"Suspicious" Salivary Gland FNA: Risk of Malignancy and Interinstitutional Variability

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BACKGROUND: Fine-needle aspiration (FNA) cytology is well accepted as a safe, reliable, minimally invasive, and cost-effective method for the diagnosis of salivary gland lesions. Salivary gland neoplasms are often difficult to diagnose because of morphologic heterogeneity and a variety of epithelial metaplastic changes. Hence, a number of salivary gland FNA specimens yield indeterminate results. For indeterminate FNA specimens, the suspicious-for-malignancy (SFM) category is used when a specific neoplasm falls short in quantity or quality for the criteria for malignancy. Therefore, the findings are not sufficient for a conclusive diagnosis of malignancy. **METHODS:** This study was designed to evaluate the risk of malignancy (ROM) for the SFM group at 5 tertiary medical centers worldwide with the aforementioned criteria. Among 12,606 salivary gland FNA cases between 1997 and 2014, 276 (2.2%) were reported to be SFN. Specifically, 114 suspicious cases (41%) had histological follow-up. **RESULTS:** Histological follow-up of the 114 suspicious cases showed 95 malignant tumors indicating a risk of malignancy (ROM) of 83.3%. The ROM varied between 74% and 88% for the 5 participating institutions, and a Fisher's exact test with significance set to $p<.05$ showed no significant difference in ROM among the institutions ($p = .78$). **CONCLUSIONS:** Overall, 83.3% of SFM salivary gland FNA specimens turned out to be malignant; there was no significant interinstitutional variability in the ROMs. The SFM category for salivary gland FNA is very homogeneous, and the ROMs are quite similar worldwide. ***Cancer Cytopathol* 2018;126:94-100.** *© 2017 American Cancer Society.*

KEY WORDS: cytology; fine-needle aspiration (FNA); interinstitutional variability; risk of malignancy; salivary gland; suspicious.

INTRODUCTION

Salivary gland carcinomas are morphologically distinct and rare malignancies constituting only 0.5% of all malignancies and approximately 5% of head and neck cancers.[1] Fine-needle aspiration (FNA) is a well-accepted diagnostic tool used in the preoperative evaluation of salivary gland mass lesions to distinguish nonneoplastic lesions from neoplastic tumors and benign tumors from malignant ones.[2] FNA is a minimally invasive, cost-effective,[3-5] and relatively well-tolerated procedure performed in an outpatient clinical setting or under ultrasound guidance. The cytomorphologic findings of aspirated material from salivary glands play an important role in the risk stratification and management of patients presenting with a salivary gland mass. Patients with nonneoplastic lesions are followed by watchful waiting, whereas patients with a neoplastic diagnosis are candidates for surgical intervention. Furthermore, the extension of surgical operations of salivary gland neoplasms heavily relies on the FNA

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diagnosis.[6,7] Salivary gland FNA has been reported to have a high specificity for the detection of neoplasia (98%) and malignant processes (96%). However, the sensitivity has been reported to be lower and more variable: 96% and 79% for the detection of neoplasia and malignancy, respectively.[8] The lower sensitivity has been attributed to morphologic heterogeneity, a variety of epithelial metaplastic changes, and even occasionally cystic changes.[9-13] Moreover, morphologic overlap between primary neoplasms of salivary glands and metastatic neoplasms contributes to the complexity of the diagnosis. Limited diagnostic material is another reason for the lower sensitivity, which precludes ancillary testing to reach a definitive diagnosis. Small-core biopsy, which is routinely performed concurrently with fine-needle aspiration biopsy (FNAB), is not an option for salivary gland lesions. Therefore, cytomorphologic findings for these lesions are the only means for rendering a diagnosis. The morphologic overlap between primary and secondary neoplasms of salivary glands along with the scarcity of aspirated material has led to the diagnostic category of suspicious for malignancy (SFM). Salivary gland FNA constitutes a small portion of cytology cases; however, this remains one of the most challenging areas in cytopathology. To address the lack of guidelines, risk-stratification classification schemes for reporting findings of salivary gland FNA have recently been suggested.[14-16] In fact, at the European Congress of Cytology meeting in Milan, Italy, in 2015, a group of pathologists initiated the development of an international classification scheme for salivary gland FNA.[17] Although there is much information on the general performance of salivary gland FNA, much less is known specifically about SFM salivary gland lesions and the impact that this category would have on a tiered classification scheme.

The aim of this study was to investigate the risk of malignancy (ROM) in the SFM category of salivary gland lesion FNA. Furthermore, we evaluated the variability in the ROM among different institutions from the United States, Europe, and China.

MATERIALS AND METHODS

Salivary gland FNAB cases (n = 12,606) were collected from 5 academic institutions, including 2 in the United States (John Hopkins Hospital [JHH] in Baltimore, Maryland, and Temple University Hospital [TUH] in Philadelphia, Pennsylvania), 2 in Europe (Catholic University of Rome [CUR] in Rome, Italy, and Guy's and St Thomas' Hospital NHS Foundation Trust [GST] in London, United Kingdom), and 1 in China (Fudan University Cancer Hospital in Shanghai, People's Republic of China). The salivary gland FNA cases were identified retrospectively through a search of the electronic medical records of the aforementioned institutions for an 18-year period (January 1, 1997, to December 31, 2014). Then, a search for salivary gland FNA cases diagnosed as SFM was performed. Subsequently, the data were searched for SFM cases with surgical follow-up. Only those cases diagnosed as SFM on cytology and involving surgical resection were included in this study. The total number of salivary gland FNAB procedures performed during this time frame and the number of cases carrying the diagnosis of SFM FNAB at each participating institution were as follows: 7809 FNAB procedures with 54 SFM cases at Fudan, 2186 FNAB procedures with 23 SFM cases at JHH, 1424 FNAB procedures with 17 SFM cases at GST, 987 FNAB procedures with 13 SFM cases at CUR, and 200 FNAB procedures with 7 SFM cases at TUH. The following information was collected and analyzed for each patient: age and sex, ethnicity, location of the salivary gland nodule or nodules (based on ultrasound), and cytological and surgical diagnoses. SFM refers to cases with certain cytomorphologic features of malignancy, but the findings are not sufficient to make a conclusive diagnosis. The suggested diagnostic criteria for an SFM entity in the current cohort were the presence of markedly atypical cells, including epithelial, lymphoid, or other cell types, suggestive of malignancy but insufficient for a definitive diagnosis or a hypocellular specimen with features suggestive of a particular malignancy such as adenoid cystic carcinoma. All the collected patient data were reviewed further by 2 pathologists (J.A.M. and Z.M). The cytology samples in this study were prepared with Diff-Quik staining on air-dried slides and with Papanicolaou staining on slides fixed with an alcohol-based fixative. The cases from CUR were diagnosed with both conventional and liquid-based cytology (ThinPrep 5000 method; Hologic Co, Marlborough, Massachusetts). A conclusive diagnosis was made with an evaluation of both cytological samples.

The risk of neoplasia (RON) and the ROM for each institution were calculated. The statistical analysis was performed with Fisher's exact test with significance set at $P < .05$, and the R statistical programming environment (version 3.2.1) was used.

This study was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations (Title 45, Part 46) and the Code of European Commonwealth Regulations and was performed under institutional review board approval (22833; TUH).

RESULTS

Among the 12,606 salivary gland FNA cases from the participating institutions between 1997 and 2014 (18 years), 276 (2.2%) were reported to be SFM. One hundred fourteen SFM cases (41%) had histological follow-up. Among the 114 study cases, 23 were from JHH, 17 were from GST, 54 were from Fudan, 7 were from TUH, and 13 were from CUR. There were 55 males and 59 females (male:female ratio, 0.93:1), and the mean age of the patients with SFM salivary gland FNA at the time of diagnosis was 51.38 years (range, 6 days to 87 years). The FNA sites included the parotid gland (n = 92), submandibular gland (n = 17), sublingual gland (n = 3), and minor salivary glands (n = 2). A 25-gauge needle was used for aspiration, and the average number of passes was 3. The FNA procedure was performed under ultrasound guidance by a radiologist in the majority of cases, and a rapid onsite evaluation was performed by a pathologist for specimen adequacy. Rare cases were performed by palpation at the clinic by a clinician. The "suspicious" or "favored" diagnosis in the cytology report was accurate the majority of the time; for instance, in 25 of 47 cases, the diagnosis of suspicious for adenoid cystic carcinoma was confirmed by histology. Scant cellularity (n = 6), poorly preserved cells (n = 3), extensive necrosis (n = 2), and a cystic background (n = 3) were possible explanations for a suboptimal specimen. Two cases were accompanied by cell blocks. One cell block was used for periodic acid–Schiff and mucicarmine staining (JHH), and the other cell block was insufficient (GST). MNF116, CD68, and BerEP4 immunostaining was performed on a case's cytospin sample (GST). Overall, the mean prevalence of SFM salivary gland FNAB cases among the 5 institutions participating in this cohort was 2.2% in general and 0.9% (range, 0.7%-3.5%) for cases with surgical follow-up. The number of cases and the prevalence at each institution were as follows: 7809 FNA cases with a 0.7% SFM prevalence at Fudan, 2186 FNA cases with a 1% SFM prevalence at JHH, 1424 FNAB cases with a 1.2% SFM prevalence at GST, 987 FNA cases with a 1.3% SFM prevalence at CUR, and 200 FNA cases with a 3.5% SFM prevalence at TUH. Follow-up of the 114 SFM cases showed 95 malignant tumors (83.3% [76 carcinomas and 19 lymphomas]), 13 benign tumors (11.4%), and 6 nonneoplastic lesions (5.3%). The proportions of malignant and neoplastic cases and the surgical correlation of FNA cases are shown in Tables 1 and 2, respectively.

TABLE 1. Surgical Correlation of Fine-Needle Aspiration Biopsies of Salivary Glands Diagnosed as Suspicious for Malignancy at Multiple International Institutions and the Associated Risk of Malignancy

Institution	Malignant, No. (%)	Nonmalignant, No. (%)	Total, No. (%)
Johns Hopkins Hospital (Baltimore, Maryland)	17 (74)	6 (26)	23 (100)
Catholic University of Rome (Rome, Italy)	11 (85)	2 (15)	13 (100)
Temple University (Philadelphia, Pennsylvania)	6 (86)	1 (14)	7 (100)
Guy's and St Thomas' Hospital (London, United Kingdom)	15 (88)	2 (12)	17 (100)
Fudan University Cancer Hospital (Shanghai, China)	46 (85)	8 (15)	54 (100)
Total	95 (83)	19 (17)	114 (100)

TABLE 2. Surgical Correlation of Fine-Needle Aspiration Biopsies of Salivary Glands Diagnosed as Suspicious for Malignancy at Multiple International Institutions and the Risk of Neoplasm

Institution	Neoplastic, No. (%)	Nonneoplastic, No. (%)	Total, No. (%)
Johns Hopkins Hospital (Baltimore, Maryland)	20 (86.96)	3 (13.04)	23 (100)
Catholic University of Rome (Rome, Italy)	13 (100)	0 (0)	13 (100)
Temple University (Philadelphia, Pennsylvania)	7 (100)	0 (0)	7 (100)
Guy's and St Thomas' Hospital (London, United Kingdom)	16 (94.11)	1 (5. 82)	17 (100)
Fudan University Cancer Hospital (Shanghai, China)	53 (98.14)	1 (1.86)	54 (100)
Total	109 (95.61)	5 (4.39)	114 (100)

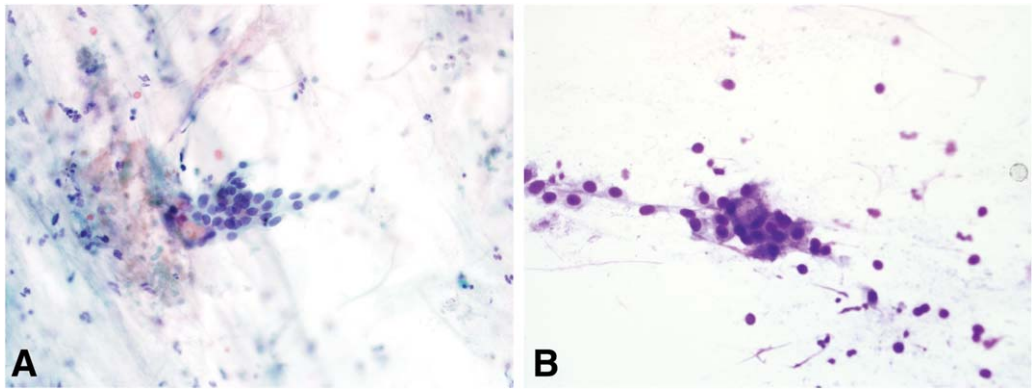

Figure 1. (A) A small fragment of epithelial cells can be seen. There is a cell with a large intracytoplasmic mucin vacuole. The background shows strands of mucin and debris (Papanicolaou stain, ×400). (B) A small fragment of loosely cohesive uniform cells with 1 goblet cell in the center can be seen against a relatively clean background. This case was diagnosed as suspicious for mucoepidermoid carcinoma (Diff-Quik stain, ×400).

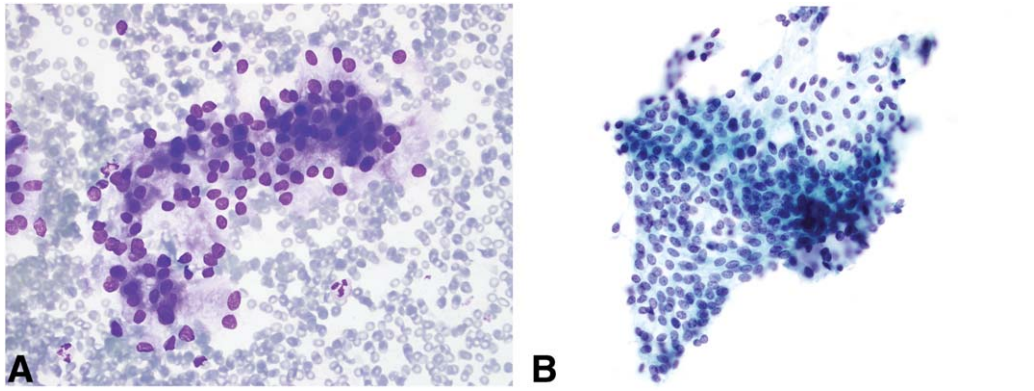

Figure 2. (A) A fragment of epithelial cells can be seen. The nuclei are relatively uniform with minimal atypia. The cytoplasm is moderate to abundant and finely granular (Diff-Quik stain, ×400). (B) A large fragment of epithelial cells with a deceptively bland morphology can be seen. The cytoplasm is delicate and lacy. This case was diagnosed as suspicious for malignancy on cytology, and the histology showed well-differentiated acinic cell carcinoma (Papanicolaou stain, ×400).

Final Diagnosis of the SFM Salivary Gland FNA Category

The histological follow-up of the 114 FNAB cases diagnosed as SFM revealed 95 malignant cases, which composed 83% of the total salivary gland SFM cases (Table 1). The malignant cases included 76 carcinoma cases and 19 lymphoma cases. The carcinoma cases included 19 mucoepidermoid carcinomas (Fig. 1A,B), 14 adenoid cystic carcinomas, 11 acinic cell carcinomas (Fig. 2A,B), 8 adenocarcinomas not otherwise specified, 7 squamous cell carcinomas (Fig. 3A,B), 6 carcinoma ex pleomorphic adenomas, 2 lymphoepithelial carcinomas, 1 nasopharyngeal carcinoma, 1 epithelial-myoepithelial carcinoma, 1 sialoblastoma, 1 basal cell adenocarcinoma, 1 metastatic breast carcinoma, 1 metastatic renal cell carcinoma, 1 metastatic adenocarcinoma of the orbit primary, 1 metastatic nonpulmonary carcinoma, and 1 carcinoma not otherwise specified. The lymphoma cases included 4 diffuse large B-cell lymphomas, 4 follicular lymphomas, 3 low-grade mucosa-associated lymphoid tissue lymphomas, 2 low-grade B-cell lymphomas, 2 Burkitt lymphomas, 1 high-grade lymphoma, 1 Hodgkin lymphoma, 1 small lymphocytic lymphoma/cell lymphocytic leukemia, and 1 lymphoma not otherwise specified. Additional material was collected for flow cytometry studies in multiple cases with a high suspicion for lymphoma. The ROM combining carcinomas and lymphomas was 83.33% in this cohort (Table 1).

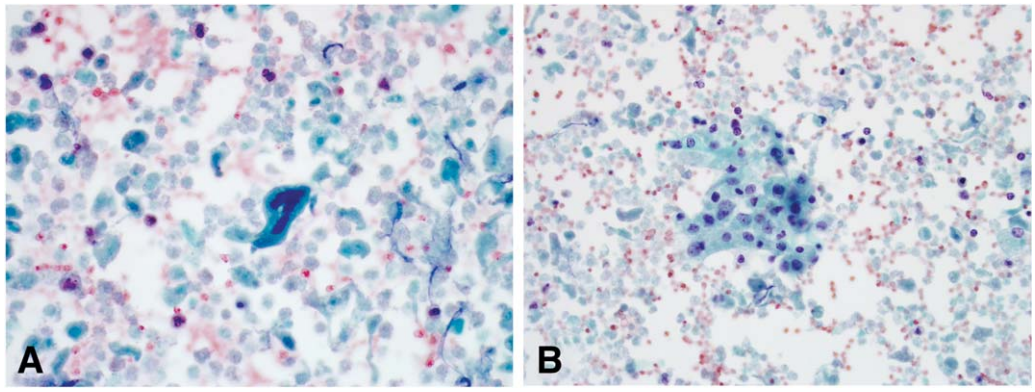

Figure 3. (A) A markedly atypical squamous cell can be seen against a background of numerous necrotic cells (Papanicolaou stain, ×400). (B) A small fragment of loosely cohesive squamous cells with nuclear atypia can be seen against a background of tumor necrosis. This case was diagnosed as suspicious for squamous cell carcinoma (Papanicolaou stain, ×400).

The surgical follow-up of 14 cases showed benign neoplasms, including 6 pleomorphic adenomas, 3 oncocytomas, 2 basal cell adenomas, 1 Warthin tumor, 1 myoepithelioma, and 1 lymphoepithelial cyst.

The surgical follow-up of the 4 remaining cases showed nonneoplastic conditions, including 1 case of chronic sialadenitis, 1 reactive intraparotid lymph node, 1 parotid parenchyma with dense fibrosis, and 1 intraparotid cyst without lining cells. The last remaining case was subjected to repeat FNA, which showed abscess formation. The RONs for the individual participating institutions are listed in Table 2. The histological diagnoses were specifically and correctly mentioned in the cytology reports for 15 nonlymphoma cases (eg, suspicious for adenoid cystic carcinoma). The specimen with a histological diagnosis of Warthin tumor was initially labeled a neck mass.

Interinstitutional Variability of ROM and RON

Fisher's exact test with sensitivity of $p < .05$ shows that there is no statistically significant association between ROM and institution ($p = .78$). The risk of neoplasm (RON) combining both benign and malignant neoplasms was 95.61% in this cohort, ranging from 87% to 100% among the 5 institutions. Fisher's exact test shows no association between institution and RON ($p = .18$).

DISCUSSION

In this study, data collected from multiple institutions in the United States, Europe, and China showed that 83.33% of SFM salivary gland FNAB cases turned out to be malignant at surgical resection, whereas 95.61% were neoplastic (including both malignant and benign neoplasms). The most common malignant neoplasms were mucoepidermoid carcinomas, which were followed by adenoid cystic carcinomas and acinic cell carcinomas. The most common benign neoplasms were pleomorphic adenomas, which were followed by oncocytomas and basal cell adenomas. Mucoepidermoid carcinomas and pleomorphic adenomas were reported as the most common malignant and benign neoplasms, respectively, in the SFM category according to the data extracted from 13 studies,[18] and this is in concordance with our findings. Only 4.39% of the cases were nonneoplastic with reactive atypia concerning for malignancy. Furthermore, the ROMs for the SFM category were within a very tight range for all participating institutions except for one (JHH), whose ROM was slightly outside the range. A high ROM can be translated into surgical excision by surgeons. Only 1 SFM case was followed by FNA, which was probably due to a high clinical suspicion for an inflammatory/infectious process (abscess). Nineteen of the 114 cases (16.67%) were diagnosed as lymphoma. The postoperative diagnosis was a reactive lymph node with a mixed population of B and T cells in 1 case. A differential diagnosis between reactive and malignant lymphoproliferative processes can be challenging with only a microscopic evaluation of aspirated material. A rapid onsite evaluation and the collection of additional material for flow cytometry will increase the definitive diagnosis rate and decrease the SFM diagnosis rate. Flow cytometry can be useful for the diagnosis of non-Hodgkin lymphoma.[19]

A recent review article[18] showed that the SFM diagnosis was used for diagnosing salivary gland FNAB

specimens in 13 of 29 international studies, which contributed 1.6% of the cases (70 of 4506). Surgical follow-up of the SFM category revealed 41 malignant neoplasms (58.6%), 25 benign neoplasms (35.7%), and 4 nonneoplastic conditions (5.7%). The ROM of the study was 58.6%. Our overall ROM of 83.33% is much higher than the reported study's ROM. Our SFM cases were neoplastic at a rate of 95.61%. Another study found an SFM diagnosis for 28 of 709 salivary gland FNAB cases (3.95%) with a surgical correlation; they included 22 malignant neoplasms and 6 benign cases. Their ROM was 78.6% for SFM cases, and this falls within the range of our study.[16] Scant cellularity of malignant cells, a necrotic or mucinous background, poor preservation of the aspirated material, and the presence of lymphocytes were reported in multiple cases in this study and contributed to the diagnosis of SFM. Scant cellularity of aspirated malignant neoplasms may result in a diagnosis of SFM,[20] whereas hypercellular aspirates of inflammatory nonneoplastic lesions with reactive atypia may mimic a malignant process diagnosed as SFM (eg, the case of chronic sialadenitis in this study). Squamous metaplasia, a clear cell pattern, and hyaline stromal globules are other features resulting in diagnostic challenges.[12] Clear cell changes caused diagnostic difficulty in 1 case of oncocytoma and in 1 case of pleomorphic adenoma in our study. The accurate designation of the FNA site can improve the sensitivity of salivary gland FNA. For example, the Warthin tumor most likely would have been diagnosed properly if the body site had been initially labeled as the parotid gland and not as the neck. Notably, FNA of salivary gland lesions is more sensitive and specific for benign lesions than malignant neoplasms.[21] Most benign neoplasms are treated with surgical resection with facial nerve preservation,[6,22,23] whereas complete resection by parotidectomy with facial nerve preservation is recommended for malignant neoplasms in select cases.[6,7] Lymph node dissection for malignant salivary gland neoplasms is not a general practice; although some surgeons may perform elective neck dissection for all patients with a malignant salivary gland neoplasm because of the high rate of occult metastases, others reserve it for pathologic high-grade malignancies and those at a high clinical stage.[24,25] Therefore, a diagnosis of SFM warrants surgical resection.

Recent advances in the molecular characterization of salivary gland neoplasms have shed light on the cytological diagnosis and surgical management of these neoplasms. Fifty to sixty percent of pleomorphic adenomas show the t(3;8)(p21;q12) translocation involving the *PLAG1* gene.[26-28] Sixty to seventy-five percent of mucoepidermoid carcinomas harbor the t(11;19)(q14-q21;p12-13) translocation with a CRTC1-MAML2 fusion.[29-33] Moreover; mammary analogue secretory carcinoma harbors the t(12;15)(p13;q25) translocation with a fusion of the *ETV6* and *NTRK3* genes.[34-36] The application of molecular studies may promote a definitive diagnosis. It is understandable that the experience of the pathologist will play an important role in rendering a diagnosis because salivary gland lesions are not common and the neoplasms can be very heterogeneous. However, as in our series from different institutions, there is also a subset of SFM cases that do not benefit from the application of ancillary techniques, and for these cases, the diagnosis of SFM is the more accurate diagnostic solution. Therefore, for SFM cases, consultation with pathologists experienced in this area is recommended when it is feasible. We recommend conservative surgical follow-up accompanied by an intraoperative frozen section consultation because of the high ROM of 83% and the high RON of 95.61% in the SFM category.

In conclusion, our careful examination of data from 5 academic institutions across the world shows that SFM is a diagnostic category with a high ROM and an even higher RON. Adequate specimens, accurate labeling of the biopsy site, optimal preparation of the slides, familiarity of the practicing cytopathologists with salivary gland lesions, and the application of ancillary tests when they are feasible will reduce the rate of this diagnosis and/or improve the ROM.

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The authors made no disclosure.

AUTHOR CONTRIBUTIONS

Zahra Maleki: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **James Adam Miller:** Methodology, software, formal analysis, data curation, writing–original draft, writing–review and editing, and visualization. **Seyedeh Elham Arab:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, and visualization. **Guido Fadda:** Investigation, resources, and writing–review and editing. **Ping Bo:** Methodology, validation, formal analysis, resources, and writing–review and editing. **Olga Wise:** Investigation and resources. **Esther Diana Rossi:** Resources and writing–review and editing. **Nirag Jhala:** Resources,

writing–original draft, and writing–review and editing. **Chandra Ashish:** Conceptualization, methodology, validation, investigation, resources, writing–original draft, writing–review and editing, and visualization. **Syed Z. Ali:** Conceptualization, methodology, formal analysis, and writing–review and editing. **He Wang:** Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration.

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