Recent genetic insights into endometrial cancer and sarcoma – Diagnostic and Management implications

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I do not have an affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.
Educational Objectives

1). The participants will understand why recent genetic insights are prompting changes to the classification of endometrial cancer and sarcoma.

2). The participants will understand the clinical significance of these proposed changes in tumor classification.

3). The participants will be able to effectively combine ancillary studies (immunohistochemical and genetic) together with histologic evaluation to improve the diagnosis of endometrial cancer and sarcoma.
Uterine tumors

- Different molecular types of endometrial carcinoma
- Different molecular types of endometrial stromal sarcoma
ENDOMETRIAL CARCINOMA
Histologic subtyping of Endometrial Ca

Type 1 ~ 80%
- Endometrioid

Type 2 ~ 20%
- Non-Endometrioid
  - Serous
  - Clear Cell
  - Mixed
  - Undifferentiated
  - Squamous
  - Transitional
  - Small Cell
  - Other
Challenges with histotyping endo ca

- Studies have shown suboptimal diagnostic agreement in endometrial carcinomas, especially in high-grade cases

<table>
<thead>
<tr>
<th>Study</th>
<th>Total # Cases</th>
<th>Cases with Diagnostic Disagreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomo et al. (2008)</td>
<td>103</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>Garg et al. (2010)</td>
<td>35</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Sidhu et al. (2010)</td>
<td>116</td>
<td>31 (27%)</td>
</tr>
<tr>
<td>Gilks et al. (2013)</td>
<td>56</td>
<td>21 (37%)</td>
</tr>
</tbody>
</table>
**Study samples:**
- 373 endometrial ca
  - 307 endometrioid-type
  - 66 serous-type

**Study methods:**
- Genomic analysis
  - Whole exon seq
  - MSI analysis
  - Affy SNP 6.0 microarray
- mRNA/miRNA expression analysis
- DNA methylation analysis
- Protein array

TCGA molecular subtype of Endometrial Ca

Histologic subtype

- Serous carcinoma
- Endometrioid carcinoma

Molecular subtype

- Copy number-high serous-like
  - TP53, PPP2R1A
- Copy number-low endometrioid
  - PTEN, ARID1A, CTNBB1
- MSI (hypermutated)
- POLE (ultramutated)
  - ++ mutations
  - +++ of mutations
  - ++++ of mutations

POLE (polymerase epsilon)

- Family B polymerase with both
  - Replicative function (polymerase domain)
  - Repair function (exonuclease domain)
- Balanced Exonuclease/Polymerase activity important
- Mutations in exonuclease domain lead to mutator phenotype
Prognostic significance of *POLE EDM* mutation in Grade 3 Endometrioid Carcinoma

**Progression-free survival**

- EC3 *POLE* mutated: N=16, zero events
- EC3 *POLE* wild type: N=82, 25 events

**Overall survival**

- EC3 *POLE* mutated: N=16, zero events
- EC3 *POLE* wild type: N=86, 21 events

**G3 endometrioid: n=53** – 8 (15%) showed *POLE EDM* mutation

*Meng et al, Gynecol Oncol. 2014;134:15-9.*
## PORTEC-1 and PORTEC-2 series - POLE mutation

<table>
<thead>
<tr>
<th>Demographic/clinicopathological characteristic</th>
<th>POLE wild-type (n = 740)</th>
<th>POLE mutant* (n = 48)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>68.5</td>
<td>63.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Range</td>
<td>41–90</td>
<td>46–81</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>106 (14.3)</td>
<td>16 (33.3)</td>
<td>.002</td>
</tr>
<tr>
<td>60–70</td>
<td>325 (43.9)</td>
<td>16 (33.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>309 (41.8)</td>
<td>16 (33.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEC</td>
<td>723 (97.7)</td>
<td>47 (97.9)</td>
<td>.92</td>
</tr>
<tr>
<td>NEEC</td>
<td>17 (2.3)</td>
<td>1 (2.1)</td>
<td></td>
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<td><strong>HGO stage (1988)</strong></td>
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<tr>
<td>IB</td>
<td>177 (23.9)</td>
<td>17 (35.4)</td>
<td>.19</td>
</tr>
<tr>
<td>IC</td>
<td>519 (70.1)</td>
<td>29 (60.4)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>44 (5.9)</td>
<td>2 (4.2)</td>
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</tr>
<tr>
<td><strong>Depth of invasion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>208 (28.1)</td>
<td>20 (41.7)</td>
<td>.045</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>532 (71.9)</td>
<td>28 (58.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>543 (73.4)</td>
<td>28 (58.3)</td>
<td>.001</td>
</tr>
<tr>
<td>2</td>
<td>103 (13.9)</td>
<td>5 (10.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>94 (12.7)</td>
<td>15 (31.3)</td>
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<td><strong>LVSI</strong></td>
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<tr>
<td>Absent</td>
<td>670 (90.5)</td>
<td>48 (100)</td>
<td>.03</td>
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<tr>
<td>Present</td>
<td>70 (9.5)</td>
<td>0 (0)</td>
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<td><strong>Radiotherapy</strong></td>
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<td></td>
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</tr>
<tr>
<td>NAT</td>
<td>199 (26.9)</td>
<td>13 (27.1)</td>
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<tr>
<td>EBRT</td>
<td>361 (48.8)</td>
<td>24 (50)</td>
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<tr>
<td>VBT</td>
<td>180 (24.3)</td>
<td>11 (22.9)</td>
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<tr>
<td><strong>Chemotherapy</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>740 (100.0)</td>
<td>48 (100.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Church et al. J Nati Cancer Inst. 2014 Dec 12;107(1):402*
PORTEC-1 and PORTEC-2 series - *POLE* mutation

![Graphs showing cancer specific survival for *POLE* wild-type and *POLE* proofreading-mutant](#)

- Left graph: *POLE* wild-type vs. *POLE* proofreading-mutant
  - *P* = 0.11

- Right graph: G3 *POLE* wild-type vs. G3 *POLE* proofreading-mutant
  - *P* = 0.03
POLE-mutated Endometrial ca

• Histology
  Variable - tends to display high-grade nuclear features (serous-like)
  Dense tumor –infiltrating/peri-tumoral lymphocytes
  No reliable predictive histologic features

• Clinical behavior
  Excellent prognosis (despite a tendency for higher tumor grade, outer-half myometrial invasion, frequency lymphovascular invasion)

• Diagnosis (no surrogate immunomarker)
  Targeted sequencing of exon 9-14 (exonuclease domain) of POLE (Sanger or NGS) - > 2/3 harbor P286R or V411L missense mutation

Hussein et al. Mod Pathol. 2015 Apr;28(4):505-14
Salwa et al, Histopathology, in press
MSI-H Endometrial ca

• Microsatellite instability secondary to mutation/loss of expression of mismatch repair (MMR) protein
  • Germline mutation in HNPCC/Lynch Syndrome
  • Somatic mutation/epigenetic silencing

• Morphology not an ideal predictor for MMR/MSI status
  • Dedifferentiated endometrial carcinoma (50-70% MMR-deficient)
    • BMI status, age and lower uterine segment location

• Diagnosis
  • Microsatellite stability analysis (NCI markers) → MSS/MSI-Low/MSI-high
  • MMR protein immunohistochemistry (MLH1, MSH2, MSH6, PMS2)
• MMR IHC a sensitive surrogate marker for MSI-H (>90% sensitivity*)
  • Some types of MMR protein mutation that renders the protein non-functional (resulting in MSI-H) may retain its antigenicity
  • Reflex MMR IHC screen instituted in some centers for all endometrial ca and non-serous/non-mucinous ovarian ca (CCC and EC)

• Risk of Lynch Syndrome in endometrial ca varies depending on the pattern of MMR protein loss
  • Most patients with loss of MLH1 do not have LS (80% due to MLH1 methylation → methylation and BRAF mutation study)
  • Most patients with loss of MSH2, MSH6 or PMS2 do have LS

Gynecologic Oncology 2015 May;137(2):306-10.
Tumor genetics-driven Diagnostic insights

Improved molecular understanding provides an opportunity for us to,

1). Refine our tumor classification system

2). Improve our diagnostic accuracy (reproducibility)
• 36 high-grade endometrial carcinomas were genotyped

• Endometrioid/clear cell genotype cases:
  • *PTEN* + *ARID1A* mutations, or
  • *PTEN* or *ARID1A* mutations without *PPP2R1A* and *TP53* mutations

• Serous genotype cases:
  • *TP53* and/or *PPP2R1A* mutations, without *ARID1A* or *PTEN* mutations

• Pathologists were provided immunohistochemical (IHC) results for p53; and diagnoses were re-submitted

• Diagnoses (both before and after IHC) were divided into:
  • histotype-genotype *concordant* diagnoses
  • histotype-genotype *discordant* diagnoses

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Description</th>
<th>Not recommended</th>
</tr>
</thead>
</table>
| Aberrant/ Abnormal  | “All or none”  
All: overexpression: strong intensity in > 70% cells (usually ~100%, 70% accounts areas of poor fixation/necrosis)  
None: complete absence with retained internal control) | Positive, +           |
| Wild-type           | Heterogeneous intensity in 1-70%                                             | Negative, -           |
Aberrant (diffuse strong nuclear staining in tumor cells)

Aberrant (absence of nuclear staining in tumor cells in the presence of stromal positive control)
Key Points:
1) 20% of diagnoses were histotype-genotype discordant
2) After IHC, 1/3 of those discordant diagnoses improved

Kappa Values for individual pathologists

<table>
<thead>
<tr>
<th></th>
<th>Dx</th>
<th>Dx after IHC</th>
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<tbody>
<tr>
<td></td>
<td>0.30</td>
<td>0.64</td>
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<tr>
<td></td>
<td>0.48</td>
<td>0.57</td>
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<tr>
<td></td>
<td>0.63</td>
<td>0.76</td>
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<td></td>
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<td>0.76</td>
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<tr>
<td></td>
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<td>0.76</td>
</tr>
<tr>
<td></td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>0.67</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>0.48</td>
<td>0.54</td>
</tr>
</tbody>
</table>
• Histotype-genotype concordance in 80% of diagnoses
• Two problematic scenarios identified:
  I. Tumors with **papillary** growth pattern
  II. Tumors with **solid** growth pattern
• In tumors with predominantly or exclusively papillary/villoglandular growth pattern
  • p53 IHC is recommended in cases with more than low-grade nuclear features (intermediate to high-grade) and/or increased mitotic activity
  • Mutated p53 immunostaining ("all or none") suggests serous carcinoma
  • Normal p53 immunostaining suggests non-serous type carcinoma
  • p16 IHC not as useful (emphasis should be placed on p53 IHC result)

Serous genotype (papillary pattern)
p53 IHC
Endometrioid genotype (papillary pattern)
• In tumors with predominantly solid/confluent growth pattern
  • p53 IHC result in the solid area is not as informative
  • Need to identify and examine for more classic, better differentiated areas (additional tissue sampling)
  • Perform p53 IHC on the more classic area is more informative
    • Mutated p53 IHC → serous carcinoma
    • Normal p53 IHC → non-serous type carcinoma
Insights from Mixed-type Endo Ca

• **Study sample**: 18 mixed-type endometrial carcinomas (with spatially distinct areas of differentiated histotype)

• **Study methods**:
  - DNA extracted from the different areas (0.6 mm tissue cores) of tumor in FFPE block (*tissue re-embedded after core sampling to confirm the same histology on the opposite side*) and normal
  - **Mutation analysis**: Full exon sequencing of 26 genes previously found to be recurrently mutated in endometrial ca using Truseq (Illumina) custom panel
  - **IHC analysis**: p53, MSH6, PMS2, HNF1β, napsin A

CASE 1
Serous carcinoma

- p53 (mutated; complete loss)
- p53 (mutated; complete loss)
Mixed endometrioid and serous POLE ultramutated (Endometrioid)

Shared mutations

**POLE (L424V), POLE (R1879C), ARID1A (G2087R), FBXW7 (R385C). PIK3R1 (A277T), MAP3K4 (E154K), MAP3K4 (R558H), PTEN (R173H), PPP2R1A (R183W, 27% and 25%), PPP2R1A (R527C, 25% and 27%), FGFR2 (++), ZFHX3(++), GRLF1 (++), EP300 (++), CSMD3(++)....**
Mixed endometrioid and serous

- p53 – wild-type
- p53 – mutated (diffuse)

Somatic mutations:
- PIK3CA (E542K)
- CSMD3 (I2936R)
- PTEN (D92E)
- PPP2R1A (R183Q)
- ARID1A (R1989X and FS)
- RPL22 (FS)
- CTCF (FS)
MSI hypermutated

? endometrioid

HNF1β and napsin A+

++ mutations identified

Shared

MAP3K4, PTEN, CHD4, CSMD3, ZFHX3, FGFR2

ARID1A (FS), PTEN (FS), CSMD3 (R1276C), SPOP (R121Q), PPP2R1A (R527H), PIK3R2 (FS) and TPSYL2 (FS)

RPL22, ARID1A, CTNNB1, PIK3R1, EP300, CSMD3, ZFHX3

IHC

Wild-type p53 staining and
PMS2 loss in both
Serous carcinoma

HNF1β- and napsin A+

p53 – mutated (diffuse)

Shared somatic mutations:

TP53 (G105C)
PPI2R1A (P179R)
PIK3CA (G106V)
“Mixed-type endometrial ca”

• In 16 of 18 cases there was molecular evidence that both components shared a clonal origin
  • SC genotype with area that mimicked another histotype (EC or CCC)
  • MSI-H or POLE-mutated tumors showing morphologic heterogeneity

• In 2 of 18 cases (both mixed SC/EC) Biologically unrelated synchronous tumors (collision tumor)
Tumor genetics-driven Diagnostic insights

• Morphology can be deceiving
  • High-grade tumors
  • Mixed-histotype
  • POLE-mutated tumors (κ=0.55*)

• p53 and MMR IHC can be useful
  • p53 IHC in mixed EC/SC scenarios and in tumors showing cyto-architectural discordance (i.e. higher nuclear grade or mitotic rate than expected)
  • MMR IHC in mixed EC/CCC scenarios (to be validated)

• POLE exonuclease domain mutation status also useful

Where do these fit in?

- Dediff/Undiff endo ca
- Carcinosarcoma/MMMT
- Clear cell ca
Dedifferentiated endometrial carcinoma

- A low-grade endometrioid-type carcinoma + an undifferentiated carcinoma

- 50-70% in a MSI-H (DNA mismatch repair protein-deficient) setting

- The low-grade endometrioid component (differentiated component) and undifferentiated component shares the same somatic mutations*; hence clonally related

- Speculation: Low-grade endometrioid → undifferentiated (“Dedifferentiation”)

- WHAT IS THE MOLECULAR SWITCH???

Loss of CK7 in undiff ca
Loss of ER in undiff ca
Wild-type p53 (TP53)
• Sequencing analysis
  • **SMARCA4** (frame-shift + Q756X) only in the undifferentiated component *
  • Other mutated genes: **ARID1A, PTEN, PIK3CA, KRAS**

• Immunohistochemical analysis
  • MLH1/PMS2 loss (MSI-H) in both differentiated and undifferentiated components

Loss of BRG1 (SMARCA4) in undifferentiated ca
Loss of INI1 (SMARCB1) in undifferentiated ca
Dedifferentiated endometrial carcinoma (DDEC)

- About half of DDEC shows loss of core SWI/SNF proteins - SMARCA4 (BRG1) or SMARCB1 (INI1) in the undifferentiated component

- Given the known roles of SWI/SNF in chromatin remodeling and transcriptional regulation + documented SMARCA4/SMARCB1 inactivation in other cancers (same undifferentiated histology), it is likely that SMARCA4 or SMARCB1 inactivation contributes to cellular dedifferentiation and more aggressive biologic behavior
Endometrial Clear Cell Carcinoma

- All cases demonstrate pure CCC histology and Napsin A/HNF1B positivity
- No distinct mutation profile identified
- 1/3 shows TP53 mutation
- Some of the TP53-mutated CCC showed identical mutation profiles (TP53 and PPP2R1A mutation) as that of Serous ca → WHAT ARE THEY???

Hoang et al. Histopathology. 2015 Apr;66(5):664-74
Histologic subtype

- Clear cell
- Serous carcinoma
- Endometrioid carcinoma

Molecular subtype

- ??? (ARID1A...)
- Copy number-high serous-like
- Copy number-low endometrioid
- MSI (hypermethylated)
- POLE (ultramethylated)

Disease progression

- Carcinosarcoma*
  - Frequent PI3K pathway mutations
- Dedifferentiated/Undifferentiated carcinoma
  - SMARCA4
  - SMARCB1

Improved molecular understanding provides an opportunity for us to,

1). Improve our ability to prognosticate

2). Improve our ability to deliver more optimal therapies
A clinically applicable molecular-based classification for endometrial cancers

A Talhouk\textsuperscript{1}, M K McConkey\textsuperscript{1}, S Leung\textsuperscript{2}, H H Li-Chang\textsuperscript{1,3}, J S Kwon\textsuperscript{4}, N Melnyk\textsuperscript{1}, W Yang\textsuperscript{1}, J Senz\textsuperscript{1}, N Boyd\textsuperscript{1}, A N Karnezis\textsuperscript{1}, D G Huntsman\textsuperscript{1}, C B Gilks\textsuperscript{1} and J N McAlpine\textsuperscript{1,4}

\textsuperscript{1}Department of Pathology and Laboratory Medicine, University of British Columbia and BC Cancer Agency, 509-2660 Oak Street, Vancouver, British Columbia, Canada V6H 3Z6; \textsuperscript{2}Genetic Pathology Evaluation Centre, Department of Pathology and Laboratory Medicine, University of British Columbia, 509-2660 Oak Street, Vancouver, British Columbia, Canada V6H 3Z6; \textsuperscript{3}Department of Laboratory Services, Royal Victoria Regional Health Centre, 201 Georgian Drive, Barrie, Ontario, Canada L4M 6M2 and \textsuperscript{4}Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, University of British Columbia, 2775 Laurel St. 6th Floor. Vancouver. British Columbia. Canada V5Z 1M9
**POLE and IHC marker (p53 and MMR)-based molecular subtyping and prognostication**

- **POLE (ex9-14) testing**
  → POLE-ultramutated

- **MMR IHC testing**
  → MSI-H hypermutated

- Wild-type POLE and MSS (MMR-intact)
  - **p53 IHC**
    → Copy number high serous-like
    → Copy number low endometrioid

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*Talhouk et al. Br J Cancer. 2015 Jul 14;113(2):299-310*
Current management of endometrial cancer

High stage cancer
- Endometrioid ca
- Serous ca
- Clear cell ca
- Dedifferentiated/undiff ca
- Carcinosarcoma

Chemotherapy (platinum and taxol-based)

- **Vaginal brachytherapy** for tumors with high-grade histology (stage 1A) and stage 1B low-grade tumors
- **Vaginal brachytherapy +/- pelvic RT** for stage 1B/stage 2 high-grade histology
Molecular subtype-driven management

Chemotherapy
PIK3CA/mTOR inhibitor...

Chemotherapy
Hormone therapy
PIK3CA/mTOR

Immunotherapy
+/- chemotherapy

Need for chemotherapy?
Brachy/Pelvic RT?

Copy number-high serous-like

Copy number-low endometrioid

MSI (hypermutated)

POLE (ultramutated)

Carcinosarcoma

Carcinosarcoma

Carcinosarcoma

Dedifferentiated/Undifferentiated carcinoma

Clear cell carcinoma

Chemotherapy
PIK3CA/mTOR inhibitor...

Chemotherapy
PIK3CA/mTOR inhibitor...

Epigenetic therapy
(HDAC/Polycomb) +/- chemotherapy

Anti-angiogenic Epigenetic therapy (ARID1A)
Endometrial Stromal Sarcoma

- Low-grade tumor: Chromosomal translocations → genetic fusions of genes/proteins in chromatin remodelling (i.e. polycomb complex proteins, histone acetyl/methyltransferase)
  - \( t(7;17)(p15;q21) \rightarrow JAZF1-SUZ12 \)
  - 6p21 rearranged \( \rightarrow JAZF1-PHF1, EPC1-PHF1^* \)
  - \( t(1;6)(p34;p21) \rightarrow MEAF6-PHF1^* \)
  - \( t(X;17) \rightarrow MBTD1-CXORF67 \)
  - \( t(X;22) \rightarrow ZC3H7B-BCOR^* \)

- These genetic fusions are seen in about 70% of LGESS (limited diagnostic value) – may be useful if unusual site or morphology

Variant Histology of LGESS

- Smooth muscle differentiation (*JAZF1-SUZ12, PHF1*-rearranged) (DDX: LM, LMS, ESN)
- Fibrous and fibromyxoid (*JAZF1-SUZ12, PHF1*-rearranged) (DDX: myxoid LM/LMS)
- Sex-cord-like elements (*JAZF1-SUZ12, PHF1*-rearranged) (DDX: UTROSCT)
- Epithelioid-type (*JAZF1-SUZ12*) (DDX: carcinoma, epithelioid LMS, PEComa)
- Gland differentiation (*EPC1-PHF1*) (DDX: Gland-poor adenomyosis)

*Oliva E, de Leval L, Soslow RA, Herens C. AJSP. 2007;31:1277-84.*
*Chiang et al, AJSP. 2011;35:1364-72.*
High-grade Endometrial Stromal Sarcoma

Lee et al, Proc Natl Acad Sci USA. 2012
17;109(3):929-34

Wild type

Fusion

Split reads

NUTM2A (FAM22)

Chr 17

Chr 10

NUTM2A (10p22.1)

NUTM2B (10p22.3)

YWHAE (17p13.3)
YWHAE-NUTM2 HGESS – Histologic Features

- Myopermeative tumor with LVI (similar to LGESS)

- High grade round cell area (present in nearly all cases)
  - Monomorphic nuclear features but with greater nuclear atypia compared to LGESS
    - Larger nuclei with more irregular contour
    - > 10MF/10HPF (average 21)
    - Tumor necrosis present

YWHAE-HGESS - high-grade area consistently shows diffuse strong cyclin D1 nuclear positivity (Low-grade variable)

Lee et al, AJSP. 2012;36(10):1562-70.
## YWHAE-NUTM2 ESS – Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>Average Age</th>
<th>Extrauterine spread</th>
<th>Adjuvant treatment</th>
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</thead>
<tbody>
<tr>
<td>LGESS JAZF1 (n=77)</td>
<td>48 (19-71)</td>
<td>16%</td>
<td>24%</td>
</tr>
<tr>
<td>HGESS YWHAE (n=38)</td>
<td>45 (23-67)</td>
<td>32%</td>
<td>75%</td>
</tr>
<tr>
<td>UUS/UES* (n=65)</td>
<td>59 (34-89)</td>
<td>35%</td>
<td>78%</td>
</tr>
</tbody>
</table>

*Negative for YWHAE, JAZF1 or PHF1 rearrangement by FISH
UES: undifferentiated endometrial sarcoma; UUS: undifferentiated uterine sarcoma
Molecular classification defines prognostically distinct groups of endometrial sarcoma

**WHO 2003 Classification**
- LGESS
- Undifferentiated endometrial sarcoma (UES)

**WHO 2014 Classification**
- LGESS w JAZF1-SUZ12
- LGESS fusion-neg
- HGESS w YWHAE-NUTM2
- UUS (UES) fusion-neg

![Graph showing survival curves for LGESS and UES with Log rank test P<0.001.]

![Graph showing survival curves for LGESS (JAZF1 and fusion-neg) and HGESS (YWHAE-NUTM2) with Log rank test P<0.001.]

Log rank test $P<0.001$
WHO 2014

**UUS*\(^\text{†}\):**
- Complex karyotype
- Post-menopausal
- Poor prognosis
  - (no effective treatment)

**HG ESS:**
- YWHAE-NUTM2
- Pre- and post-menopausal
- Intermediate prognosis
  - (adjuvant radiation/chemotherapy strategy if stage 2 or higher)

**LG ESS:**
- JAZF1-SUZ12
- JAZF1-PHF1
- EPC1-PHF1
- MEAF6-PHF1
- ZC3H7B-BCOR
- MBTD1-CXorf67
- Peri-menopausal
- Good prognosis
  - (anti-estrogenic therapy)

* Very rare dedifferentiated JAZF1-SUZ12 ESS
Next generation sequencing based assay - uses primers that target multiple “fusion genes of interest” to identify specific fusion transcript → ideal for ESS (with multiple known genetic fusions)

http://archerdx.com/fusionplex-assays/sarcoma
Summary

1. Molecular insights critical to further improve our tumor classification system (*POLE* mutated and MSI-H tumors tend to show heterogeneous and/or ambiguous histologic features)

2. Biomarkers (IHC and genetic) can improve diagnostic accuracy (*p53* and MMR IHC markers)

3. More work needed to determine the best management strategies (integrating molecular subtype in clinical trial design)