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SALIVA – Nature's miracle in our mouth

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Abstract

Salivary gland is any cell or organ discharging a secretion into the oral cavity. These are exocrine glands whose secretions flow into the oral cavity. There are three pairs of large glands located extra-orally known as the major salivary glands and numerous small glands widely distributed in the mucosa and sub mucosa of the oral cavity, known as the minor salivary glands. Both the major and minor glands are composed of parenchymal elements invested in and supported by connective tissue. The parenchymal elements are derived from the oral epithelium and consist of terminal secretory units leading into ducts that eventually open into the oral cavity.

Secretory proteins represent the main category of organic substances in the saliva. These include various enzymes, large carbohydrate rich glycoproteins, antibacterial substances, and a group of proteins involved principally in enamel pellicle formation and calcium phosphate homeostasis in the saliva. Certain constituents such as albumin, blood-clotting factors, microglobulin, and immunoglobulins are also found in the saliva. Other organic molecules present in saliva include cyclic AMP and cyclic AMP-binding factors, amino acids, urea, uric acid, various lipids and corticosteroids.

Keywords: Saliva, Blood supply, Flow rate, Histology.

Introduction

"Saliva is a clear, tasteless, odourless slightly acidic viscous fluid, consisting of secretions from the parotid, sublingual, submandibular salivary glands and mucous glands of oral cavity". It is one of the most complex, versatile, and important body fluids, supplying a large range of physiological needs.[1]

In 1656 Thomas Wharton wrote of the duct which now bears his name. He described a canal that opens into the mouth and issues salivary fluid; thus the concept of salivary secretion was born. It is these secretions that have been referred to “aqua vita” i.e. water of life.[2]

99% of saliva is water and the other 1% is composed of organic and inorganic molecules. The average daily volume of saliva production is 500-1000 ml.[3] While the quantity of saliva is important, so is its quality, as each of its components performs a series of specific functions which play an important role in the maintenance of oral health. These include homeostatic processes, lubrication, antimicrobial activity, and the control of demineralization/remineralization of teeth.[4]

Composition of saliva is influenced by flow rate. Biological and environmental factors significantly affect the flow. Reduced salivary flow rate may occur due to hypo-function of the salivary glands. It can be also be caused by a variety of other reasons like dehydration, mouth breathing, medications and radiotherapy. Lack of saliva (xerostomia) not only has a negative impact on oral health but also on the health of the body as a whole. Less frequently, salivary secretion can increase. This is called hypersalivation, ptyalism or sialorrhea and it may be physiological or pathological.[5, 6]

Research on salivary functions is not that old, perhaps partly because saliva has not been one of the "popular" body fluids. Historically saliva has been scorned in literature and viewed by many cultures as the ultimate insult. The pithy expression by Mandel (1990) was that "saliva lacks the drama of blood, the sincerity of sweat and the emotional appeal of tears". Despite the absence of charisma, however, research on salivary functions and the underlying molecules has been intensive for the last three decades. Interest in saliva increased more with the finding that saliva is filled with hundreds of components that may serve to detect systemic disease or evidence of exposure to various harmful substances, as well as provide biomarkers of health and disease status. [6, 7, 8]

Many dental researchers call saliva the miracle fluid of the 21st century. As the "Mirror of Body", saliva is a perfect medium to be explored for health and disease surveillance. The use of saliva has many advantages, including the simple and non-invasive method of collection and its easy, low-cost storage. With the addition of modern techniques and chemical instrumentation equipment, there has been an increase in its use for laboratory investigations, applicable for basic and clinical analyses in the fields of medicine and dentistry. [8]

The salivary research field is rapidly advancing due to the use of novel approaches that include metabolomics, genomics, proteomics and bioinformatics. Tests using saliva as a diagnostic tool have made substantial inroads into an array of clinical and research areas, such as virology, immunology, microbiology, endocrinology, epidemiology and forensics.[9, 10]

This is provides an overview of the composition of saliva, its functions in maintaining oral health, the main factors that cause alterations in salivary secretion and the latest advances using salivary biomarkers for disease detection.

The True Beginnings

The history of the subject really began in London with the publication in 1656 of 'Adenographia' by Thomas Wharton (1614-73), of mnemonic fame. In his book, he gave the first ever description of the duct of the submandibular gland. He wrote 'Hinc canalis dictus... in os aperitur...humorem salivem impertit' ['this said canal... opens into the mouth... and issues the salivary fluid'] and so the concept of salivary secretion was born. His fundamental observation about the submandibular duct and its function opened out the road to all further thinking.

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It was not long before Niels Steensen (1638-86) from Copenhagen described the duct of the parotid gland in his thesis in 1661. He claimed that the stimulation of the gland came from the brain via the nerves to the gland - a view that was subsequently forgotten. Having observed that saliva may squirt out into the mouth in response to a stimulus, he believed that the nerves may stimulate some motor function, but he realized that they must also be doing more than just this in stimulating a more continuous flow. He also believed that the blood carried all the elements which appear in the secretion. In his work on glands he was the first to differentiate the exocrine glands from the lymph nodes.

Malpighi, the founder of histology, devoted much time to studying the structure of glands and in 1665 introduced the word 'acini' for the ultimate end bodies in glands. He realized that secreting glands are essentially composed of tubes with blind ends.[11]

Recent History of Salivary Research

The diagnostic value of saliva was first recognized by ancient judicial community who employed salivary flow as the basis for a primitive lie detector test. The past 50 years of salivary research has been marked by a series of changing perceptions as new techniques and technologies have illuminated the complexities of the secretory mechanism, salivary composition, and function. However, salivary research blossomed in mid 1950s to mid 1960s with the advent of electrophoresis, chromatography, histochemistry, immunochemistry, electron microscopy, and microphysiology. [12]

- In 1954 the two stage hypothesis for salivary formation was proposed.[13]
- In 1956 Burgen used isolated, perfused gland preparation and demonstrated the initial loss of potassium on stimulation.[14]
- In 1958 Fundberg gave the hypothesis to explain the initiation of the secretory process.[15]
- In 1960 Immunoglobulins in saliva were identified by immunochemical technique and identification of secretary IgA in the secretion was the major event of this period.[16]
- In 1963 It was shown that IgA predominated in saliva and not IgG.[17]
- In 1965 major amino acid i.e. proline in saliva was identified.[18]
- In 1969 basic proline rich glycoprotein of parotid saliva was characterized.[19]
- In 1974 isoamylases were identified by Mayo and Carlton.[20]
- In 1980 Cystine rich proteins were identified.[21]
- In 1983 the ability of saliva to accelerate wound healing in animals was recognized, and growth factors were also related and studied for therapeutic use.[22]
- In 1990 Epidermal Growth Factor (EGF) receptor in buccal mucosa was identified and it was supposed to have a protective role in oral cavity.[23]
- In 1990 the level of EGF in various systemic diseases was identified and decreased EGF was demonstrated with rheumatoid arthritis and peptic ulcer.[24]
- In 1990 saliva was found to have diagnostic use in clinical situations and systemic diseases that can affect salivary gland function and composition, in addition to it all steroids of diagnostic significance were also measured in saliva, drug monitoring was done.[25]
- In 1990's the role of saliva as a diagnostic tool was identified in number of diseases.
- In 2001 it was recognized that saliva has potential to replace serum in IgG antibody prevalence surveys.[26]

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Salivary Glands

The human salivary gland system can be divided into two distinct exocrine groups. The *major salivary glands* include the paired parotid, submandibular, and sublingual glands. Additionally, the mucosa of the upper aerodigestive tract is lined by hundreds of small, *minor salivary glands*. The major function of the salivary glands is to secrete saliva, which plays a significant role in lubrication, digestion, immunity, and the overall maintenance of homeostasis within the human body.

Anatomy Of The Glands

Major salivary glands: The parotid is the largest of the salivary glands. It weights about 15g. It is situated below the external acoustic meatus, between the ramus of the mandible and the sternocleidomastoid muscle.[27] Anteriorly the gland also overlaps the masseter muscle. A part of this forward extension is often detatched is known as the accessory parotid and it lies between the zygomatic arch and parotid duct. [28]

External features : The gland resembles a three sided pyramid. The apex of the pyramid is directed downwards.[28]

Relations: The apex overlaps the posterior belly of the digastric and the adjoining part of carotid. The cervical branch of facial nerve and two divisions of the retromandibular vein emerge through it.

1) The superior surface or base is formed by the upper end of the gland which is small and concave. This is related to
    a) Cartilaginous part of external acoustic meatus.
    b) The posterior surface of the TMJ
    c) The superficial temporal vessels and
    d) The auriculotemporal nerve.
2) The superficial surface is the largest of the four surfaces. It is covered with
    a) Skin
    b) Superficial fascia containing the anterior branches of the great auricular nerve, the preauricular or superficial lymphnodes, posterior fibers of platysma and risorius
    c) Parotid fascia
    d) Few deep parotid lymph nodes.
3) Anteromedial surface related to the masseter, lateral surface of TMJ posterior border of ramus of the mandible the medial pterygoid and emerging branches of facial nerve, stylomandibular ligament.
4) Posteromedial surface is related to the mastoid process, with the sternocleido mastoid and posterior belly of the digastric, the styloid process, carotid sheath, internal carotid artery, vagus, glossopharyngeal, accessory and facial nerve. [29]

Parotid duct: The parotid excretory duct (Stensen's duct) has a diameter of 1-2mm and averages 4 cm in length.[30] Emerging from the anterior border of the superficial lobe, at the level of the masseter extension, this duct runs forwards, lateral to the masseter, together with the transverse facial artery. After running deeply towards the buccal surface of the cheek, the duct pierces the buccinators muscle and drains via a prominent papilla into the oral cavity, opposite the second upper molar. In approximately 20% of individuals, Stensen's duct receives the duct of an accessory parotid gland as it crosses the masseter muscle (Silvers and Som 1998)

Blood supply: by the external carotid arteryLymphatic drainage: Lymph vessels drain into the upper deep cervical nodes.

Structures within the parotid gland:[31]

1) Facial nerve: It emerges from stylomastoid foramen and enters the posteromedial surface of the gland. It passes forward within the gland, superficial to retromandibular vein and external carotid artery and divides into 5 terminal branches.

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2) Retromandibular nerve
3) External carotid artery

Submandibular salivary gland: This is a large salivary gland, situated in the anterior part of the digastric triangle. The gland is about the size of walnut. It is roughly J-shaped and is indented by the posterior border of the mylohyiod which divides it into a larger part superficial to the muscle and a small part lying deep to the muscle.[32]

Superficial part

This part of the gland fills the digastric triangle it extends upwards deep to the mandible up to the mylohyoid line. It has inferior, lateral and medial surfaces.

The gland is partially enclosed between 2 layers of deep cervical fascia. The superficial layers of fascia cover the inferior surface of gland and it is attached to the base of the mandible. The deep layer covers the medial surface of the gland and is attached to mylohyoid line of mandible.[31]

Relations:

A. Inferior surface: It is covered by: Skin, platysma, cervical branch of the facial nerve, deep fascia, facial vein, submandibular lymph nodes

B. Lateral surface: It is related to

- Submandibular fossa on the mandible
- Facial artery
- Insertion of the medial pterygoid.

Medial surface may be divided into 3 parts:

- Anterior part: Related to mylohyoid muscle, nerve and vessels.
- Middle part: Related to hyoglossus, styloglossus, lingual nerve, submandibular ganglion and hypoglossal nerve.

Posterior part: Related to hyloglossus, stylohyoid ligament, the ninth nerve, wall of the pharynx and inferiorly it overlaps the stylohyoid and the posterior belly of digastric. [33]

Deep part

It lies deep to the mylohyoid and superficial to hyoglossus and the styloglossus. **Submandibular Duct:** It is thin walled and is about 5 cm long and 2-3 mm in diameter. It emerges at the anterior end of the deep part of the gland and runs forwards on the hyoglossus between the lingual and hypoglossal nerve the anterior border of the hyloglossus, the duct is crossed by lingual nerve. It opens on the floor of the mouth on the summit of the sublingual papilla at the side of frenulum of the tongue called caruncula sublingualis.[29]

Blood supply: Facial artery

Lymphatic drainage: Lymph vessels drain into submandibular lymph nodes

Sublingual gland: It is the smallest of the three main salivary glands. It is of almond shape and weighs about 3-4g. It contains both serous and mucous acini, mucous acini is predominating.[33]

Situation: It lies beneath the mucous membrane of the floor of the mouth close to the midline.[28]

Relations: Anteriorly: It is related to the gland of the opposite side.

Posteriorly: It is related to the deep part of submandibular gland.

Medially: It is related to genioglossus muscle, lingual nerve and submandibular duct.

Laterally: It is related laterally to the sublingual fossa of the medial surface of mandible.

Superiorly: The mucous membrane of the floor of the mouth, which is elevated by the gland to form the sublingual fold.

Inferiorly: The gland is supported by mylohyoid muscle.[31]

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Sublingual ducts: They are 8-20 in number. (Bartholin's duct)

Opening of duct: they open into the mouth on the summit of the sublingual fold. But few may open into submandibular duct.

Blood supply: Branches of facial and lingual arteries

Lymph drainage: Lymph vessels drain into submandibular and deep cervical lymph nodes.[33]

Minor Salivary Glands

There are over 600 minor salivary glands located throughout the oral cavity within the submucosal of the oral mucosa.

1. Labial and buccal glands
2. Glossopalatine glands
3. Palatine glands
4. Lingual glands
   a. Blandin and Nuhn
   b. Von Ebner's gland

Histology Of Salivary Glands

The glands develop from the epithelium and usually composed of two parts

1) The duct
2) The secretory unit (acini)

The secretory unit is composed of cells that produce a cell product that is expelled into the center or lumen of the secretary unit.[34]

1) Serous secreting unit

- Serous secreting units have many protein granules in their cytoplasm.
- Serous cells secretes polysaccharide therefore these are seromucous cells.
- Serous cells are pyramid in shape with their apex situated towards the central lumen.
- Nucleus is spherical and situated in the basal third of the cell.
- Cytoplasm stains intensely with hematoxylin and eosin (H & E)
- Seromucous cells have all the features of a cell specialized for the synthesis, storage and secretion of protein.
- It has large amount of rough endoplasm i.e. reticular arranged in parallel stalks, parked basally and laterally to the nucleus.
- Has prominent golgi apparatus complex
- Apical cytoplasm filled with secretary granules each surrounded by the unit membrane.
- In a seromucous end piece the cells are supported by a basement membrane that separates the parenchyma from the connective tissue.
- A well defined intracellular space continues from the lumen of the end piece between these cells.
- A canaliculus terminates in the form of classic junctional complexes consisting of in order a light junction (zena occludense) and intermediate junction (zena adherence) and desmosome (macula adherence).[35, 36]

2) Mucous cells: They are clear because of the mucous produced within the cells the secretary product of mucous cells different from that of the seromucous cells in that there is a smaller enzymatic component and proteins are linked to greater amount of carbohydrate material forming mucins.

Demilunes: Many of the mucous acini (tubule) exhibits in histologic section a crescent shaped group of serous cells at their distal ends. These structures are named for their histologic appearance the demilunes or crescent. In three dimensions they would resemble a cap of cells.[37]

Myoepithelial cells: Myoepithelial cells are found close to the terminal secretary end piece and the intercalated duct occupying the space between basement membrane of the secretory epithelial cells.

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- Each cell consists of central body from which four to eight processes radiate and embrace the long axis of the secretory unit.
- These processes contain microfilaments that frequently aggregate to form dark bodies along the course of the process and this microfilament can be demonstrated by using immunofluorescence techniques.
- Myoepithelial cells are considered to be epithelial origin because they are situated between paranchymal cells and its basement membrane.
- Rapid emptying of saliva in the mouth and a maintained flow at a high rate of the viscous saliva is promoted by contractions of the myoepithelial cells.[38]

Formation of Saliva

Production of saliva: Saliva contains both serous and mucous secretions secreted by salivary glands and major contribution is by major salivary glands.[39]

Salivary Gland Secretions	
Gland Type	Saliva Type
Parotid, and Von Ebner's (on the tongue)	Serous
Submandibular	Mixed, more serous than mucous
Sublingual	Mixed, but mostly mucous
Most minor	Mucous

Mechanism of formation of saliva is a two step process (Thaysen et al in 1954):[40]

1) Primary secretion of saliva

The acinar cells of salivary glands secrete the initial saliva into the salivary ducts. The initial saliva is formed by transudation (pressure filtration) of plasma and therefore is isotonic, i.e. has the same Na^+, K^+ and HCO^{-3} concentrations as plasma. However, the initial saliva is soon modified by the salivary ducts.

2) Modification of saliva

The ductal cells that line the tubular portions of the salivary ducts change the composition of initial saliva by following processes:

- Reabsorption of Na^+ and Cl^- occurs in the ductal cells, therefore, the concentration o these ions is lower than their plasma concentration.
- Secretion of K^+ and HCO^{-3} is caused by the ductal cells; therefore, the concentrations of these ions are higher than their plasma concentrations.
- Modified saliva becomes hypotonic in their ducts because the ducts are relatively impermeable to water. Because more solutes than water are reabsorbed by the ducts, the saliva becomes dilute relative to plasma.

Usually cell membranes have very low intrinsic water permeabilities and the large water permeabilities observed in the membranes of many tissues are because of the presence of **aquaporins**, a family of plasma membrane water channel proteins (Borgnia et al, 1999). Recent studies have shown that a new aquaporin isoform, **AQP5**, is localized to the apical membranes of many secretory epithelia, including salivary acinar cells.[41]

Control of Salivation

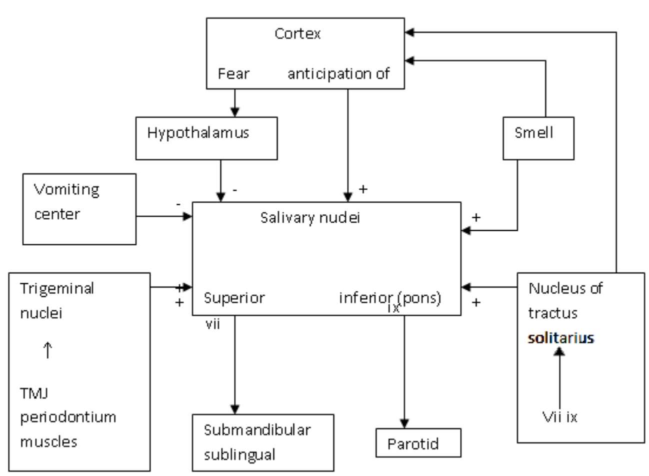

Fig. 1: Flow chart showing influences controlling the reflex secretion of saliva

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Neurophysiologic control of salivation

- Salivary secretion is controlled entirely by autonomic nervous system (ANS) reflexes.
- There is no hormonal regulation of salivary secretion.
- Salivary secretion production is unique in that it is increased by both parasympathetic and sympathetic activity; however the activity of former is more important.[42]

Two subunits are receptor molecules which bind with cAMP (2R cAMP), thereby liberating the other two catalytic subnits (2C) to activate effector proteins (Pr) by phosphorylation (Pr-P). The activated effector proteins then stimulate exocytosis. Diacylglycerol (from the phospholipase C pathway) also promotes exocytosis.[43, 44, 45]

This complex sequence of intracellular events thus leads to the formation of the primary fluid.

Salivary protein secretion

Salivary proteins exhibit vectorial transport from the rough endoplasmic reticulum, where they are synthesized, through a succession of membrane bounded compartments including the Golgi complex, condensing vacuoles and secretory granules. The secretory granules migrate to particular locations within the cell close to the apical membrane prior to the release of their contents into the acinar lumen.

Cells release the contents of their secretory granules. This involves the fusion of the granule membrane with the luminal plasma membrane of the secretory cell followed by the rupture of the fused membranes. This process is continuous in most cells, but it can be greatly accelerated following an appropriate cellular signal such as neural stimulation. In parotid, submandibular and sublingual, exocytotic protein secretion is primarily controlled by the autonomic nervous system; sympathetic stimulation elicits protein release from parotid and submandibular gland acini, and parasympathetic stimulation elicits protein release from sublingual gland acini as well as some release from parotid acini.[46, 47, 48]

cAMP - dependent amylase secretion

Salivary protein secretion, like fluid secretion, is evoked when neurotransmitters bind to specific receptors on the basolateral membrane of the secretory cells and generate intracellular second messengers that, in turn, activate the cellular mechanisms responsible for secretion. cAMP is the primary second messenger for amylase secretion from rat parotid acinar cells. Noradrenaline, released from sympathetic nerves, binds to and activates β adrenergic receptors leading to increased intracellular cAMP levels. cAMP is thought to mediate most of its effects through the activation of a cAMP-dependent protein kinase, also known as PKA. PKA activation is essential for cAMP-dependent exocytotic secretion.

Ca^{2+} - dependent amylase secretion:

Stimulation of muscarinic, substance P peptidergic or α-adrenergic receptors also elicits significant amylase release. These receptors are activated by acetylcholine and sybstance P released from parasympathetic nerves, and by noradrenaline released from sympathetic nerves, respectively. The stimulation of these receptors activates phosphatidylinositide metabolism and induces an increase in intracellular Ca^{2+} concentration without affecting intracellular cAMP levels.[49]

Factors Affecting Salivary Flow Rate

Circadian variation

Unstimulated flow peaks at approximately 5 pm in most individuals, with a minimum flow during the night. This variation is independent of eating and sleeping behaviour. SF attains its peak at the end of the afternoon but goes down to almost zero during sleep. Salivary

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composition is not constant and is related to the Circadian cycle. The concentration of total proteins attains its peak at the end of the afternoon, while the peak production levels of sodium and chloride occur at the beginning of the morning.[50, 51]

Light and arousal:

If one is blindfolded, or in an unlit room, the unstimulated flow rate falls. This is probably associated with the effect of visual input in maintaining a state of arousal. Saliva flow is much reduced during sleep.[52]

Hydration: The degree of individual hydration is the most important factor that interferes in salivary secretion. When the body water content is reduced by 8%, salivary flow virtually diminishes to zero, whereas hyperhydration causes an increase in salivary flow. During dehydration, the salivary glands cease secretion to conserve water.[52]

Stress: Anxiety and depression may lead to decrease in salivary flow rate. Acute stress conditions also induce significant salivary changes such as a decrease in secretory IgA, increase in salivary amylase and prompt changes of bacterial adherence to salivary mucins.[50]

Psychic flow: A ‘mouthwatering’ sensation is a universal experience on the anticipation or sight of food, especially if temptingly presented when hungry. In man, a small increase in flow can usually be demonstrated on thinking about food, or seeing it being prepared.[52]

Unconditional reflexes: The most important stimuli to salivation are those associated with feeding: masticatory movement, and especially taste.[50]

Mastication: Chewing a flavourless bolus such as wax or chewing gum base leads to an increase in saliva flow of about three-fold. This is a reflex response: receptors in the muscles of mastication, temporomandibular joint, periodontal ligament and mucosa detect the presence of a bolus and its mastication, and stimulate the salivary nuclei to increase the parasympathetic secretomotor discharge.[50]

Aging: Salivary flow rate data in healthy elderly--that are persons without any medication and not suffering from any (treatment related) salivary gland disorder have revealed no significant age-related decrease other than a slight decrease of the secretion from the (sero)mucous glands under conditions of minimal or extended stimulation.[53]

Gustatory stimuli: The reflex effects of taste stimuli are more dramatic, giving rise to perhaps a ten fold increase in saliva flow. Sour stimuli are most effective, followed by sweet, salt and bitter. Most food also elicits olfactory stimuli, and a reflex response to smell can be demonstrated.

Smoking: Studies have shown that men who smoke present significantly higher stimulated salivary flow than non-smoking men. The irritating effect of tobacco increases glandular excretion, and nicotine causes severe morphologic and functional alterations in the salivary glands.[54]

Other stimuli: Connections between the salivary nuclei and the vomiting center in the medulla, since copious reflex salivation as well as nausea frequently occur just before vomiting, perhaps as an attempt to dilute or neutralize the irritant which is giving rise to the nausea.

Conclusion

Despite these limitations, the use of saliva for diagnostic purposes is increasing in popularity. Several diagnostic tests are commercially available and are currently used by patients, researchers, and clinicians. Salivary diagnosis provides an attractive alternative to more invasive, time-consuming, complicated, and expensive diagnostic approaches. However, before a salivary diagnostic test can replace a more conventional one, the diagnostic value of a new salivary test has to be

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compared with accepted diagnostic methods. The usefulness of a new test has to be determined in terms of sensitivity, specificity, correlation with established disease diagnostic criteria, and reproducibility.

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