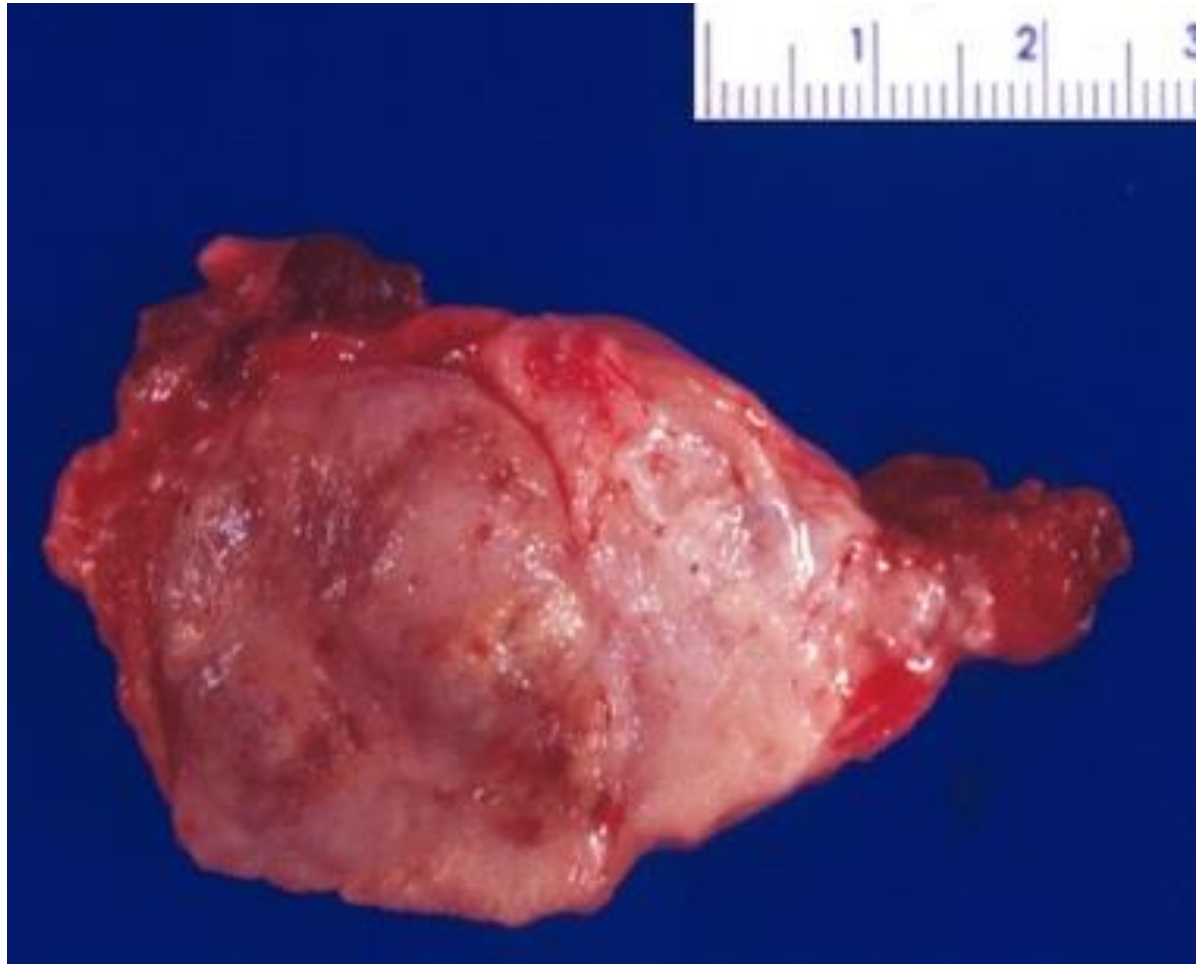
- Infiltrative
- Moderate to marked atypia
- Focal necrosis
- Vessel wall invasion and replacement



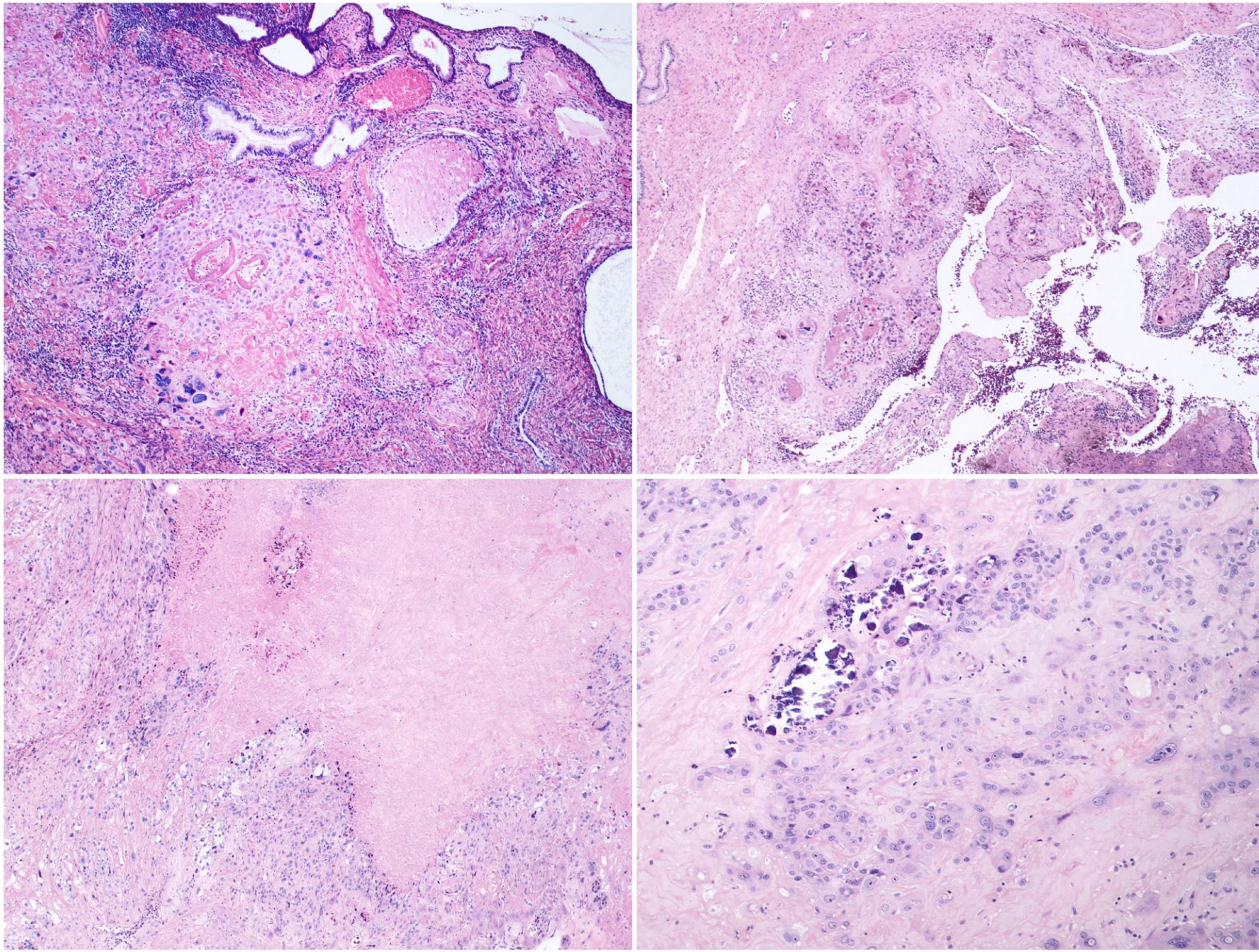
Epithelioid Trophoblastic Tumor

Epithelioid Trophoblastic Tumor (ETT)

- Reproductive age with vaginal bleeding
- ~6 yrs after pregancy
- 50% arising from cervix
- 2/3 after normal pregnancy, 15% after mole, 15% after abortion
- Serum hCG <3000 mIU/ml
- Recurrence rate: 25-30%



- Expansile, well-defined mass
- Geographic necrosis
- Hyalinization, calcifications
- Mild to moderate nuclear atypia
- Mitoses



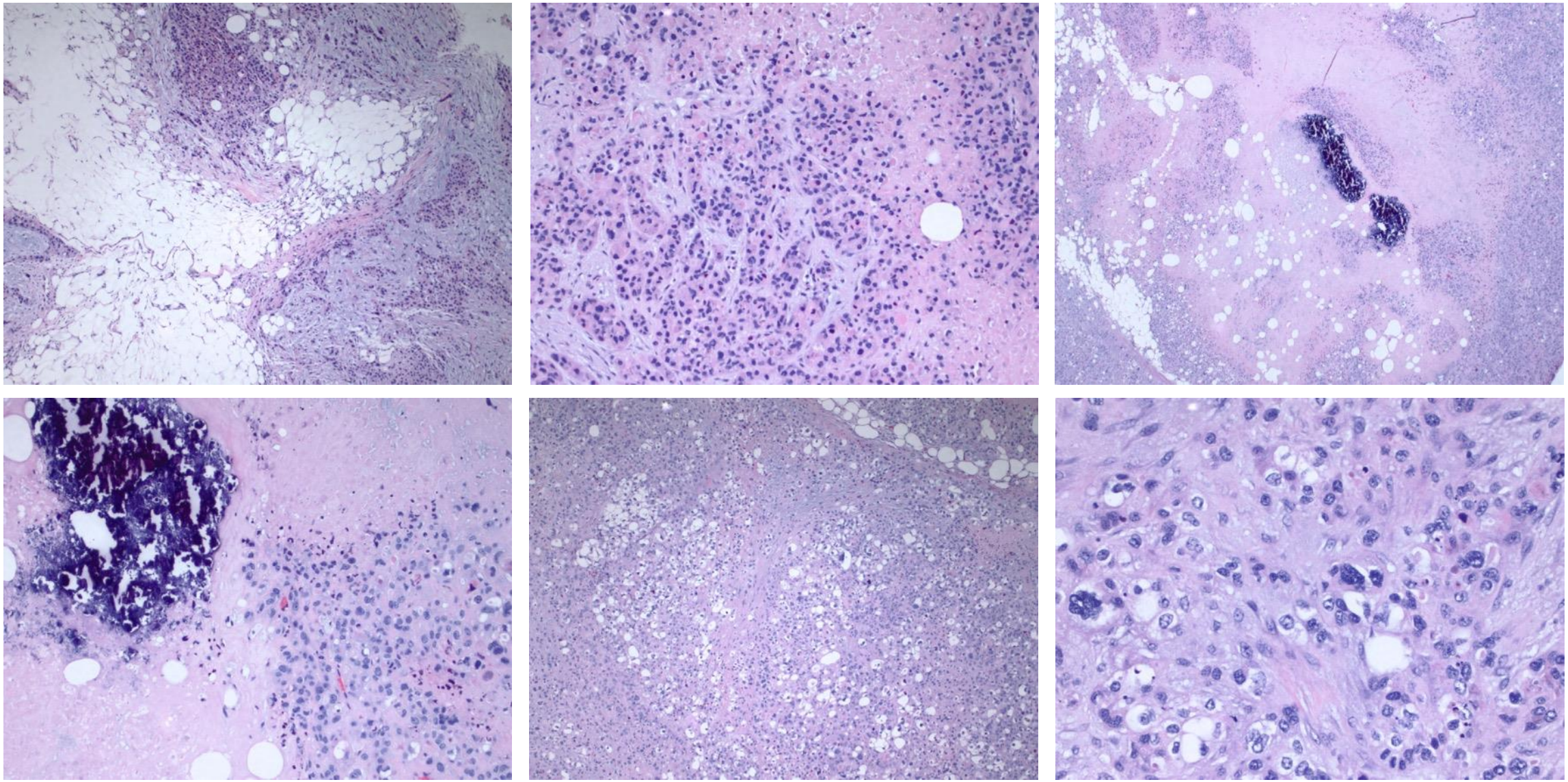
Ancillary Studies in GTN

- Immunohistochemistry
  - Separation of CC, ETT, PSTT and other mimics
  - PD-L1
- Short tandem repeat (STR) genotyping
  - Establish *gestational origin* of neoplasia – Rule out germ cell or somatic origin
  - Identify *causative gestation* for prognostication

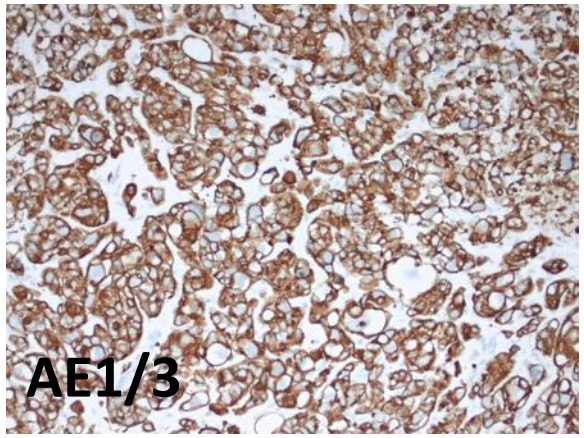
Metastatic Epithelioid Trophoblastic Tumor

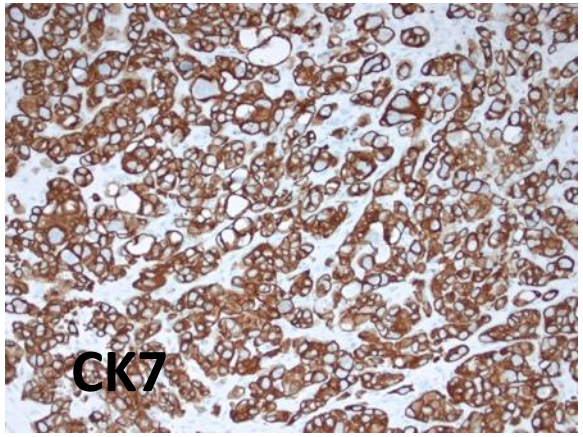
- 61-year-old G1P1 presenting pain, bleeding and discharge
- EMB: poorly differentiated carcinoma with necrosis and calcification
- CT: enlarged uterus with calcified masses, fistula and pleural effusion
- TAH-BSO: omental caking and frozen pelvis
- Omental excisional biopsy
- Original diagnosis: poorly differentiated carcinoma with squamous features

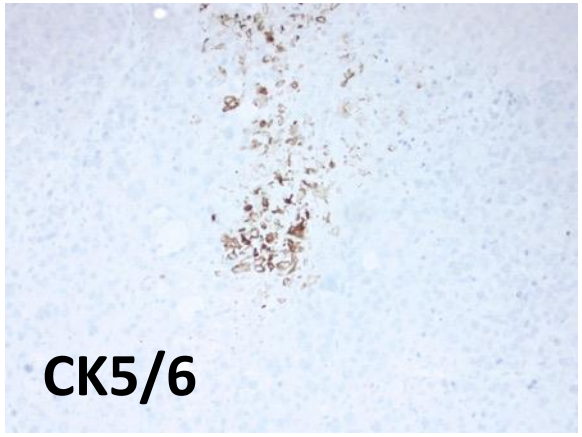
Original Dx: Poorly Differentiated Carcinoma with Squamous Features

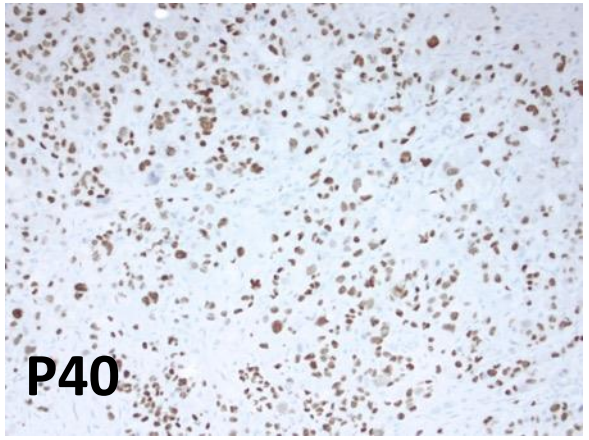


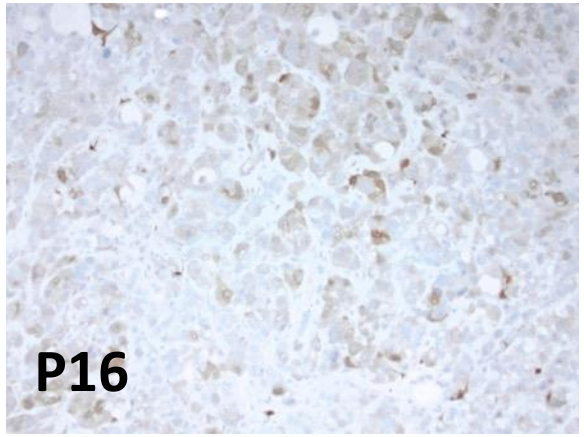
Original Dx: Poorly Differentiated Carcinoma with Squamous Features

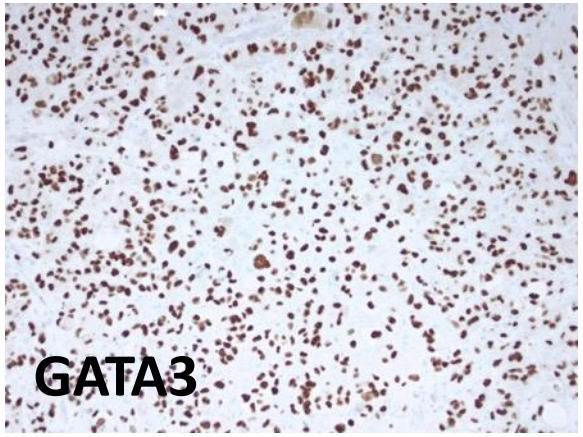


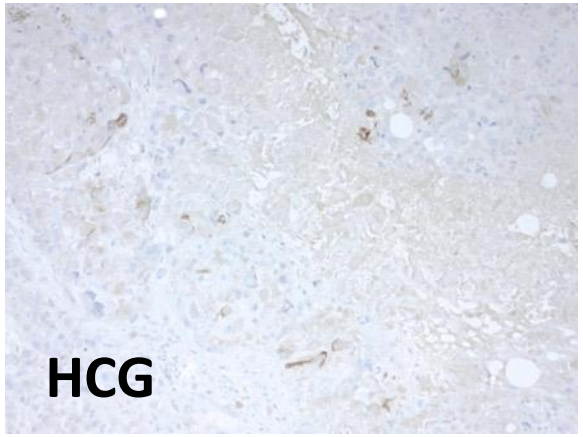


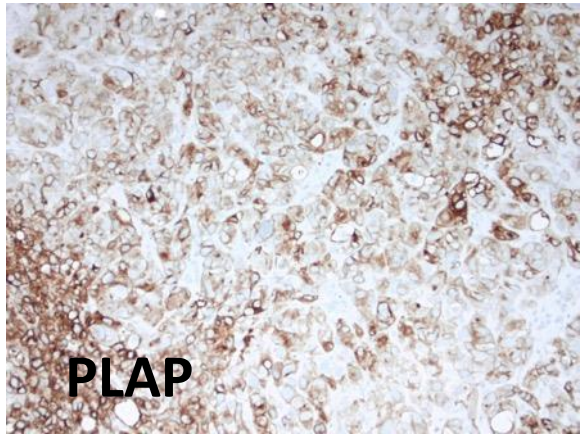




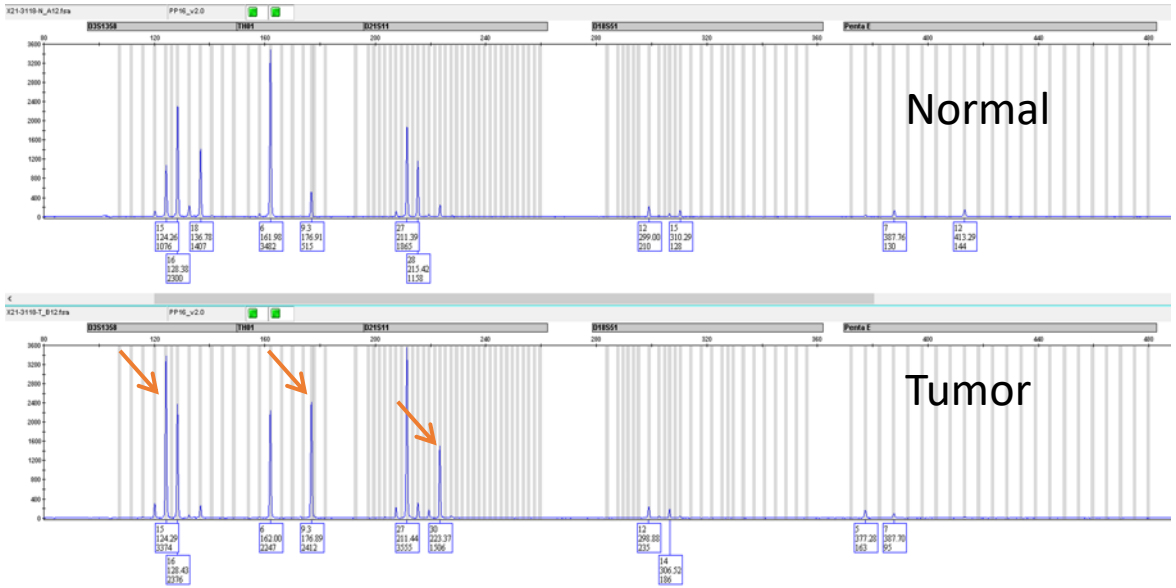


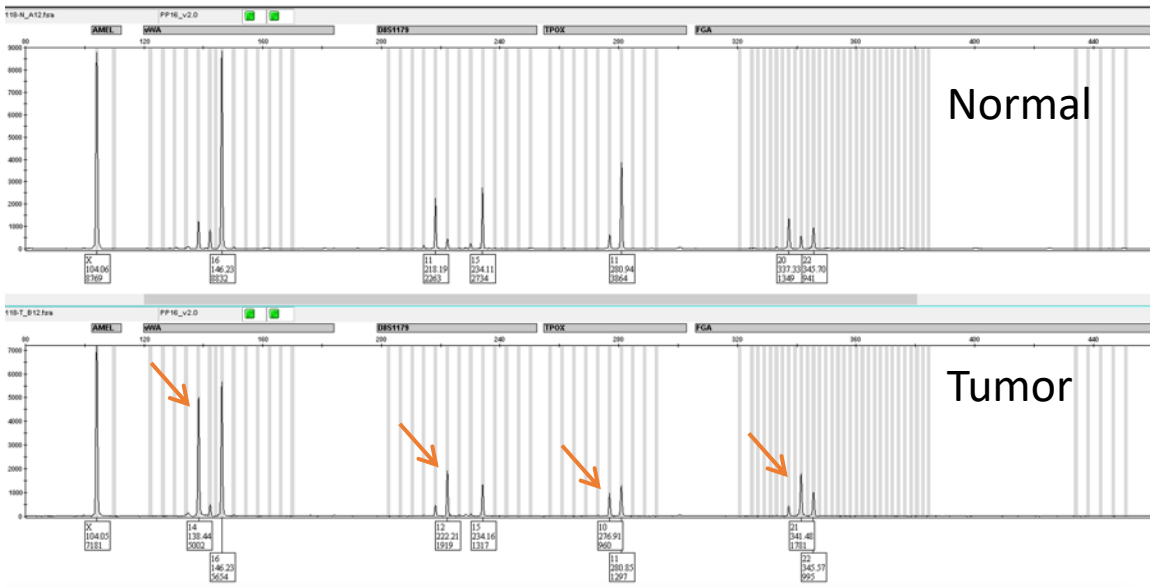






STR Genotyping – Distinct Paternal Alleles at SRT Loci





Histopathology

Histopathology 2023 DOI: 10.1111/his.15054

Extrauterine epithelioid trophoblastic tumour and its somatic carcinoma mimics: short tandem repeat genotyping meets the diagnostic challenges

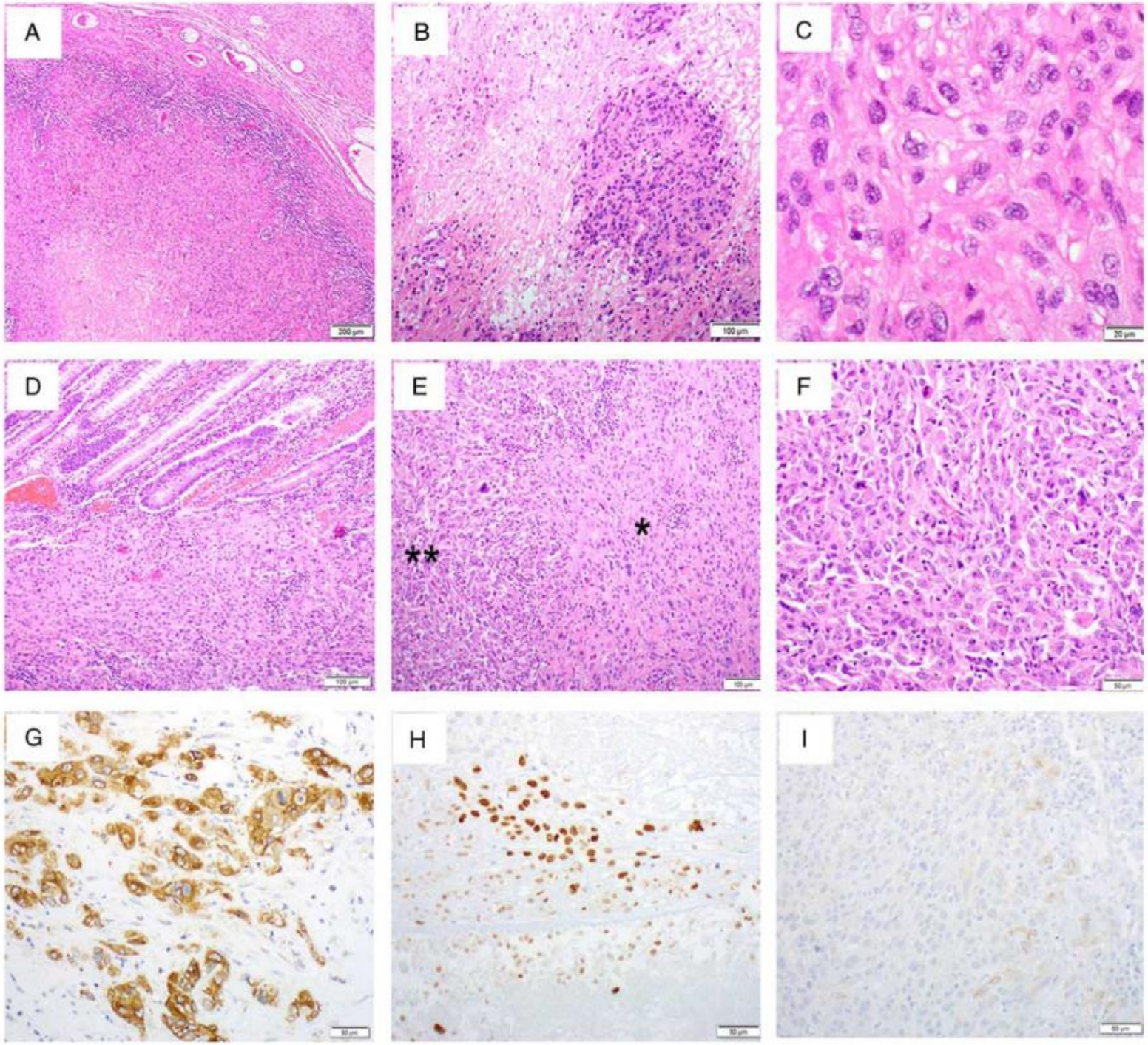
Na Niu,[1] Zehra Ordulu,[2] Zeybek Burak,[3] Natalia Buza[1] & Pei Hui[1]

[1]Department of Pathology, Center for the Precision Medicine of Trophoblastic Disease, Yale School of Medicine, New Haven, CT, [2]Department of Pathology, Immunology and Laboratory Medicine and [3]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Florida, Gainesville, FL, USA

Table 2. Summary of the clinicopathological information and STR genotyping results

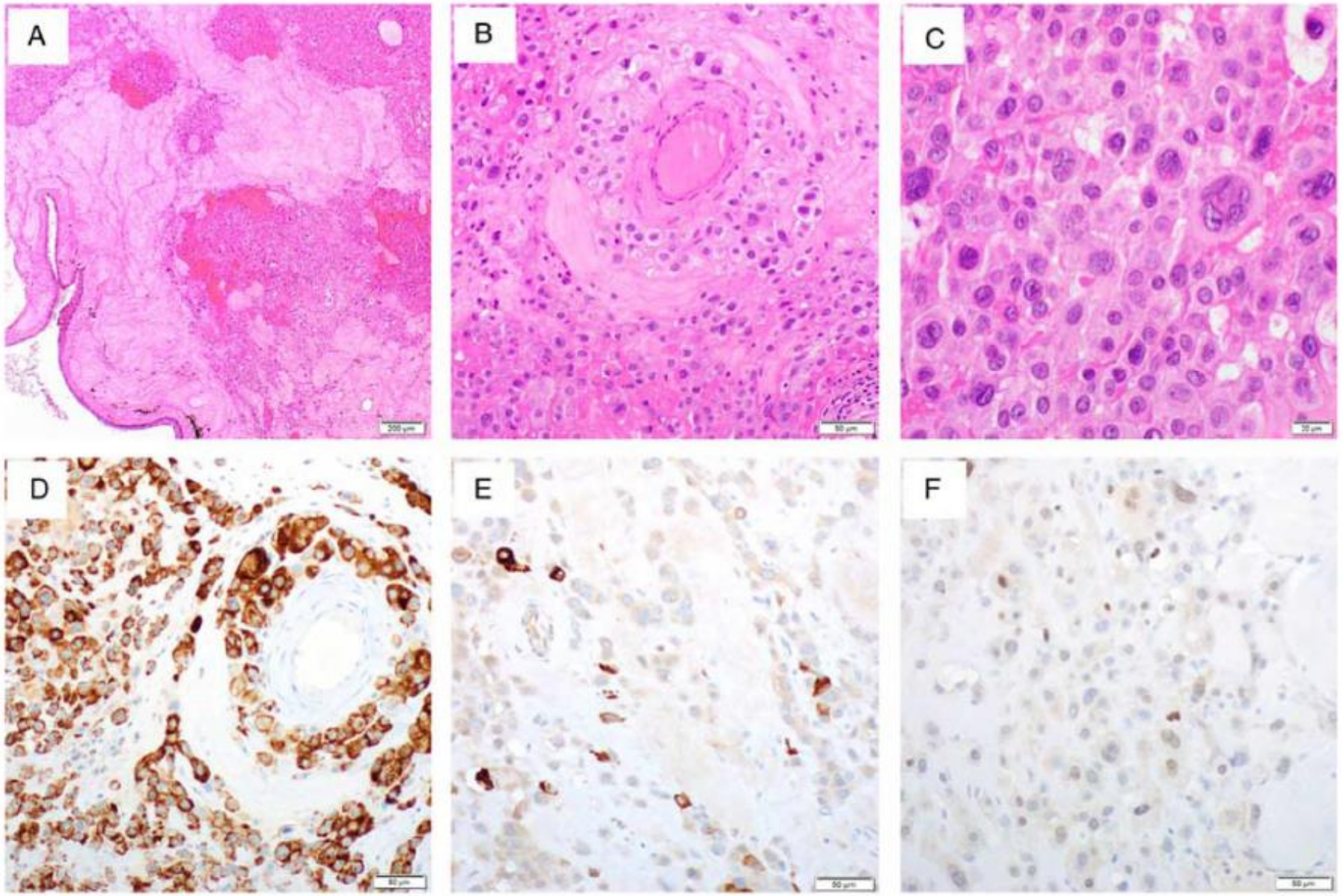
	Case 1	Case 2	Case 3	Case 4
Patient age (years)	61	26	65	57
Prior gestations	G1P0	G3P0A1	NA	G7P3
Presenting symptoms	Vaginal bleeding, abdominal pain weight loss	Home pregnancy test positive	Supraclavicular lymphadenopathy and liver nodules	Dyspnoea
Reported PMH	Endometrial cancer, poorly differentiated	Abortion	Triple-negative breast cancer, stage IV	NA
Lesion site	Anterior abdominal wall, omentum, intestine	Multiple lung nodules	Multiple nodules in the liver	Multiple bilateral lung nodules, neck and mediastinal lymphadenopathy
Initial diagnosis at outside institution	Poorly differentiated carcinoma with squamoid features and extensive necrosis	Malignant neoplasm with trophoblastic features involving lung	ETT	ETT
Treatment/ procedure	Exploratory laparotomy, omentectomy	Lung wedge resection	First-round chemotherapy for trophoblastic tumour without response	Right lung core biopsy
Molecular genotyping	Distinct paternal alleles (not present in normal tissues)	Distinct paternal alleles (not present in normal tissues and recent full-term pregnancy)	Matching alleles with the patient's normal tissues	Matching alleles with the patient's normal tissues
Final diagnosis	Metastatic ETT	Metastatic ETT	Somatic carcinoma with trophoblastic differentiation	Somatic carcinoma with trophoblastic differentiation

ETT, Epithelioid trophoblast tumour; NA, Not available; PMH, Past medical history.



Ovarian non-gestational ETT, germ cell origin

Xing, D et al., Am J Surg Pathol 2020



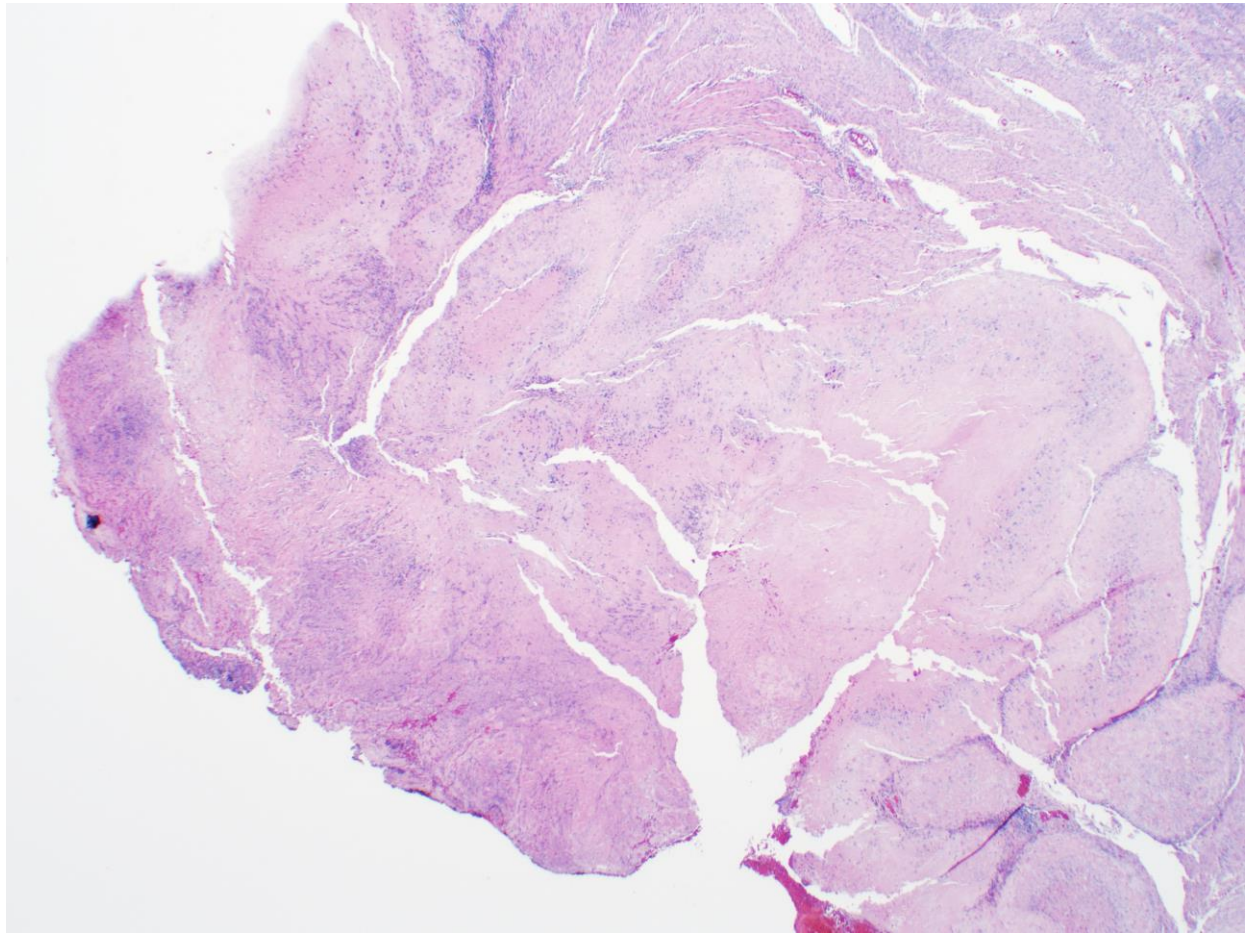
Ovarian non-gestational PSTT, germ cell origin

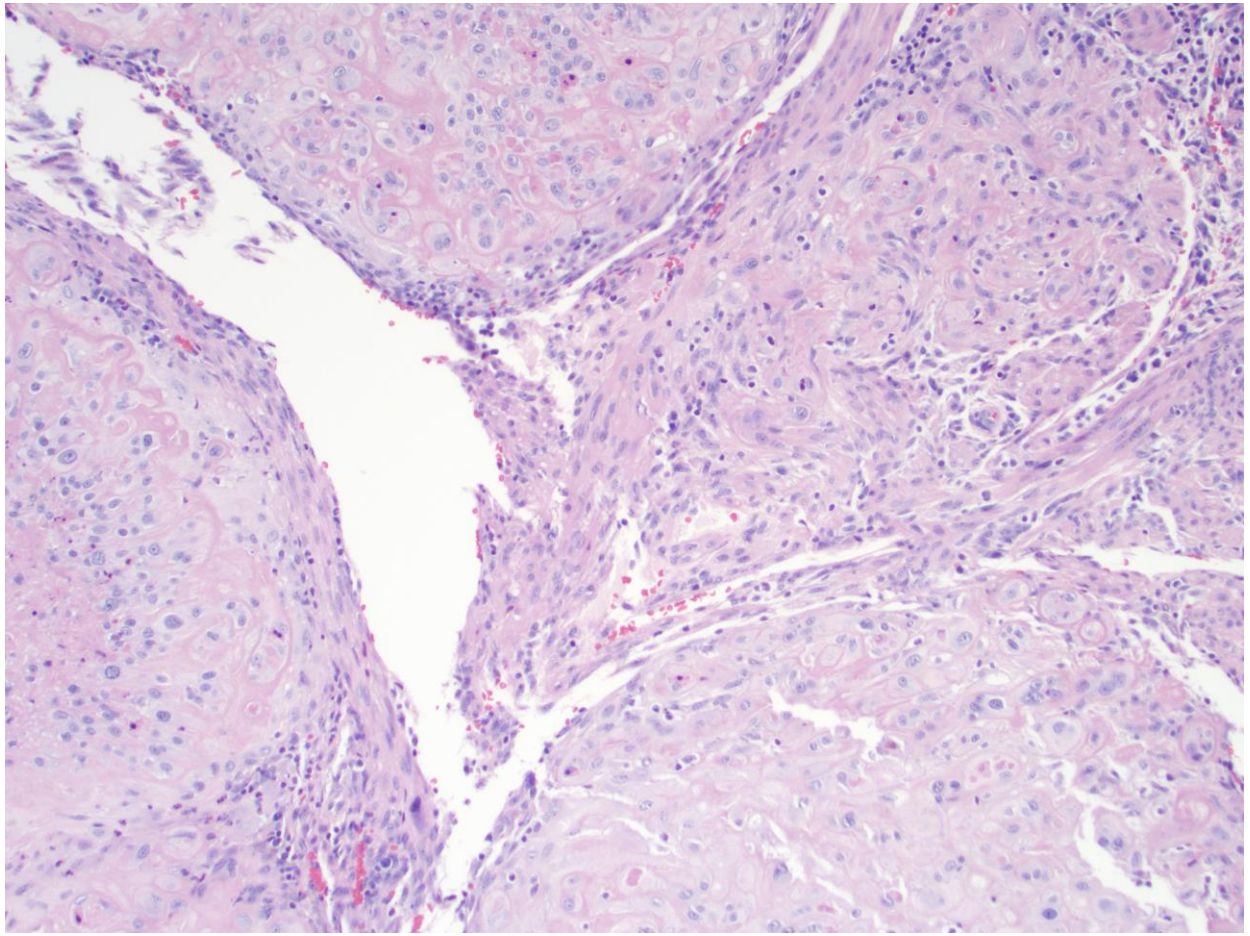
Xing, D. et al., Am J Surg Pathol 2020

Prognostic Indicators for ETT and PSTT

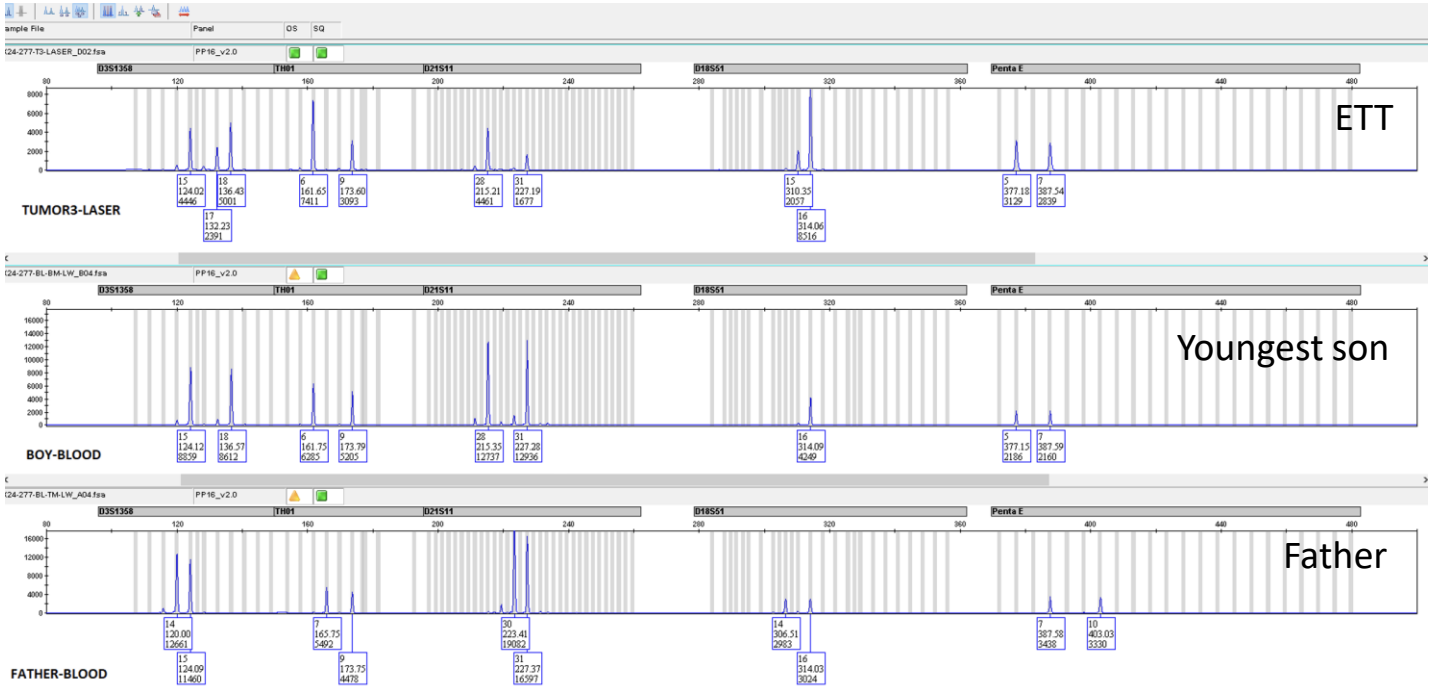
- **TNM/ FIGO stage**
- **Interval time of ≥ 4 years from causative gestation**
- Larger tumor size
- Deep myometrial invasion
- High mitotic count (≥ 5/ 10 HPF)
- Necrosis
- Clear cytoplasm (PSTT)

41-year-old woman with a 3.0 cm ETT confined to uterus for determination of the interval time





41-year-old woman with a 3.0 cm ETT confined to uterus for determination of the interval time



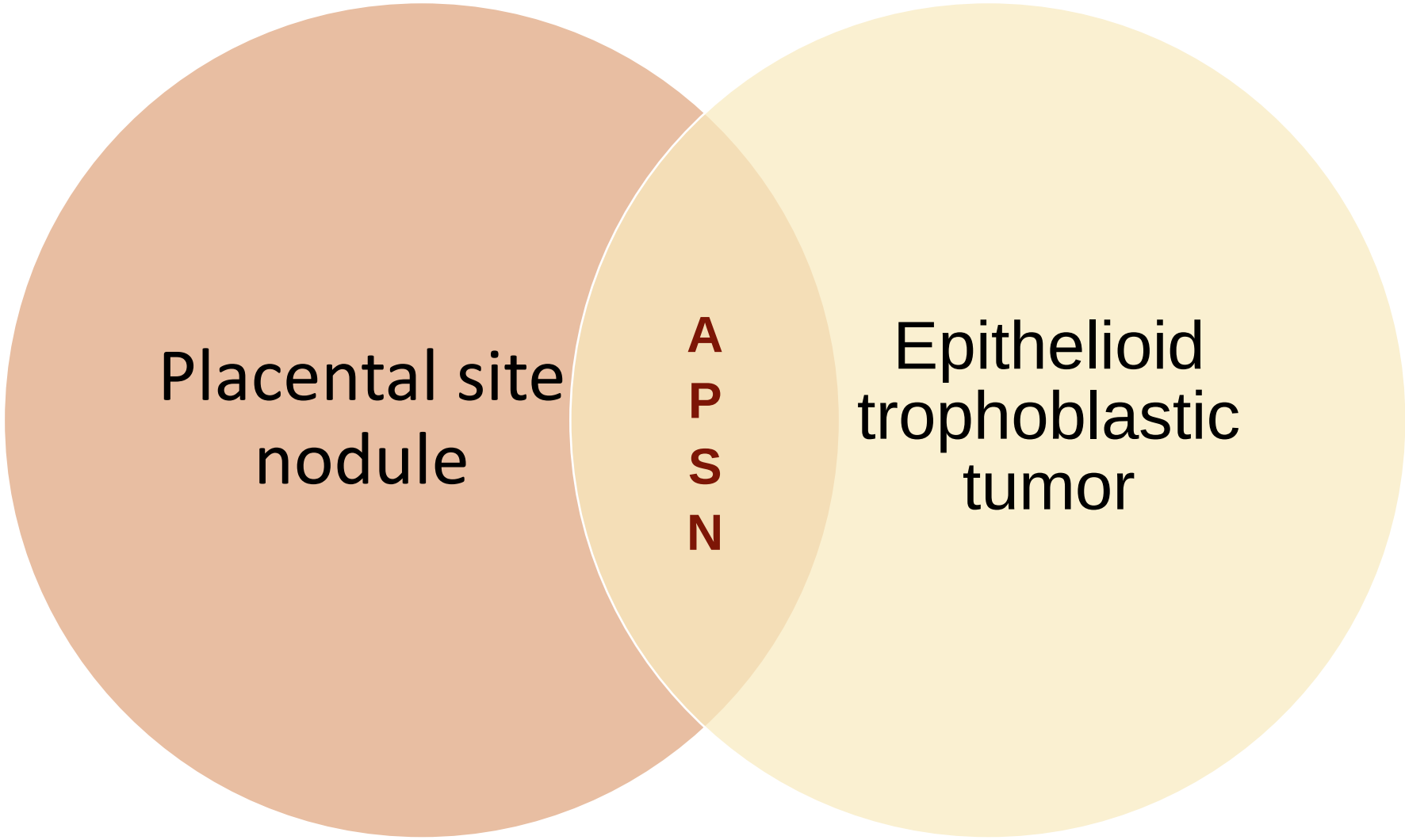
- ETT genetic profile matches with that of the youngest son among the three children with age of 1, 7, 9 years
- Interval time of < 4 years – low risk factor

Case#: X24-277			Patient name: Mudd, Cambridge M				
STR Loci	Tumor #1	Tumor #2	Mother (CM, DOB:1-23-82)	Father (TM, DOB:5-10-77)	Child#1 (AM, DOB:6-12-15)	Child#2 (VM, DOB:1-6-17)	Child#3 (BM, DOB:2-2-23)
D3S1358	15,17,18	15,17,18	17,18	14,15	15,18	15,17	15,18
TH01	6,9	6,9	6	7,9	6,7	6,9	6,9
D21S11	28,31	28,31	28	30,31	28,30	28,30	28,31
D18S51	15,16	15,16	15,16	14,16	14,16	16	16
Penta E	5,7	5,7	5,7	7,10	5,10	7,10	5,7
D5S818	10,11,13	10,11,13	10,11	11,13	10,13	10,11	10,13
D13S317	8,11	8,11	8,11	11,14	8,11	8,11	8,11
D7S820	10,12,13	10,12,13	10,12	11,13	10,13	10,11	10,13
D16S539	9,11,13	9,11,13	9,11	13	11,13	9,13	11,13
CSF1PO	11,12,13	11, 12,13	12,13	8,11	8,13	8,13	11,13
PENTA D	9,13	9,13	9	11,13	11	11	9,13
AMEL (XY)	XY	XY	X	XY	X	X	XY
vWA	14,17,18	14,17,18	14,17	17,18	14,18	14,18	14,18
D8S1179	12,13	12,13	12,13	12	12	12	12
TPOX	8,11	8,11	8,11	8,11	8,11	8,11	8,11
FGA	19,21,24	19,21,24	19,21	22,24	21,24	19,22	21,24

Potential Precursor Lesions – ETT, PSTT

	Benign	Potential Precursor	Malignant
Chorion Laeve (Chorionic) Intermediate Trophoblast	Placental Site Nodule	**Atypical Placental Site Nodule (WHO 2020)**	Epithelioid Trophoblastic Tumor
Implantation Site Intermediate Trophoblast	Exaggerated Placental Site Reaction	? Atypical Implantation Site Trophoblastic Proliferation	Placental Site Trophoblastic Tumor

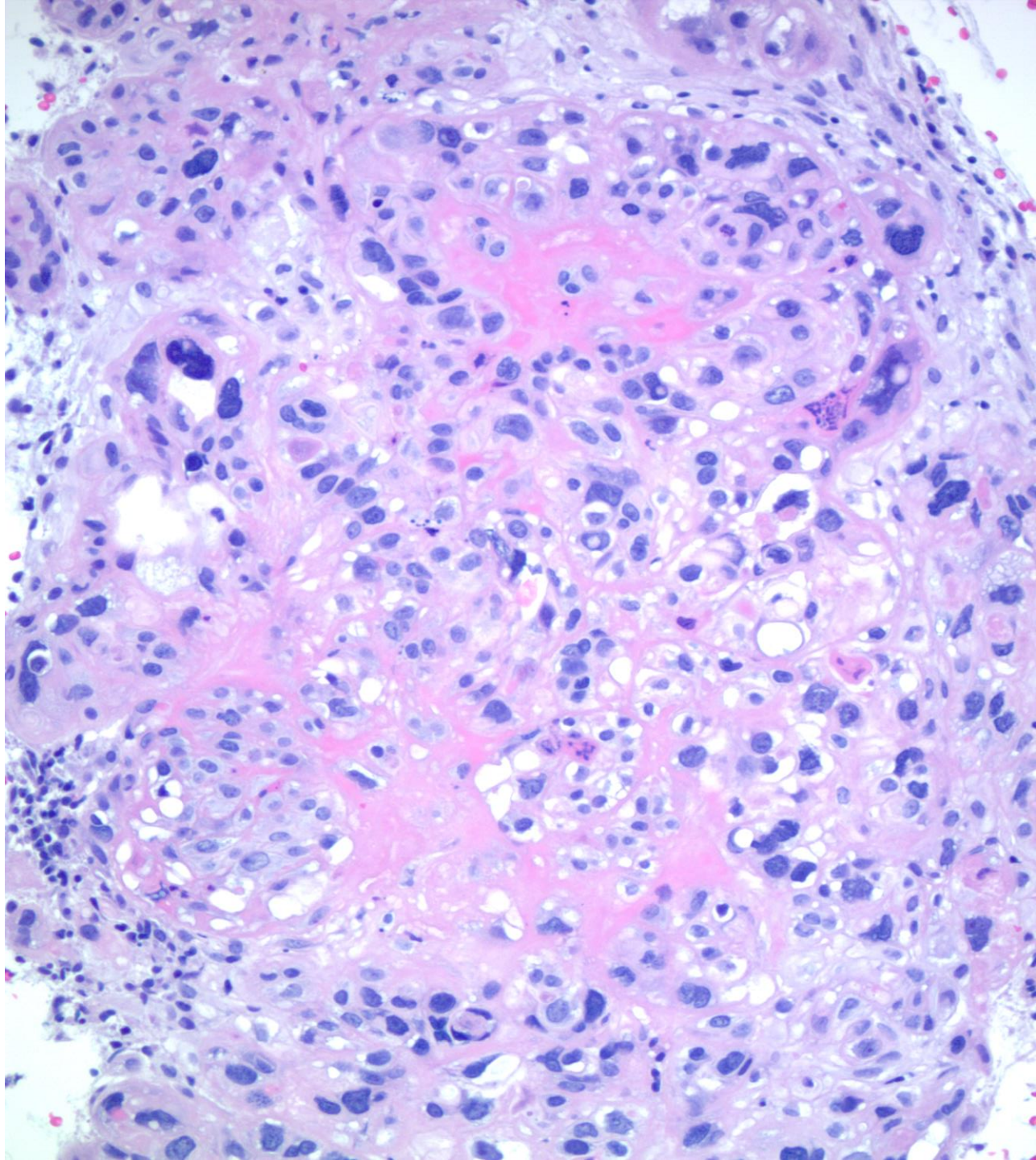
Atypical Placental Site Nodule

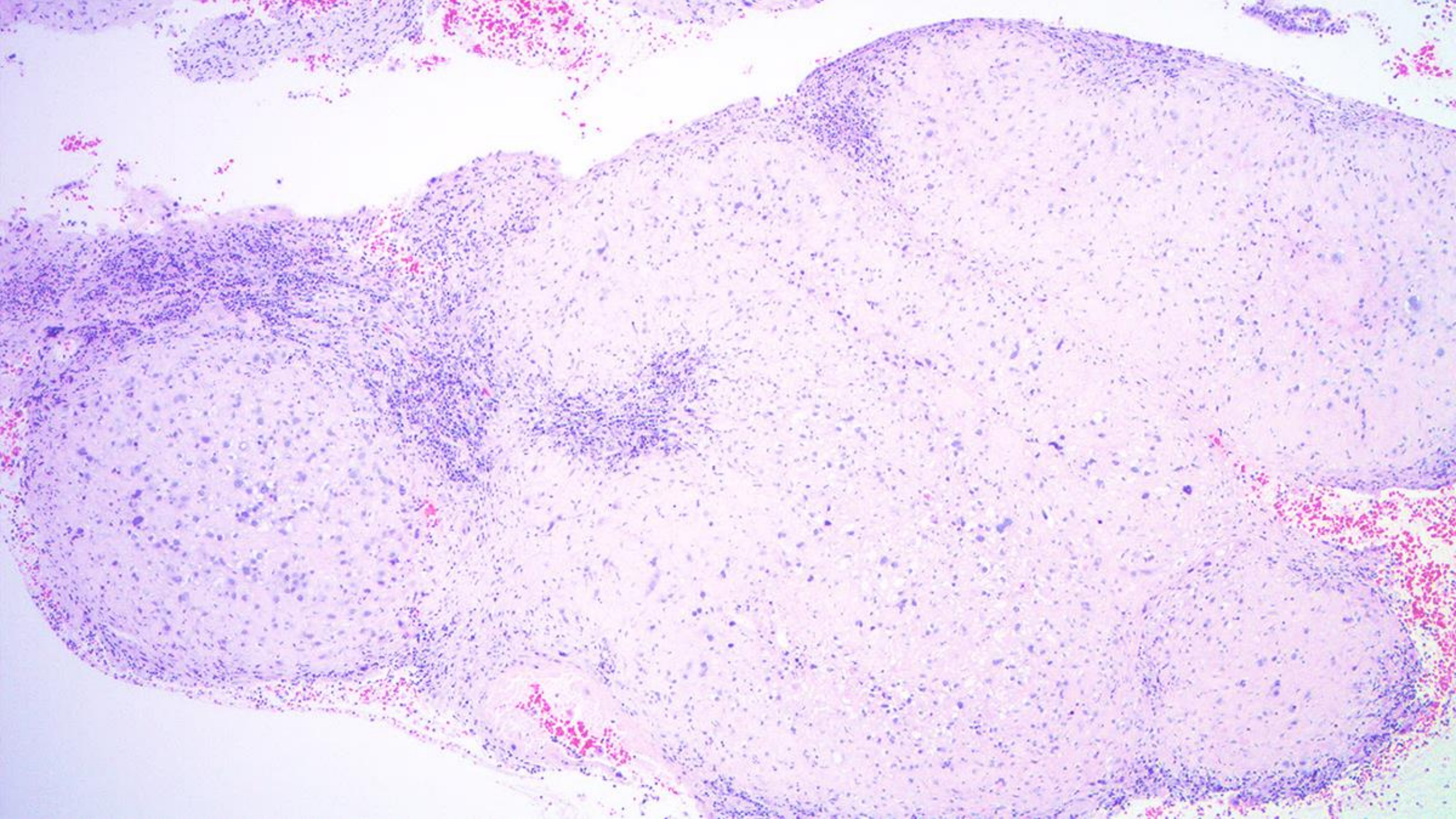


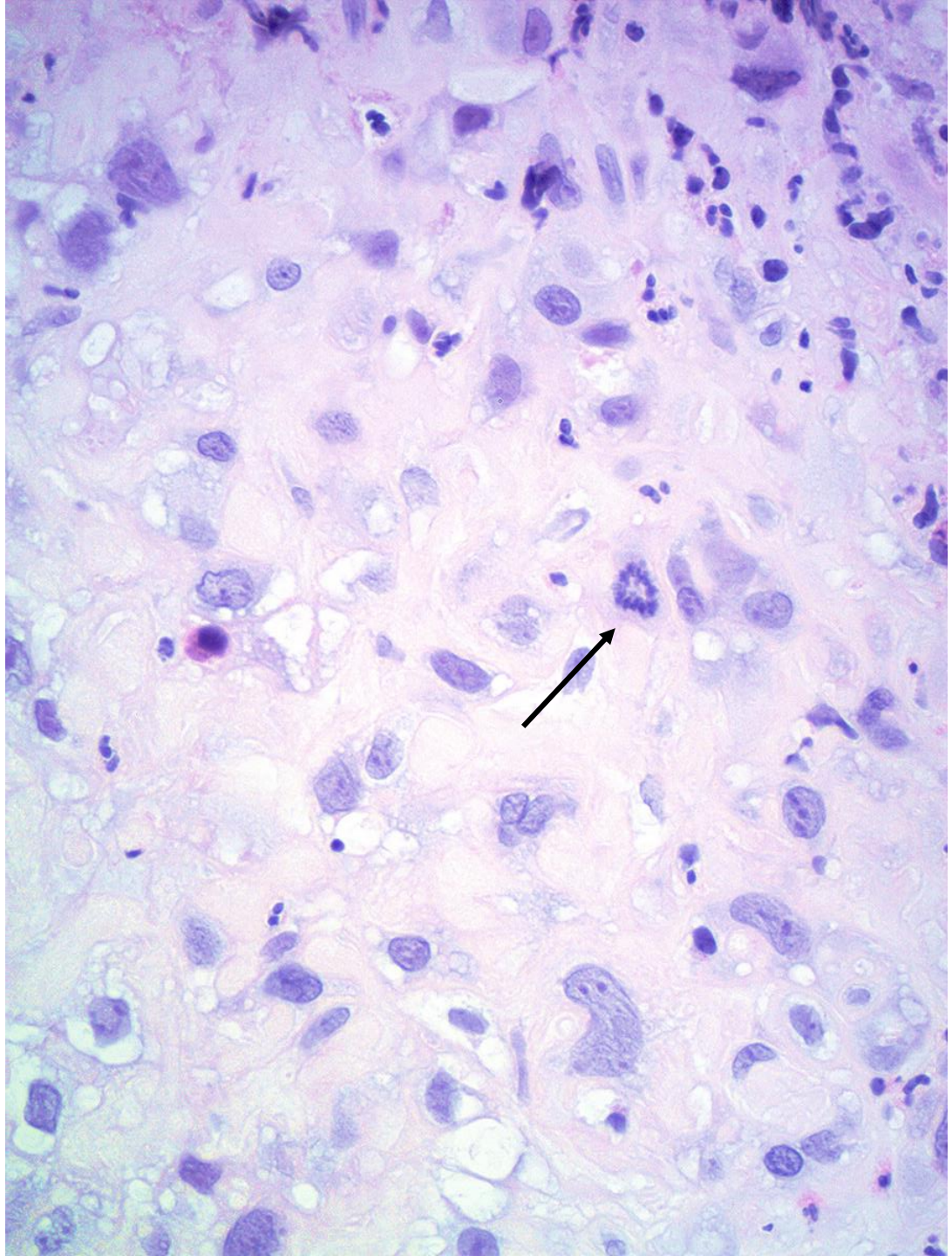
Curtesy of Dr. Buza

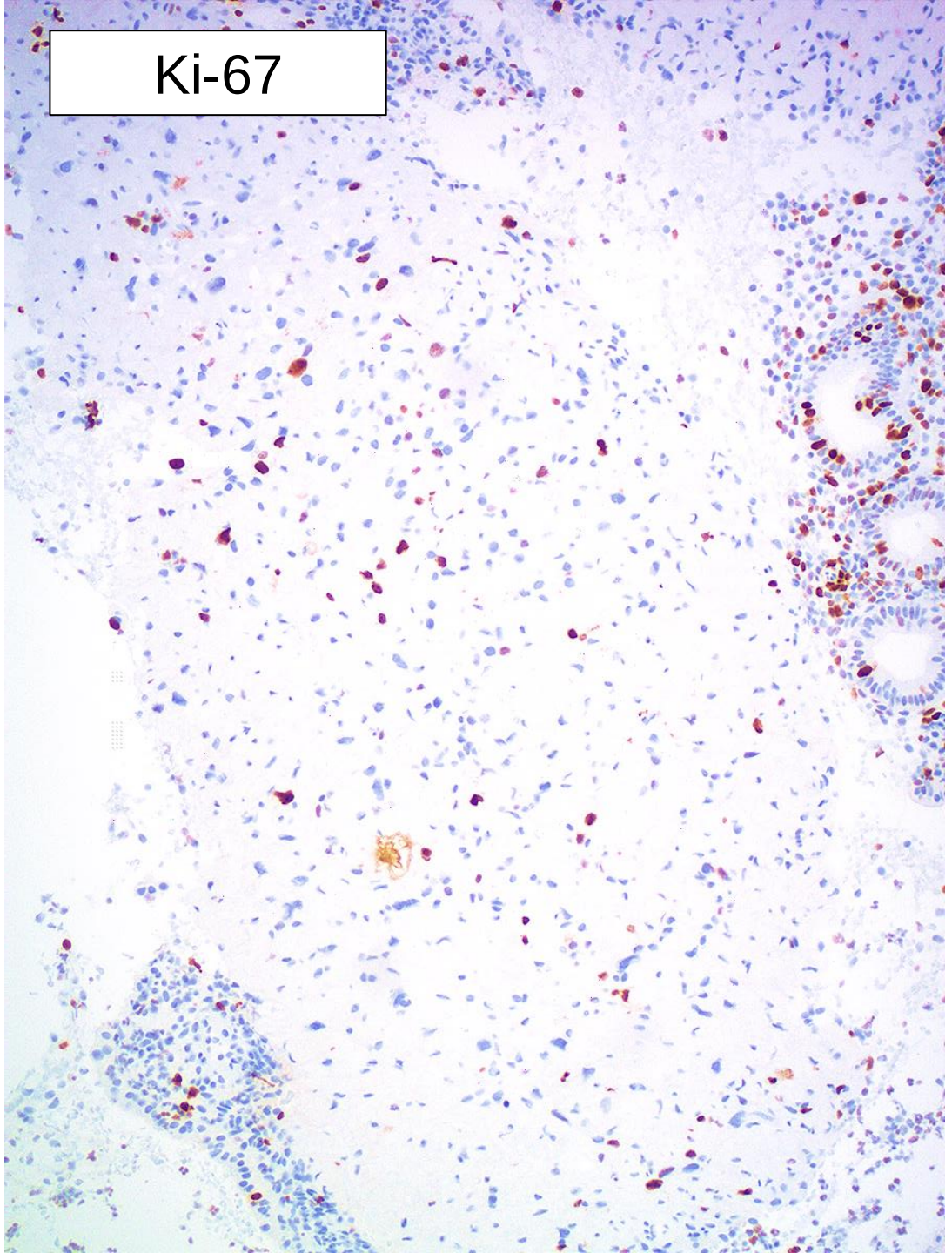
Atypical Placental Site Nodule (APSN)

- Larger size (5-10 mm)
- Hypercellularity
- Cytological atypia
- Mitotic activity
- Ki-67 index of 5-10%








Ki-67

International Journal of Gynecological Pathology
34:152–158, Lippincott Williams & Wilkins, Baltimore

Original Article

Atypical Placental Site Nodule (APSN) and Association With Malignant Gestational Trophoblastic Disease; A Clinicopathologic Study of 21 Cases

Baljeet Kaur, F.R.C.Path., Dee Short, Rosemary A. Fisher, Ph.D., F.R.C.Path., Philip M. Savage, Ph.D., F.R.C.P., Michael J. Seckl, Ph.D., F.R.C.P., and Neil J. Sebire, F.R.C.Path.

> Int J Gynecol Pathol. 2023 Sep 1;42(5):482-490. doi: 10.1097/PGP.0000000000000934. Epub 2023 Jan 3.

Application of Current Pathologic Criteria for Atypical Placental Site Nodule Suggests That Refined Criteria Are Needed

Catherine E Perez, David B Chapel, Stephanie L Skala

PMID: 36728542 DOI: 10.1097/PGP.0000000000000934

3 of 21 (14%) APSN developed GTN:

- 1 concurrent PSTT
- 1 PSTT after 16 months
- 1 ETT after 6 months

SUMMARY

- Ancillary studies, particularly STR genotyping are important for accurate diagnosis and subtyping of hydatidiform moles
- STR genotyping is important for precision diagnosis of trophoblastic tumors at extrauterine sites and WHO/FIGO prognostic scoring of GTN
- Recognition of intraplacental and intra-molar choriocarcinoma
- Recognition of atypical placental site nodule

THANK YOU

	Yale Direct STR Genotyping Approach (This Study)	Johns Hopkins Direct P57 IHC Approach (Ref. 1)
Total Study Cohort	2871 cases (41% consults)	2217 cases (87% consults)
Definitive diagnosis achieved	99.5% (14 inconclusive cases)	94% (137 inconclusive cases)
CHM Exclusively Observed	<14 and >50 years of age	<21 and >45 years of age
Non-molar	2006 cases (69.8%)	900 cases (40.6%)
PHM	564 Cases (19.6%)	498 cases (22.5%) (497 genotyped)
CHM	282 cases (9.2%)	571 cases (25.7%) (153 genotyped)
Androgenetic/ Biparental mosaicism	3 cases	56 cases (16 genotyped)
Laser microdissection	138 cases (97% success rate)	Not Applicable
Turnaround time	5.3 days	Unknown

Table 2. Comparison of test performance of STR genotyping/laser microdissection versus p57 IHC followed by genotyping in p57-positive cases. STR genotyping test turnaround time is represented in days with mean ± SE.

Ancillary Studies – Cost Estimate (2024)

- p57 immunohistochemistry: ~ $100
- Conventional karyotyping: ~ $300
- DNA ploidy by flow cytometry: ~ $400**
- Cytogenetics – SNP Array: ~ $1,160
- FISH
  - Single chromosome: ~ $400
  - Multiple chromosomes (UroVysion): ~ $600
- STR Genotyping: ~ $500

** based on billing codes of 2010

2024 www.cms.gov
2024 www.cap.org

Immunotherapy for Gestational Trophoblastic Tumors

References	Tumor Type	PD-L1 Expression	Pembrolizumab Cycles to hCG Normalization	Pembrolizumab Cycles as Consolidation	Response
Huang et al., 2017 [45]	Choriocarcinoma	Strong	2	4	CR
Ghorani et al., 2017 [46]	Choriocarcinoma	100%	4	5	CR
	PSTT/ETT	>90%	5	0	PD
	PSTT	>90%	8	5	CR
Chul Choi et al., 2019 [47]	Choriocarcinoma	100%	2	5	CR
	PSTT	100%	1	13	CR
	ETT	50%	11	4	PR
Goldfarb et al., 2020 [48]	Choriocarcinoma	100%	3	3	CR
Clair et al., 2020 [49]	Choriocarcinoma	Strong	10	0	CR
Pisani et al., 2021 [50]	ETT	Not evaluated	Undeclared	Undeclared	CR
Bell et al., 2021 [51]	ETT	>5%	Ongoing	Ongoing	PR (Cut-off of 29 cycles)
Paspalj et al., 2021 [52]	Choriocarcinoma	>90%	4	7	CR

Review

Current Evidence on Immunotherapy for Gestational Trophoblastic Neoplasia (GTN)

Giorgia Mangili [1], Giulia Sabetta [1], Raffaella Cioffi [1,2], Emanuela Rabaiotti [1], Giorgio Candotti [1], Francesca Pella [1], Massimo Candiani [1,2] and Alice Bergamini [1,2,*]

Cancers. 2022,14,2782