Salivary Gland Cytology and The Milan System for Reporting

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Conflict of Interest

- None with vendors of cytology equipment or HPV testing
- Amirsys (now Elsevier) and McGraw Hill
  - (Book publishers/Royalties)

Conditions Affecting Salivary Glands

- Stones
- Cysts
- Infections/Inflammatory
- Sialadenosis
- Neoplasms
  - Benign
  - Low grade
  - High grade
- Others like intra or adjacent to salivary Lymph nodes
### Salivary Gland FNA Diagnosis
- Based on cystic or solid
- Neoplastic or non neoplastic
  - Neoplasms divided into matrix producing or not
    - Basaloid
    - Oncocytic
    - Clear cell
    - Spindle cell cystic and mucinous
  - Lymphocytic or not...lymph node/lymphoepithelial cyst
- Other characteristics

### Salivary Gland Aspiration Patterns
#### Cystic Lesions
- Acellular clear fluid
- Sialocele
- Lymphoepithelial cyst
- Cloudy/mucoid fluid+/- cells
- Lymphoepithelial cyst
- Abscess
- Mucocele
- Warthin's tumor
- Low Grade Mucoepidermoid ca
  - Acinic cell.ca(rare)
  - Cystic degeneration in any neoplasm

#### Inflammatory cells
- Abscess
- Chronic sialadenitis
- Lymphoepithelial sialadenitis
- Warthin's
- Lymph node
- Lymphoma(monotonous)

#### Granulomas
- Sarcoid
- TB
- Fungal

### Salivary Gland Aspiration Patterns
#### Oncocytic cell Pattern
- Nodular Oncocytic hyperplasia
- Oncocytoma
- Warthin's
- Oncocytic carcinoma
- Mucoepidermoid ca, oncocytic variant
  - Acinic cell carcinoma
  - Salivary duct carcinoma
  - MASC

#### Lymphocytic Cell pattern
- Chronic sialadenitis
- Lymphoepithelial sialadenitis
- Lymphoepithelial cyst
- Lymph node
- Lymphoma
- Warthin's tumor
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
Salivary Gland Aspiration Patterns

**Basaloid cell Pattern**
- Basal cell (monomorphic) adenoma/carcinoma
- Cellular Pleomorphic adenoma
- Adenoid cystic carcinoma
- Myoepithelial carcinoma
- Polymorphous low grade adenocarcinoma
- Small cell carcinoma, prim/met
- Cutaneous basal cell carcinoma
- Sialoblastoma

**Clear cell Pattern**
- Normal salivary gland
- Lipoma
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Clear cell myoepithelioma
- Epithelial/myoepithelial carcinoma
- Sebaceous lymphadenoma
- Metastatic clear cell carcinoma

**Neoplasms with stromal pattern**
- Pleomorphic Adenoma: Fibrillary stroma
- Adenoid Cystic carcinoma: discrete, defined globules
- Basal cell adenoma/carcinoma: dense membrane-like stroma
- Polymorphous low grade adenocarcinoma
- Myoepithelioma/carcinoma
- Nodular fasciitis: loose myxoid

**High grade malignant neoplasms**
- High grade Mucoepidermoid carcinoma (MEC)
- Carcinoma ex Pleomorphic Adenoma
- Adenocarcinoma NOS
- Salivary duct carcinoma
- Mammary Analogue Salivary Carcinoma (MASC)
- Squamous cell carcinoma
- Merkel cell carcinoma
- Melanoma
- Angiosarcoma
- Other variants

**Mucinous**
- Normal submandibular or sub-lingual glands
- Florid adenomatoid hyperplasia
- Mucocele
- Low grade Mucoepidermoid carcinoma

**Spindle cells**
- Schwannoma/NF
- Myoepithelioma
- PA with predominance of myoepithelioma
- Angiosarcoma
- Other variants

**Crystals**
- Tyrosine: Daisy petals in Pleomorphic adenoma (PA)
- Amylase: elongated hexagons in chronic sialadenitis/cysts
- Cholesterol: clear and colorless in Warthin's and various cysts
- Atelectasis: round, clear, and colorless inWarthin's
- Calcium oxalate: round, clear, and colorless
- Calcium phosphates: purple on pap, colorless on DQ
- Retained products of saliva
- Psammoma bodies: normal or inflamed salivary gland and neoplasms, benign and malignant
Problem with old way of reporting...

- No consistency
- Salivary gland neoplasms are the most heterogeneous group, and hence also the most challenging, even more so on cytology and minute Core needle biopsies
  - Matrix containing tumors
  - Basaloid tumors
  - Oncocytic lesions/tumors
  - Cystic and mucinous lesions/tumors
  - High grade carcinomas
  - Clear cell tumors
  - Spindle cell lesions/neoplasms

Problem with old way of reporting… continued…

- Surgical pathology terminology often used
- Too many DIDGO’s (describe it to death and let it go)…not helpful at all! Clinicians confused

- Agreement for need of defined diagnostic categories
- Clarity of communication
- Exchange of information across institutions
- Uniform management, improvement patient care

Salivary FNA Variances

- **False Positive**
  - Interpretive
  - Monomorphic Adenoma
  - Warthin’s with squamous and mucinous metaplasia with atypia
  - Intraparotid lymph node
  - Oncocytoma
  - Granulomatous sialadenitis

- **False negative**
  - Sampling
  - Interpretive
  - Acinic cell carcinoma
  - Low grade MECarcinoma
  - Lymphoma
  - Adenoid cystic carcinoma
  - Low grade angiosarcoma(cutaneous)
Salivary Glands Statistics

<table>
<thead>
<tr>
<th></th>
<th>Our results (%)</th>
<th>Literature results (%)</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>80.6</td>
<td>86-100</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.5</td>
<td>81-100</td>
</tr>
<tr>
<td>Positive Predictive value</td>
<td>92.6</td>
<td></td>
</tr>
<tr>
<td>Negative Predictive value</td>
<td>92.8</td>
<td></td>
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<tr>
<td>Accuracy</td>
<td>92.7</td>
<td>48-94 (specific neoplasm) (B vs Malig) 81-100</td>
</tr>
<tr>
<td>Pleomorphic Adenoma</td>
<td>97.1 (concordance)</td>
<td></td>
</tr>
<tr>
<td>Warthin's</td>
<td>88.9 (concordance)</td>
<td></td>
</tr>
</tbody>
</table>

Salivary Gland Lesions/Neoplasms

<table>
<thead>
<tr>
<th>Usually Diagnostic</th>
<th>Sometimes Diagnostic</th>
<th>Descriptive I call them DDDDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/chronic sialadenitis</td>
<td>Mucocele</td>
<td>Basal adenoma (other than membranous)</td>
</tr>
<tr>
<td>Reactive lymph node</td>
<td>Adenoid cystic carcinoma</td>
<td>Basal cell adenocarcinoma</td>
</tr>
<tr>
<td>Lympho epithelial cyst</td>
<td>Acinic cell carcinoma</td>
<td>Mucoepidermoid ca High grade</td>
</tr>
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<td>Pleomorphic adenoma</td>
<td>Mucoepidermoid ca (low grade)</td>
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<td>Polymorphous low grade adenocarcinoma</td>
</tr>
<tr>
<td>Basal cell adenoma, membranous type</td>
<td>Carcinoma ex PA</td>
<td>Epithelial-myoepithelial carcinoma</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Small cell carcinoma</td>
<td>(Mammary analogue) Secretory carcinoma</td>
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Management of Salivary Gland Lesions/conditions

- If inflammatory: Medical management
- Lymphoma: Heme Onc referral
- Metastasis: Resection or radical neck dissection
- Benign or low grade primary neoplasm: Limited resection
- High grade carcinoma: Radical resection

The Milan System for Salivary Gland Cytopathology

- ASC and IAC co sponsors
- Over 40 participants, 14 countries
- Evidence based
- Print atlas in early 2018...already out!
- Web based atlas also available through ASC
- Co chairs Drs Bill Faquin and Diana Rossi
- Others include Drs Baloch, Barkan, Foschini, Kurtyz, Pusztaszeri, Vielh
- Online survey data: 49 questions, 515 participants, 54% academic
- >95% agreed with new reporting structure
- Both Romanowsky and pap staining essential
The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

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<td>IVb. Salivary gland Neoplasm of Uncertain malignant potential (SUMP)</td>
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<td>~90%</td>
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Salivary Gland Mass sampling

- Palpation or Ultrasound guidance
- FNA preferred
- Both Romanowsky and Pap/H&E stains preferred
- Cell block preparation encouraged
- Core needle biopsies an option but...
  - Tracking
  - Facial nerve injury, especially with larger cores
Non Diagnostic

- Currently no validated criteria in literature
- Call non diagnostic after everything is processed and examined and correlated clinically and radiologically
- Insufficient material qualitative or quantitative for a diagnosis
- 10% or less targeted reporting rate (hopefully!)
- Exceptions: matrix material, mucinous cyst contents, acute inflammation, any atypia
- Minimum of 60 lesional cells for adequacy…like thyroid?

Non Diagnostic..continued

- E.g. Salivary duct stone with cyst…aspiration yields clear fluid, no more mass…then adequate as it explains the scenario
- Bilateral enlarged salivary glands with no definite mass, then adequate
- However, if mass, and all you get is normal salivary gland tissue…
  - Then non diagnostic as it does not explain the mass/"it"

Normal Salivary Gland Cytology

- E.g. Salivary duct stone with cyst…aspiration yields clear fluid, no more mass…then adequate as it explains the scenario
- Bilateral enlarged salivary glands with no definite mass, then adequate
- However, if mass, and all you get is normal salivary gland tissue…
  - Then non diagnostic as it does not explain the mass/"it"
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Non Neoplastic

- Chronic and granulomatous Sialadenitis
- Sialolithiasis
- Lymph nodes (reactive) within or adjacent to salivary gland
  - Recommend flow if clinically and cytologically worrisome, older age
- Other benign conditions like cysts etc.
- Risks of malignancy should be low if adequately sampled
- A subset will need surgical excision to exclude a poorly sampled neoplasm
Lymph nodes on Salivary FNA

- Reactive lymph nodes
- Polymorphous population
- Age, usually <50
- Tingible body macrophages
- But all of above can be seen in lymphomas
- Flow cytometry if worrisome or older patient
  - Even that may be problematic as some large cell lymphomas, Hodgkin's, T cell rich B cell Lymphomas negative by flow
  - Recommend excision if uncertain
  - Make sure representative of lesion
  - Note of caution, consider follow up/excision if does not go away

Milan 3: Atypia of Undetermined Significance

- Heterogeneous category with majority being due to poor sampling or preparation/compromised specimen (air drying, blood clot, artefact)
- Cannot entirely exclude a neoplasm
- <10% reporting rate (hopefully!)
- Example is mucinous cyst contents only (cannot exclude a low grade Mucoepidermoid carcinoma)

Atypia of Undetermined Significance..Scenarios

- Oncocytic metaplasia (vs neoplasm)
- Reactive/reparative atypia, cannot rule out a neoplasm
- Low cellularity specimen, worrisome for but not diagnostic of a neoplasm
- Salivary gland lymph nodes, indefinite for a lymphoma on morphology alone (do flow or excise)
- Sclerosing polycystic adenosis
- Lymphoepithelial cyst with squamous atypia in cyst lining
Cystic salivary Gland Aspirates .Intrinsic

- Non neoplastic
  - Salivary duct cyst
  - Lymphoepithelial cyst
  - Polycystic disease

- Neoplastic
  - Warthin’s, Pleomorphic adenoma
  - Mucoepidermoid ca, Acinic cell ca
  - Cystadenoma/ca
  - Secretory carcinoma

Atypia of Undetermined Significance…Examples

Cystic salivary Gland Aspirates .Extrinsic

- Non neoplastic
  - Branchial cleft cyst

- Neoplastic
  - Metastatic carcinoma (with cystic degeneration/necrosis to an intra or peri salivary gland lymph node (especially parotid and sometimes sub mandibular).
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<td>~85-90%</td>
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Diagnosis depends on salivary gland site and nature of specimen.

**Personal communication Drs Faquin and Rossi and presentation at ASC Meeting in Phoenix AZ Nov 2017**

**Atypia of Undetermined Significance sample reports**

**Evaluation limited by scant cellularity**

**Atypia of Undetermined Significance**

Histiocytes with scant epithelial cells in an abundant mucinous background. Differential includes a mucocele, mucus retention cyst and low grade mucoepidermoid carcinoma.

**Satisfactory for evaluation**

Atypia of Undetermined Significance

Aspirate is suggestive of a reactive lymph node. However, in absence of flow cytometry, a low grade lymphoma cannot be ruled out. Clinical and radiological considerations recommended.

From The Milan System for Reporting Salivary Gland Cytopathology by Faquin and Rossi, Springer 2018

**Milan 4. Neoplasm**

- Benign Neoplasm
- Salivary gland neoplasm of uncertain malignant potential
Neoplasm: Benign
- Pleomorphic Adenomas
- Warthin's
- Lipomas
- Schwannomas

Pleomorphic Adenoma (Benign Mixed Tumor)
- Most common salivary neoplasm
- Parotid most common site
- Fibrillary chondromyxoid stroma
  - Metachromatic on DQ
  - Greyish blue on Pap
- Ductal cells
  - Small cuboidal to polygonal cells
- Myoepithelial cells
  - Plasmacytoid, dyshesive, bland
Carcinoma ex Pleomorphic Adenoma
- Carcinoma arising from Pleomorphic adenoma
- Requires concurrent PA or history of PA at same site
- 80% occur in major salivary glands especially Parotid
  - 7-10% of PAs (especially long standing), 6th to 8th decade (20 yrs later than PA)
  - 6th most common salivary gland malignancy in adults
- Cellular specimen with predominantly epithelial cells
- 2 distinct patterns, benign PA with malignant or equivocally malignant cells with or without necrosis, mitosis
  - Malignant component could be adenocarcinoma, salivary duct carcinoma, ACC, MEC, PLGA, epi-myoepithelial carcinoma

Warthin’s Tumor
- 2nd most common benign salivary gland tumor
- Smokers, typically 5th -7th decade, M>F
- Almost exclusively Parotid, superficial lobe in the tail
- Painless mass with a doughy feel
- Aspiration usually yields a drop or two of thick, tan brown fluid (looks like motor oil)
- Bimorphic population of lymphocytes and oncocytes, some papillary configuration
- DD MECarcinoma, Oncocytoma, lymphnode, Sq ca
Warthin's with atypical Squamous metaplasia

Myoepithelioma
- Benign myoepithelial tumor, 2% of salivary gland neoplasms, 6% of minor salivary gland tumors
- 3rd-5th decade, M:F (1:1), slowly growing, painless mass
- Two cell types, spindle or plasmacytoid or may be mixed.
- Collagenized stroma, chondroid or chondromyxoid areas
- Looks like PA but without ductal cells
- DD PA, Plasmacytoma, myoepithelial carcinoma (has necrosis, atypical mitosis, invasion into surrounding)
Neoplasm: Uncertain Malignant Potential (SUMP)

- Can diagnose as a neoplasm but cannot tell what type/specific diagnosis
- Malignancy cannot be excluded
- Majority will consist of cellular benign neoplasms with atypical/confusing features or low grade carcinomas
  - Myoepithelioma
  - Stroma poor Pleomorphic adenoma
  - Warthin’s with atypical metaplasia
  - Basaloid tumors (adenoma vs carcinoma)

Neoplasm: Uncertain Malignant Potential (SUMP)

- Subgroups include:
  - Cellular Basaloid neoplasm
    - (fibrous stroma) Pleomorphic adenoma (PA), Myoepithelioma/ca, Basal cell adenoma/ca
    - (hyaline stroma) Basal cell adenoma/ca, Adenoid cystic ca (Adcc), Polymorphous ACA, epi-my-epithelial carcinoma
    - (Mixed/other stroma) Adenoid cystic ca, Polymorphous ca
    - Scant Stroma: Cellular PA, Adcc, canalicular adenoma, myoepith ca
  - Cellular oncocytic/Oncocytoid neoplasm
    - Warthin’s, Oncocytoma, acinic cell ca, MASC, meta RCC, MEC, myoepithelioma
  - Cellular neoplasm with clear cell features
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ROM depends on salivary gland site and nature of specimen. Personal communication Drs Faquin and Rossi and presentation at ASC spring meeting Phoenix AZ Nov 2017

### Neoplasm: SUMP
- Pleomorphic Adenoma with myoepithelial cell prominence
- PA with focal areas questionable for Adenoid cystic carcinoma

### Sample Reports
- Neoplasm, Benign: Satisfactory for evaluation
- Neoplasm, Benign: Pleomorphic Adenoma

From: The Milan System for reporting salivary gland cytopathology by Faquin and Rossi, Springer 2018
Suspicious for Malignancy

- Aspirates with features highly suggestive of carcinoma but qualitatively or quantitatively fall short of a definitive diagnosis
- An attempt should be made to subcategorize if worried about low or high grade malignancy
- Majority (but not all) will be cases of high grade carcinomas with compromised sampling/preparation

Suspicious for malignancy...sample reports

- Satisfactory for evaluation
- Evaluation limited by scant cellularity
- Rare highly malignant cells, suspicious for high grade carcinoma
- Atypical cells in a mucinous background, suspicious for low grade muco epidermoid carcinoma

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<td>~50%</td>
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<tr>
<td>IIIA. Neoplasia: Benign</td>
<td>~0%</td>
<td>Follow or conservative surgery</td>
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ROM depends on salivary gland site and nature of specimen
Personal communication Drs Faquin and Rossi and presentation at ASC meeting in Phoenix AZ Nov 2017
Malignant

- Aspirates diagnostic of malignancy
- Every attempt should be made to classify into specific type/grade when possible as grading is critical for management
  - Low grade (low grade mucoepidermoid carcinoma)
  - High Grade (Salivary duct carcinoma)
- Other malignancies like Metastasis, Lymphomas and Sarcomas also belong here but should be specified as to type etc..

Mucoepidermoid Carcinoma

- Most common malignant salivary gland tumor in children and adults, wide age range
- Major and minor glands affected, size varies
- Low and High grade types
- Low grade, 98% Disease Specific Survival
- High grade metastatize, 65% DSS
- 3 cell types, mucus, intermediate and epidermoid cell
- High grade difficult to diagnose on cytology, often called high grade carcinoma/squamous ca

Mucoepidermoid Carcinoma…continued

- Low grade may have abundant Mucin and few cells
- MEC has 3 cell types: Clusters of bland intermediate, epithelial cells and mucocytes
- Mucin producing cells may be columnar, cuboidal or histiocyte like
- Intermediate cells often found in nests or sheets, can be polygonal/epidermoid in appearance
- Epidermoid cells are polygonal and appear in nests or scattered
Mucoepidermoid Carcinoma

- IHC: Her 2+ in 60% of high grade MECs
- EGFR high copy numbers in high grade
- P16 + in 60%. NOT HPV related
- Molecular: t(11;19)(q21;p13) seen in 55-65% of MEC
  - This translocation fuses CREB-regulated transcription coactivator 1 (CRTC1, formerly MECT1) (exon 1 of gene at 19p13) with Mastermind-like gene family (MAML2) (exons 2–5 of gene at 11q21)
  - Identified in low- to intermediate-grade tumors usually
  - Tumors with few copy number alterations (usually CRTC1-MAML2) seem to have better prognosis
**Acinic Cell carcinoma**

- 80% occur in Parotid gland, 2nd most common malignant salivary gland tumor (10-12%), 6% of all salivary tumors
- F:M=3:2, wide age range, mean mid 40s
- 2nd most common malignant salivary tumor in kids
- Slowly growing, may have pain or facial nerve paralysis
- High cellularity, loose or tight acinar structures
- Many stripped bare tumor nuclei in background
- Ample granular vacuolated fragile cytoplasm

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**Acinic Cell carcinoma**

- High false negative rate
- Mistaken for normal salivary gland (note ducts and adipocytes missing, acini tight in normal)
- Other DD Warthin's, MEC, other clear cell tumors
- PAS+ diastase resistant granules (not useful in cytology)
- No specific IHC profile
- No specific genetic/molecular test
- 5 yr survival around 90%, local recurrence in 35%
Adenoid Cystic Carcinoma

- 4th most common malignant salivary gland tumor, F:M=3:2, peak age 6th decade
- Major and minor salivary glands, Parotid most frequent
- Mass, pain, tenderness, facial nerve paralysis
- Treated with radical excision
- Poorly circumscribed infiltrative tumor with multiple patterns
- Survival based on stage, stage I 75%, II 43%, III & IV 15%

Adenoid Cystic Carcinoma

- Variety of patterns (cribiform, tubular, solid, combination)
- Small to medium cells with clear to eosinophilic cytoplasm
- Cohesive cellular clusters surrounding balls of metachromatic material (distinct cells and stroma)
- High N:C ratio, dark nuclei with scant cytoplasm
- Difficult to distinguish from other salivary neoplasms in absence of metachromatic stroma
- DD PA, other basaloid salivary tumors, B9 or malignant
Adenoid Cystic Carcinoma...Ancillary tests

- Immunohistochemistry of limited practical use as tumors in DD react similarly
- Ckit
- Molecular testing:
  - MYB-NFIB fusion protein up-regulates MYB protein expression
  - Rare cases do not rely on MYB overexpression for tumorigenesis

Salivary Duct Carcinoma

- High grade carcinoma resembling breast ca
- 7th decade, parotid, M:F-2:4:1
- Rapid growth with facial nerve involvement
- Cytology shows features of high grade adenocarcinoma with necrosis and mitosis
- Cribiform, papillary, sheets and single cells
- Immunoreactive for epithelial markers, Androgen receptor and Her 2
Carcinoma ex Pleomorphic Adenoma

- Carcinoma arising from Pleomorphic adenoma
- Requires concurrent PA or history of PA at same site
- 80% occur in major salivary glands especially Parotid
  - 7-10% of PAs (especially long standing), 6th to 8th decade (20 yrs later than PA)
  - 6th most common salivary gland malignancy in adults
- Cellular specimen with predominantly epithelial cells
- 2 distinct patterns, benign PA with malignant or equivocally malignant cells with or without necrosis, mitosis
  - Malignant component could be adenocarcinoma, salivary duct carcinoma, ACC, MEC, PLGA, epi-myoepithelial carcinoma
Other Primary and Metastatic Malignancies in Salivary Gland

- Squamous cell carcinoma, primary or mets/direct extension
- Lymphomas primary or secondary
- Melanomas usually mets or direct extension
- Small cell carcinoma/Merkel cell ca
- Angiosarcomas, usually direct extension from cutaneous
- Other metastasis
- Parotid most frequent recipient of mets
**Milan System Reporting**

- Statement on adequacy
- Brief description of cytological features
- Specific diagnosis as to nature of process (neoplastic or non-neoplastic)
- If above not possible, then reason for categorization
- Do not use category numbers without the category name
- Optional to report ROM, depends on laboratory

**Molecular Testing specific to Salivary Gland Tumors**

- **Pleomorphic Adenoma & ca ex PA**
  - Most show overexpression of PLAG1 protein
  - Some show PLAG1 protein overexpression or HMGA2 gene amplification or rearrangement
- **Mucopeidermoid Carcinoma**
  - CRTC1-MAML2 or CRTC3-MAML2 fusion proteins disrupt Notch signaling pathway
  - By FISH or NGS
- **Adenoid Cystic Carcinoma**
  - MYB-NFIB fusion protein up-regulates MYB protein expression
  - Rare cases do not rely on MYB overexpression for tumorigenesis
- **(Mammary Analog) Secretory Carcinoma**
  - ETV6-NTRK3 gene fusion
  - ETV6: Transcriptional regulator
  - NTRK3: Membrane receptor kinase
- **Hyalinizing Clear Cell Carcinoma**
  - EWSR1-ATF1 gene fusion

**Additional Molecular Testing for Salivary Gland Tumors**

- **Basal cell adenoma**
  - CTNNB1 mutations
- **Cribriform adenocarcinoma**
  - PRKD rearrangement
### Immunocytochemistry for Salivary Gland Neoplasms

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Positive Markers</th>
<th>Negative Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic Adenoma</td>
<td>epithelial: CK7, CEA, SOX10, SMA, S-100, Calponin, p63, GFAP, PLAG1, HMGA2</td>
<td>MYB</td>
</tr>
<tr>
<td>Adenoid Cystic carcinoma</td>
<td>epithelial: CK7, CEA, SMA, calponin, S-100, CK5/6, CD117 (&gt;90%+) MYB+ MYB translocation by FISH is specific for ACC</td>
<td></td>
</tr>
<tr>
<td>Basal cell adenomarca</td>
<td>CK7, CEA, SMA + for myoep markers</td>
<td></td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>DOG1 strong diffuse staining SOX10, strong diffuse nuclear staining in most ACC, PAS-D</td>
<td></td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>DOG1, SOX10, PAS-D</td>
<td></td>
</tr>
</tbody>
</table>

### IHC and Molecular profiles of Salivary Gland Neoplasms

(Information that we know of now...)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Genetic Alteration</th>
<th>Genes</th>
<th>FISH probe</th>
<th>IHC markers +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma (ca ex)</td>
<td>Translocation 8q12</td>
<td>PLAG1, HMGA2</td>
<td>PLAG1, HMGA2</td>
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</tr>
<tr>
<td>Basal cell adenoma</td>
<td>3p22.1 mutation</td>
<td>CTNNB1, CYLD</td>
<td>Beta catenin, LEF-1</td>
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</tr>
<tr>
<td>Adenoid Cystic carcinoma</td>
<td>T(6;9)(q21-23;p23-24)</td>
<td>MYB</td>
<td>MYB (82% test + ?)</td>
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</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>T(11;19)(q21;p13) T(11;15)(q21;q26)</td>
<td>CRTCL1-MAK2</td>
<td>CRTCL1-MAK2, MAML2, P63/p40</td>
<td></td>
</tr>
<tr>
<td>Salivary carcinoma (MASC)</td>
<td>T(11;15)(q21;q26)</td>
<td>CRTC3-MAML2</td>
<td>P63/p40</td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>T(12;22)(q13;q12)</td>
<td>EWSR1-ATF1</td>
<td>EWSR1</td>
<td></td>
</tr>
</tbody>
</table>

*From presentation by Dr. Krane at American Society of Cytopathology meeting, Phoenix AZ, Nov 2017*

* shakesqueak cells help that patient*
## SOX10 in Salivary Gland neoplasms

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinic cell carcinoma</td>
<td>Salivary duct carcinoma</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>Mucoepidermoid carcinoma</td>
</tr>
<tr>
<td>Epithelial-Myoepithelial carcinoma</td>
<td>Warthin's</td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td>Oncocytoma</td>
</tr>
<tr>
<td>Pleomorphic Adenoma</td>
<td></td>
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