**Template for Reporting Results of Biomarker Testing of Specimens From Patients With Tumors of the Head and Neck**

**Version:** HeadNeckBiomarkers 1.0.0.0

Template posting date: February 2017

**Authors**

Raja R. Seethala, MD\*
Department of Pathology, University of Pittsburgh, Pittsburgh, PA

Alain Algazi, MD
Melanoma Center, University of California San Francisco Medical Center, San Francisco, CA

Philip Cagle, MD
Department of Pathology, Houston Methodist Hospital, Houston, TX

Diane L. Carlson, MD

Department of Laboratory Medicine and Pathology, Cleveland Clinic Florida, Weston, FL

Deborah Chute, MD
Department of Pathology, Cleveland Clinic, Cleveland, OH

William Faquin, MD,PhD
Department of Pathology, Massachusetts General Hospital, Boston, MA

Karen Hood, RHIA, CTR
Surgical Services, VA Medical Center, Birmingham, AL

James S. Lewis Jr, MD
Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN

Jason Pettus, MD
Department of Pathology, **Dartmouth-Hitchcock Medical Center**, Lebanon, NH

Mary S. Richardson, MD, DDS,
Department of Pathology, Medical University of South Carolina, Charleston, SC

Lester D.R. Thompson, MD
Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, CA

Bruce M. Wenig, MD
Department of Pathology and Laboratory Medicine, Beth Israel Medical Center, St. Luke’s and Roosevelt Hospitals, New York, NY

For the Members of the Cancer Biomarker Reporting Committee, College of American Pathologists

\* Denotes primary author. All other contributing authors are listed alphabetically.

**© 2017 College of American Pathologists (CAP). All rights reserved.**

The College does not permit reproduction of any substantial portion of these templates without its written authorization. The College hereby authorizes use of these templates by physicians and other health care providers in reporting results of biomarker testing on patient specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these templates for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the templates solely for their individual use in reporting results of biomarker testing for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified templates for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified templates into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the template data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the templates in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from the CAP.

Any public dissemination of the original or modified templates is prohibited without a written license from the CAP.

The College of American Pathologists offers these templates to assist pathologists in providing clinically useful and relevant information when reporting results of biomarker testing. The College regards the reporting elements in the templates as important elements of the biomarker test report, but the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these templates as educational tools to assist pathologists in the useful reporting of relevant information. It did not issue them for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the templates might be used by hospitals, attorneys, payers, and others. The College cautions that use of the templates other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.

CAP Head and Neck Biomarker Template Revision History

**Version Code**

The definition of version control and an explanation of version codes can be found at www.cap.org
(search: cancer protocol terms).

**Summary of Changes**

This is a new template.

Head and Neck Biomarker Reporting Template

Template posting date: February 2017

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient’s medical record and thus readily available to the treating clinical team.

**HEAD AND NECK**

**Select a single response unless otherwise indicated.**

***Note:*** *Use of this template is optional.*

**+ RESULTS**

**+ Head and Neck Squamous Cell Carcinoma (HNSCC)**

***+* Human Papillomavirus (HPV) Testing**

+ p16 Expression (by immunohistochemistry) as a Surrogate for Transcriptionally Active High-Risk HPV

+ \_\_\_ Negative (<50% diffuse and strong nuclear and cytoplasmic staining)

+ \_\_\_ Equivocal (<70% but >50% diffuse and strong nuclear and cytoplasmic staining)

+ \_\_\_ Positive (>70% diffuse and strong nuclear and cytoplasmic staining)

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ HPV-DNA (by in situ hybridization [ISH])

+ \_\_\_ Negative (no signal)

+ \_\_\_ Positive (check all that apply)

+ \_\_\_ Punctate

+ \_\_\_ Diffuse

+ Subtype(s) (if available): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ HPV E6/E7 mRNA (by ISH)

+ \_\_\_ Negative (no signal)

+ \_\_\_ Positive (cytoplasmic and/or nuclear signals)

+ Subtype(s) (if available): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ HPV-DNA (by polymerase chain reaction [PCR])

+ \_\_\_ Negative (no signal)

+ \_\_\_ Positive

+ Subtype(s) (if available): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ HPV E6/E7 mRNA (by reverse transcriptase polymerase chain reaction [RT-PCR])

+ \_\_\_ Negative (no signal)

+ \_\_\_ Positive

+ Subtype(s) (if available): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ Epstein-Barr Virus (EBV) Testing

*+ EBV Early mRNA (EBER) (by ISH)*

+ \_\_\_ Negative (no signal)

+ \_\_\_ Positive (nuclear signal)

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ NUT Midline Carcinoma

*+ NUT Expression (by immunohistochemistry [IHC])*

+ \_\_\_ Negative

+ \_\_\_ Positive

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*+ NUT Rearrangements (by Fluorescence ISH [FISH])*

+ \_\_\_ No *NUT* rearrangement detected

+ \_\_\_ *NUT* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

*+ BRD4-NUT Fusion (by RT-PCR)*

+ \_\_\_ No *BRD4-NUT* fusions detected

+ \_\_\_ *BRD4-NUT* fusions detected

*+ Other NUT Fusion (by RT-PCR)*

+ \_\_\_ No *NUT* translocation detected

+ \_\_\_ *NUT* translocation detected

+ Fusion partner: \_\_\_\_\_\_

**+ Salivary Gland Carcinoma**

**+ (Hyalinizing) Clear Cell Carcinoma**

+ *EWSR1* Rearrangements (by FISH)

+ \_\_\_ No *EWSR1* rearrangement detected

+ \_\_\_ *EWSR1* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *EWSR1-ATF1* Fusion (by RT-PCR)

+ \_\_\_ No *EWSR1-ATF1* fusions detected

+ \_\_\_ *EWSR1-ATF1* fusions detected

+ Other *EWSR1* Fusion (by RT-PCR)

+ \_\_\_ No EWSR1 translocation detected

+ \_\_\_ EWSR1 translocation detected

+ Fusion partner: \_\_\_\_\_\_

**+ Mammary Analogue Secretory Carcinoma**

+ *ETV6* Rearrangements (by FISH)

+ \_\_\_ No *ETV6* rearrangement detected

+ \_\_\_ *ETV6* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*+ ETV6-NTRK3 Fusion (by RT-PCR)*

+ \_\_\_ No *ETV6-NTRK3* fusions detected

+ \_\_\_ *ETV6-NTRK3* fusions detected

**+ Mucoepidermoid Carcinoma**

+ *MAML2* Rearrangements (by FISH)

+ \_\_\_ No *MAML2* rearrangement detected

+ \_\_\_ *MAML2* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *CRTC1-MAML2* Fusion (by RT-PCR)

+ \_\_\_ No *CRTC1-MAML2* fusions detected

+ \_\_\_ *CRTC1-MAML2* fusions detected

+ *CRTC3-MAML2* Fusion (by RT-PCR)

+ \_\_\_ No *CRTC3-MAML2* fusions detected

+ \_\_\_ *CRTC3-MAML2* fusions detected

**+ Adenoid Cystic Carcinoma**

+ MYB Expression (by IHC)

+ \_\_\_ Negative

+ \_\_\_ Positive

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *MYB* Rearrangements (by FISH)

+ \_\_\_ No *MYB* rearrangement detected

+ \_\_\_ *MYB* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *MYB*-*NFIB* Fusion (by FISH)

+ \_\_\_ No *MYB-NFIB* fusions detected

+ \_\_\_ *MYB-NFIB* fusions detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic fusion (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex fusion (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *MYB-NFIB* Fusion (by RT-PCR)

+ \_\_\_ No *MYB-NFIB* fusions detected

+ \_\_\_ *MYB-NFIB* fusions detected

**+ Carcinoma ex Pleomorphic Adenoma/Pleomorphic Adenoma**

+ *HMGA2* (by FISH)

+ \_\_\_ No *HMGA2* rearrangement detected

+ \_\_\_ *HMGA2* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ PLAG1 Expression (by IHC)

+ \_\_\_ Negative

+ \_\_\_ Positive

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *PLAG1* (by FISH)

+ \_\_\_ No *PLAG1* rearrangement detected

+ \_\_\_ *PLAG1* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Salivary Duct Carcinoma**

+ Human Epidermal Growth Factor-2 (HER2 [ERBB2]) Expression (by IHC)

+ \_\_\_ Negative (score 0)

+ \_\_\_ Negative (score 1+)

+ \_\_\_ Equivocal (score 2+)

+ \_\_\_ Positive (score 3+)

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ *HER2* (*ERBB2)* Expression (by FISH)

+ \_\_\_ Negative (not amplified)

+ \_\_\_ Positive (amplified)

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ Number of observers: \_\_\_\_\_\_

+ Number of invasive cancer cells counted: \_\_\_\_\_\_

+ \_\_\_ Using dual-probe assay

+ Average number of *HER2* (*ERBB2*) signals per cancer cell: \_\_\_\_\_\_

+ Average number of CEP17 signals per cancer cell: \_\_\_\_\_\_

+ *HER2* (*ERBB2*):CEP17 ratio: \_\_\_\_\_\_

+ \_\_\_ Using single-probe assay

+ Average number of *HER2* (*ERBB2*) signals per cancer cell: \_\_\_\_\_\_

+ Androgen Receptor (by IHC)

+ \_\_\_ Negative

+ \_\_\_ Positive

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Sinonasal Malignancies**

**+ INI-Deficient Sinonasal Carcinoma/Rhabdoid Tumor**

+ INI-1 (by IHC)

+ \_\_\_ Intact (staining retained, negative for INI1 deletion)

+ \_\_\_ Lost (staining lost, positive for INI1 alteration)

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ Biphenotypic Sinonasal Sarcoma**

+ *PAX3* Rearrangements (by FISH)

+ \_\_\_ No *PAX3* rearrangement detected

+ \_\_\_ *PAX3* rearrangement detected

+ Percentage of positive cells: \_\_\_\_\_\_%

+ Percentage of positive cells with classic rearrangement (if applicable): \_\_\_\_\_\_%

+ Percentage of positive cells with complex rearrangement (if applicable): \_\_\_\_\_\_%

+ *PAX3-MAML3* Fusion (by RT-PCR)

+ \_\_\_ No *PAX3-MAML3* fusions detected

+ \_\_\_ *PAX3-MAML3* fusions detected

**+ Paraganglioma**

+ SDHB (by IHC)

+ \_\_\_ Intact (staining retained, negative for SDH alteration)

+ \_\_\_ Lost (staining lost, positive for SDH alteration)

+ \_\_\_ Indeterminate (explain): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**+ METHODS**

**+ Head And Neck Squamous Cell Carcinoma (HNSCC)**

**+ HPV Testing**

+ \_\_\_ P16 (by IHC)

+ Primary Antibody

+ \_\_\_ E6H4

+ \_\_\_ Other (specify clone): \_\_\_\_\_

+ \_\_\_ HPV DNA (by ISH)

+ Subtypes Separately Tested

+ \_\_\_ High-Risk (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Low-Risk (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Specific Subtype: \_\_\_\_\_ (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ HR-HPV E6/E7 mRNA (by ISH) (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ HPV DNA (by PCR)

+ Subtypes Separately Tested

+ \_\_\_ High-Risk (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Low-Risk (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Specific Subtype: \_\_\_\_\_ (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ HR-HPV E6/E7 mRNA by RT-PCR

+ EBV Testing

+ \_\_\_ EBER by ISH

+ \_\_\_ EBV DNA by PCR

**+ NUT Midline Carcinoma**

+ *NUT* Rearrangements

+ \_\_\_ Breakapart FISH

+ \_\_\_ *BRD4-NUT* fusion transcript RT-PCR

+ \_\_\_ NUT immunohistochemistry

**+ Salivary Gland Carcinoma**

**+ (Hyalinizing) Clear Cell Carcinoma**

+ *EWSR1* Rearrangements

+ \_\_\_ Breakapart FISH

+ \_\_\_ *EWSR1-ATF1* fusion transcript RT-PCR

**+ Mammary Analogue Secretory Carcinoma**

+ *ETV6* Rearrangements

+ \_\_\_ Breakapart FISH

+ \_\_\_ *ETV6-NTRK3* fusion transcript RT-PCR

**+ Mucoepidermoid Carcinoma**

+ *MAML2* Rearrangements

+ \_\_\_ Breakapart FISH

+ \_\_\_ *CRTC1-MAML2* fusion transcript RT-PCR

+ \_\_\_ *CRTC3-MAML2* fusion transcript RT-PCR

**+ Adenoid Cystic Carcinoma**

+ *MYB* Rearrangements

+ \_\_\_ Breakapart FISH

+ \_\_\_ *MYB-NFIB* fusion FISH

+ \_\_\_ *MYB-NFIB* fusion transcript RT-PCR

+ \_\_\_ MYB immunohistochemistry

**+ Carcinoma ex Pleomorphic Adenoma/Pleomorphic Adenoma**

+ *HMGA2*

+ \_\_\_ Breakapart FISH

+ *PLAG1*

+ \_\_\_ Breakapart FISH

+ \_\_\_ PLAG1 Immunohistochemistry

**+ Salivary Duct Carcinoma**

+ Her2 Expression (by IHC)

+ \_\_\_ US Food and Drug Administration (FDA) cleared (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Laboratory-developed test

+ Primary Antibody

+ \_\_\_ 4B5

+ \_\_\_ HercepTest

+ \_\_\_ A0485

+ \_\_\_ SP3

+ \_\_\_ CB11

+ \_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*+ HER2 (ERBB2*) Expression (by FISH)

+ \_\_\_ FDA cleared (specify test/vendor): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Laboratory-developed test (specify probe): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

+ \_\_\_ Androgen receptor immunohistochemistry

**+ Sinonasal Malignancies**

+ \_\_\_ INI-1

+ \_\_\_ PAX-3

**+ Paraganglioma**

+ \_\_\_ SDHB immunohistochemistry

**+ COMMENT(S)**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Note: Fixative type, time to fixation (cold ischemia time), and time of fixation should be reported if applicable in this template or in the original pathology report.*

*Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee (www.genenames.org; accessed May 9, 2016).*

*All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (http://varnomen.hgvs.org; accessed June 21, 2016).*

Explanatory Notes

**A. Head and Neck Squamous Cell Carcinoma (HNSCC)**

Human Papillomavirus Testing

Human papillomavirus (HPV)-related head and neck lesions have garnered much attention in recent years, mainly due to the rising incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC).1 Transcriptionally active, high-risk HPV is present in the majority of OPSCC in the United States and at least a significant minority of OPSCC patients worldwide, with rates rapidly increasing over the past several decades, despite the decrease in smoking rates.2 This change has been linked to changes in sexual practices, and the disease is overwhelmingly one of white men in their 50s and 60s. Patients typically have smaller primary tumors (often clinically occult), present with neck metastases (80% to 85%) that are often cystic, and have tumors that are nonkeratinizing in appearance. High-risk HPV types cause the cancers, and more than 90% of the time it is HPV type 16. While there are many carcinogenic/transforming HPV proteins, the early gene products E6 and E7 appear to play the most significant roles. Although both E6 and E7 can interact with many host proteins, their main contribution to tumorigenesis is through negative regulation of the tumor suppressor proteins p53 and Rb, respectively. Of particular importance is the degradation of Rb by E7, because this leads to a paradoxical overexpression of the tumor suppressor protein p16, which is consistently overexpressed in the nuclei and cytoplasm of tumors with transcriptionally active, high-risk HPV. P16 immunohistochemistry thus serves as a very good surrogate marker of active HPV in these tumors.

Despite the tendency for HPV-related tonsillar squamous cell carcinoma (SCC) to metastasize to neck lymph nodes early in the course of disease (a feature that is usually associated with aggressive disease in cancers), the prognosis is better than for HPV-negative carcinomas. HPV-related oropharyngeal SCC is associated with a 30% to 50% reduction in the risk of death compared to HPV-negative SCC.3 However, the improved prognosis may be offset in patients who have a strong history of tobacco use and/or are current (heavy) smokers. HPV-related oropharyngeal SCC responds better to both primary chemoradiation and surgical treatment. This may be because these tumors have lower mutation rates and are less genetically complex than HPV-negative cancers. There are now definitive prospective studies showing that the prognosis of HPV-related OPSCC patients has improved such that the head and neck oncology community is essentially united in the concept that all new patients should be tested for high-risk HPV.4

How to test for high-risk HPV is not clearly defined, however, and different groups vary in recommendations about use of HPV-specific testing, surrogate marker testing such as p16, or a combination of these. Further, many of the recommendations are site and clinical scenario specific. For OPSCC, for instance, there is broad acceptance of p16 as a good surrogate marker for HPV. The cutoffs listed above refer mainly to these tumors. For other sites this is not well vetted.

Currently, for OPSCC, prognosis and counseling critically depends on these test results. Small changes in treatment within the standard of care are made for HPV-positive OPSCC patients currently, and there are many clinical trials underway to de-intensify and tailor treatments specifically for these patients. There are many HPV-specific detection methods, including those that detect HPV DNA (PCR, ISH, fluid-based tests such as those used in gynecologic cytology) and those that detect HPV mRNA (RT-PCR, ISH, fluid-based tests). These have quite variable sensitivity, specificity, prognostic power, and availability. Tests can be performed on formalin-fixed paraffin-embedded small biopsies and resection specimens; on cytology cell blocks, fluid aspirates, and smears; or on saliva specimens. Given the predominance of bulky cervical nodal disease in patients with OPSCC, both surgical and cytology specimens from the neck are common. Cytology specimen-based diagnosis, confirming metastatic carcinoma and then providing HPV-specific and/or surrogate marker testing, is increasingly common.

High-risk HPV has been detected in most of the specific SCC variants in the oropharynx. When associated with active HPV, these SCC variants appear to have the same favorable prognosis.5 Although its significance is not established, active high-risk HPV has also been detected in most oropharyngeal small cell carcinomas, although many of these patients have developed progressive and metastatic carcinoma much more akin to the clinical behavior of a high-grade neuroendocrine carcinoma at any site. Although a minority of non-oropharyngeal SCC have transcriptionally active high-risk HPV (particularly those of the sinonasal tract and nasopharynx, and less often oral cavity, larynx, and hypopharynx), current data have not clearly demonstrated prognostic benefit or altered treatment responses for these tumors.

Epstein-Barr Virus Testing

Epstein-Barr virus is an established etiologic agent for cancer development, specifically for nasopharyngeal carcinomas, lymphoepithelial carcinomas at other sites, and also for several types of hematopoietic malignancies. Exposure to EBV is widespread in humans, and the virus establishes persistent asymptomatic infection in lymphocytes. It also infects epithelial cells, specifically in the oropharynx and nasopharynx, establishing replicative status and shedding virus into the saliva throughout a host's life. EBV also establishes several different forms of latency in cells, resulting in complex and varying expression profiles in infected cells. EBV is strongly associated with nasopharyngeal carcinoma worldwide. Tumors are particularly concentrated in distinctive geographical regions such as southern China and Southeast Asia, among the Inuit in Alaska and Greenland, and in the Middle East and north Africa.6,7

Nasopharyngeal carcinoma is highly associated with viral infection, predominantly EBV, but also rarely HPV. The World Health Organization classifies nasopharyngeal carcinoma into 3 major types: keratinizing, same morphology as conventional SCC at other anatomic subsites; nonkeratinizing, further subdivided into differentiated and undifferentiated; and basaloid.

EBV is universally seen in undifferentiated tumors regardless of geographic location. In endemic areas, keratinizing tumors are often positive as well, but in Western countries, these are consistently negative. Basaloid nasopharyngeal carcinoma is very rare and is frequently, but not consistently, EBV related.6,7

Plasma and serum EBV DNA, assessed by RT-PCR, is highly sensitive and specific for nasopharyngeal carcinoma. EBV early RNA (EBER) is strongly and diffusely expressed by EBV-related tumors, and in situ hybridization for EBER in is very helpful diagnostically, as well, particularly in specimens from nodal metastases where nasopharyngeal carcinoma is suspected. EBER is strongly and diffusely expressed by EBV-related tumors, so the assay is highly sensitive and specific.8 There are a number of commercially available assays, and individual laboratory-developed ISH assays are common as well. Routine ISH testing of new nasopharyngeal carcinoma cases in clinical practice is common since studies suggest that EBV-related tumors have somewhat better prognosis and treatment response and, further, to differentiate from the subset of nonkeratinizing (and perhaps basaloid) nasopharyngeal carcinomas that are related to HPV, rather than EBV.

NUT Midline Carcinoma

NUT midline carcinoma is a rare, aggressive, squamous cell carcinoma variant uniquely defined by *NUT* gene translocations.9 It has a predilection, as its name implies, for midline sites and can occur in both children and adults. About one-third occur in the head and neck, frequently, the sinonasal tract.10 The majority (approximately two-thirds) show a *NUT*-*BRD4* fusion [t(15;19)(q14, p13.1)], while the remainder show a *NUT-BRD3* fusion [t(9;15)(q34.2;q14)], the newly described *NSD3-NUT* fusion, or another uncharacterized *NUT* fusion.11 The presence of a *NUT* fusion is specific for this entity and can be used to diagnostically define it.

Both breakapart fluorescence in situ hybridization (FISH) or RT-PCR for the fusion transcript are commonly used testing methodologies. But perhaps the most common method of testing is by immunohistochemistry for NUT protein since the fusions result in overexpression. As with many other immunohistochemical surrogates for fusion, NUT overexpression performs well (sensitivity 87%, specificity almost 100%),12 but NUT protein-positive, fusion-negative cases can occur.13-15

Clinical response to BRD inhibitor OTX015/MK-8628 has recently been documented.16

**B. Salivary Gland Carcinoma**

(Hyalinizing) Clear Cell Carcinoma – *EWSR1* Translocation Analysis

Hyalinizing clear cell carcinoma is a distinct, typically low-grade salivary tumor with clear cell features, characteristic fibrohyaline stroma, and a largely squamous phenotype. It is essentially defined by the *EWSR1-ATF1* translocation [t(12;22)(q13;q12)] in over 80% of cases.17 This translocation is seen in nonsalivary tumors as well, notably clear cell sarcoma (soft parts melanoma) and angiomatoid fibrous histiocytoma, among others.18 Within tumors of the head and neck region, this specific translocation is largely restricted to clear cell carcinoma and its odontogenic counterpart, clear cell odontogenic carcinoma.19 The major value of testing for the translocation is to aid in distinction from mimics like clear cell mucoepidermoid carcinoma and squamous cell carcinoma with clear cell change, as these entities have a different biologic behavior.

Both breakapart FISH and RT-PCR for the fusion transcript are viable testing methodologies in the appropriate morphologic and immunophenotypic context. Without this context, however, *EWSR1* FISH is not specific. Aside from other *EWSR1* translocated tumors (Ewing sarcoma, extraskeletal myxoid chondrosarcoma, desmoplastic small round cell tumor, soft tissue type myoepithelioma, among others) that may occur in this region, a subset of salivary, high-grade, clear cell myoepithelial carcinomas have been recently reported to show *EWSR1* rearrangements as well, though the translocation partner here is unknown.20

Mammary Analogue Secretory Carcinoma – *ETV6* Translocation Analysis

Mammary analogue secretory carcinoma is a recently described, distinct, low-grade salivary gland tumor, historically categorized under acinic cell carcinoma and adenocarcinoma not otherwise specified, but now recognized to show a striking resemblance to secretory carcinoma of the breast.21,22 In addition to this shared morphologic appearance, this tumor also shares an *ETV6-NTRK3* translocation [t(12;15)(15)(p13;q25)].22-28 Of note, this translocation is well described in other nonsalivary tumors: infantile fibrosarcoma, cellular mesoblastic nephromas, acute myeloid leukemias, and a subset of radiation-associated papillary thyroid carcinomas.21,24,29,30

In the context of primary salivary gland tumors, application of testing for the translocation is diagnostic, mainly to distinguish this tumor from zymogen-poor acinic cell carcinoma, low-grade cribriform cystadenocarcinoma, and mucoepidermoid carcinoma.22 Similarly, translocation studies may aid in establishing the diagnosis of mammary analogue secretory carcinoma with high-grade transformation.25 In these scenarios, both breakapart *ETV6* FISH and RT-PCR for the fusion transcript are viable testing methods, though traditionally RT-PCR only detects about 65% of cases detected by paired breakapart FISH in paraffin tissue.21,25-27 Aside from technical limitations of RNA-based testing on paraffin tissue, a small subset of mammary analogue secretory carcinomas may have an alternate translocation with a currently unknown partner.26

A phase 1a/1b clinical trial of the oral TRK Inhibitor LOXO-101 is available and may thus be relevant in the rare aggressive cases of mammary analogue secretory carcinoma.

Mucoepidermoid Carcinoma – *MAML2* Translocation Analysis

Mucoepidermoid carcinoma is still the most common salivary gland carcinoma and serves as prototypical translocation-associated salivary gland carcinoma, known to frequently harbor a *CRTC1-MAML2* translocation [t(11;19)(q21;p13)] in 40% to 80% of cases,31 and a *CRTC3-MAML2* translocation [t(11;15)(q21;q26)] in roughly 5% of cases.32,33 This translocation may be of potential prognostic and diagnostic significance.

Both translocations historically favored low- to intermediate-grade mucoepidermoid carcinomas and were even purported as an independent prognosticator.33-35 However, in others, the *MAML2* translocations have been documented in sizeable subsets of high-grade tumors, and the prognostic value is actually muted to absent,31,36-38 suggesting that the perceived prognostic value was an artifact of misclassification of high-grade mucoepidermoid carcinomas in earlier series. Conversely, other genetic events (ie, CDKN2A/p16 alterations)39 adversely modulate the favorable prognosis of a translocation-positive tumor.

Ultimately, rather than prognostic value, *MAML2* translocation testing has evolved into a diagnostic capacity serving as adjuncts in separating variant morphologies of mucoepidermoid carcinoma (ie, oncocytic) from their mimics40 or delineating high-grade mucoepidermoid carcinoma from more aggressive entities such as adenosquamous carcinoma and salivary duct carcinoma.36

While highly prevalent in mucoepidermoid carcinoma, *MAML2* rearrangements are not considered diagnosis defining; translocation negativity does not necessarily supersede the histomorphologic diagnosis, let alone conventional staging for prognosis. Both *MAML2* FISH using breakapart methodology and RT-PCR for *CRTC1* or *CRTC3-MAML2* fusion transcripts are feasible techniques for detection in paraffin tissue, though the former is more widely utilized and provides coverage of both translocations.33,36 While there is some controversy regarding the presence *CRTC1-MAML2* translocations in some Warthin tumors, the diagnostic verification of these cases is suspect, and in large series focusing on Warthin tumors with high-quality morphologic verification, the translocation is nonexistent.41-43

Adenoid Cystic Carcinoma – MYB Expression and Translocation Analysis

Adenoid cystic carcinoma is among the earliest described salivary gland carcinomas and is defined by a highly infiltrative biphasic salivary gland neoplasm composed of epithelial (luminal) and myoepithelial (basal) cells arranged in cribriform, tubular, and solid growth patterns. Overexpression of MYB and activation of its downstream targets are now implicated in the pathogenesis of this tumor.44 Specifically, an *MYB-NFIB* translocation [t(6;9)(q22-23;p23-24)] is the main mechanism for this.

While not diagnosis defining, MYB status can thus be used diagnostically, especially on small biopsies. Translocation of *MYB* protooncogene (nearly always with transcription factor *NFIB*) has been demonstrated by breakapart or fusion FISH or fusion transcript RT-PCR in 30% to 80% of cases.45-47 Furthermore, MYB protein overexpression, which can be detected by IHC, is seen in 60% to 80% of adenoid cystic carcinomas, including a large proportion of fusion-negative cases.45-47

*MYB-NFIB* is highly specific for adenoid cystic carcinoma, regardless of tissue of origin (eg, salivary gland, breast, bronchus, sinus); however, as implied above, sensitivity is variable and may be quite low. While MYB protein expression is more sensitive, showing strong and diffuse nuclear immunohistochemical staining for MYB within the abluminal component, it is not entirely specific since a subset of other salivary gland tumor types can also show immunoreactivity for MYB.45 It is now known that a subset (approximately one-third) of MYB negative tumors have an alternate translocation, *MYBL1-NFIB.*48

Carcinoma ex Pleomorphic Adenoma/Pleomorphic Adenoma – *PLAG1* and *HMGA2* Translocation Analysis

Pleomorphic adenoma is the most common salivary gland tumor type overall, and can undergo malignant transformation, designated generically as *carcinoma ex pleomorphic adenoma*. By conventional karyotyping, translocations involving 12q13-1549 or 8q1250 have been reported in 40% to 70% of pleomorphic adenomas. The genes involved are now known to be *HMGA2* [12q13-15] and *PLAG1* [8q12].

Translocation-positive pleomorphic adenomas tend to have more of a classic morphology and occur in younger individuals.50 Translocation assessment may provide value on fine-needle aspirates or small biopsies of pleomorphic adenomas. However, these translocations are also useful in confirming origin from pleomorphic adenoma in histologically malignant tumors (carcinoma ex pleomorphic adenoma). It must be noted that over half of carcinoma ex pleomorphic adenomas show imbalanced translocations, with amplification of *PLAG1* or *HMGA2.*51,52

As the translocations may be complex and may involve a variety of partners, FISH is among the most viable clinical methods for testing. Additionally, for PLAG1, IHC for overexpression has also been utilized. However, like other immunohistochemical markers used as surrogate markers, PLAG is sensitive, present in over 90% of pleomorphic adenomas and carcinoma ex pleomorphic adenomas, but not specific, as it can be expressed in other tumor types and can be difficult to interpret.53,54

Salivary Duct Carcinoma – Her2 and Androgen Receptor Analysis

Salivary duct carcinoma is generally a high-grade malignant neoplasm, most commonly arising in the parotid gland, with poor outcomes. While morphologically akin to a high-grade ductal carcinoma of breast, it is now understood that, when properly classified, the vast majority of salivary duct carcinomas recapitulate the “luminal AR-positive/molecular apocrine” type of breast carcinoma.55 Less common histologic variants, papillary, micropapillary, mucin-rich, basal like, and sarcomatoid,56,57 are still under the umbrella of this phenotype.55 In situ disease has also been reported.

Given the similarities to ductal carcinoma of breast, assessment for ERBB2 (HER2) is of potential therapeutic interest, though it has no diagnostic utility. There are no established meaningful thresholds for HER2 IHC and *HER2* FISH testing in salivary duct carcinoma, but by extrapolation and for standardization, breast criteria are generally adopted. Roughly 20% to 40% of salivary duct carcinomas show 3+ positivity for HER2 by IHC,58,59 and FISH amplification of *HER2* is noted in 20% to 30% of cases.55,58,59 Objective tumor responses in patients treated with HER2-directed therapy in combination with bevacizumab60 and chemotherapy61 have been reported, though complete responses are rare. A subset of salivary duct carcinomas may harbor mutations in *TP53*, *HRAS,* or *PTEN* loss, which may decrease efficacy of anti-ERBB2 therapy.55

Androgen receptor (AR) positivity essentially defines salivary duct carcinoma; most high-grade ductal carcinomas that are AR negative represent high-grade transformation of another tumor type.62 Aside from its diagnostic utility, a subset of cases has been shown to benefit from antiandrogen therapy either alone or concurrently with radiation.63,64 There are currently no thresholds for defining positivity for AR from a diagnostic or therapeutic standpoint.

**C. Sinonasal Malignancies**

INI-Deficient Sinonasal Carcinoma/Rhabdoid Tumor

Recently, a subset (up to 6% of primary sinonasal carcinomas) of poorly differentiated/undifferentiated carcinomas of the sinonasal tract have now been characterized by loss of SMARCB1 (INI-1) on chromosome 22q11.2 akin to rhabdoid tumors. Tumors are usually phenotypically undifferentiated but may show squamous or glandular differentiation and do show some rhabdoid morphology.65,66 The current diagnosis rests on establishing INI-1 deficiency in the context of the aforementioned morphology. Currently this is most frequently documented by IHC, though *SMARCB1* deletions can be evaluated by FISH. Limited data suggest that the latter is only 75% sensitive in detecting the INI-1–deficient phenotype.65

Biphenotypic Sinonasal Sarcoma – *PAX3* Translocation Analysis

Biphenotypic sinonasal sarcoma, or low-grade sinonasal sarcoma with neural and myogenic features, is an increasingly recognized, locally aggressive sarcoma of the sinonasal tract, seen most commonly in middle-aged women.67 Key morphologic features include a cellular, spindled, herringbone architecture; “hemangiopericytomatous” vasculature; and secondary proliferation of respiratory glandular elements. While, initially, confirmation of diagnosis was established by expression of neural (typically at least focal S-100) and myogenic (typically smooth muscle actin [SMA] and/or muscle specific actin [MSA] staining),67 recent work has demonstrated a recurring t(2;4)(q35;q31.1) translocation, most commonly resulting in *PAX3-MAML3* gene fusion.

The utility of testing for this translocation is currently restricted to diagnostic application: to distinguish this entity from both more indolent (ie, cellular schwannoma) and more aggressive (ie, synovial sarcoma, desmoplastic melanoma) spindle cell neoplasms of the sinonasal tract. Both breakapart FISH for *PAX3* and RT-PCR for the *PAX3-MAML3* fusion transcript are viable testing methodologies. As with other translocations, breakapart FISH appears more sensitive than RT-PCR for the *PAX3-MAML3* fusion transcript. *PAX3* rearrangements are detectable by FISH in 96% of biphenotypic sinonasal sarcomas, while *MAML3* is confirmed as the fusion partner in only 79% of cases.68 However, while this translocation is, to date, specific for biphenotypic sinonasal sarcoma68; *PAX3* rearrangements are also seen in alveolar rhabdomyosarcomas (typically partnered with *FOXO1*), which are not uncommon in the sinonasal tract.69 Thus, as with other diagnostic translocations, morphologic and immunophenotypic context is critical for appropriate use of breakapart FISH.

**D. Paraganglioma**

Familial Paraganglioma - SDHB Immunohistochemistry

Head and neck paragangliomas typically consist of carotid body, vagal, and jugulotympanic tumors; primary laryngeal and thyroid paragangliomas are uncommon. Unlike pheochromocytoma, most head and neck paragangliomas are phenotypically “parasympathetic” and rarely present with adrenergic symptomatology. While classically approximately 10% of paragangliomas are familial,70 the prevalence of germline mutations in several “sporadic” cohorts suggest that this is actually closer to 30% or higher.71,72 Most mutations in head and neck paragangliomas involve the succinate dehydrogenase complex subunits B, C, and D (SDHB, SDHC, SDHD); SDHA and SDHAF2 mutations are rare. The majority of these in head and neck paragangliomas are SDHD mutations, which are more strongly associated with multifocal disease.73 However, SDHB mutations have a higher risk of malignancy, including nonparaganglioma tumors.74

While genetic testing and counseling is the reference standard for evaluating for hereditary disease, SDHB loss by immunohistochemistry has been variably employed as a screening method on paragangliomas and pheochromocytomas to help triage patients that should be evaluated by a geneticist and/or tested for germline mutations. Destabilization of the succinate dehydrogenase complex from any mutation will result in a loss of SDHB protein, which is part of the catalytic core. Normal “intact” staining is represented as cytoplasmic granular immunopositivity. SDHB loss in SDH-deficient tumors is denoted by absence of staining, with an important caveat that the internal controls (ie, stroma, vessels) still retain granular positivity. Aside from technical failure, embolization and trauma may decrease SDHB staining, leading to a false-positive result.73

**References**

1. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst.* 2000;92(9):709-720.

2. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29(32):4294-4301.

3. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363(1):24-35.

4. Marur S, Burtness B. Oropharyngeal squamous cell carcinoma treatment: current standards and future directions. *Curr Opin Oncol.* 2014;26(3):252-258.

5. El-Mofty SK. HPV-related squamous cell carcinoma variants in the head and neck. Head and neck pathology. 2012;6(Suppl 1):S55-S62.

6. Petersson F. Nasopharyngeal carcinoma: a review. *Semin Diagn Pathol.* 2015;32(1):54-73.

7. Chan JKC, Bray F, McCarron P, et al. Nasopharyngeal carcinoma. In: Barnes L, Eveson JW, Sidransky D, eds. *Pathology and Genetics of Head and Neck Tumors. World Health Organization Classification Of Tumors.* Lyon: IARC; 2005:85-97.

8. Fan SQ, Ma J, Zhou J, et al. Differential expression of Epstein-Barr virus-encoded RNA and several tumor-related genes in various types of nasopharyngeal epithelial lesions and nasopharyngeal carcinoma using tissue microarray analysis. *Hum Pathol.* 2006;37(5):593-605.

9. French CA, Kutok JL, Faquin WC, et al. Midline carcinoma of children and young adults with NUT rearrangement. *J Clin Oncol.* 2004;22(20):4135-4139.

10. French CA. The importance of diagnosing NUT midline carcinoma. *Head Neck Pathol.* 2013;7(1):11-16.

11. French CA, Rahman S, Walsh EM, et al. NSD3-NUT fusion oncoprotein in NUT midline carcinoma: implications for a novel oncogenic mechanism. *Cancer Discov.* 2014;4(8):928-941.

12. Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. *Am J Surg Pathol*. 2009;33(7):984-991.

13. Bishop JA, Westra WH. NUT midline carcinomas of the sinonasal tract. *Am J Surg Pathol*. 2012;36(8):1216-1221.

14. Fang W, French CA, Cameron MJ, Han Y, Liu H. Clinicopathological significance of NUT rearrangements in poorly differentiated malignant tumors of the upper respiratory tract. *Int J Surg Pathol*. 2013;21(2):102-110.

15. Evans AG, French CA, Cameron MJ, et al. Pathologic characteristics of NUT midline carcinoma arising in the mediastinum. *Am J Surg Pathol*. 2012;36(8):1222-1227.

16. Stathis A, Zucca E, Bekradda M, et al. Clinical response of carcinomas harboring the BRD4-NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628. *Cancer Discov*. 2016;6(5):492-500.

17. Antonescu CR, Katabi N, Zhang L, et al. EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. *Genes Chromosomes Cancer.* 2011;50(7):559-570.

18. Thway K, Fisher C. Tumors with EWSR1-CREB1 and EWSR1-ATF1 fusions: the current status. *Am J Surg Pathol*. 2012;36(7):e1-e11.

19. Bilodeau EA, Weinreb I, Antonescu CR, et al. Clear cell odontogenic carcinomas show EWSR1 rearrangements: a novel finding and a biological link to salivary clear cell carcinomas. *Am J Surg Pathol*. 2013;37(7):1001-1005.

20. Skalova A, Weinreb I, Hyrcza M, et al. Clear cell myoepithelial carcinoma of salivary glands showing EWSR1 rearrangement: molecular analysis of 94 salivary gland carcinomas with prominent clear cell component. *Am J Surg Pathol*. 2015;39(3):338-348.

21. Skalova A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *Am J Surg Pathol*. 2010;34(5):599-608.

22. Chiosea SI, Griffith C, Assaad A, Seethala RR. Clinicopathological characterization of mammary analogue secretory carcinoma of salivary glands. *Histopathology*. 2012;61(3):387-394.

23. Connor A, Perez-Ordonez B, Shago M, Skalova A, Weinreb I. Mammary analog secretory carcinoma of salivary gland origin with the ETV6 gene rearrangement by FISH: expanded morphologic and immunohistochemical spectrum of a recently described entity. *Am J Surg Pathol*. 2012;36(1):27-34.

24. Bishop JA, Yonescu R, Batista D, Begum S, Eisele DW, Westra WH. Utility of mammaglobin immunohistochemistry as a proxy marker for the ETV6-NTRK3 translocation in the diagnosis of salivary mammary analogue secretory carcinoma. *Hum Pathol*. 2013;44(10):1982-1988.

25. Skalova A, Vanecek T, Majewska H, et al. Mammary analogue secretory carcinoma of salivary glands with high-grade transformation: report of 3 cases with the ETV6-NTRK3 gene fusion and analysis of TP53, beta-catenin, EGFR, and CCND1 genes. *Am J Surg Pathol*. 2014;38(1):23-33.

26. Ito Y, Ishibashi K, Masaki A, et al. Mammary analogue secretory carcinoma of salivary glands: a clinicopathologic and molecular study including 2 cases harboring ETV6-X fusion. *Am J Surg Pathol*. 2015;39(5):602-610.

27. Majewska H, Skalova A, Stodulski D, et al. Mammary analogue secretory carcinoma of salivary glands: a new entity associated with ETV6 gene rearrangement. *Virchows Arch*. 2015;466(3):245-254.

28. Shah AA, Wenig BM, LeGallo RD, Mills SE, Stelow EB. Morphology in conjunction with immunohistochemistry is sufficient for the diagnosis of mammary analogue secretory carcinoma. *Head Neck Pathol.* 2015;9(1):85-95.

29. Urano M, Nagao T, Miyabe S, Ishibashi K, Higuchi K, Kuroda M. Characterization of mammary analogue secretory carcinoma of the salivary gland: discrimination from its mimics by the presence of the ETV6-NTRK3 translocation and novel surrogate markers. *Hum Pathol.* 2015;46(1):94-103.

30. Leeman-Neill RJ, Kelly LM, Liu P, et al. ETV6-NTRK3 is a common chromosomal rearrangement in radiation-associated thyroid cancer. *Cancer*. 2014;120(6):799-807.

31. Seethala RR, Dacic S, Cieply K, Kelly LM, Nikiforova MN. A reappraisal of the MECT1/MAML2 translocation in salivary mucoepidermoid carcinomas. *Am J Surg Pathol*. 2010;34(8):1106-1121.

32. Fehr A, Roser K, Heidorn K, Hallas C, Loning T, Bullerdiek J. A new type of MAML2 fusion in mucoepidermoid carcinoma. *Genes Chromosomes Cancer*. 2008;47(3):203-206.

33. Okumura Y, Miyabe S, Nakayama T, et al. Impact of CRTC1/3-MAML2 fusions on histological classification and prognosis of mucoepidermoid carcinoma. *Histopathology*. 2011;59(1):90-97.

34. Behboudi A, Enlund F, Winnes M, et al. Molecular classification of mucoepidermoid carcinomas-prognostic significance of the MECT1-MAML2 fusion oncogene. *Genes Chromosomes Cancer.* 2006;45(5):470-481.

35. Noda H, Okumura Y, Nakayama T, et al. Clinicopathological significance of MAML2 gene split in mucoepidermoid carcinoma. *Cancer Sci.* 2013;104(1):85-92.

36. Chiosea SI, Dacic S, Nikiforova MN, Seethala RR. Prospective testing of mucoepidermoid carcinoma for the MAML2 translocation: clinical implications. *Laryngoscope*. 2012;122(8):1690-1694.

37. Saade RE, Bell D, Garcia J, Roberts D, Weber R. Role of CRTC1/MAML2 translocation in the prognosis and clinical outcomes of mucoepidermoid carcinoma. *JAMA Otolaryngol Head Neck Surg.* 2016;142(3):234-240.

38. Schwarz S, Stiegler C, Muller M, et al. Salivary gland mucoepidermoid carcinoma is a clinically, morphologically and genetically heterogeneous entity: a clinicopathological study of 40 cases with emphasis on grading, histological variants and presence of the t(11;19) translocation. *Histopathology*. 2011;58(4):557-570.

39. Anzick SL, Chen WD, Park Y, et al. Unfavorable prognosis of CRTC1-MAML2 positive mucoepidermoid tumors with CDKN2A deletions. *Genes Chromosomes Cancer.* 2010;49(1):59-69.

40. Garcia JJ, Hunt JL, Weinreb I, et al. Fluorescence in situ hybridization for detection of MAML2 rearrangements in oncocytic mucoepidermoid carcinomas: utility as a diagnostic test. *Hum Pathol.* 2011;42(12):2001-2009.

41. Fehr A, Roser K, Belge G, Loning T, Bullerdiek J. A closer look at Warthin tumors and the t(11;19). *Cancer Genet Cytogenet*. 2008;180(2):135-139.

42. Skalova A, Vanecek T, Simpson RH, et al. CRTC1-MAML2 and CRTC3-MAML2 fusions were not detected in metaplastic Warthin tumor and metaplastic pleomorphic adenoma of salivary glands. *Am J Surg Pathol*. 2013;37(11):1743-1750.

43. Clauditz TS, Gontarewicz A, Wang CJ, et al. 11q21 rearrangement is a frequent and highly specific genetic alteration in mucoepidermoid carcinoma. *Diagn Mol Pathol.* 2012;21(3):134-137.

44. Persson M, Andren Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. *Proc Natl Acad Sci U S A.* 2009;106(44):18740-18744.

45. Brill LB 2nd, Kanner WA, Fehr A, et al. Analysis of MYB expression and MYB-NFIB gene fusions in adenoid cystic carcinoma and other salivary neoplasms. *Mod Pathol.* 2011;24(9):1169-1176.

46. West RB, Kong C, Clarke N, et al. MYB expression and translocation in adenoid cystic carcinomas and other salivary gland tumors with clinicopathologic correlation. *Am J Surg Pathol.* 2011;35(1):92-99.

47. Mitani Y, Li J, Rao PH, et al. Comprehensive analysis of the MYB-NFIB gene fusion in salivary adenoid cystic carcinoma: incidence, variability, and clinicopathologic significance. *Clin Cancer Res.* 2010;16(19):4722-4731.

48. Mitani Y, Liu B, Rao PH, et al. Novel MYBL1 gene rearrangements with recurrent MYBL1-NFIB fusions in salivary adenoid cystic carcinomas lacking t(6;9) translocations. *Clin Cancer Res.* 2016;22(3):725-733.

49. Bullerdiek J, Hutter KJ, Brandt G, Weinberg M, Belge G, Bartnitzke S. Cytogenetic investigations on a cell line derived from a carcinoma arising in a salivary gland pleomorphic adenoma. *Cancer Genet Cytogenet.* 1990;44(2):253-262.

50. Bullerdiek J, Wobst G, Meyer-Bolte K, et al. Cytogenetic subtyping of 220 salivary gland pleomorphic adenomas: correlation to occurrence, histological subtype, and in vitro cellular behavior. *Cancer Genet Cytogenet.* 1993;65(1):27-31.

51. Persson F, Andren Y, Winnes M, et al. High-resolution genomic profiling of adenomas and carcinomas of the salivary glands reveals amplification, rearrangement, and fusion of HMGA2. *Genes Chromosomes Cancer*. 2009;48(1):69-82.

52. Katabi N, Ghossein R, Ho A, et al. Consistent PLAG1 and HMGA2 abnormalities distinguish carcinoma ex-pleomorphic adenoma from its de novo counterparts. *Hum Pathol*. 2015;46(1):26-33.

53. Rotellini M, Palomba A, Baroni G, Franchi A. Diagnostic utility of PLAG1 immunohistochemical determination in salivary gland tumors. *Appl Immunohistochem Mol Morphol.* 2014;22(5):390-394.

54. Bahrami A, Dalton JD, Shivakumar B, Krane JF. PLAG1 alteration in carcinoma ex pleomorphic adenoma: immunohistochemical and fluorescence in situ hybridization studies of 22 cases. *Head Neck Pathol.* 2012;6(3):328-335.

55. Chiosea SI, Williams L, Griffith CC, et al. Molecular characterization of apocrine salivary duct carcinoma. *Am J Surg Pathol*. 2015;39(6):744-752.

56. Simpson RH. Salivary duct carcinoma: new developments--morphological variants including pure in situ high grade lesions; proposed molecular classification. *Head Neck Pathol.* 2013;7(Suppl 1):S48-S58.

57. Di Palma S, Simpson RH, Marchio C, et al. Salivary duct carcinomas can be classified into luminal androgen receptor-positive, HER2 and basal-like phenotypes. *Histopathology*. 2012;61(4):629-643.

58. Masubuchi T, Tada Y, Maruya S, et al. Clinicopathological significance of androgen receptor, HER2, Ki-67 and EGFR expressions in salivary duct carcinoma. *Int J Clin Oncol.* 2015;20(1):35-44.

59. Clauditz TS, Reiff M, Gravert L, et al. Human epidermal growth factor receptor 2 (HER2) in salivary gland carcinomas. *Pathology*. 2011;43(5):459-464.

60. Falchook GS, Lippman SM, Bastida CC, Kurzrock R. Human epidermal receptor 2-amplified salivary duct carcinoma: regression with dual human epidermal receptor 2 inhibition and anti-vascular endothelial growth factor combination treatment. *Head Neck*. 2014;36(3):E25-E27.

61. Limaye SA, Posner MR, Krane JF, et al. Trastuzumab for the treatment of salivary duct carcinoma. *Oncologist*. 2013;18(3):294-300.

62. Williams L, Thompson LD, Seethala RR, et al. Salivary duct carcinoma: the predominance of apocrine morphology, prevalence of histologic variants, and androgen receptor expression. *Am J Surg Pathol*. 2015;39(5):705-713.

63. Soper MS, Iganej S, Thompson LD. Definitive treatment of androgen receptor-positive salivary duct carcinoma with androgen deprivation therapy and external beam radiotherapy. *Head Neck.* 2014;36(1):E4-E7.

64. Yamamoto N, Minami S, Fujii M. Clinicopathologic study of salivary duct carcinoma and the efficacy of androgen deprivation therapy. *Am J Otolaryngol.* 2014;35(6):731-735.

65. Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. *Am J Surg Pathol*. 2014;38(9):1282-1289.

66. Agaimy A, Koch M, Lell M, Semrau S, et al. SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. *Am J Surg Pathol*. 2014;38(9):1274-1281.

67. Lewis JT, Oliveira AM, Nascimento AG, et al. Low-grade sinonasal sarcoma with neural and myogenic features: a clinicopathologic analysis of 28 cases. *Am J Surg Pathol*. 2012;36(4):517-525.

68. Wang X, Bledsoe KL, Graham RP, et al. Recurrent PAX3-MAML3 fusion in biphenotypic sinonasal sarcoma. *Nat Genet.* 2014;46(7):666-668.

69. Parham DM, Barr FG. Classification of rhabdomyosarcoma and its molecular basis. *Adv Anat Pathol.* 2013;20(6):387-397.

70. Baysal BE, Willett-Brozick JE, Lawrence EC, et al. Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas. *J Med Genet*. 2002;39(3):178-183.

71. Hermsen MA, Sevilla MA, Llorente JL, et al. Relevance of germline mutation screening in both familial and sporadic head and neck paraganglioma for early diagnosis and clinical management. *Cell Oncol.* 2010;32(4):275-283.

72. Mannelli M, Castellano M, Schiavi F, et al. Clinically guided genetic screening in a large cohort of italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. *J Clin Endocrinol Metab.* 2009;94(5):1541-1547.

73. Barletta JA, Hornick JL. Succinate dehydrogenase-deficient tumors: diagnostic advances and clinical implications. *Adv Anat Pathol.* 2012;19(4):193-203.

74. Neumann HP, Pawlu C, Peczkowska M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. *JAMA*. 2004;292(8):943-951.