

CLINICAL REVIEW

Olfactory Loss and Beyond: A Practical Review of Chemosensory Dysfunction

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Background: Our ability to smell and taste is dictated by 3 chemosensory systems with distinct physiologic mechanisms – olfaction, gustation, and chemesthesis. Although often overlooked, dysfunction of these special senses may have broad implications on multiple facets of patients' lives –including safety, nutritional status, quality of life, mental health, and even cognitive function. As “loss of smell or taste” emerged as a common symptom of coronavirus disease 2019 (COVID-19), the importance of intact chemosensory function has been thrust into the spotlight. Despite the growing recognition of chemosensory dysfunction, this already highly prevalent condition will increasingly impact a larger and more diverse population, highlighting the need for improved awareness and care of these patients.

Methods: Contemporary review of chemosensory function and assessments.

Conclusions: Although patient-reported chemosensory function measures highlight the ease of screening of chemosensory dysfunction, self-reported measures underestimate both the prevalence and degree of chemosensory dysfunction and do not adequately distinguish between olfaction, gustation, and chemesthesis. Meanwhile, psychophysical assessment tools provide opportunities for more accurate, thorough assessment of the chemosenses when appropriate. Primary care providers are uniquely situated to identify patients burdened by chemosensory dysfunction and raise patient and provider awareness about the importance of chemosensory dysfunction. Identification of chemosensory dysfunction, particularly olfactory dysfunction, may raise suspicion for many underlying medical conditions, including early detection of neurodegenerative conditions. Furthermore, identification and awareness of patients with chemosensory dysfunction may help primary care providers to identify those who may benefit from additional therapeutic and safety interventions, or consultations with specialists for more detailed evaluations and management. (J Am Board Fam Med 2022;35:406–419.)

Keywords: Aging, Anosmia, Dementia, Geriatrics, Olfaction Disorders, Otolaryngology, Preventive Care, Quality of Life, Smell, Taste

Introduction

Olfaction, gustation, and chemesthesis are unique sensory functions with broad implications on daily

life, ranging from the perception of danger signals (eg, smoke) to the psychosocial implications related to the experience of food.^{1–4} Olfaction and gustation are the senses of smell and taste, respectively. Many olfactory and gustatory stimuli also activate the trigeminal nerve, resulting in chemesthesis. Chemesthesis, or trigeminal function, is a type of somatosensory stimulation which includes sensations of touch, temperature, pain, spice, and astringency.⁵ Though mediated by separate cranial nerves, these

This article was externally peer reviewed.
Submitted 12 September 2021; revised 12 November 2021; accepted 18 November 2021.

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Funding: None.

Conflicting and competing interests: Consulting, Healthy Humming, Stryker, and Optinose (RJS); grant support, Healthy Humming, Stryker, Optinose, GSK, Roche (RJS); grant support, Optinose (NRR); Sanofi-Regeneron Advisory Board (APL). All other authors declare no conflicts or competing interests.

Prior presentation: An abstract of this manuscript was virtually presented at the Triological Society Combined Sections Meeting (January 2021).

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chemosenses interact, such as in the perception of food, as the combined chemosensory input makes up what we perceive as “flavor.”⁶ Although the chemosenses are associated with unique receptors with different physiologic mechanisms, these functionally distinct senses are intimately intertwined.⁷

Chemosensory dysfunction occurs with alteration in any component of these 3 chemosenses and occurs in a wide variety of clinical settings, including upper respiratory infections (eg, SARS-CoV-2), sinonasal disorders, neurodegenerative diseases, post-traumatic states, and even normal aging, among other etiologies. Though chemosensory dysfunction was thrust into the spotlight during the COVID-19 pandemic, it was already highly prevalent before the pandemic and will only continue to increase. This is in part due to prolonged post-COVID chemosensory aberrations, but also because of an increasingly aged population with alterations due to age-related losses and various medical conditions (eg, diabetes and dementia).

Chemosensory dysfunction can alter our perception of food, but beyond the implications for diet and nutritional status, there are many other significant consequences. The chemosenses are also crucial for detection of toxic exposures, such as smoke, natural gas, and spoiled food.⁸ Dysfunction in olfaction, gustation, and chemesthesis have broad psychosocial implications, with significant impacts on patients’ quality of life, depression and anxiety, and cognition.¹⁻⁴ Olfaction, in particular, has been repeatedly shown to be a strong and independent predictor of a lack of physiologic resilience to health stressors (ie, frailty) and mortality.⁹⁻¹¹

Acknowledging its increasing prevalence and broad implications, identification and understanding of chemosensory dysfunction offers a significant opportunity to impact patient care. Although primary care providers (PCPs) are uniquely situated to identify patients with new-onset chemosensory function changes, they generally lack formal training in these unique senses. This review provides practical insights into the distinct but overlapping physiologic mechanisms of the chemosenses, highlights common etiologies of chemosensory dysfunction, increases awareness of accurate and clinically feasible chemosensory assessment tools, and provides suggestions for chemosensory assessment and management in the primary care setting.

Chemosensory Physiology and Prevalence of Dysfunction

Olfaction

Olfaction begins with the entry of odorants into the nose, specifically the olfactory cleft, via 1 of 2 routes—orthonasal or retronasal.¹² Orthonasal olfaction occurs as odorants pass through the nares to reach the olfactory cleft.¹² In contrast, retronasal olfaction occurs as odorants within the oral cavity traverse the nasopharynx—especially during swallowing, mastication, or nasal exhalation—to reach the olfactory cleft.¹² Once odorants reach the olfactory cleft, they contact olfactory epithelium, which lines the cleft between the nasal septum and superior and middle turbinates.¹³ The olfactory epithelium contains dendritic knobs and cilia of olfactory cells containing olfactory receptors, as well as axons of olfactory neurons that travel through the cribriform plate before synapsing at the olfactory bulb. The interaction of odorants with olfactory receptors sends signals to multiple areas of the brain, allowing for processing and interpretation of odorants.¹⁴

Given that the olfactory system is composed of peripheral neurons which reconnect centrally, there is remarkable capacity for regeneration. Damage occurs continuously throughout life, but proliferation of stem cells allows for regular repair of olfactory function.¹⁵ Despite this regenerative potential, olfactory loss can still occur and is classified based on 3 pathophysiologic mechanisms – conductive, sensorineural, or mixed.¹⁵ Conductive loss occurs when odorants are physically blocked from the olfactory epithelium by pathology such as nasal polyps or mucosal edema.¹⁵ Sensorineural loss occurs with olfactory neuroepithelium damage or dysfunction, while central loss occurs through damage or disruption of the olfactory pathways in the central nervous system, and mixed loss occurs when there is overlapping etiologies.¹⁵

Olfactory dysfunction is extremely common, with an estimated prevalence of 12 to 13% in the US and 25% worldwide.^{8,16} Accurate estimations of prevalence have been limited by study size, patient demographics, and variation in dysfunction definitions. Higher rates of olfactory dysfunction have been reported in men compared with women, and in Black individuals compared with White individuals, though trends are not fully understood.¹⁷⁻¹⁹

Olfactory dysfunction invariably increases with age. Though there is a broad range of prevalence estimates, up to 62.5% of those over age 80 experience olfactory dysfunction.^{2,8,20–29} In addition, people tend to underestimate both the prevalence and severity of their olfactory dysfunction on self-report,^{8,16,20,30} with 1 study reporting that up to 74.2% of people who had measured olfactory dysfunction did not recognize it clinically.²⁹ The importance of this for overall health and safety cannot be overstated, as US population-level data revealed adults age 70 and older misidentify smoke and natural gas odors at rates as high as 20.3% and 31.3%, respectively.⁸

Gustation

There are 5 basic tastants—sweet, sour, salty, bitter, and umami (“savory”). Gustation begins with the ingestion of various tastants into the oral cavity, where they are dissolved in saliva. Tastants contact taste buds located on the tongue, palate, pharynx, and larynx.^{6,31} On the tongue, taste buds are located in fungiform, foliate, and circumvallate papillae, under a keratinous layer with openings for taste pores.³¹ Unlike the receptor neurons in the olfactory system, taste buds are composed of taste receptor cells, not neurons. These taste receptor cells have microvilli that extend through the taste pores to contact tastants.⁶ The microvilli contain gustatory receptors, which are stimulated by 1 of the 5 basic taste qualities.³² Gustatory receptors then send signals to the brain for interpretation of tastants.^{6,31} The structural differences between types of gustatory receptors may provide the basis for discrimination between different taste qualities.³²

Gustatory deficits can be classified by pathophysiologic mechanism.³³ Transport dysfunction occurs when gustatory stimuli cannot contact gustatory receptors due to conditions affecting the oral cavity, such as candidiasis or salivary dysfunction, such as xerostomia.³³ In contrast, sensory dysfunction occurs when gustatory neuroepithelium is damaged, and neuronal dysfunction occurs when relevant peripheral nerves or components of the central nervous system are compromised.³³

Gustatory dysfunction impacts approximately 17.3% of Americans.¹⁶ Accurate predictions of prevalence are limited by not only variation in patient population, but also the complex interaction of olfaction and gustation. A recent study found that in patients reporting only taste disturbance,

rates of abnormal gustatory function were 25.4%, but rates of olfactory dysfunction were 44.4%.³⁴ Olfactory dysfunction leading to a perceived gustatory impairment is common, due to the complex interaction of the chemosenses creating the “flavor” of ingested foods and drinks.

Chemesthesis

Chemesthesis occurs when stimuli activate branches of the trigeminal nerve (ophthalmic or maxillary) in the nasal or oral cavity.^{5,35} Chemesthesis is the cause of many of the somatosensory sensations we perceive, including temperature (eg, cooling sensation from menthol), spice (eg, from pepper), or even ammonia (eg, from “smelling salts”). Researchers continue to discover receptors involved in chemesthesis, and the physiologic mechanisms of trigeminal function and dysfunction remain an area of active research.³⁶ The estimated prevalence of chemesthetic dysfunction is limited, but notably, isolated chemesthetic dysfunction is rare and is most often reported in conjunction with olfactory dysfunction.^{37–39}

Common Etiologies of Acquired Chemosensory Dysfunction

Viral Respiratory Infections

Acute phases of upper respiratory tract infections (eg, rhinovirus, influenza virus) are among the most frequent causes of chemosensory dysfunction.⁴⁰ This became particularly important during the COVID-19 pandemic, as “loss of taste or smell” was noted as a mechanism of detecting otherwise asymptomatic COVID-19 cases.^{41,42} Patients typically present with sudden onset chemosensory disturbances with other associated symptoms, such as fever, congestion, and fatigue.

In some instances, the chemosensory dysfunction associated with viral infections may become chronic.^{43,44} Postviral olfactory dysfunction (PVOD) is a common cause of chronic olfactory loss.^{45–47} The clinical course of PVOD is variable; some patients experience complete resolution of olfactory functioning within months of onset, while others have permanent dysfunction.⁴⁸ One study evaluating long-term prognosis of PVOD found that 31.7% of patients had complete recovery of self-reported smell function, and 85.7% had some level of self-reported improvement at least a year from their infection.⁴⁹ There is also

evidence that patients with PVOD have associated impaired chemesthesis,³⁹ which improves with olfactory function.³⁸

Sinonasal Disease

Sinonasal disease accounts for ~20% of olfactory dysfunction cases.^{50,51} There are various etiologies – including allergic rhinitis (AR) and chronic rhinosinusitis (CRS). AR and CRS affect millions of Americans, and 20 to 40% of AR patients and 70 to 80% of CRS patients experience olfactory dysfunction.^{52–59} Loss of olfactory function is a cardinal symptom of CRS. There are multiple possible causes of olfactory dysfunction in CRS, including nasal air-flow obstruction in the setting of CRS with nasal polyps, localized inflammation of the sinonasal and olfactory mucosa in CRS without nasal polyps, both of which may limit the ability for odorants to reach the olfactory cleft and/or bind to olfactory receptors. Though less well characterized, a substantial number of these patients also have independent gustatory dysfunction.⁶⁰ In patients with chemosensory dysfunction secondary to sinonasal disease, patients will often present with other symptoms associated with their sinonasal disease process.

Posttraumatic

Posttraumatic chemosensory dysfunction accounts for 10% to 20% and 20% to 25% of olfactory and self-reported gustatory dysfunction patients, respectively.^{34,51,61} The prevalence of post-traumatic chemosensory dysfunction increases with increasing head trauma severity and is estimated at 30%.^{62–64} It is generally hypothesized that shearing effects of the frontal lobe motion are responsible for the dysfunction due to head trauma.⁶³ There is also evidence that chemesthetic dysfunction occurs after head trauma, specifically in populations with known olfactory dysfunction.^{37,38} Posttraumatic chemosensory disorder may be easier to diagnose as it often presents after a known head trauma.

Aging

As we age, dysfunction occurs across a broad range of sensorineural processes, including vision and hearing, but also olfaction, gustation, and chemesthesis. As mentioned above, chemosensory dysfunction commonly occurs in otherwise healthy individuals during normal aging processes due to a multitude of mechanisms. In the case of

olfaction, age-related dysfunction is due to changes in the peripheral olfactory system, including decreased olfactory receptor neurons, impaired regeneration capacity, and impeded clearance of bacteria, to name a few.⁶⁵ Normal aging should be considered on the differential for elderly patients with chemosensory dysfunction.²⁷

Neurodegenerative Conditions

Chemosensory dysfunction is common in neurodegenerative disorders, with rates of olfactory dysfunction in Parkinson's disease ranging from 50% to 90%.⁶⁶ With gradual onset, and as 1 of the first clinical manifestations of neurodegeneration, chemosensory dysfunction may be a harbinger of multiple neurodegenerative diseases including Alzheimer's, Huntington's, and Lewy body dementia. Multiple studies have linked olfactory dysfunction to later development of cognitive decline,^{66–74} and recent studies have also revealed that intact olfactory function is associated with lack of progression to dementia.⁷⁵

Idiopathic

Finally, chemosensory loss is considered idiopathic if no other etiology can be identified after evaluation. Chemosensory dysfunction is idiopathic in 18% and 34% of olfactory and gustatory loss patients, respectively.^{50,51,61} These numbers are anticipated to decrease as understanding of chemosensory dysfunction mechanisms and evaluation improves.

Types of Chemosensory Assessment

A variety of assessments have been developed to quantify patients' chemosensory capabilities. Subjective tests require participants to consciously report findings, while objective tests are imaging or electrophysical tests involving recording electric changes after stimuli presentation.⁷⁶ Psychophysical tests, on the other hand, have both subjective and objective components. These require more rigorous testing than subjective self-report options but still require subjects to report perceptions of stimuli. Although individual subjective and objective tests are categorized as separately measuring olfaction, gustation, or chemesthesis, it may be challenging to clinically distinguish these senses, as stimuli typically simultaneously activate multiple sensory modalities.^{7,76}

Olfaction

There are multiple validated self-report assessments for the measurement of olfaction.^{77–79} These instruments make information easily attainable and are often modified to reflect regional variations in scent awareness, but they are often not closely associated with validated psychophysical tests.⁷⁶ As many as 74.2% of healthy individuals with psychophysically measured olfactory dysfunction fail to detect and accurately self-report their sensory deficits.²⁹ As this data suggests, when physicians ask patients to describe or rate their olfactory dysfunction in general clinical settings, patients' responses may be inaccurate.^{29,76,80} Therefore, psychophysical olfactory assessments are the gold standard for olfactory testing because of their accuracy.^{81,76,82}

Psychophysical tests most commonly measure odor identification, the ability to detect and accurately recognize a certain odor. Psychophysical tests may also evaluate olfactory discrimination, the ability to distinguish 1 odor from another; olfactory threshold, the lowest concentration of an odorant that can be reliably detected; or olfactory memory, the ability to correctly identify an odor on repeat administration.^{76,82} Most of the psychophysical assessments for olfaction focus on the orthonasal route (Table 1).^{69,76,81,83–92} Measurements of retronasal olfaction are significantly less developed and are not used in routine clinical practice.⁹³

Two commonly used assessments are the 40-item University of Pennsylvania Smell Identification Test (UPSIT) and the “Sniffin’ Sticks.”^{76,86,92} The UPSIT is a suprathreshold test that assesses odor identification, which benefits from ease of clinical use, high sensitivity and reliability (test–retest $r=0.94$), and extensive normative data.^{76,86} Meanwhile, “Sniffin’ Sticks” evaluates threshold, discrimination, and identification, and provides a composite score (TDI) that describes reliability and psychometric characteristics.⁹² Though this instrument is robust, its completion requires increased time and resources, limiting its use in primary care settings.^{76,92}

The UPSIT has been abbreviated as the 3-item Pocket Smell Test (PST) and the 12-item Brief Smell Identification Test (B-SIT).^{69,83} These shortened assessments allow clinicians to detect chemosensory dysfunction in a time-efficient, cost-effective manner. A subset of olfactory assessments instruments—including the PST and B-SIT—are

self-administered as opposed to clinician-administered, allowing patients to perform the testing at their convenience, which may be advantageous in primary care settings.^{69,83–86}

In addition, electroolfactogram, electroencephalography, positron emission tomography, and functional magnetic resonance imaging (fMRI) have all been utilized to measure olfactory function objectively.^{94–98} Though these techniques have improved our understanding of olfaction-related cortical networks in research settings, they are not appropriate for clinical olfactory assessment even in tertiary care centers, as they are more invasive and costly, require extensive resources, and have high false positive and false negative rates.^{76,95,97}

Gustation

Measuring the subjective experience of taste is difficult considering the significant contribution of olfaction and trigeminal input to the perception of flavor.⁷ Moreover, many individuals who report gustatory deficits oftentimes exhibit measurable olfactory impairment (particularly retronasal olfaction), instead of gustatory impairment.^{34,81} As a result, few self-report questionnaires have been used or validated to assess taste in various populations,^{99–101} and psychophysical assessments are the most clinically appropriate tests for gustation and allow clinicians to isolate gustatory dysfunction from olfactory dysfunction.^{76,102}

Psychophysical assessments often measure identification, the ability to identify stimuli, and threshold, the lowest concentration of stimuli that can be reliably detected.¹⁰² Whole mouth tests assess the subject's entire oral cavity, while regional taste tests isolate dysfunction to specific areas of the tongue.^{102–104} As gustatory assessments generally require significant time and resources, they are normally reserved for use by trained specialists (generally at academic institutions), and therefore patients with suspected isolated gustatory dysfunction may warrant referral for further testing. Psychophysical gustatory assessments that PCPs should be aware of are summarized in Table 2.¹⁰²

In addition, electrogustometry is a method of assessing gustatory losses in research settings.¹⁰⁵ This resource intensive instrument is not clinically practical, because it requires specific materials and is not predictive of function in daily life.^{102,105}

Table 1. Olfactory Psychophysical Clinic-Based Assessments

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
Brief or Cross-Cultural Smell Identification Test ⁸³	Identification	Banana, chocolate, cinnamon*, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, turpentine	Derived from the UPSIT. Using microencapsulated odorants, subjects progress through 12-item multiple-choice test for 12 odors	Requires less time, cost efficient Can be self-administered	Less thorough evaluation
Pocket Smell Test ⁶⁹	Identification	Lemon, lilac, smoke	Derived from the UPSIT. Using microencapsulated strips, subjects progress through 3-item multiple-choice test for 3 odors.	Requires less time, cost efficient Can be self-administered	Less thorough evaluation
Q-Sticks ⁸⁴	Identification	Cloves*, coffee, rose	Using felt-tip pens with odorants, subjects progress through 3-item multiple-choice test for 3 odors.	Can be self-administered	Less thorough evaluation
Quick Smell Identification Test ⁸⁵	Identification	Chocolate, banana, smoke	Using microencapsulated odorant strips, subjects progress through 3-item multiple-choice test for 3 odors.	Can be self-administered	Less thorough evaluation
University of Pennsylvania Smell Identification Test ⁸⁶	Identification	Banana, bubble gum, cedar, cheddar cheese, cherry, chocolate, cinnamon*, cloves*, coconut, dill pickle, fruit punch, gasoline, gingerbread, grape, grass, leather, lemon, lilac, lime, licorice, menthol*, mint, motor oil, natural gas, onion, orange, peach, peanut, pine, pineapple, pizza, root bear, rose, smoke, soap, strawberry, thinner, turpentine, watermelon, wintergreen*	Using scratch and sniff scented strips, subjects progress through 40-item multiple-choice test for 40 odors.	High sensitivity and reliability; Extensive normative data Can be self-administered	More time intensive
Snap & Sniff Threshold Test ⁸⁷	Threshold	PEA, dilutions ranging from 10 ⁻² (strongest) to 10 ⁻⁹ (weakest) volume/volume concentrations	The kit contains 20 smell "wands." Five contain no smell, while the other 15 contain PEA dilutions. Examiners plan the wand under subjects' noses and briefly present the dilution scent. A single staircase forced-choice paradigm is recommended.	Time efficient, rapid assessment of general olfactory function Newer test but recently validated	Less thorough evaluation – only evaluates detection threshold
Alcohol Threshold Test ⁸⁸	Threshold	Ethyl alcohol (10%, 25%, 50%, 70%, 96%)	Examiners place 100 mL bottles with saline and with varying concentrations of ethyl alcohol under subjects' noses. The threshold scores of 1, 2, 3, 4, and 5 correspond to the weakest detectable alcohol concentrations of 10%, 25%, 50%, 70%, and 96%, respectively. The threshold score of 6 corresponds to participants not detecting 96% alcohol.	Time efficient, rapid assessment of general olfactory function	Less thorough evaluation Requires clinician administration
Smell Threshold Test ⁶⁹	Threshold	Polypropylene, PEA	Examiners place 120 mL polypropylene squeeze bottles with mineral oil and varying concentrations of PEA in mineral oil under		Less thorough evaluation Requires clinician administration

Continued

Table 1. Continued

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
"Sniffin' Sticks" ⁹⁰	Identification, discrimination, threshold	Apple, anise seed, banana, cinnamon*cloves*, coffee, fish, garlic*, lemon, licorice, orange, peppermint*, pineapple, rose, shoe leather, turpentine, n-butanol	<p>subjects' noses. The threshold is the mean of the last 4 of 7 staircase reversals.</p> <p>Using felt-tip pens with odorants, subjects progress through 16-item multiple-choice test of 16 odors for identification, triple forced choice for 16 pairs of odorants for discrimination, and the presentation of n-butanol in varying concentrations for threshold. Threshold was calculated as the mean of the last 4 of 7 staircase reversals.</p>	Enables testing of three smell domainsCan be self- or clinician-administered	More time intensive

Abbreviations: PEA, phenyl ethyl alcohol; UPSIT, University of Pennsylvania Smell Identification Test.
 * Indicates potential olfaction and chemesthesis overlap.

Chemesthesis

Clinicians are increasingly developing assessments to specifically measure chemesthesis.¹⁰⁶ Currently, there are no validated, self-report questionnaires which solely focus on assessing trigeminal function. However, targeted questions have been used to attempt to distinguish olfactory, gustatory, and chemesthetic functions.¹⁰⁶ Chemesthetic function can be evaluated psychophysically by evaluating subjects' ability to lateralize trigeminal stimulation (Table 3).^{107,108} Two new psychophysical assessments of chemesthesis have been reported since 2016, both of which are awaiting validation (Table 3).^{109,110} The further development and utilization of such assessments provides an opportunity to standardize trigeminal function testing, but these tests are not currently appropriate for routine clinical use.¹⁰²

Chemosensory Testing in Primary Care Settings

Chemosensory function is an underrecognized but critical contributor to patients' overall health and quality of life, specifically impacting patients' nutritional status, safety around fire or toxins, and overall psychological well-being.^{3,4} Hearing and sight frequently come to mind as vital human sensory functions, but studies suggest that olfactory dysfunction is independently associated with an increased risk of dementia, frailty, and all-cause mortality.^{9-11,28,68,69,111} Besides the known psychosocial effects of chemosensory dysfunction, this underscores the increasingly recognized connection between chemosensory function and other domains of health, such as physical and cognitive function. As interventions which improve patients' chemosensory functioning are associated with improved quality of life, the identification and management of chemosensory dysfunction should be an important element of comprehensive care.^{112,113}

For patients with chemosensory dysfunction, as with any patient encounter, it is of the utmost importance to first perform a comprehensive history and physical. History should focus on identifying risk factors (eg, age, recent head injury) and characterizing the chemosensory dysfunction (eg, sudden onset, associated symptoms) to help distinguish between common types of chemosensory dysfunction. Patients should also be screened for warning signs such as epistaxis, headache, vision changes, or

Table 2. Gustatory Psychophysical Clinic-Based Assessments

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
Taste sprays	Identification	Substances diluted in 100 mL distilled water: sweet (10g D-saccharose), sour (5g citric acid), salty (7.5g NaCl), bitter (0.025g quinine hydrochloride), and umami (4g MSU)	Whole mouth evaluation Patients open mouth for spray application and close mouth as they identify flavor. Patients receive 1 point for each correctly identified taste. The score is graded 0 to 5.	Indicates whether “suprathreshold” taste perception has been preserved, provides overall taste quality perception data, short time needed for testing, good reproducibility of results, long shelf life	Examiners cannot test individual parts of the oral cavity Requires clinician administration
“Sip and spit” tests	Identification	Patients imbibe flavors from cups or other vessels and then report on the detected flavor.			
Taste strips	Identification, threshold	20 taste-impregnated filter-paper strips presented in randomized order with taste qualities in increasing concentrations: sweet (0.4, 0.2, 0.1, 0.05 g/mL sucrose), sour (0.3, 0.165, 0.09, 0.05 g/mL citric acid), salty (0.25, 0.1, 0.04, 0.016 g/mL NaCl), bitter (0.006, 0.0024, 0.0009, 0.0004 g/mL quinine hydrochloride), and umami (0.25, 0.1, 0.04, 0.016 g/mL MSG)	Regional evaluation Patients identify the taste quality on a form. Patients receive 1 point for each correctly identified taste. The score is graded 0 to 20. An overall score ≤ 9 is considered hyposgeusia.	Allows examiners to test each side of the tongue independently, provides basic data on detection threshold and intensity of flavor, short time needed for testing, good reproducibility of results, long shelf life	Certain areas of the tongue may be difficult to isolate or reach with strips or drops Requires clinician administration

Abbreviations: MSG, monosodium glutamate; MSU, monosodium urate; NaCl, sodium chloride.

Table 3. Chemesthesis Psychophysical Assessments

Instrument	Function assessed	Substances used	Protocol	Advantages	Disadvantages
Stimuli lateralization ¹⁰⁸	Lateralization	Benzaldehyde, eucalyptol	Subjects were presented with two bottles, one for either nostril. Bottles are filled with chemicals dissolved in propylene glycol or propylene glycol alone. A 15 mL puff of air from each bottle is simultaneously administered into one nostril. Subjects report which nostril was presented with the stimuli.	Simple administration, distinguishes olfactory function from chemesthesis	Requires clinician administration, protocol requires ~30 minutes per stimuli
Odorant Detection Test ¹¹⁰	Detection threshold, discrimination, identification, lateralization	Camphor, diallyl sulfide, ethanol, eucalyptol, menthol, propranolol	Using felt-tip pens with chemicals dissolved in propylene glycol, subjects progress through identification of the sensation quality and triple-forced-choice procedure for discrimination for the 6 chemicals. Threshold and lateralization were assessed with menthol. Threshold was calculated as the mean of the last 4 of 7 staircase reversals.	Simple administration, similar protocol to Sniffin' Sticks	Not validated Requires clinician administration
CO ₂ device ¹¹¹	Pain responsiveness	CO ₂ stimuli with various durations (multiples of 50 ms)	CO ₂ stimuli is provided through standard nasal cannula in 10 seconds intervals. With each interval, stimulus duration is increased by 50ms until the subject pushes a button, indicating a painful sensation.	Assesses "mass of a stimulus" rather than concentration	Not validated Requires clinician administration

watery rhinorrhea, which may indicate a more malignant process and warrant expedited referral and assessment. A thorough head and neck examination should be performed, as well as a full neurologic examination. PCPs should consider the possible etiologies of a patient's chemosensory dysfunction and tailor their assessment based on this to develop a plan for work up and management of chemosensory dysfunction. Notably, this review focuses on acquired forms of chemosensory dysfunction, but congenital forms such as Kallmann syndrome and congenital anosmia are possible, and a lifelong history of dysfunction would be present.^{114,115}

Simply by identifying patients with self-reported chemosensory dysfunction and performing an initial history and physical, PCPs can improve patient care by providing specialist (ie, otolaryngologist) referrals for further management. In addition, patients at risk for associated conditions, including anxiety and depression, can be identified and treated as indicated. For PCPs interested in performing additional testing in their practice, psychophysical chemosensory tests can be administered quickly and inexpensively with few, if any, risks to the patient. As the value of time cannot be overstated in the primary care setting, we recognize the importance of brevity in these tests and therefore recommend the use of a short, psychophysical olfactory assessment that can be self-administered by patients, such as the abbreviated B-SIT. Finally, for those with the resources necessary to implement such a change, routine chemosensory dysfunction screening in certain at-risk populations (eg, elderly populations) may raise awareness and provide opportunities to educate patients about the risk factors associated with dysfunction and advise on how to improve safety and overall quality of life. Given the association of chemosensory dysfunction and dementia progression, the utility of routine chemosensory testing in the elderly is currently being investigated,¹¹⁶ and there is some evidence that evaluation of olfactory function subscores may help distinguish neurodegeneration from normal aging.¹¹⁷

Management of Chemosensory Dysfunction

In patients with identified chemosensory dysfunction, management should first begin with safety counseling, with emphasis on using smoke/natural gas detectors, monitoring food expiration dates,

and maintaining proper nutrition. In many cases, relying on family or friends for assistance in monitoring for food spoilage or for hygiene may be necessary. Patients should also be counseled on the possible etiologies of their chemosensory dysfunction, and the associated psychosocial implications. Although many patients with olfactory dysfunction may have some improvement in olfaction without treatment, many chemosensory deficits are longstanding. Efficacious treatment options are limited, but treatment of the inciting pathology is generally an appropriate first approach. For example, treatments for CRS without nasal polyps and AR with topical steroids may improve inflammation and thereby improve conductive olfactory dysfunction.^{53,55,118,119} On the other hand CRS with nasal polyps may require systemic steroids to notice clinical improvement. In addition, patients with gustatory dysfunction from throughsh may benefit from antifungals and improved oral hygiene.¹²⁰

In patients with olfactory dysfunction, olfactory training represents a novel treatment strategy for a variety of olfactory loss etiologies.^{45,121–125} Olfactory neurons demonstrate neuroplasticity, and similar to physical therapy after a stroke, olfactory training aims to strengthen and “retrain” neural pathways.^{112,125} Radiologic studies suggest that the olfactory system may be strengthened by the act of practicing sniffing alone, with 1 study demonstrating an increased in signal intensity in the olfactory network on fMRI following olfactory training.¹²²

Most olfactory training regimes use twice daily sessions including 1 scent from each of 4 odor categories: flowery, fruity, spicy, resinous—commonly with essential oils. Though recommendations regarding timeline, duration of therapy, and adjunctive use of topical steroids are varied, it is generally agreed on that earlier initiation of olfactory training following olfactory loss is associated with improved outcomes.^{45,50,112,125} It may take 3 months to 6 months of olfactory training before patients notice an improvement and communicating this may aid in compliance.⁴⁵

Additional therapies have been trialed with varying success, including topical or systemic steroids, nonsteroidal topicals, and nonsteroid oral medications (eg, vitamins, antioxidants, antibiotics, phosphodiesterase inhibitors).⁴⁵ There have been studies demonstrating benefit, no improvement, or no obvious conclusion in multiple of these

modalities.⁴⁵ Given additive risks of additional treatments, it is important to carefully consider which patients may benefit from additional medical therapies. In patients who are having persistent chemosensory dysfunction despite treatment, or those with significant consequences of their chemosensory dysfunction (eg, depression), referral to the proper specialist is warranted for more complex work up or management. For example, referral to an otolaryngologist would allow for a more thorough head and neck examination, including nasal endoscopy to determine if a lesion is present.

Conclusion

The 3 chemosensory functions of olfaction, gustation, and chemesthesis have distinct but overlapping physiologic mechanisms. Chemosensory dysfunction has broad implications and is therefore an important aspect of patients’ health. Identification and management of chemosensory dysfunction allows for safety education and risk stratification, as olfactory loss may occur on a continuum from healthy patients, to ill (ie, frail) patients, to even death. Awareness and screening for chemosensory dysfunction in primary care settings can enable PCPs to provide more comprehensive medical care.

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References

1. Rebholz H, Braun RJ, Ladage D, Knoll W, Kleber C, Hassel AW. Loss of olfactory function—early indicator for COVID-19, other viral infections and neurodegenerative disorders. *Front Neurol* 2020;11:569333.
2. Boesveldt S, Postma EM, Boak D, et al. Anosmia—a clinical review. *Chem Senses* 2017;42:513–23.
3. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses* 2014;39:185–94.
4. Doty RL. Age-related deficits in taste and smell. *Otolaryngol Clin North Am* 2018;51:815–25.
5. Slack JP. Molecular pharmacology of chemesthesis. In: Zufall F, Munger SD, eds. *Chemosensory Transduction: The Detection of Odors, Tastes, and Other Chemostimuli*. 2016:375–91: Academic Press.
6. Duffy VB, Hayes JE. Biological basis and functional assessment of oral sensation. In: Meiselman HL, ed. *Handbook of Eating and Drinking*. Springer; 2020:1–25.

7. Tremblay C, Frasnelli J. Olfactory and trigeminal systems interact in the periphery. *Chem Senses* 2018;43:611–6.
8. Hoffman HJ, Rawal S, Li CM, Duffy VB. New chemosensory component in the U.S. National Health and Nutrition Examination Survey (NHANES): first-year results for measured olfactory dysfunction. *Rev Endocr Metab Disord* 2016;17:221–40.
9. Ekstrom I, Sjölund S, Nordin S, et al. Smell loss predicts mortality risk regardless of dementia conversion. *J Am Geriatr Soc* 2017;65:1238–43.
10. Bernstein IA, Roxbury CR, Lin SY, Rowan NR. The association of frailty with olfactory and gustatory dysfunction in older adults: a nationally representative sample. *Int Forum Allergy Rhinol* 2021;11:866–76.
11. Choi JS, Jang SS, Kim J, Hur K, Ference E, Wrobel B. Association between olfactory dysfunction and mortality in US adults. *JAMA Otolaryngol Head Neck Surg* 2021;147:49–55.
12. Blankenship ML, Grigorova M, Katz DB, Maier JX. Retronasal odor perception requires taste cortex, but orthonasal does not. *Curr Biol* 2019;29:62–9 e3.
13. Pinna F D R, Ctenas B, Weber R, Saldiva PH, Voegels RL. Olfactory neuroepithelium in the superior and middle turbinates: which is the optimal biopsy site? *Int Arch Otorhinolaryngol* 2013;17:131–8.
14. Morrison EE, Costanzo RM. Morphology of olfactory epithelium in humans and other vertebrates. *Microsc Res Tech* 1992;23:49–61.
15. Goncalves S, Goldstein BJ. Pathophysiology of olfactory disorders and potential treatment strategies. *Curr Otorhinolaryngol Rep* 2016;4:115–21.
16. Liu G, Zong G, Doty RL, Sun Q. Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the US population: a cross-sectional study. *BMJ Open* 2016;6:e013246.
17. Dong J, Pinto JM, Guo X, et al. The prevalence of anosmia and associated factors among U.S. Black and White older adults. *J Gerontol A Biol Sci Med Sci* 2017;72:1080–6.
18. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. The rate of age-related olfactory decline among the general population of older U.S. adults. *GERONA* 2015;70:1435–41.
19. Yang J, Pinto JM. The Epidemiology of Olfactory Disorders. *Curr Otorhinolaryngol Rep* 2016;4:130–41.
20. Murphy C, Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA* 2002;288:2307–12.
21. Devanand DP, Lee S, Manly J, et al. Olfactory identification deficits and increased mortality in the community. *Ann Neurol* 2015;78:401–11.
22. Kern DW, Wroblewski KE, Schumm LP, Pinto JM, Chen RC, McClintock MK. Olfactory function in Wave 2 of the National Social Life, Health, and Aging Project. *J Gerontol B Psychol Sci Soc Sci* 2014;69:S134–43.
23. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann Neurol* 2008;63:167–73.
24. Schlosser RJ, Desiato VM, Storck KA, et al. A community-based study on the prevalence of olfactory dysfunction. *Am J Rhinol Allergy* 2020;34:661–70.
25. Schubert CR, Cruickshanks KJ, Fischer ME, et al. Olfactory impairment in an adult population: the Beaver Dam Offspring Study. *Chem Senses* 2012;37:325–34.
26. Seubert J, Laukka EJ, Rizzuto D, et al. Prevalence and correlates of olfactory dysfunction in old age: a population-based study. *J Gerontol A Biol Sci Med Sci* 2017;72:1072–9.
27. Attems J, Walker L, Jellinger KA. Olfaction and aging: a mini-review. *Gerontology* 2015;61:485–90.
28. Wilson RS, Yu L, Bennett DA. Odor identification and mortality in old age. *Chem Senses* 2011;36:63–7.
29. Adams DR, Wroblewski KE, Kern DW, et al. Factors associated with inaccurate self-reporting of olfactory dysfunction in older US adults. *Chem Senses* 2017;42:223–31.
30. Rawal S, Hoffman HJ, Chapo AK, Duffy VB. Sensitivity and specificity of self-reported olfactory function in a home-based study of independent-living, healthy older women. *Chemosens Percept* 2014;7:108–16.
31. Olofsson JK, Freiherr J. Neuroimaging of smell and taste. *Handb Clin Neurol* 2019;164:263–82.
32. Yoshida R, Miyauchi A, Yasuo T, et al. Discrimination of taste qualities among mouse fungiform taste bud cells. *J Physiol* 2009;587:4425–39.
33. Maheswaran T, Abikshyeet P, Sitra G, Gokulanathan S, Vaithyanadane V, Jeelani S. Gustatory dysfunction. *J Pharm Bioallied Sci* 2014;6:S30–3.
34. Hunt JD, Reiter ER, Costanzo RM. Etiology of subjective taste loss. *Int Forum Allergy Rhinol* 2019;9:409–12.
35. Hummel T, Frasnelli J. The intranasal trigeminal system. *Handb Clin Neurol* 2019;164:119–34.
36. Roper SD. TRPs in taste and chemesthesis. *Handb Exp Pharmacol* 2014;223:827–71.
37. Hummel T, Barz S, Lotsch J, Roscher S, Kettenmann B, Kobal G. Loss of olfactory

- function leads to a decrease of trigeminal sensitivity. *Chem Senses* 1996;21:75–9.
38. Frasnelli J, Schuster B, Hummel T. Interactions between olfaction and the trigeminal system: what can be learned from olfactory loss. *Cereb Cortex* 2007;17:2268–75.
 39. de Haro-Licer J, Roura-Moreno J, Vizitiu A, Gonzalez-Fernandez A, Gonzalez-Ares JA. Long term serious olfactory loss in colds and/or flu. *Acta Otorrinolaringol Esp* 2013;64:331–8.
 40. Soler ZM, Patel ZM, Turner JH, Holbrook EH. A primer on viral-associated olfactory loss in the era of COVID-19. *Int Forum Allergy Rhinol* 2020;10:814–20.
 41. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis. *Mayo Clin Proc* 2020;95:1621–31.
 42. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol* 2020;10:944–50.
 43. Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope* 2007;117:272–7.
 44. Imam SA, Lao WP, Reddy P, Nguyen SA, Schlosser RJ. Is SARS-CoV-2 (COVID-19) post-viral olfactory dysfunction (PVOD) different from other PVOD? *World J Otorhinolaryngol Head Neck Surg* 2020;6:S26–S32.
 45. Hura N, Xie DX, Choby GW, et al. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2020;10:1065–86.
 46. Iannuzzi L, Salzo AE, Angarano G, et al. Gaining back what is lost: Recovering the sense of smell in mild to moderate patients after COVID-19. *Chem Senses* 2020;45:875–81.
 47. Potter MR, Chen JH, Lobban NS, Doty RL. Olfactory dysfunction from acute upper respiratory infections: relationship to season of onset. *Int Forum Allergy Rhinol* 2020;10:706–12. Jun.
 48. Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Arch Otolaryngol Head Neck Surg* 2006;132:265–9.
 49. Lee DY, Lee WH, Wee JH, Kim JW. Prognosis of postviral olfactory loss: follow-up study for longer than one year. *Am J Rhinol Allergy* 2014;28:419–22.
 50. Kim DH, Kim SW, Hwang SH, et al. Prognosis of olfactory dysfunction according to etiology and timing of treatment. *Otolaryngol Head Neck Surg* 2017;156:371–7.
 51. Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg* 2002;128:635–41.
 52. D'Alonzo GE. Jr. Scope and impact of allergic rhinitis. *J Am Osteopath Assoc* 2002;102:S2–S6.
 53. Stuck BA, Hummel T. Olfaction in allergic rhinitis: A systematic review. *J Allergy Clin Immunol* 2015;136:1460–70.
 54. DeConde AS, Soler ZM. Chronic rhinosinusitis: Epidemiology and burden of disease. *Am J Rhinol Allergy* 2016;30:134–9.
 55. Ahmed OG, Rowan NR. Olfactory dysfunction and chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2020;40:223–32.
 56. Alt JA, Mace JC, Buniel MC, Soler ZM, Smith TL. Predictors of olfactory dysfunction in rhinosinusitis using the brief smell identification test. *Laryngoscope* 2014;124:E259–66.
 57. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;50:1–12.
 58. Jiang RS, Lu FJ, Liang KL, et al. Olfactory function in patients with chronic rhinosinusitis before and after functional endoscopic sinus surgery. *Am J Rhinol* 2008;22:445–8.
 59. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *Laryngoscope* 2017;127:309–20.
 60. Xie DX, Leland EM, Seal SM, Lin SY, Rowan NR. A systematic review and meta-analysis of taste dysfunction in chronic rhinosinusitis. *Laryngoscope* 2021;131:482–9.
 61. Fark T, Hummel C, Hahner A, Nin T, Hummel T. Characteristics of taste disorders. *Eur Arch Otorhinolaryngol* 2013;270:1855–60.
 62. Haxel BR, Grant L, Mackay-Sim A. Olfactory dysfunction after head injury. *J Head Trauma Rehabil* 2008;23:407–13.
 63. Howell J, Costanzo RM, Reiter ER. Head trauma and olfactory function. *World J Otorhinolaryngol Head Neck Surg* 2018;4:39–45.
 64. Reiter ER, DiNardo LJ, Costanzo RM. Effects of head injury on olfaction and taste. *Otolaryngol Clin North Am* 2004;37:1167–84.
 65. Doty RL, Kamath V. The influences of age on olfaction: a review. *Front Psychol* 2014;5:20.
 66. Fullard ME, Morley JF, Duda JE. Olfactory dysfunction as an early biomarker in Parkinson's disease. *Neurosci Bull* 2017;33:515–25.
 67. Yoo HS, Jeon S, Chung SJ, et al. Olfactory dysfunction in Alzheimer's disease and Lewy body-related cognitive impairment. *Alzheimers Dement* 2018;14:1243–52.
 68. Bathini P, Brai E, Auber LA. Olfactory dysfunction in the pathophysiological continuum of dementia. *Ageing Res Rev* 2019;55:100956.

69. Solomon GS, Petrie WM, Hart JR, Brackin HB, Jr. Olfactory dysfunction discriminates Alzheimer's dementia from major depression. *JNP* 1998;10:64–7.
70. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters E, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol* 2004;56:173–81.
71. Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA. Olfactory identification and incidence of mild cognitive impairment in older age. *Arch Gen Psychiatry* 2007;64:802–8.
72. Yaffe K, Freimer D, Chen H, et al. Olfaction and risk of dementia in a biracial cohort of older adults. *Neurology* 2017;88:456–62.
73. Schubert CR, Carmichael LL, Murphy C, Klein BE, Klein R, Cruickshanks KJ. Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. *J Am Geriatr Soc* 2008;56:1517–21.
74. Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Neurology* 2015;84:182–9.
75. Devanand DP, Lee S, Luchsinger JA, et al. Intact global cognitive and olfactory ability predicts lack of transition to dementia. *Alzheimers Dement* 2020;16:326–34.
76. Doty RL. Olfactory dysfunction and its measurement in the clinic. *World J Otorhinolaryngol Head Neck Surg* 2015;1:28–33.
77. Lin SH, Chu ST, Yuan BC, Shu CH. Survey of the frequency of olfactory dysfunction in Taiwan. *J Chin Med Assoc* 2009;72:68–71.
78. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses* 2003;28:691–4.
79. Zou LQ, Linden L, Cuevas M, et al. Self-reported mini olfactory questionnaire (Self-MOQ): a simple and useful measurement for the screening of olfactory dysfunction. *Laryngoscope* 2020;130:E786–E790.
80. Gözen ED, Aliyeva C, Tevetoglu F, et al. Evaluation of olfactory function with objective tests in COVID-19-positive patients: a cross-sectional study. *Ear Nose Throat J* 2021;100:169S–73S. Apr.
81. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinology* 2016;56:1–30.
82. Doty RL. Psychophysical testing of smell and taste function. *Handb Clin Neurol* 2019;164:229–46.
83. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope* 1996;106:353–6.
84. Sorokowska A, Oleszkiewicz A, Minovi A, Konnerth CG, Hummel T. Fast screening of olfactory function using the Q-Sticks Test. *ORL J Otorhinolaryngol Relat Spec* 2019;81:245–51.
85. Jackman AH, Doty RL. Utility of a three-item smell identification test in detecting olfactory dysfunction. *Laryngoscope* 2005;115:2209–12.
86. Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. *Laryngoscope* 1984;94:176–8.
87. Doty RL, Wylie C, Potter M, Beston R, Cope B, Majam K. Clinical validation of the olfactory detection threshold module of the Snap & Sniff(R) olfactory test system. *Int Forum Allergy Rhinol* 2019;9:986–92.
88. Calvo-Henriquez C, Maldonado-Alvarado B, Chiesa-Estomba C, et al. Ethyl alcohol threshold test: a fast, reliable and affordable olfactory Assessment tool for COVID-19 patients. *Eur Arch Otorhinolaryngol* 2020;277:2783–92.
89. Pierce JD, Jr., Doty RL, Amoore JE. Analysis of position of trial sequence and type of diluent on the detection threshold for phenyl ethyl alcohol using a single staircase method. *Percept Mot Skills* 1996;82:451–8.
90. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. *Rhinology* 1996;34:222–6.
91. Doty R. The Odor Threshold Test administration manual. Haddon Hts., NJ: Sensonics. Inc; 2000. [Database]
92. Rumeau C, Nguyen DT, Jankowski R. How to assess olfactory performance with the Sniffin' Sticks test. *Eur Ann Otorhinolaryngol Head Neck Dis* 2016;133:203–6.
93. Ozay H, Cakir A, Ecevit MC. Retronasal olfaction test methods: a systematic review. *Balkan Med J* 2019;36:49–59.
94. Furukawa M, Kamide M, Ohkado T, Umeda R. Electro-olfactogram (EOG) in olfactometry. *Auris Nasus Larynx* 1989;16:33–8.
95. Roberts RJ, Sheehan W, Thurber S, Roberts MA. Functional neuro-imaging and post-traumatic olfactory impairment. *Indian J Psychol Med* 2010;32:93–8.
96. Rombaux P, Huart C, Mouraux A. Assessment of chemosensory function using electroencephalographic techniques. *Rhinology* 2012;50:13–21.
97. Soler ZM, Pallanch JF, Sansoni ER, et al. Volumetric computed tomography analysis of the olfactory cleft in patients with chronic rhinosinusitis. *International Forum of Allergy and Rhinology* 2015;5:846–54.
98. Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AL. Contingent negative variation: an electric sign of sensorimotor association and expectancy in the human brain. *Nature* 1964;203:380–4.

99. Rawal S, Hoffman HJ, Honda M, Huedo-Medin TB, Duffy VB. The taste and smell protocol in the 2011–2014 US National Health and Nutrition Examination Survey (NHANES): Test–retest reliability and validity testing. *Chemosens Percept* 2015;8:138–48.
100. Bernhardson BM, Olson K, Baracos VE, Wismer WV. Reframing eating during chemotherapy in cancer patients with chemosensory alterations. *Eur J Oncol Nurs* 2012;16:483–90.
101. Mathey MF. Assessing appetite in Dutch elderly with the Appetite, Hunger and Sensory Perception (AHSP) questionnaire. *J Nutr Health Aging* 2001;5:22–8.
102. Doty RL. Measurement of chemosensory function. *World J Otorhinolaryngol Head Neck Surg* 2018;4:11–28.
103. Stinton N, Atif MA, Barkat N, Doty RL. Influence of smell loss on taste function. *Behav Neurosci* 2010;124:256–64.
104. Bartoshuk LM, Gent J, Catalanotto FA, Goodspeed RB. Clinical evaluation of taste. *Am J Otolaryngol* 1983;4:257–60.
105. Frank ME, Smith DV. Electrogustometry: A simple way to test taste. In: Getchell TV, Doty RL, Bartoshuk LM, Snow Jr JB eds. *Smell and Taste in Health and Disease*. New York, NY: Raven Press; 1991:503–514.
106. Parma V, Ohla K, Veldhuizen MG, GCCR Group Author, et al. More than smell—COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chem Senses* 2020;45:609–22.
107. Hummel T, Futschik T, Frasnelli J, Huttenbrink KB. Effects of olfactory function, age, and gender on trigeminally mediated sensations: a study based on the lateralization of chemosensory stimuli. *Toxicol Lett* 2003;140–141:273–80.
108. Kobal G, Van Toller S, Hummel T. Is there directional smelling? *Experientia* 1989;45:130–2.
109. Huart C, Hummel T, Kaehling C, et al. Development of a new psychophysical method to assess intranasal trigeminal chemosensory function. *Rhinology* 2019;57:375–84.
110. Hummel T, Kaehling C, Grosse F. Automated assessment of intranasal trigeminal function. *Rhinology*. Mar 2016;54:27–31.
111. Van Regemorter V, Hummel T, Rosenzweig F, Mouraux A, Rombaux P, Huart C. Mechanisms linking olfactory impairment and risk of mortality. *Front Neurosci* 2020;14:140.
112. Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink K-B. Effects of olfactory training in patients with olfactory loss. *Laryngoscope* 2009;119:496–9.
113. Birte-Antina W, Ilona C, Antje H, Thomas H. Olfactory training with older people. *Int J Geriatr Psychiatry* 2018;33:212–20.
114. Fechner A, Fong S, McGovern P. A review of Kallmann syndrome: genetics, pathophysiology, and clinical management. *Obstet Gynecol Surv* 2008;63:189–94.
115. Yousem DM, Geckle RJ, Bilker W, McKeown DA, Doty RL. MR evaluation of patients with congenital hyposmia or anosmia. *AJR Am J Roentgenol* 1996;166:439–43.
116. Luchsinger JA, Devanand DP. Testing olfaction in primary care to detect Alzheimer’s disease and other dementias (TOPAD). Reporter. <https://reporter.nih.gov/search/0QxT-MyFhEWXIdUXtkGzCA/project-details/10192624>.
117. Krismer F, Pinter B, Mueller C, et al. Sniffing the diagnosis: Olfactory testing in neurodegenerative parkinsonism. *Parkinsonism Relat Disord* 2017; 35:36–41.
118. Mori E, Merkonidis C, Cuevas M, Gudziol V, Matsuwaki Y, Hummel T. The administration of nasal drops in the “Kaiteki” position allows for delivery of the drug to the olfactory cleft: a pilot study in healthy subjects. *Eur Arch Otorhinolaryngol* 2016; 273:939–43.
119. Sur DK, Scandale S. Treatment of allergic rhinitis. *Am Fam Physician* 2010;81:1440–6.
120. Sakashita S, Takayama K, Nishioka K, Katoh T. Taste disorders in healthy “carriers” and “non-carriers” of *Candida albicans* and in patients with candidosis of the tongue. *J Dermatol* 2004;31:890–7.
121. Huang T, Wei Y, Wu D. Effects of olfactory training on posttraumatic olfactory dysfunction: a systematic review and meta-analysis. *Int Forum Allergy Rhinol* 2021;11:1102–12.
122. Kollndorfer K, Fischmeister FP, Kowalczyk K, et al. Olfactory training induces changes in regional functional connectivity in patients with long-term smell loss. *Neuroimage Clin* 2015;9:401–10.
123. Pekala K, Chandra RK, Turner JH. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. *Int Forum Allergy Rhinol* 2016;6:299–307.
124. Kattar N, Do TM, Unis GD, Mignerol MR, Thomas AJ, McCoul ED. Olfactory training for postviral olfactory dysfunction: systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2021;164:244–54.
125. Whitcroft KL, Hummel T. Clinical diagnosis and current management strategies for olfactory dysfunction: a review. *JAMA Otolaryngol Head Neck Surg* 2019;145:846–53.