Molecular Gynaecological Pathology

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Outline

• What is Molecular Pathology?
• Lower Genital Tract
  – HPV infection
  – p16 immunostaining
• Endometrium
  – Molecular changes
  – Molecular classification
  – Stromal tumours
• Ovary, Fallopian tube and Peritoneum
  – Origins and types of epithelial tumour
  – Non-epithelial tumours
  – Patterns of genomic complexity
• Hereditary Gynaecological Tumours
Molecular Pathology

• Diagnostic Histopathology
  – Surrogate markers e.g. p16
  – ‘Genogenic’ immunohistochemistry
    • Identification of specific mutations e.g. TP53, BRAF
    • Identification of products of translocation e.g. t(2:5)
    • Identification of therapeutic targets e.g. HER2
    Gown AM Diagnostic Histopathology 2002; 8: 193-200
  – In situ hybridisation
    • FISH/CISH e.g. HER2, translocations, viruses

• Ancillary Molecular Testing
  – PCR-based methods – DNA/RNA
  – ‘omics’ technology
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Human Papillomavirus Infection and Anogenital Disease

- HPV infection is present in 99.7% of invasive cervical carcinomas
- Mucosal HPV infection can also cause vulval and vaginal pre-cancerous lesions and genital warts
p16^{INK4A} in Squamous Lesions
p16^{INK4A} in Glandular Lesions
Cervical Epithelial Lesions

Squamous cell tumours and precursors
- **Squamous intraepithelial lesions**
  - Low-grade squamous intraepithelial lesion (HPV only, CIN 1)
  - High grade squamous intraepithelial lesion (CIN 2, CIN 3)
- **Squamous cell carcinoma (keratinising, non-keratinising etc)**

Glandular tumours and precursors
- **Adenocarcinoma in situ (High grade CGIN)**
- **Adenocarcinoma**
  - Endocervical adenocarcinoma, usual type
  - Mucinous carcinoma, NOS
    - Gastric type (including adenoma malignum / minimal deviation adenocarcinoma)
    - Intestinal type
    - Signet-ring cell type
  - Villoglandular adenocarcinoma
  - Endometrioid adenocarcinoma
  - Clear cell adenocarcinoma
  - Serous adenocarcinoma
  - Mesonephric adenocarcinoma
  - Adenocarcinoma admixed with neuroendocrine carcinoma

Two Pathways to Vulval Neoplasia

HPV-related

• Young women
• Warty/basaloid (undifferentiated) vulvar intraepithelial neoplasia (VIN)
• Warty/basaloid carcinoma
• Associated with other intraepithelial lesions
• Same HPV types as CIN
• Predominance of HPV 16
• Mechanisms probably similar
• p16 is a surrogate marker
Two Pathways to Vulval Neoplasia

Non-HPV-related

- Older women
- Associated with lichen sclerosus
- Differentiated (simplex type) VIN
- Often well differentiated squamous cell carcinoma but clinically aggressive
- p16 negative
- ? p53 mutation important (Pinto et al, Mod Pathol 2010; 23: 404-412)
BUT
p16 as a Surrogate Marker of High-Risk HPV Infection

- In lower anogenital squamous intraepithelial lesions
  - Discrimination between high-grade SIL and mimics
  - Triage of ‘CIN 2’
  - Not for diagnosis of low-grade SIL
  - Only ‘block-type’ positivity should be considered positive
    Darragh et al Int J Gynecol Pathol 2013; 32: 76-11

- In lower genital tract tumours
  - Strong diffuse p16 positivity supports an HPV-associated aetiology
  - Endometrioid endometrial adenocarcinomas can be diffusely positive
  - Serous carcinomas are typically diffusely positive
  - Context is important and p16 should be used as part of a panel
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Endometrial Carcinoma

‘Type I’ tumours

- Endometrioid and mucinous phenotypes
- *PTEN, CTNNB1, KRAS, PIK3CA* mutations
- *PTEN* loss and mutation identifiable in morphologically normal proliferative glands
- Microsatellite instability
  - Germline mutation of MMR genes
  - Promoter hypermethylation esp *hMLH1*
Endometrial Carcinoma

• ‘Type II’ tumours
  – Serous and clear cell phenotypes
  – p53 mutation and overexpression
  – Inactivation of p16 and E-cadherin
  – PPP2R1A mutation in 41% of serous
    McConathy et al J Pathol 2011; 223: 567-573

• Ambiguous and mixed tumours
  – Overlapping morphological and molecular features
  – More frequently MSI-high
  – Dedifferentiation by acquisition of p53 mutation
    Soslow RA. Histopathology 2013; 62: 89-110
Endometrioid Ca

Non-endometrioid Ca

Normal epithelium

High-grade endometrioid Ca

Chromosome Instability
- LOH
- Amplification
- E-cadherin
- Cyclin D1
- Cyclin E
- STK15

p53
- MI, PTEN
- β-catenin

BAX
- TGFβ-RII
- IGF-IIR
- MSH3
- MSH6

p53
- PPP2R1A?
Diagnostic Algorithm?

• Tumours associated with *POLE* mutation
  – 65% microsatellite stable, 35% p53 mutant
  – Often high grade and morphologically ambiguous
    Hussein et al Mod Pathol 2014; doi: 10.1038/modpathol.2014.145
  – Excellent outcome
    Meng et al Gynecol Oncol 2014; 134: 15-19

• Microsatellite unstable tumours
  – MMR protein immunohistochemistry

• Serous-like tumours
  – *TP53* mutation

• Endometrioid tumours
  – None of the above
Translocations in Endometrial Stromal Tumours

- Recurrent translocations present in endometrial stromal nodules and sarcomas
- $t(7;17)(p15;q21)$ leads to fusion of $JAZF1$ and $SUZ12$
- Present in 92% of ESNs and 70% of low-grade ESSs
  
  
  
  Chiang & Oliva Adv Anat Pathol 2011; 42: 609-617

- $t(10;17)(q22;p13)$ $YWHAE$-$FAM22$ fusion identifies high-grade endometrial stromal sarcoma
  
  
  

- Undifferentiated uterine sarcoma
  - No specific pattern
**TABLE 3.** Molecular Translocations Identified in Endometrial Stromal Tumors, Named Sarcomas, and Other Tumors in Differential Diagnosis

<table>
<thead>
<tr>
<th>ESN</th>
<th>LG-ESS</th>
<th>HG-ESS*</th>
<th>UUS</th>
<th>LMS</th>
<th>LM</th>
<th>AS</th>
<th>CS</th>
<th>UTROSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAZF1-SUZ12</strong></td>
<td><strong>JAZF1-SUZ12</strong></td>
<td><strong>JAZF1-SUZ12</strong></td>
<td>Complex karyotype</td>
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<tr>
<td>(formerly <strong>JAZF1-JJAZ1</strong>)</td>
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<tr>
<td><strong>PHF1-JAZF1</strong></td>
<td><strong>MEAF6-PHF1</strong></td>
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<tr>
<td><strong>EPC1-PHF1</strong></td>
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</tbody>
</table>

*As defined by the **YWHAE-FAM22** translocation.

AS indicates adenosarcoma; CS, carcinosarcoma; ESN, endometrial stromal nodule; HG-ESS, high-grade endometrial stromal sarcoma; LG-ESS, low-grade endometrial stromal sarcoma; LM, leiomyoma; LMS, leiomyosarcoma; UTROSCT, uterine tumor resembling ovarian sex cord tumor; UUS, undifferentiated uterine sarcoma.
## WHO Classification of tumours of the uterine corpus

### Epithelial tumours and precursors

**Precursors**
- Hyperplasia without atypia
- Atypical hyperplasia / Endometrioid intraepithelial neoplasia 8380/2*

**Endometrial carcinomas**
- Endometrioid carcinoma 8380/3
- Squamous differentiation 8570/3
- Villoglandular 8263/3
- Secretory 8382/3
- Mucinous carcinoma 8480/3
- Serous endometrial intraepithelial carcinoma 8441/2*
- Serous carcinoma 8441/3
- Clear cell carcinoma 8310/3

### Neuroendocrine tumours

- Low-grade neuroendocrine tumour
  - Carcinoid tumour 8240/3
- High-grade neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma 8041/3
  - Large cell neuroendocrine carcinoma 8013/3
- Mixed cell adenocarcinoma 8323/3
- Undifferentiated carcinoma 8020/3
- Dedifferentiated carcinoma

### Miscellaneous mesenchymal tumours
- Dissecting (cotyledonoid) leiomyoma 8890/0
- Diffuse leiomyomatosis 8890/1
- Intravenous leiomyomatosis 8890/1
- Metastasizing leiomyoma 8898/1
- Smooth-muscle tumour of uncertain malignant potential 8897/1
- Leiomyosarcoma 8890/3
- Epithelioid leiomyosarcoma 8891/3
- Myxoid leiomyosarcoma 8896/3
- Endometrial stromal and related tumours
  - Endometrial stromal nodule 8930/0
  - Low-grade endometrial stromal sarcoma 8931/3
  - High-grade endometrial stromal sarcoma 8930/3
  - Undifferentiated uterine sarcoma 8805/3
  - Uterine tumour resembling ovarian sex cord tumour 8590/1
- Rhabdomyosarcoma 8900/3
- Perivascular epithelioid cell tumour
  - Benign 8714/0
  - Malignant 8714/3
- Others
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# Ovarian Epithelial Tumours

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<tr>
<td>Grade 1</td>
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<td>![Diagonal Stripe]</td>
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<tr>
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Modified from Gilks CB. Int J Gynecol Pathol 2004; 23: 200-205
High-Grade Serous, Endometrioid and Unclassified Tumours

- Loss of BRCA1/BRCA2 function
  - Germline/somatic mutation; loss of heterozygosity
  - Promoter hypermethylation
  - Amplification of EMSY

- Unable to repair dsDNA breaks
  - Complex karyotypes

- TP53 mutation common in high-grade serous carcinoma (almost 100%)
  - Ahmed et al J Pathol 2010; 221: 49-56

- WT1 immunopositive and p53 aberrant (diffuse or absent)

- Most of tubal origin?
High Grade Serous Carcinoma
Low-grade Serous Tumours

- *BRAF* and *KRAS* mutation common in borderline and invasive tumours (60-65%)
- *p53* mutation uncommon (<10%) and often diploid
- Fewer karyotypic and other molecular abnormalities than high-grade tumours
- Diagnosis
  - Two-tier grading system based on nuclear atypia alone
- Treatment
  - Differences in chemosensitivity
    - Santillan A et al Int J Gynecol Cancer 2007; 17: 601-606
Immunohistochemical Detection of *BRAF* V600E Mutation
Low-grade serous tumours

- **KRAS** mutation in serous borderline tumours associated with recurrent low-grade serous carcinoma
  Tsang et al J Pathol 2013; 231: 449-456

- **BRAF V600E** mutation associated with senescent phenotype in serous borderline tumours

- **NRAS** mutation restricted to invasive component in serous carcinomas with adjacent borderline regions
  Emmanuel et al Clin Cancer Res 2014; Epub Oct 14, 2014
## Ovarian Epithelial Tumours

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<th>Borderline/LMP</th>
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<th>Grade 3</th>
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Mucinous Tumours

• Borderline tumours, microinvasive and invasive carcinomas

• *KRAS* but not *BRAF* mutations common

• True primary tumours are uncommon (6 of 220 ovarian carcinomas - Seidman et al. Int J Gynecol Pathol 2004; 23: 41-4)

• *HER2* amplification in approx 20% of primary mucinous carcinomas (clinical significance unclear) (Anglesio et al J Pathol 2013; 229: 111-120)

• Must rigorously exclude metastases
# Ovarian Epithelial Tumours

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Clear Cell Carcinoma

- Associated with endometriosis
- Also associated with Lynch syndrome
- Not clear if can separate low and high grade groups
- Some evidence that tumours associated with endometriosis less aggressive than those associated with clear cell adenofibroma


- Inactivating mutation of *ARID1A* in approx 50%, activating mutation of *PIK3CA* in approx 50%, deletion of *PTEN* in approx 20%

  Kurman and Shih *Hum Pathol* 2011; 42: 918-931
  Lowery et al *Int J Gynecol Cancer* 2012; 22: 9-14
# Ovarian Surface Epithelial Tumours

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Low-Grade Endometrioid Tumours

- Association with endometriosis and endometrioid hyperplasia
- Also associated with Lynch syndrome
- Borderline endometrioid tumours
  - Borderline adenofibroma
  - Atypical hyperplasia in endometriosis
- *Beta-catenin* mutation common (16 - 54%)
  - occurs in endometriosis and tumours
- *ARID1A* mutation in approx 50%
- *PTEN* mutation in approx 20%
- Boundary with high-grade tumours?
  - WT1 and p53 useful
Kurman and Shih Hum Pathol 2011; 42: 918-931
Kurman and Shih Hum Pathol 2011; 42: 918-931
FOXL2 in ovarian sex cord-stromal tumours

- C134W FOXL2 mutation identified in 4 index adult-type granulosa cell tumours
- Present in 86/89 (97%) aGCTs, 3/14 thecomas, 1/10 jGCTs
- Absent in 49 other sex cord stromal tumours and 329 other ovarian and breast tumours
  - Shah et al NEJM 2009; 360: 2719-2729
FOXL2 in ovarian sex cord-stromal tumours

- C134W mutation in 53/56 aGCTs, 2/6 thecomas but none of remaining 1281 tumours from a range of sites
  - Kim et al J Pathol 2010; 221: 147-152
- Mutation present in 18/20 aGCT and 0/3 jGCTs
  - Kim et al Histopathology 2010; 56: 408-410
- Mutation present in 52/56 aGCTs; ?3/4 negative cases mis-diagnosed
  - Jamieson et al Mod Pathol 2010; 23: 1477-1485
- FOXL2 immunohistochemistry sensitive (80%) and specific (99%) marker of SCSTs but not aGCT specifically
- Mutation testing useful in ambiguous cases
  - Kommoss et al Histopathology 2014; 64: 380-388
Small Cell Carcinoma of Hypercalcaemic Type

- *SMARCA4* mutation redefines this tumour as a rhabdoid tumour
- Identified by whole-exome sequencing
- Mutation may be germline
- Leads to loss of expression of BRG1

Witkowski et al Nat Genet 2014; 46: 438-443
BRG1 Loss in Small Cell Carcinoma, Hypercalcaemic Type

Foulkes et al J Pathol 2014; 233: 209 - 214
## Possible Therapeutic Approaches

<table>
<thead>
<tr>
<th>Mutational spectrum</th>
<th>High Complexity Cancer</th>
<th>Moderate Complexity Cancer</th>
<th>Low Complexity Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian tumour example</td>
<td>High-grade serous carcinoma</td>
<td>Clear cell carcinoma</td>
<td>Granulosa cell tumour</td>
</tr>
<tr>
<td>Inter- and intratumoural heterogeneity</td>
<td>Profound</td>
<td>Unknown</td>
<td>Minimal</td>
</tr>
<tr>
<td>Therapeutic approach</td>
<td>Personalised</td>
<td>Stratified</td>
<td>Generic</td>
</tr>
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Concept courtesy of David Huntsman
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Hereditary Gynaecological Tumours

- Breast-ovarian cancer syndrome
- Site-specific ovarian cancer syndrome
- Lynch syndrome
- Other syndromes
  - Peutz-Jeghers
  - Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)
  - Gorlin syndrome
  - Cowden syndrome
  - (Small cell carcinoma, hypercalcaemic type)

BRCA 1 and 2 Mutation

High-grade serous and undifferentiated carcinomas

# Lynch Syndrome

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Probability</th>
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<tbody>
<tr>
<td>Colorectum</td>
<td>25-50%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>25-70%</td>
</tr>
<tr>
<td>Ureter and renal pelvis</td>
<td>10%</td>
</tr>
<tr>
<td>Ovary</td>
<td>10%</td>
</tr>
<tr>
<td>Stomach</td>
<td>10%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>5%</td>
</tr>
<tr>
<td>Brain (usually glioblastoma)</td>
<td>4%</td>
</tr>
<tr>
<td>Skin (sebaceous adenoma/carcinoma)</td>
<td>4%</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
</tr>
</tbody>
</table>
Lynch Syndrome – Ovarian Carcinomas

- 2-4% of ovarian carcinomas
- Occur at younger age
- 85% clear cell
- 10% endometrioid
- Associated particularly with MSH2 and MSH6 mutations
MMR deficiency identified in 10/48 consecutive non-serous ovarian carcinomas

All were of endometrioid or clear cell type

‘Given the widespread availability of MMR-IHC, reflex testing for MMR deficiency is recommended for non-serous OCs, particularly of endometrioid or clear cell type’.

# Other Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Gynaecological Tumours</th>
<th>Associated Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td><em>STK11/LKB1</em></td>
<td>Ovary – sex cord stromal tumours (5-15% risk) Cervix – adenoma malignum</td>
<td>Hamartomatous GI polyps Breast, GI, lung, pancreas, testis cancers</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)</td>
<td><em>Fumarate hydratase</em></td>
<td>Uterus – leiomyomas with prominent nucleoli and perinuclear halos</td>
<td>Renal cell carcinoma (15% risk) Cutaneous leiomyomas</td>
</tr>
<tr>
<td>Gorlin syndrome (neviod basal cell syndrome)</td>
<td><em>PTCH</em></td>
<td>Ovary – fibromas, bilateral and calcified (2-25% risk)</td>
<td>Basal cell carcinomas Odontogenic keratocysts Medulloblastomas</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td><em>PTEN</em></td>
<td>Uterus – leiomyomas, endometrial carcinoma (5-20% risk)</td>
<td>Hamartomas of GI tract, skin etc Breast (25-50% risk) and thyroid (3-10% risk) carcinomas</td>
</tr>
</tbody>
</table>

Summary

• Lower Genital Tract
  – p16 is a useful surrogate marker of high-risk HPV infection
  – Staining pattern and context are important

• Endometrium
  – Improved molecular understanding may lead to a diagnostic algorithm for endometrial carcinomas, involving p53 and MMR protein immunostaining
  – Endometrial stromal tumours have characteristic translocations

• Ovary, Fallopian tube and Peritoneum
  – The different types of epithelial ovarian carcinoma have different anatomical and molecular origins
  – Identification of specific molecular abnormalities may indicate type (e.g. p53, WT1) and possibly behaviour (e.g. BRAF)
  – Some (rare) ovarian tumours have defining mutations e.g. FOXL2, SMARCA4

• Hereditary Gynaecological Tumours
  – Patients with high-grade serous carcinoma should have BRCA gene testing
  – MMR immunohistochemistry should be performed on ovarian endometrioid and clear cell carcinomas