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[88] Intracystic Papillary Carcinoma (IPC) of the Breast: A Clinicopathological Study of 125 Cases

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- **Background:** IPC is an uncommon breast neoplasm. Because of its rarity, data about its epidemiology is limited. On the other hand, IPCs have traditionally been considered to be a variant of ductal carcinoma in situ, however, it is not clear if some of these lesions might represent a special type of invasive carcinoma. The goals of this study were: to identify specific characteristics of patients (pts) with IPCs and investigate its natural history (behavior).
- **Design:** We searched the pathology database from 1990-2010 for IPC and solid papillary carcinomas (SPCs). Two pathologists reviewed all H&E slides. We evaluated the expression of myoepithelial cell (MEC) markers, p63 and calponin as well as the expression of Estrogen Receptors (ER), Progesterone Receptors(PR) and HER2 in all cases. Clinical management and follow-up were obtained from clinical charts.
- **Results:** 106 (85%) intracystic and 19 (15%) solid papillary carcinomas were the study group. The mean age at diagnosis was 59 years and the mean tumor size 2.2cm. From 106 IPCs cases, 82 were pure, 14 were IPC with microinvasion (IPC+Mi), and 10 cases were IPC with invasive carcinoma (IPC+IC). Six (32%) of SPCs were associated with invasive carcinoma (SPC+IC). All 125 cases showed complete absence of MEC at the periphery of the nodules, also, all tumors were ER and PR positive and HER2 negative. 52 pts underwent mastectomy, of these, 6 cases with IPC+IC, 3 with SPC+IC, 2 with pure IPC and 1 with pure SPC, respectively, had lymph node metastases. 73 pts underwent lumpectomy, of these pts, 48 received radiation and 25 hormonal treatment. Eight of 73 (11%) pts treated conservatively (1 with pure IPC, 4 with IPC+IC, one with IPC +Mi, and 2 with SPC+IC) recurred locally, including one who later developed lung metastases.
- **Conclusions:** Pure IPCs and SPCs: have excellent prognosis; because they are strongly ER and PR positive, hormonal therapy should be pursued for its management; routine use of chemotherapy is clearly not appropiate. Sentinel Lymph node biopsy may be a prudent way to evaluate axillary involvement.

Category: Breast

[102] Patterns of Oncotype DX Recurrence Scores – Analysis Based on Levels of ER & PR Expression and Proliferation Markers

Meredith Burge, Steven Frame, Patrick McGrath, Edward Romond, Marie-Louise Fjallskog, Cecilia Ahlin, Michael Cibull, Yolanda Brill, Luis M Samayoa. University of Kentucky, Lexington, KY; Uppsala University, Uppsala, Sweden

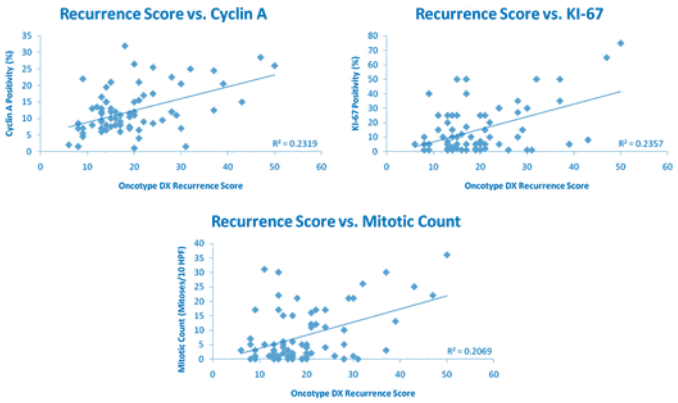
- **Background:** In 2010 we reported that in 20 – 30% of patients undergoing Oncotype DX, the test was probably of no clinical significance, since Low (L) and High (H) Recurrence Scores (RS) for Grade (G) I & GIII tumors could be accurately predicted based on tumor differentiation, Progesterone (PR) status (+/-) and high Estrogen (ER) expression (95% of tumor cells). We currently test the possibility of identifying other groups of ER (+) patients with predictable RS by analyzing the role of proliferation markers (PM) and levels of PR expression in the same patient population.
- **Design:** Histopathologic material from 72 patients with known Oncotype DX RS was analyzed for the following: tumor grade (Elston Modification of Bloom-Richardson Score), levels (%) of ER and PR expression, proliferating index (PI) according to Cyclin A and Ki-67 expression (%), and number of mitoses in 10 high power fields (HPF). All analyses were performed in sections from definitive surgical specimens. Levels of ER, PR, Ki-67 and Cyclin A were performed by Immunohistochemistry (IHC) and scored by a consensus of 3 pathologists. Each variable was then correlated with the corresponding RS.

Results: See Figures I and 2

Table 1. Oncotype DX Recurrence Scores according to PR expression and average Cyclin A and Ki-67 levels

Patients with > 80% ER (+)	PR expression (%)				Oncotype DX (RS)			Avr RS	Aver Cyclin A (%)	Aver Ki-67 (%)	Aver Mitotic count/10H PF
	0	1 - 30	31 - 75	76 - 100	Low (0 - 18)	Int (19 - 31)	High (31 - 50)				
GI PR (+/-) (n = 18)	3	3	1	11	16	2 (<20)*	-	13	8.8	4.5	1.6
GII PR (+) (n = 18)	-	-	-	18	11	7 (<21)*	-	16	11	10	4.4
GII PR (+) (n = 15)	-	11	4	-	5	9	1	20	12	17	5
GII PR (-) (n = 4)	4	-	-	-	-	4	-	25	8	11.6	3.6
GIII PR (+) (n = 11)	-	-	4	7	7	2	2	21	17	21	23
GIII PR (+) (n = 3)	-	3	-	-	-	2	1	33	16	30	20
GIII PR (-) (n = 3)	3	-	-	-	-	1	2	40	22	37	26

*Actual RS



Conclusions: 1) The combination of tumor grade and levels of PR expression in patients with tumors showing >80% (+) ER are predictors of Oncotype RS. 2) Although average values of Cyclin A, Ki-67 and mitotic counts correlated with average RS accordingly, regression analysis failed to show an acceptable correlation in predicting RS scores individually. 3) Depending on clinical judgement, these observations may result in stricter indications for Oncotype DX, i.e.: only in patients with GII < 75% PR (+) tumors and GIII > 30 % PR (+) tumors, ultimately resulting in cost containment equivalent to > 50% (28/72) of resources currently disbursed without clinical validation.

Category: Breast

[106] Lobular Neoplasia on Core Needle Biopsy: Clinical and Radiopathologic Correlation Study with Follow-Up Excision Biopsy of 87 Cases

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- **Background:** Lobular neoplasia(LN) which includes Lobular carcinoma in situ (LCIS) and Atypical lobular hyperplasia (ALH) may be identified in breast core biopsies as an incidental finding with microcalcifications, mass lesion or indeterminate enhancements. Several studies have shown variable upgrade rates (1-40%), but many of these are limited by small sample size, selection bias and discordant radiopathologic correlation. The aim of our study was to assess the risk of invasive carcinoma/DCIS at the site of the isolated LN diagnosis on core biopsy and to assess any significant factors associated with the upgrade.
- **Design:** The data base was searched for breast core biopsies from Jun 06- Jun 11 with the diagnosis of LCIS/ALH. Any case with coexistent pleomorphic LCIS, ADH, flat epithelial atypia, papilloma or radial scar was excluded from the study. Core and excision biopsy slides of all cases were reviewed using Page's criteria. Radiopathologic correlation was done for all cases. 87 cases with follow up excision biopsy qualified for study. Presence of invasive carcinoma/DCIS in direct correlation to initial biopsy site with LN defined the lesion as upgrade. The proportion of upgrade on excision and 95% confidence intervals (CI) were calculated.
- **Results:** Our study consisted of 83 females, mean age 55 yrs (age range=37-88yrs) with 87 core biopsies showing isolated LN (22 ALH, 44 LCIS and 21 ALH&LCIS). Of these, 13 had family history and 28 had history of breast cancer (2 bilateral, 16 contralateral and 10 ipsilateral). Core biopsy indication included calcification in 36 (41%), non mass like enhancements in 17 (20%) and solid nodules or mass enhancement 34 (39%). 3/87 (3.4%) cases upgraded on excision biopsy. The upgraded lesions included low grade invasive ductal carcinoma (6mm), invasive lobular carcinoma (4mm) and pleomorphic LCIS with focal low grade DCIS. 2 of the upgraded cases were BIRADS 6 and 1 was BIRADS 4a. LCIS extent and associated microcalcifications showed no correlation with upgrade.
- **Conclusions:** With a good sample size and radiopathologic correlation, our study showed a 3.4%(95%CI, 1-10%) upgrade on follow up excision for core biopsy with isolated LN. Our study essentially highlights benign outcome for isolated ALH/LCIS on core biopsy and gives a valid reason for rethinking the current practice of surgical excision for these patients.

Category: Breast

[121] Pathologic Upgrade (PU) Rates on Subsequent Excisional Biopsy (EXBX) When Lobular Carcinoma In Situ (LCIS) Is Found in a Needle Core Biopsy (NCB) with Emphasis on Radiologic Correlation

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- **Background:** Management of lobular carcinoma in situ (LCIS) on NCB is uncertain as studies report a wide range of PU (3-35%) in the EXBX. This range can be attributed to the design of individual studies [pre-selection bias, radiologic correlation, and characteristics of LCIS [classical vs. non-classical; nuclear grade; extent; calcifications (calcs), if applicable]. We set out to determine the PU rate when LCIS is found in NCB at our institution.
- **Design:** NCB samples containing LCIS as the most significant lesion in patients (pts) who underwent subsequent EXBX were identified (2001-2011). Microscopic features including architecture (florid vs. non-florid vs. both), nuclear grade, percentage of cores involved by LCIS, concurrent columnar cell lesion (CCL), and the presence/absence of calcs within LCIS were recorded. The most significant lesion was recorded from each corresponding EXBX. PU was defined as the presence of invasive carcinoma, ductal carcinoma in situ (DCIS), and pleomorphic LCIS (in cases where only classical LCIS was present in NCB) in the EXBX.
- **Results:** 62 pts with LCIS in NCB who underwent EXBX were identified. Analyzed as a single group, PU was 11% (7/62). The percentage of cores involved by LCIS was significantly associated with PU (p=0.02). Characteristics present in the NCB such as architectural type of LCIS, nuclear grade, presence of CCL, or presence of calcs within LCIS did not correlate with PU. The results were re-analyzed with radiologic correlation. Of 62 cases, 51 (82%) were targeted for calcs, where 11 (22%) had calcs only in LCIS. Of these 11 cases, 3 (27%) had a PU on EXBX (1-microinvasive carcinoma; 2-DCIS). In 26 cases (51%), targeted calcs were found in both LCIS and benign lesions; of these, 3 (12%) had a PU on EXBX (1-invasive ductal carcinoma, 1-invasive lobular carcinoma, 1-pleomorphic LCIS). Cases of purely incidental LCIS (24/62; 39%) showed a PU of 4% (1/24) (1-DCIS).
- **Conclusions:** PU in EXBX is significant (27%) if the targeted lesion is calcs which are exclusively associated with LCIS. If targeted calcs are found in both a benign lesion as well as LCIS, PU in EXBX remains significant (12%). However, for purely incidental LCIS found in NCB, PU is much lower (4%) and thus, foregoing EXBX may be reasonable in these pts. Our study underscores the importance of radiologic correlation when determining the PU in EXBX for pts with LCIS on NCB.

Category: Breast

[130] Routine Excision Is Necessary for Lobular Neoplasia Detected on Breast Core Needle Biopsy: Experience from a Large Women's Health Center

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- **Background:** Lobular neoplasia (LN) is regarded as a risk indicator for the development of breast carcinoma. The significance of these lesions in core biopsy with respect to the need for surgical re-excision is controversial. The specific aim of this study was to ascertain pathologic findings of surgical follow-up excision (FUE) on patients who had LN on core biopsy.
- **Design:** Core biopsies of breast from 2006-2011 with a diagnosis of LN with or without ADH, with no h/o invasive carcinoma (IC) or DCIS were studied. Cases were divided into: group 1 (pure LN) and group 2 (LN+ADH). Each group was further sub-divided into ALH or LCIS. Cases were considered to be upstaged if FUE showed IC or DCIS. Radiologic images, BIRADS and time between biopsy and FUE were recorded from the data files.
- **Results:** 807 cases of LN were identified out of 20260 breast core biopsies (4%). 240 cases were excluded due to history or synchronous IC or DCIS (29.7%). Among the remaining 567 cases, 466 (82.2%) with FUE were included in the study. Patients were divided into groups as follow: ALH (235; 50%), LCIS (125; 27%), ALH+ADH (80; 17%) and LCIS+ADH (26; 6%). LN was confirmed by E-cad/P120 dual stain (263/466; 56.4%) or E-cad (70; 15%). The radiological abnormalities were calcification (78.5%), mass (14.2%) or other in 7.3%. The BI-RADS for group 1 were: score 4 in 256/260 (98.5% only 1 case score 5), and scores 3&5 in 4 cases (1.5%). For group 2, the BIRADS were: 4 in 78/80 (97.5%) and score 3 in 2 cases (2.5%) with no significant difference in relation to upstaging. The time interval between the core biopsy and FUE range from 0.3-7 month (mean 1.4) with significant difference in relation to upstaging in group 2. 28/360 (7.8%) and 17/106 (16.0%) of group 1 and group 2 cases upstaged to IC or DCIS (Table 1).

Table (1) Upstaging of LN on surgical follow-up excision

	ALH (%)	LCIS (%)	ALH+ADH (%)	LCIS+ADH (%)	Total (%)
IC	5 (2.1)	8 (6.4)	6 (7.5)	5 (19.2)	24 (5.2)
DCIS	8 (3.4)	7 (5.6)	3 (3.8)	3 (11.5)	21 (4.5)
ADH	47 (20)	25 (20)	40 (50)	7 (26.9)	119 (25.5)
Not upstaged	175 (74.5)	85 (68)	31 (38.7)	11 (42.4)	302 (64.8)
Total	235	125	80	26	466

Chi square test, P=0.0001

- **Conclusions:**

1. This is the largest study on patients with diagnosis of LN on core biopsy and FUE.
2. LN with or without ADH is a definite risk factor for upstaging to IC and/or DCIS.
3. The risk of upstaging on FUE for LCIS is more than that of ALH (15.2% vs. 7.0%) (p=0.0001).
4. Our data indicate that excision of the biopsy site is prudent for all patients with LN on core biopsy due to the significant percentage of cases which found to be upgraded to IC or DCIS.

Category: Breast

[138] Do Combined Histopathological Features of ER Positive Breast Carcinoma Correlate with OncotypeDx Recurrence Score?

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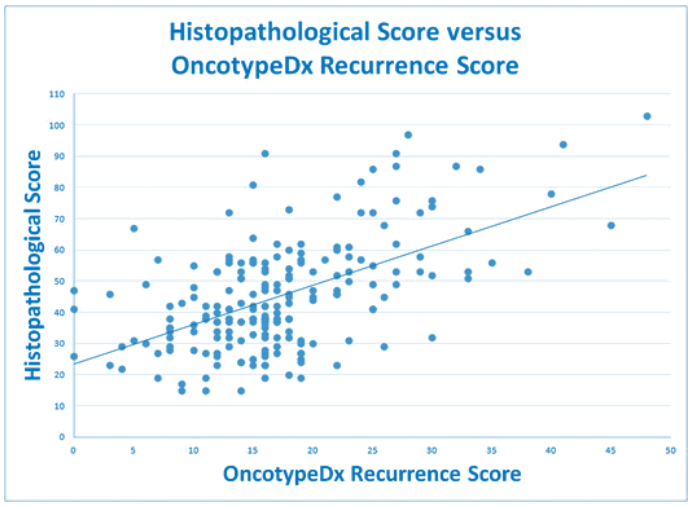
- **Background:** Gene expression assays, such as OncotypeDx (ODx), show promise to predict recurrence and help guide treatment of the heterogeneous group of estrogen receptor (ER) positive breast carcinomas, including cases with metastatic disease in lymph nodes. However, this technology is relatively costly and patient selection criteria are subjective. Histopathological features, along with ER, progesterone receptor (PR), and HER2 status, are routinely reported and remain the current gold standard for predicting response to treatment and prognosis. This study aims to correlate routine histopathological features with ODx Recurrence Score (ODxRS) and seeks to determine if a subgroup of cases may not benefit from the added cost of ODx.
- **Design:** The slides and charts of 206 patients who had ODx performed between July 2004 and July 2011 were examined. Ten histopathological parameters were evaluated and assigned value including tumor size, tubule formation, nuclear grade, mitotic count, lymphovascular invasion, lymph node status, quantitative ER and PR (using current CAP reporting standards), HER2 status, and extent of adjacent DCIS. A formula was developed to calculate a Histopathological Score (HS) combining nine weighted parameters (DCIS was excluded). The weight of each parameter was based on the strength of correlation with the reported ODxRS. The total HS for each case was compared to the ODxRS.
- **Results:** Histopathological grade along with ER, PR, and HER2 status significantly correlated with ODxRS. Additionally, cases with a combined HS of ≤50 correlated with an ODx score of ≤30 (n=141, 69% of total cases). All resultant scores correlated with ODx scores with an R=0.565 (Figure 1). The extent of DCIS did not correlate with ODxRS. Nodal status, lymphovascular invasion, and tumor size did not independently correlate with the ODxRS.



- **Conclusions:** Routinely obtained histopathological parameters can predict an ODxRS of ≤30 when the calculated HS is ≤50 (69% of our cases); therefore, it may not be necessary to perform ODx testing in these cases. Further studies are needed to validate the utility of combined HS in selecting cases for ODx testing.

Category: Breast

[153] The University of Kentucky Model for Selecting Breast Cancer Patients for Oncotype DX Testing

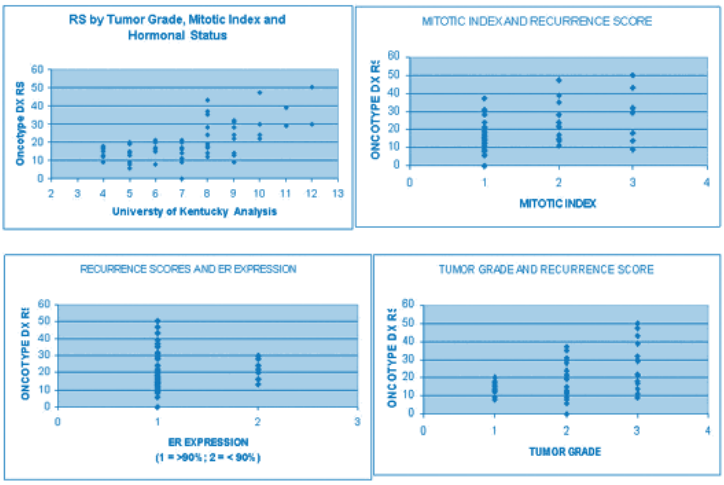
Steven Frame, Meredith Burge, Nicole Miller, Yolanda Brill, Rahul Matnani, Patrick McGrath, Marie-Louise Fjallskog, Luis M Samayoa. University of Kentucky, Lexington, KY; VAMC, Lexington, KY; Uppsala University, Uppsala, Sweden

- **Background:** Currently, the decision on treatment of Estrogen Receptor (ER) (+), Her2-neu (-), N0-1a patients is largely supported by molecular tests such as Oncotype DX. While the benefits of this test are indisputable, the guidelines for ordering it are non-specific and may lead to over-utilization at a significant cost. This study presents a model for Oncotype DX testing, based on common morphologic (H&E) and Immunohistochemical (IHC) variables already established in our daily practices.
- **Design:** Recurrence Scores (RS) from 72 randomly selected N0 patients were compared to levels (%) of ER, Progesterone Receptors (PR), Ki – 67, Cyclin A, Mitotic Index (MI) and Tumor Grade (TG) using univariate regression analyses. Although no one variable showed a significant R value, the ones that correlated the most were selected and given a numerical score according to cut-off levels either previously described (MI and TG) or encountered while performing the analyses (ER and PR) (see table 1). Subsequently, all patients were scored accordingly and paired with their corresponding RS.

Univeristy of Kentucky Model for Oncotype DX testing					
	1	2	3	4	5
ER expression %	>90	<90			
PR expression %	90 - 100	70 - 90	30 - 70	1 - 30	0
Mitotic Index*	I	II	III		
Tumor Grade*	1	2	3		

Based on the modified combined Bloom Richardson Score

- **Results:** See Figures 1A-D



- **Conclusions:** Although limited by the number of patients and depending on individual practices, results from this study suggest that only patients with scores of 8 and 9 will benefit from Oncotype DX. Patients with scores of 4-7 and > 10 will probably not benefit from the test since their RS are predictable to be low (< 21) and high (>25) respectively. In addition, RS of < 10 were not found in patients with tumors showing <90% ER (+), MI > I and in grade III tumors. These observations indicate that the model may be useful even after the results from the TAILOR X trial become available.

Category: Breast

[155] Clinical Outcome of Intracystic and Solid Papillary Carcinomas of the Breast

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- **Background:** Papillary carcinoma (PC) of the breast accounts for 0.5 to 1% of breast cancer. The localized form of PC encompasses both the intracystic/encysted (IPC) and solid (SPC) variants, which are typically circumscribed and often encapsulated (separated from the surrounding mammary stroma by a fibrous capsule) and lack myoepithelial layer at their periphery. Hence the term encapsulated PC (EPC) has been introduced. IPC is usually confined to a dilated cystic space and is surrounded by a fibrous capsule. Compared to IPC, SPC is typically solid, characterized by mucin production and neuroendocrine features, and is more often multinodular. IPC and SPD have long been regarded as a form of in-situ carcinoma but the observation of the absence of a myoepithelial cells at the tumor stromal interface has led to the proposal that these lesions are, in fact, invasive carcinomas with an expansile growth pattern. This concept is supported by the results of some studies which reported cases of axillary nodal or distant metastases. The purpose of our study is to assess the clinical features, behavior and outcome of IPC and SPC in our population in regards to its clinical outcome in order to better understand the pathophysiology of these lesions.
- **Design:** All cases of IPC and SPC were retrieved using SnoMed search from 1994 to 2011. The clinical-pathologic features including post-surgical treatment and outcome (recurrence, metastasis and death) were investigated and recorded. Descriptive and inferential analysis was performed.
- **Results:** See Table 1

Table 1. Results

Variables	IPC (21)	SPC (12)
Median age (mean)	68.7 (70.3)	72.2 (69.9)
Histologic grade	100 % low grade	91.7% low grade, 8.3% immediate grade
Mean tumor size (range)	1.4 cm (0.5- 2.5 cm)	1.8 cm (0.6 - 4.3)
Associated DCIS	38.1% (8/21)	25%(3/12)
Invasive ductal carcinoma IDC	33.3% (7/21)	50.0% (6/12)
Lymph node (LN) status (positive)	0.09% (1/11)	0.12% (1/8)
Reccurence	0.05% (1/21)	0
Mean folow up time (years)	4.2 (0-11)	1.5 (0.1-5.4)
Metastasis or death of disease	None	None

- **Conclusions:** These lesions tend to occur in older women. Almost one third of the cases were accompanied by DCIS or IDC. Only patients with invasive disease developed LN metastasis, however recurrence is very rare and so its distant metastasis. As previously reported, these patients had excellent survival.

Category: Breast

[182] Prediction of Oncotype DX Recurrence Score: Use of Equations Derived by Linear Regression Analysis

Molly E Klein, David J Dabbs, Yongli Shuai, Rohit Bhargava. University of Wisconsin, Madison, WI; Magee-Womens Hospital of UPMC, Pittsburgh, PA; University of Pittsburgh Cancer Institute, Pittsburgh, PA

- **Background:** *Oncotype* DX® is a quantitative reverse transcription polymerase chain reaction based assay, shown to have prognostic and predictive value in estrogen receptor (ER) positive breast cancers. The *Oncotype* DX® recurrence score (RS) ranges from 0-100, divided into low, intermediate or high risk categories (LR <18, IR 18-30, HR ≥31). Morpho-immunohistologic correlation studies have shown that RS is heavily influenced by ER and progesterone receptor (PR) H-scores, HER2 status, Ki-67 proliferation index, and tumor grade. Our pilot study of 42 cases (Mod Pathol. 2008;21:1255-1261) showed that RS can be predicted by the following (old Magee equation, oME): RS =13.424 + 5.420*(nuclear grade) + 5.538*(mitotic count) - 0.045*(ER H-score) - 0.030*(PR H-score) + 9.486*(0 for HER2 negative, 1 for positive).
- **Design:** We used a dataset of over 800 cases to formulate three new RS equations, then used each equation to calculate a RS for an independent set of 162 cases.

  new Magee Equation 1 (nME1): RS = 15.31385 + Nottingham score*1.4055+ ER H-score*(-0.01924) + PR H-Score*(-0.02925) + (0 for HER2 negative, 0.77681 for equivocal, 11.58134 for positive) + Tumor size*0.78677 + Ki-67*0.13269.

  nME2: RS = 18.8042+ Nottingham score*2.34123 + ER H-Score*(-0.03749) + PR H-Score*(-0.03065) + (0 for HER2 negative, 1.82921 for equivocal, 11.51378 for positive) + Tumor size*0.04267.

  nME3: RS = 24.30812+ ER H-Score*(-0.02177) + PR H-Score*(-0.02884) + (0 for HER2 negative, 1.46495 for equivocal, 12.75525 for positive) + Ki-67*0.18649.

- **Results:** The concordance between RS category by *Oncotype* DX® and Magee equations was 54.6% (88/161), 55.7% (87/156), 59.7% (95/159), and 54% (86/159) for oME, nME1, nME2, and nME3 respectively. When the IR category was eliminated, the concordance increased to 95.4% (62/65), 100% (52/52), 98.1% (52/53), and 98.1% (53/54) for oME, nME1, nME2, and nME3 respectively. The mean (median) RS for *Oncotype* DX® was 20 (19), compared to 17.5 (16) for oME, 19.9 (18.8) for nME1, 19.8 (19.6) for nME2 and 19.3 (18.5) for nME3.
- **Conclusions:** Any of the four equations may be used to calculate a RS, using reported pathologic findings. When the calculated RS is LR or HR, the concordance with the *Oncotype* DX® RS is very high, and *Oncotype* DX® testing may even be avoided. Conversely, pathologists should investigate any *Oncotype* DX® RS that is dramatically different than expected based on pathologic findings, to ensure accuracy of the *Oncotype* DX® result.

Category: Breast

[255] Invasive Lobular Carcinoma and Oncotype Dx®: Impact of Pathology and Recurrence Score on Treatment Plan

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- **Background:** Oncotype Dx® Breast Cancer Assay is a 21-gene assay that predicts whether certain patients with ER-positive breast cancer will benefit from chemotherapy. The goal of this project is to examine the impact of pathology and Oncotype Dx® Recurrence Score (RS) on the treatment plan for invasive lobular carcinoma (ILC).
- **Design:** A search of the 2008-2011 pathology database was performed for cases of ILC submitted for Oncotype Dx® testing. The pathology, test results and treatment regimen for each patient was obtained. The histopathologic features of the tumors were recorded as were the results of their Oncotype Dx® RS. The latter was categorized into different risk categories based on the guidelines set forth by Oncotype Dx®: low risk (LR) <18, intermediate risk (IR) 18-30, high risk (HR) >30.
- **Results:** A total of 1489 specimens were sent for Oncotype Dx® testing during the study period. Of these, 135 (9%) cases were classified as ILC. The age of the patients, tumor size and subtype, nodal status, Oncotype Dx® RS and treatment for the 3 risk groups are summarized in Table 1. The overall mean age was 58 years-old (range 34-79) and the overall mean tumor size was 1.6 cm (range 0.3-4.3 cm). The histology of the ILC was classical (n=108, 80%), pleomorphic (n=13, 10%), classical and pleomorphic (n=14, 10%). Twelve (9%) out of 133 patients that had axillary lymph node (LN) sampling had metastases (range 1-2 positive LN). All tumors were Her-2/neu negative by immunohistochemistry. The overall mean Oncotype Dx® RS was 16 (range 5-33), with the following distribution: LR 85 (63%), IR 48 (36%), HR 2 (1%). No patients with classical or mixed type ILC or with LN metastases were classified as HR. Two (15%) out of 13 pleomorphic ILC were in the HR category with scores of 31 and 33. Forty-two (31%) patients received chemotherapy (CT), 108 (80%) hormone therapy (HT) and 72 (53%) radiation therapy (RT).

ILC Characteristics			
	LR (<18)	IR (18-30)	HR (>30)
N (total 135)	85	48	2
Age (yrs)	57 (34-79)	59 (45-77)	69 (61-76)
Tumor Size (cm)	1.7 (0.5-4.3)	1.4 (0.3-3.6)	1.8 (1.2-2.4)
Histology			
Classical	73	35	0
Pleomorphic	2	9	2
Classical & Pleomorphic	10	4	0
LN Metastasis	9	3	0
Recurrence Score	13 (5-17)	21 (18-29)	32 (31-33)
Treatment			
CT	15	25	2
HT	72	34	2
RT	42	29	1

- **Conclusions:** 1) Regardless of subtype, 99% of ILC are in the LR/IR categories. 2) The clinical decision for administering CT in our study population was not based on Oncotype Dx® RS but determined by clinicopathologic variables. 3) Oncotype Dx testing does not provide additional predictive information for clinical management of patients with ILC.

Category: Breast

[271] Progesterone Receptor and Ki-67 Immunohistochemistry Predict Oncotype Dx® Recurrence Score in Lymph Node Negative and Positive Breast Cancers

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- **Background:** Oncotype Dx® is a proprietary molecular assay that detects the expression level of RNA associated with behavior of invasive breast cancer. Results are reported as a Recurrence Score (RS) and stratified into low, intermediate, and high risks groups which theoretically correlate with risk of recurrence at 10 years after surgical treatment only. RS may used by oncologists as a tool to guide initiation of chemotherapy. The ongoing prospective TAILORx trial utilizes a modification of the standard RS risk stratification values which expands the number of patients in the intermediate group.
- **Design:** Our objective was twofold: 1) to test whether routinely performed histology and immunohistochemical studies could be used to predict the RS in a cohort of lymph node negative and lymph node positive patients, and 2) to assess the prediction of recurrence using both the standard RS and the modified TAILORx RS. H&E stained slides were used to assess morphology including the components of the Nottingham combined histologic grade. Immunohistochemistry was used to assess hormone receptor expression, Ki-67 positivity, and Her-2/neu expression.
- **Results:** The most recent 92 cases with invasive carcinoma and Oncotype DX® results were evaluated. Of those, 69 cases were node negative and 23 were node positive. Using the standard RS, 56 cases were low risk, 26 were intermediate risk, and 10 were high risk. Using the modified TAILORx stratification, 19 cases were low risk, 57 were intermediate risk, and 16 were high risk. Bivariate analysis demonstrated that PR status, Nottingham grade, nuclear score, mitotic rate, and Ki-67% were significantly associated with RS using both the standard and modified TAILORx risk stratifications. However, multivariate logistic regression analysis demonstrated that only a positive PR status and low Ki-67% were predictive of a low RS using the standard risk stratification. None of the variables remained predictive of RS when the modified TAILORx values were applied.
- **Conclusions:** Our study demonstrates that PR status and Ki-67% are predictive of Oncotype DX® RS values using the currently clinically applicable standard risk stratification in a cohort of lymph node negative and lymph node positive patients.

Category: Breast

[253] Comprehensive Genomic Profiling of Breast Cancer by Massively Parallel Sequencing Reveals New Routes to Targeted Therapies

Jeffrey Ross, Christine Sheehan, Alex Parker, Mirna Jarosz, Sean Downing, Roman Yelensky, Doron Lipson, Philip Stephens, Gary Palmer, Maureen Cronin. Albany Medical College, Albany, NY; Foundation Medicine Inc., Cambridge, MA

- **Background:** The recent introduction of massively parallel (next-generation) DNA sequencing to clinical samples has enabled the discovery of novel and unanticipated genomic-derived drug targets of therapy for patients with refractory metastatic breast cancer.
- **Design:** After DNA was extracted from 4 formalin-fixed paraffin embedded sections cut at 10 microns from 15 cases of primary invasive breast carcinomas, the exons of 145 cancer-related genes were fully sequenced by next-generation technology using the Illumina HiSeq 2000 (Illumina Inc. San Diego, CA) to at an average sequencing depth of 253X. Tumoral DNA was evaluated for point mutations, insertions, deletions, copy number alterations and translocations.
- **Results:** 15/16 (94%) of the tumors revealed 33 total somatic genomic alterations (mean 2.2 alterations per tumor) with a range of 0 to 4 alterations per sample. Standard of care alterations consisted of 3(19%) tumors with *HER2* copy number increases. The NGS *HER2* copy number measurements by NGS in the *HER2* amplified cases averaged 80% of the counted *HER2* copies on FISH assessment of the same tumor block. Genes co-amplified with HER2 included RARA. 10/16 (63%) of tumors harbored at least one alteration that potentially could have led to clinical trials of novel targeted therapies including copy number increases for IGF-1R in 2 (13%) tumors [IGF-1R inhibitors], *MDM2* in 1 (6%) tumor [nutlins], *CCND1* in 3 (19%) tumors [CDK inhibitors], *CCNE1* in 1 (6%) tumor [CDK inhibitors] *CDK4* in 1 (6%) tumor (CDK inhibitors), and *FGF1R* in 1 (6%) tumor (FGF1R inhibitors). 5 (31%) of tumors had 1 or more *PIK3CA* mutations [PIK3CA and mTOR inhibitors]. 6/16 (38%) of tumors had alterations classically associated with adverse clinical outcome including *TP53* and *PTEN* mutations and *HER2* copy number increases.
- **Conclusions:** Deep massively parallel DNA sequencing of clinical breast cancer samples uncovers an unexpectedly high frequency of genomic alterations that could influence therapy selection for the disease. Deep sequencing of genomic DNA can provide a broad cancer-related gene survey at a depth of coverage that provides sensitive detection for all classes of genomic alterations, and when applied to breast cancer patients can reveal actionable genomic abnormalities that inform treatment decisions.

Category: Breast

[1101] Levels and P16 Are Valuable Adjuncts in the Evaluation of Cervical Cone or Loop Electrosurgical Excision Procedure (LEEP) Specimens Initially Considered Negative for Dysplasia

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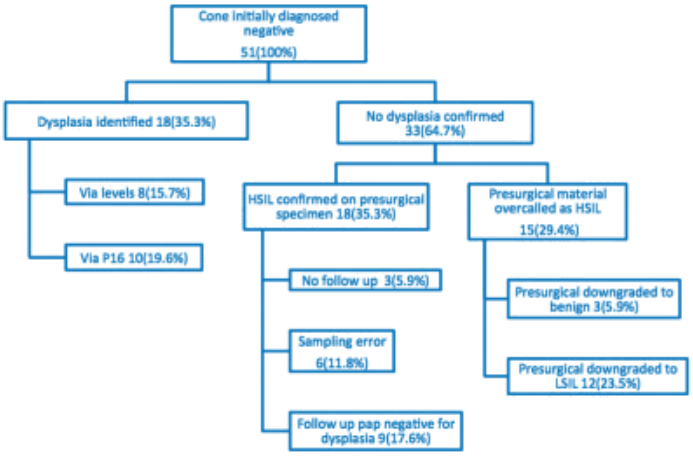
- **Background:** At University of California San Diego Medical Center an average of 19% of the cervical cone biopsies are negative for dysplasia or malignancy. In order to identify sources of misdiagnosis and error, we evaluated the cause and outcomes of these cervical conization specimens.
- **Design:** Fifty one cone biopsies with an original negative diagnosis were selected at UCSDMC. These specimens and the presurgical Pap smears, biopsies and endocervical curettages (ECC) were reviewed by up to 6 surgical pathologists in order to obtain a consensus diagnosis. Deeper levels and then p16 immunostains were performed on all the cone cases and select biopsy sections.
- **Results:** Please see figure 1.



- **Conclusions:** Our results suggest four categories of cases.

  MISSED DYSPLASIA IN CONE SPECIMEN: In 35.3% of cases the original cone diagnosis was overturned to positive (SIL, LSIL or HSIL).

  SAMPLING ERROR: For cases with confirmed pre-surgical diagnosis of HSIL but negative cone specimen, 6 of the original 51 cases (11.8%) were found to have dysplasia or even invasive squamous cell carcinoma on subsequent follow-up, suggesting that the conization sampling may have been incomplete due to factors that complicated the surgical procedure.

  PRESURGICAL SPECIMEN OVERCALLED AS HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL): In 29.4%, conization was not clinically indicated, due to an overcall of HSIL on the preceding Pap smear, cervical biopsy, or ECC.

  PRESURGICAL MATERIAL CONFIRMED AS HSIL, WITH NEGATIVE CONE AND NEGATIVE FOLLOWUP: In 17.6% of cases, no errors were detected in either pre-surgical or conization diagnosis and the patient had negative subsequent follow-up. The implications of this category are unclear, but could result from either incomplete tissue examination, regression of the lesion, or possibly complete excision of small foci of HSIL by biopsy.

  Our results, taken as a whole, emphasize the necessity for close clinical follow up, liberal use of p16 immunohistochemistry, examination of deeper level sections, review of prior material, and consensus group review to reduce errors in the pathologic workup of cervical dysplasia.

  Category: Gynecologic & Obstetrics

[1109] YWHAE Rearrangement Identified by FISH in a Series of Undifferentiated Endometrial Stromal Sarcomas: Genetic and Pathological Correlations

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- **Background:** Endometrial Stromal tumors (EST) of the uterus represent less than 10% of all uterine mesenchymal tumors. Undifferentiated Stromal Sarcomas (U-ESS) are aggressive malignant tumors with moderate to marked cytological atypia and little resemblance to proliferative-phase endometrial stroma. Unlike ESS, U-ESS doesn't generally harbor a JAZF1/JJAZ1 chromosomal rearrangement. Recently, a rearrangement of (WYHAE) on 17p13 with FAM 22 A-B on chromosome (Chr) arm 10q has been described in U-ESS. The aim of our study was to evaluate the frequency of WYHAE rearrangement and to look for a correlation with morphology.
- **Design:** We collected 29 cases of U-ESS from our Department diagnosed between 1995 and 2011. At the morphological level, we distinguished the U-ESS Uniform (U-ESS-U) and pleiomorphic (U-ESS-P) types according to Kurihara S et al criteria. An immunohistochemical study including CD10, H-caldesmon and desmin was performed. *FISH analysis* using *break-apart* probes targeting the WYHAE gene on chr17p13 and JAZF1gene on chr7p15 was performed on paraffin-embedded tissue sections. In-house FISH probes were selected and validated on chromosome spreads.
- **Results:** Mean age at diagnosis was 58.6 years (31 to 93). 22/29 (76%) tumors expressed CD10 marker. Only 2/29(7%) and 2/29(7%) cases showed a weak and heterogeneous positivity for desmin and H-caldesmon, respectively. The tumors expressed estrogen and progesterone receptors in 6/27 (22%) and 8/28 (28%) respectively. FISH was interpretable in 22/29 cases. 9/22 (41%) cases showed a WYHAE chromosomal rearrangement of which 8/9 (89%) showed a uniform morphology (U-ESS-U): 2 with fibromyxoid features, 3 with spindle morphology and 1 with spindle and epithelioid appearance. Only one case (1/9) (11%) showed a pleomorphic morphology (U-ESS-P). No chromosomal rearrangement for JAZF1-JJAZ was detected. Three hybridization profiles were observed: 1 chromosomal rearrangement for YWHAE and 1 normal Chr 17; 1 chromosomal rearrangement for YWHAE and the loss of other Chr 17 and 1 chromosomal rearrangement for YWHAE and a gain of the non-rearranged Chr 17. Never less these tumors showed a very unstable chromosomal profile with loss or gain of part of chromosomes.
- **Conclusions**: YWHAE t(10;17) rearrangement was found in 41% U-ESS in our series and correlated with the uniform, spindle and fibro-myxoid variant.

Category: Gynecologic & Obstetrics

[1118] Conventional Screening Criteria May Miss a High Proportion of Lynch Syndrome Patients with Endometrial Carcinoma Due to PMS2 Loss

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- **Background:** Loss of mismatch repair (MMR) protein expression (MLH1, PMS2, MSH2 and MSH6) occurs in Lynch syndrome, while MLH1 loss can also be found in sporadic endometrial tumors due to promoter methylation. Experience with endometrial cancers with PMS2 loss is limited. In this study, we describe the clinical and pathological features of 7 such tumors, the largest case series to date.
- **Design:** Using MMR immunohistochemistry, we investigated the following two different cohorts of endometrial cancer patients: 154 sequential patients, unselected for age or personal and family history of Lynch associated cancers, and 45 patients with a clinical suspicion of Lynch syndrome (age less than 50 and/or a relative with Lynch associated cancer).
- **Results:** 7 patients with PMS2 loss and intact expression of other MMR proteins were identified. Their clinicopathologic characteristics are summarized below.

Case	Age	Personal Cancer History	Family Cancer History	Tumor Histotype and FIGO Grade	Stage
Unselected 1	87	No	No	Endometrioid 2	1b
Unselected 2	45	No	No	Endometrioid 2	1b
Unselected 3	75	No	Colon ca in mother at 92; Other Non-Lynch ca	Endometrioid 2	1a
Unselected 4	66	No	Non-Lynch ca	Endometrioid 3	1b
Unselected 5	51	No	Non-Lynch ca	Endometrioid 2	1a
Lynch Suspicious 1	58	Non-Lynch ca	Colon ca in mother at 58	Endometrioid 2	1b
Lynch Suspicious 2	70	No	Colon ca in father at 66	Endometrioid 2	3c

The average patient age was 64.6 years, with only one patient younger than 50. Only 3 patients had first degree relatives with colon cancer, with an average age of 72 years. In comparison with published data, MLH1, MSH2 and MSH6 mutation carriers had an average age of 45.8, 45.5 and 51.2 respectively at the time of endometrial cancer diagnosis, and first degree relatives with colon cancer at an average age of 48.0, 46.2 and 60.9 respectively. All tumors with PMS2 loss were of endometrioid histology. In contrast, non-endometrioid endometrial cancers with MLH1, MSH2 and MSH6 mutations have been reported.

- **Conclusions:** Endometrial tumors with PMS2 loss have a predilection toward the endometrioid histotype. The patients tend to be older and either lack relatives with Lynch associated cancers or have relatives with colon cancer diagnosed later in life that may be confused with sporadic tumors. Therefore, Lynch syndrome patients with PMS2 abnormalities and endometrial cancer may be missed by screening criteria that use young patient age and family history as determinants for further testing.

Category: Gynecologic & Obstetrics

[1128] Loss of BAF250a *(ARID1A)* Expression in Endometrial Clear Cell Carcinoma: Assessment of Frequency and Clinicopathologic Implications

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- **Background:** SWI/SNF chromatin-modification complexes use the energy of ATP hydrolysis to remodel nucleosomes and to affect transcription in a manner that is critical for proliferation and differentiation. Accordingly, their loss of function has been associated with malignant transformation. *ARID1A* (the expression of whose product, BAF250a, a key complex component, is lost when mutated) has recently been identified as a tumor suppressor gene that is mutated in 50% of ovarian clear cell carcinoma (CCC). The purposes of this study are to assess the frequency of loss of BAF250a expression in *endometrial* CCC and whether this loss has any discernable clinicopathologic implications.
- **Design:** 34 endometrial carcinomas with a CCC component (including 22 pure CCC, 8 mixed carcinomas with a ≥10% CCC component, and 4 carcinosarcomas with a CCC epithelial component), were evaluated by immunohistochemistry using a monoclonal antibody directed against the human BAF250a protein.
- **Results:** 5 (22.7%) of 22 pure CCC were entirely BAF250a[-], whereas the remainder showed diffuse immunoreactivity. None of 4 carcinosarcomas and only 1 (12.5%) of 8 mixed carcinomas were BAF250a[-]. Of the 22 pts with pure CCC, 14, 2, 3, and 3 were FIGO stages 1, II, III & IV respectively. Interestingly, all 5 BAF250a[-] cases were late stage [III,IV], meaning that 83% of all late stage cases were BAF250a[-], as compared with only 1 (6.25%) of the 16 early stage cases (p=.001). 1 of 5 BAF250a[-] cases showed lymphovascular invasion, as compared with 6 of 17 BAF250a[-] cases, an insignificant difference (p>.05). As may be anticipated from the concentration of late stage cases in the BAF250a[-] group, pt outcomes were worsened, at least on univariate analysis, in that group. Pt outcomes for the pure CCC group were as follows: Alive with disease, 6 pts; No evidence of disease, NED, 11 pts; Dead of disease, DOD, 4 pts; f/u unavailable, 1 pt. 60% of the 5 BAF250a[-] pts were DOD (the other 2 were NED), as compared with only 1 (6.25%)of 16 BAF250a[+] pts (p=0.02)
- **Conclusions:** 22.7% of endometrial CCC display complete loss of BAF250a expression. Although formal outcome analyses cannot be performed on this dataset, some noteworthy and intriguing trends *did* emerge, including the disproportionate concentration of BAF250a[-] cases in the late stage group and the attendant possibility of an associated worsened prognosis. These preliminary findings suggest the need for larger analyses to evaluate the prognostic significance, if any, of the loss of BAF250a expression in CCC.

Category: Gynecologic & Obstetrics

[1172] Immunohistochemical Profile of Gastric Type Endocervical Adenocarcinoma, Including HER2/Neu Status

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- **Background:** Gastric type (GA) and minimal deviation adenocarcinoma (MDA) are subtypes of endocervical adenocarcinoma not related to infection by human papillomavirus (HPV) and are characterized by expression of gastric pyloric gland type mucin as evinced by HIK1083 immunoreactivity. The extent to which these tumors express other Mullerian or gastrointestinal (GI) immunophenotype has not been previously studied. We evaluated a series of GA/MDA for expression of such markers. Since gastric and ovarian mucinous carcinomas have been shown to overexpress HER2/neu with concurrent amplification (and are therefore amenable to targeted therapy with traztuzumab), we also included this stain in our panel.
- **Design:** A retrospective review of GA or MDA from the pathology databases of two institutions was performed. Using standard protocols, immunohistochemical (IHC) studies were performed on formalin-fixed, paraffin embedded tissue for CK7, p16, CK20, CDX2, p53, PAX8 and Her2/neu. Her2/neu expression was scored according to the ASCO/CAP guidelines (0 to 3+). All others were scored semiquantitatively as POS (>50%), NEG (0), FOC (any to 50%).
- **Results:** 16 cases with blocks available for staining were identified. Results are summarized in Tables 1 and 2. Four cases also had tissue from metastatic sites available for staining.

Table 1

	POS (%)	FOC (%)	NEG (%)
CK7	16 (100)	0	0
CK20	3 (19)	2 (13)	11(69)
p16	0	1 (6)	15 (94)
CDX2	0	4 (19)	12 (81)
p53	3 (19)	13 (81)	0
PAX8	7 (47)	3 (20)	5 (33)

POS >50% staining; NEG no staining; FOC <=50% staining

Table 2

	3+ (%)	2+ (%)	0/1+ (%)
Her2/neu	1 (6)	1 (6)	14 (82)

The metastatic tumors had similar staining patterns to the primary, except for 3 cases where CK20/CDX2 was either lost or focally gained. One case also lost PAX8 in the metastasis.

- **Conclusions:** Gastric type and minimal deviation adenocarcinoma are characteristically CK7 and many, but not all, are PAX8 positive as well. p16 is negative, further supporting HPV-independent tumorigenesis. A minority of tumors express focal "GI markers" CK20 and CDX2 but are usually negative. p53 is overexpressed in 19% of these tumors which may indicate presence of TP53 mutation. Her2/neu shows 2+ or greater expression in 12% of cases which may be indicative of Her2 amplification.

Category: Gynecologic & Obstetrics

[1183] Cyclin D1 Is a Sensitive and Specific Diagnostic Immunomarker for *YWHAE-FAM22A/B* Endometrial Stromal Sarcoma

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- **Background:** We recently described a novel genetic fusion *YWHAE-FAM22A/B* resulting from translocation t(10;17)(q22;p13) in a subset of endometrial stromal sarcomas (ESS) which are histologically higher-grade and clinically more aggressive than *JAZF1*-rearranged ESS. We describe here the utility of cyclin D1 as a diagnostic immunomarker for *YWHAE-FAM22A/B ESS*.
- **Design:** Gene expression profiling was performed by 3' end sequencing in 3 *YWHAE-FAM22A/B* ESS, 4 *JAZF1* ESS and 4 uterine leiomyosarcomas. Significance analysis of microarray data was used to identify genes (immunomarkers) substantially upregulated in *YWHAE-FAM22A/B* ESS. Immunomarker specificity and sensitivity were evaluated in a series of *YWHEA-FAM22A/B* ESS and other uterine tumors.
- **Results:** The 3' end sequencing profiles demonstrated cyclin D1 overexpression in *YWHAE-FAM22A/B* ESS compared to *JAZF1* ESS and leiomyosarcomas: this candidate immunomarker was selected for further evaluation because of its general availability in pathology laboratories. Immunohistochemically, > 70% of nuclei in the round cell/epithelioid cell component of all *YWHAE-FAM22A/B* ESS (N = 10) demonstrated diffuse moderate-to-strong nuclear cyclin D1 staining (comparable to that seen in Mantle cell lymphoma) and such diffuse positivity was rarely seen (0.4%) in other uterine tumors (Table 1). Other than *YWHAE-FAM22A/B* ESS, most uterine sarcomas (98%) displayed cyclin D1 straining in < 20% of tumor nuclei.

Cyclin D1 (Thermoscientific) immunostaining results in 267 uterine tumors.		
	Number of cases examined	Cyclin D1 positive cases (>70% moderate-strong nuclear positivity)
ESS with JAZF1/SUZ12/PHF1/EPC1 rearrangement	34	0 (0%)
ESS with YWHAE-FAM22A/B rearrangement	10	10 (100%)
Sarcoma NOS	12	0 (0%)
Adenosarcoma*	25	0 (0%)
Leiomyosarcoma	111	1 (1%)
Malignant mixed mullerian tumor	14	0 (0%)
Leiomyoma	49	0 (0%)
Endometrial stromal nodule	3	0 (0%)
Polypoid endometriosis	7	0 (0%)
Uterine tumors resembling ovarian sex cord tumor (UTROSCT)	2	0 (0%)

* 8 cases showed sarcomatous overgrowth

- **Conclusions**: We have identified a cyclin D1 as a sensitive and specific diagnostic immunomarker for *YWHAE-FAM22A/B* ESS. When evaluating uterine sarcomas where the differential of ESS with high grade histologic features is considered, cyclin D1 should be included in the immunohistochemical work-up to evaluate the possibility of *YWHAE-FAM22A/B* ESS.

Category: Gynecologic & Obstetrics

[1203] P504S (AMACR-alpha-Methylacyl-coA Racemase): A Novel Marker of Clear Cell Carcinoma of the Female Genital Tract

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- **Background:** Clear cell carcinoma (CCC) of the female genital tract (FGT) poses a diagnostic challenge as its histologic features can overlap with other carcinomas particularly when they demonstrate clear cell change. Currently, CCC is diagnosed primarily on morphologic features with poor interobserver reproducibility. As yet, there are no specific immunohistochemical markers to assist in the diagnosis of CCC. P504S (AMACR-alpha-methylacyl-coA racemase) is widely used in the diagnosis of prostate cancer and papillary renal cell carcinomas. In addition, studies have show the expression of this marker in CCCs of the urinary bladder and urethra. However, P504S expression has not been extensively studied in tumors of the FGT, particularly CCC. The aim of our study is to determine if P504S is expressed by tumors of Müllerian origin with attention to its value, if any, in the diagnosis of CCC.
- **Design:** 30 CCCs of FGT were retrieved from our pathology files covering a period of 26 years (1985 to the present). CCC from the following sites were included: endometrium (9), ovary (10), cervix (8), pelvis (1), vagina (1) and metastasis to a pelvic lymph node (1).13 serous carcinomas (SC), 15 endometrioid carcinomas (EC) of the endometrium and ovary, and 9 cases of endometriosis were used as controls. All cases were stained for P504S (Zeta Corp., Arcadia, CA). Granular cytoplasmic staining was interpreted as positive. Staining in the neoplastic cells was graded as follows: 0: no detectable staining, 1+: 1-5%, 2+: 6 to 25%, 3+: 26 to 50%, 4+: 51 to 75% and 5+: >76%.
- **Results:** P504S was positive in 19 of 30 (70%) CCCs. Of these, 3 cases showed 1+, 4 showed 2+, 5 showed 3+, 3 showed 4+ and 6 showed 5+ staining for P504S. Only 1 of 13 (8%) SC was positive (1+) for P504S. Ten of 15 (67%) ECs were completely negative for P504S. Three of 5 ECs showed 1+ staining, 1 case showed 2+ staining and 1 case showed 5+ staining in the tumor cells. The positive staining of ECs, including the case with 5+ staining, was mostly confined to areas of necrosis and showed only weak to moderate intensity. None of the SC or EC showed strong diffuse staining for P504S.
- **Conclusions:** We found that P504S is expressed in 70% of CCC of the FGT. Strong, diffuse, granular cytoplasmic staining of P504S, when present, is highly suggestive of CCC histotype. P504S is negative in majority of SC and EC and can be a useful marker to differentiate them from CCC, in challenging cases. Staining in areas of necrosis can be seen in SC and EC and must be interepreted with caution.

Category: Gynecologic & Obstetrics

[1254] Mismatch Repair Protein Expression in Clear Cell Carcinoma of the Endometrium: Frequency and Clinicopathologic Correlation of 41 Cases

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- **Background:** Lynch Syndrome is associated with a >40% risk of developing endometrial carcinoma, with quite variable frequency of the different histologic subtypes reported, including high-grade endometrioid carcinomas (EEC), clear cell and serous carcinomas. Recently, an increased incidence of clear cell carcinomas (CCC) of the ovary has also been described in the setting of Lynch Syndrome. However, no large series of endometrial CCC have been studied. The goals of this study are to evaluate the overall incidence of loss of DNA mismatch repair (MMR) protein expression in a series of endometrial clear cell carcinomas and its potential association with Lynch Syndrome.
- **Design:** After IRB approval, 41 endometrial CCC were retrieved from our files from 1986 till 2010. All available H&E slides (2-12 per case) were reviewed by two gynecologic pathologists and clinicopathologic parameters were recorded. Immunohistochemical expression of MMR proteins (MLH1, MSH2, MSH6, and PMS2) was assessed.
- **Results:** The mean age of the patients was 67.8 years (range: 40-92; 5 patients < 50). Twenty patients were diagnosed at early stage (FIGO I and II), and 21 at advanced stage (FIGO III and IV). Combined loss of MLH1 and PMS2 expression was seen in 2 patients (40 and 59 years), while combined loss of MSH2 and MSH6 expression was seen in 2 other patients (46 and 48 years). A predominant solid growth was seen in 3/4 tumors (also present in 8/37 CCC with preserved MMR proteins) and abundant peri- and intratumoral lymphoplasmacytic infiltrate in 2/4 (both with absent MSH2/MSH6) (also seen in 9/37 CCC with preserved MMR proteins). All 4 patients were diagnosed with FIGO IA tumors, and had no evidence of disease with a mean follow-up of 148 months (range: 80-220). None of these 4 patients had metachronous ovarian or colorectal carcinoma. Eleven out of the other 16 patients with early stage CCC also had no evidence of disease with a mean follow-up of 96 months (range: 6-205). Two patients with a history of colorectal carcinoma had preserved MMR protein expression and advanced stage CCC.
- **Conclusions:** In this study, the overall frequency of DNA MMR protein abnormalities in endometrial CCC is relatively low (4/41; 9.8%) compared to a mean of 25% reported in EEC. Among patients aged ≤ 50 in our cohort, 3/5 (60%) showed loss of DNA MMR protein expression and they did not have high-stage tumors, however, clinical behavior was similar to patients without abnormal MMR protein profile, and they had not developed other evidence of Lynch Syndrome.

Category: Gynecologic & Obstetrics

[1267] BAF250a *(ARID1A)* Combined with HNF-1b, ER and P53 Can Distinguish between Ovarian Clear Cell Carcinoma and Papillary Serous Carcinoma

Wenbin Xiao, Amad Awadallah, Wei Xin. University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH

- **Background:** Ovarian epithelial carcinoma consists of a heterogeneous group of different types of carcinoma. Most studies have shown that clear cell carcinoma (CCC) and endometrioid adenocarcinoma might have similar genetic pathway and more commonly associated with endometriosis, while high grade papillary serous carcinoma (PSC) has a different tumorogenesis pathway with common P53 mutation. However, morphologically, high grade clear cell carcinoma and papillary serous carcinoma are not always readily distinguishable. Recent studies suggest that loss of expression of BAF250a, a tumor suppressor encoded by *ARID1A*, and up-regulation of hepatocyte nuclear factor (HNF)-1b were commonly present in CCC, but not PSC. In our study, we would like to show whether we could differentiate these 2 carcinomas by using a panel of immunohistochemical stains including BAF250a, HNF-1b, P53, estrogen receptor (ER) and progesterone receptor (PR).
- **Design:** Formalin-fixed paraffin-embedded blocks of ovarian resection specimens were selected. Cases of CCC (n=26) and high grade PSC (n=24) were selected. Immunohistochemical staining for BAF250a, HNF-1b, P53, ER and PR was performed by our diagnostic lab.
- **Results:** BAF250a, HNF-1b, P53 and ER all have different expression patterns between CCC and PSC (P<0.01), as shown in table below. Most CCCs are negative for BAF250a, ER, P53 and positive for HNF-1b, while PSC are positive for BAF250a, ER, P53 and negative for HNF-1b.

Table 1 Immunoprofiles of ovarian CCC versus PSC

	BAF250a	HNF-1b	ER	P53	PR
CCC (N=26)	42.3% (11/26)	92.3% (24/26)	7.7% (2/26)	7.7%(2/26)	15.4% (4/26)
PSC (N=24)	100% (24/24)*	4.2% (1/24)*	91.8% (22/24)*	62.5% (15/24)*	16.7% (4/24)

* p<0.001 by Fisher's exact test

- **Conclusions:** Our data support that ARIDA and HNF-1b involves ovarian CCC carcinogenesis but not in PSC. PSC and CCC are two biologically different carcinoma types and can be readily differentiated by a panel of immunohistochemical stains of BAF250a, HNF-1b, P53 and ER in morphologically challenged cases.

Category: Gynecologic & Obstetrics

[1269] Array CGH Analysis Reveals Amplification of Met and AKT2 in Clear Cell Carcinoma of the Ovary

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- **Background:** Clear cell carcinoma of the ovary (OCCC) is a chemo-resistant tumor with relatively worse prognosis and is frequently associated with endometriosis. Frequent mutations of the ARID1A gene and activating mutations of the PI3CA gene are reported in OCCC, but positive array CGH results for specific gene amplification have rarely been reported.
- **Design:** In this study, we performed an array CGH analysis using formalin-fixed, paraffin-embedded samples from 13 OCCC patients to comprehensively evaluate gene copy number changes in OCCC samples. We also performed Taqman gene copy number analysis, fluorescence in situ hybridization, immunoblotting, and immunohistochemistry to confirm the array CGH results.
- **Results:** Array CGH analysis revealed that Met gene amplification was present in 4 / 13 OCCC patients and 2 / 8 OCCC cell lines. Amplification of the AKT2 gene, which is a component of one of the downstream signaling pathway of Met together with PI3CA, was also detected in 3 / 13 OCCC patients and 2 / 8 OCCC cell lines. Totally 73 OCCC cases were examined by Taqman PCR for Met amplification, and 37.0% revealed to have Met gene amplification (>4 copies). Furthermore, stage 1 and 2 patients with Met gene amplification had significantly worse overall survival than patients without Met gene amplification (p=0.037).
- **Conclusions:** We demonstrated for the first time Met and AKT2 amplification by array CGH in approximately half of the OCCC cases. Met amplification was significantly related to worse prognosis. Activation of the Met/PI3CA/AKT pathway may be one of the most important molecular events in OCCC carcinogenesis.

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