Review Article

Advanced Diagnostic Methods for Salivary Glands Diseases: A Narrative Review Study

Abstract

Effective diagnosis of salivary gland lesions and tumors requires a comprehensive understanding of the intricate composition of these glands. Salivary glands consist of diverse cell types, including epithelial, mesenchymal, ductal, and myoepithelial cells. The complex cellular architecture poses challenges in accurately diagnosing lesions or tumors. Furthermore, external factors such as infections, viruses, and genetic abnormalities that contribute to alterations can influence salivary gland pathophysiology. Therefore, it is crucial to thoroughly grasp the latest World Health Organization classification of salivary gland neoplasms for precise diagnosis and appropriate management. This study focuses on recent advancements in diagnostic methods to establish a practical approach for identifying salivary gland diseases. The researchers found that the best results were achieved when combining multiple salivary biomarkers. The screening protocol demonstrated high accuracy in diagnosing early oral squamous cell carcinoma by utilizing a combination of salivary biomarkers. In conclusion, the use of salivary biomarkers shows excellent promise in the early diagnosis of oral squamous cell carcinoma.

Keywords: *Salivary gland (SG) diagnosis, Salivary gland investigations, Advanced methods for diagnosing SG tumors, Radiological investigation of salivary glands, Diagnostic approaches SGTs*

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Introduction

The mouth cavity is primarily moistened by salivary glands, crucial for digestion, defense, lubrication, taste, and buffering. Each salivary gland has a distinct secretion and can be found in large pairs or minor glands. The parotid, submandibular, and sublingual glands are the main salivary glands. The tongue, buccal mucosa, labial mucosa, and palatal surface contain small salivary glands. The submandibular gland appears next, the parotid gland, and the sublingual gland.[1] The architecture of the salivary gland contains three major cell types: acinar cells, ductal cells, and myoepithelial cells. The three significant glands consist of branched ducts that open into the oral cavity and glandular secretory endpiece. The primary role of this cell type is providing control for creating saliva from the acini through the duct system to the oral cavity, in contrast to the myoepithelial cells that wrap around the acini and intercalated ducts. All these major cell types are surrounded by extracellular matrix, immune cells, stromal cells, myofibroblasts, and nerve fibers. Each of the major salivary glands has different proportions of each acinus, affecting the composition of its secretions. The parotid contains serous acini and makes watery serous saliva. The submandibular and sublingual glands contain mucous and serous acini; therefore, they are known as mixed glands. The submandibular gland primarily presents serous acini, with only 10% being mucinous.[2, 3]

In a recent study by Kumari *et al*. (2023), conflicting theories regarding the taxonomy of the nasopharyngeal tubal glands were examined.[4] The presence of submucosal seromucous glands, accompanied by a respiratory epithelium surface lining, was observed near the nasopharyngeal end. It should be noted that although cytoplasmic alpha-SMA positive was expressed in the tubal glands, indicating myoepithelial cell presence, it was comparatively less pronounced than in the seromucous submucosal glands found in the trachea. No evidence of salivary alpha-amylase was detected in the cadaveric tissue samples analyzed during this research. Furthermore,

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A considerably lower amount was found within nasal secretion samples when comparing amylase levels between nasal and oral swab samples. These findings suggest that these nasopharyngeal tubal glands differ significantly from traditional salivary glands. Their morpho-functional similarities to seromucous gland structures located throughout various sections of the respiratory tract and their physical placement adjacent to respiratory epithelium within overlaying mucosa layers support categorizing them as integral components of both auditory tubes and parts comprising overall respiratory functioning.[5]

The most prevalent salivary gland conditions can be subdivided into malignancies and benign tumors.[6] glands can present significant challenges due to their potential similarity in cellular and structural components, making them a highly intricate and diversified subset of head and neck tumors. In contrast, adenoid cystic carcinoma and muco-epidermoid carcinoma are recognized as the most common malignant salivary gland tumors. Tumors affecting the salivary glands are an essential subset of head and neck tumors due to their complex nature and diverse histomorphological features.[7] Due to their histological diversity and complex classification, salivary gland tumors pose significant challenges to clinicians, pathologists, and surgeons.[8, 9]

Salivary biomarkers and Sialochemistry are non-invasive diagnostic tools for monitoring health and disease. Examining biochemical and molecular characteristics can help identify and monitor normal or abnormal processes. Saliva biomarkers for autoimmune illnesses such as Sjogren syndrome, periodontal disease, and neoplastic malignancy are increasingly being identified. [10, 11]

Consequently, our research will focus on the prevalent characteristics of salivary gland diseases and provide cutting-edge tools and methodologies for differentiation and diagnosis. The primary objective of this study is to provide a contemporary overview of the diagnostic procedures currently employed for diagnosing salivary gland diseases.

Materials and Methods

A database search using PubMed, Scopus, Web of Science, Science Direct, and Saudi Digital Library (SDL), was conducted from June 28, 2022, to August 15, 2023, in English. The following keywords were used in the search: *salivary gland (SGs) diagnosis, salivary gland investigations, advanced methods for diagnosing SG tumors, radiological investigation salivary glands, histological investigation salivary glands, and salivary gland biomarkers, diagnostic approaches SGTs.* Inclusion and exclusion criteria were discussed and designed. Case series, case reports, systemic reviews, meta-analysis studies, and any study published before 1980 were excluded. Whereas inclusion criteria involve review studies, case-control studies, cross-sectional studies, and clinical trials written in English. However, all those studies should be published from 2010 to August 15, 2023. Topics to be reviewed are *Clinical Examination, Radiological investigations, Surgical investigations, molecular and genetic testing, saliva analysis, and blood tests.* These topics were distributed among the investigators to search for relevant articles regarding each topic.

The selected articles are written in an Excel sheet by the corresponding investigator. Each article component was applied to the inclusion and exclusion criteria. A total of 142 articles were found from different databases: PubMed (n= 92 articles), SDL (n=44 articles), Web of Science (n= 1 article), ScienceDirect (n=4 articles), Scopus (n= 1 article). The mentioned articles went through the inclusion and exclusion criteria; therefore, the total number of excluded articles is (n= 45), whereas case report articles were (n= 11 articles), case series articles (n=2 articles), articles before 2018(n=9 articles), systematic review or meta-analysis articles (n=16 articles), not related to our research objective (n= 4 articles), and not in English articles (n= 3 articles). The total approved articles (n=97 articles), only 59 articles used to write this narrative review, see **Tables 1 and 2**.

Table 1. Distribution of the number of studies included in the review

Total Articles	Excluded Articles	Selected Articles	Included Articles
142	45	97	60

Table 2. Distribution of the number of studies extracted from databases in the review

Databases	Number
PUBMED	92
SDL	44
SCIENCEDIRECT	4
WEB OF SINCE DIRECT	1
SCOOP	1
Total	**97**

Results and Discussion

Type of Diagnostic Methods used in diagnosis salivary gland disease

Clinical examinations

Clinical symptoms of small slivery glands incorporated into the location can lead to pain or swelling in the paranasal, epistaxis or nasal obstruction in the sinuses, painless swelling or inappropriate tooth fitting in the sinuses, cough, or painful throat. The history of systemic disease and the drugs taken should also be carefully assessed. These gland disorders are often associated with certain systemic diseases such as diabetes, arteriosclerosis, hormone imbalances, and neurological diseases. For example, 60-year-old women with histories of rheumatoid arthritis and other spinal cord diseases have a high probability of being suffocated by

Sjögren syndrome.[12] The main salivary glands are best examined by palpation and inspection of salivary effluent during palpation; this examination step is done in the parotid and submandibular glands.[13]

Extraoral examination

Extraoral inspections involve the following steps

- The patient should stand 1–2 meters away, facing the examiner directly.
- The examiner should inspect symmetry, color, possible pulsation and any discharge of sinuses on both sides of the patient.
- Observe for any major or minor salivary gland enlargement, which may occur on one or both sides.
- Inspect of any preauricular swelling, but it may not be visible if deep in the parotid tail or within the substance of the gland.
- Ask the patient to squeeze the jaws together, which activates the masseter muscle; this step is use to differentiate between the Submandibular swelling, which presents just medial and inferior to the angle of the mandible.

Extraoral palpation

- The patient's head is inclined forward to expose the parotid and submandibular gland regions maximally.
- The examiner may stand in front of or behind the patient.
- Parotid glands are palpated by using fingers placed over the glands in the front of the ears to detect the swelling, for the duct can be done (Stensen duct) is most readily palpated with the jaws clenched firmly.
- A normal parotid gland is barely palpable.
- The submandibular gland is best palpated bimanually with a finger of one hand in the floor of the mouth lingual to the lower molar teeth, and a finger of the other hand placed over the submandibular triangle.
- The submandibular duct (Wharthon duct) runs anteromedially across the floor of the mouth to open at the side of the lingual frenum.
- The submandibular glands, a swelling of the sublingual glands, and the excretory ducts are palpated bimanually (whenever possible with the palmar aspect of the fingertips), noting the size of any abnormalities and assessing their consistency, surface contours, tenderness, and mobility relative to the skin and underlying tissues.
- A normal sublingual gland cannot be palpated. It should be noted that observable
- salivary or lymphatic gland swellings do not rise with swallowing, while swellings associated with the thyroid gland and larynx do elevate.
- The neck should also be carefully examined for lymphadenopathy.

Intraoral examination (Intraoral inspection)

- Identify the asymmetry, discoloration or pulsation, and assessment of the duct orifices and possible obstructions. As well as any looking for ulceration on the buccal mucosa, palate, floor of the mouth this most common type of location the malignant minor salivary glands.

Imaging investigations

Panoramic radiograph

Panorama dental radiography is one of the most commonly utilized pictures in several dental specialties and the most widely applied medical imaging procedures by general practitioners and dental specialists. The quality of the image acquired is critical to its proper interpretation.[14] Conventional radiographs have been used in dentistry and oral maxillofacial to diagnose submandibular sialoliths, oral health, fractures, decaying teeth, and other essential applications.[15] Sialolithiasis is one of the most common prominent obstructive diseases of the main salivary glands, and it is caused by the deposition of calcium salts surrounding organic debris such as mucous substances, ductal epithelial cells, bacteria, or even foreign bodies.[15, 16]

Cone beam computed tomography (CBCT)

Various salivary gland diseases, such as infections, obstructions, immunological disorders, and benign and malignant tumors, can potentially emerge at any stage of life.[17] The use of radiology in diagnosis, treatment, and evaluation has become more critical. With the continuous development of health care, especially dental health, dental X-rays have increased.[18] CBCT is a type of oral radiology that provides us with 3-dimensional, accurate images.[19] The CBCT is short for "cone-beam computed tomography" and was introduced to dental imaging by Piero Mozzo *et al*. in 1998. It has excellent spatial resolution for bones and teeth and is considered a high-contrast structure. It has been noted that using standard techniques such as the orthopantomogram (OPG) or panorama image has been replaced by cone beam computed tomography (CBCT). CBCT has higher accuracy measurements and low radiation doses. However, there are limitations of CBCT, including poor soft-tissue resolution, and dental practitioners need to know how to use the units and the machine to get a quality image. The dentists who use CBCT must have adequate knowledge of head and neck anatomy and how it appears on the screen to recognize normal and abnormal variations.[20, 21] Cone Beam Computed Tomography in diagnosing sialolithiasis has shown promising results. The CBCT image, which provides three-dimensional imaging of the salivary glands, has been found to have certain advantages over other imaging techniques, such as ultrasonography. One of the main advantages of CBCT is its high sensitivity in detecting salivary stones. A recent comparative study found that CBCT detected a higher number of salivary stones than US. This increased sensitivity can be attributed to the ability of CBCT to provide detailed and precise images of the salivary stones in a patient with signs and symptoms of obstructed salivary glands.[22]

Computed tomography (CT) scan

CT scans are often considered the preferred modality for evaluating masses in or around the salivary glands and studying noninflammatory gland enlargement. This approach yields valuable clinical insights directly applicable when determining appropriate treatment strategies. In contrast to traditional sialography, CT scans offer a less invasive alternative as they typically do not require contrast material. Furthermore, CT scans exhibit high sensitivity in identifying a mass's presence, extent, and origin within or outside a salivary gland. They also provide detailed anatomical information that enables precise localization of a mass in the parotid gland. Consequently, this data can be leveraged to make informed assessments regarding its potential impact on facial nerve positioning. Similarly, CT scans can assess the vascularity of tumors and their relationship to adjacent neurovascular structures.[23]

Sialography

Sialography is a radiographic examination in which soluble contrast material is injected into the ducts. It helps in determining the duct anatomy and abnormalities. It is helpful in presurgical planning to remove salivary masses. Sialography cannot be used in patients with iodine sensitivity or acute salivary gland inflammation. Using sialography helps examine the structure of the duct branches. It accurately analyzes the chronic disease pathology of the salivary ducts, such as Sjogren syndrome (SS) and acini. It also helps curative methods using mechanical distal duct dilation and gland irrigation while injecting contrast material.[24] Different minimally invasive surgical intervention techniques are available, for example, Sialoendoscopy, a transmucosal surgical approach, a combined approach, and intra- or extracorporeal stone fragmentation.[25]

Ultrasound imaging

High-frequency sound waves are utilized to produce salivary gland images, facilitating the detection of abnormalities such as cysts, tumors, or inflammation. In the 1970s and early 1980s, ultrasound emerged as a pivotal diagnostic tool in clinical medicine. Given their superficial location and ease of access with US technology, salivary glands garnered significant attention for investigation and treatment. Subsequent research findings sparked widespread interest in ultrasound imaging for diagnosing various disorders affecting the salivary glands, encompassing both inflammatory and obstructive conditions. The current body of literature increasingly supports the utilization of ultrasound as the preferred diagnostic modality for assessing these particular glandular dysfunctions. However, while ultrasound effectively diagnoses central salivary gland pathology with large masses, it is unsuitable for detecting fine parenchymal.[26]

Magnetic resonance imaging (MRI)

Head and neck magnetic resonance imaging (MRI), including functional analyses, is necessary in the presence of a suspected neoplasm to confirm the precise tumor site and its locoregional extent, especially to deep tissues or nerves. MRI also provides valuable information about lymph node and bone involvement and may help determine the lesion's probable nature on diffusion-weighted and dynamic contrast-enhanced sequencesSalivary gland carcinomas (SGCs) represent a rare and heterogeneous group of tumors. Their incidence in the pediatric population does not exceed the significant benefit because it is radiation-free.[27]

Positron emission tomography (PET)

Positron emission tomography (PET) imaging is an essential tool in clinical applications for disease detection because of its ability to obtain functional images that help distinguish between metabolic and biological activity at the molecular level. The sensor technology in the PET detector is a major limiting factor in developing efficient and accurate PET systems. On the other hand, Positron emission tomography (PET/CT) offers a comparatively non-invasive imaging technique that may be used to examine both physiological and pathological processes in the body. With the added advantage of anatomical localization. PET scanning uses radiotracers, which eventually decay by emitting positively charged particles (positrons). These positrons travel a few millimeters in tissue Before joining forces with negatively charged electrons and emitting two high energy (511 keV) photons (gamma rays) released at roughly 180º to each other. The simultaneous detection of these positrons by opposing detectors is then used to construct a three-dimensional image of these events, known as a PET image. While scanning, CT data is also collected, and when paired with PET data, it aids in the localization of these radiotracers. Furthermore, nuclear medicine has a well-defined function in clinical practice because of its use in many medical fields. It offers practical diagnostic alternatives that improve patients' healthcare and quality of life. This section will focus on radiopharmaceuticals for positron emission tomography (PET).[16]

Surgical intervention and molecular diagnosis

Sialendoscopy

Sialendoscopy can be considered safe and effective for diagnosing and treating benign obstructive salivary gland disease, with a helpful place in oral and maxillofacial surgical practice.[28, 29] The technique of sialendoscopy entails using d endoscopes to cannulate and view the interior of salivary ducts and to manage obstructions within these ducts. These endoscopes can be used as diagnostic and interventional tools as they have a hollow working channel that allows the passage of stone baskets, drills, and fiber optic lasers to fragment and remove calculi.[30] Regarding patient satisfaction, MAC and GA are acceptable anesthetic choices in sialendoscopy for appropriate cases. Patients report similar overall satisfaction and post-operative pain tolerance under either anesthetic modality. Patients who undergo GA report higher rates of preference for similar anesthetic modalities in the future. Further study is needed to determine the most appropriate criteria for anesthesia modality selection.[31, 32] Therefore, it can be concluded that sialendoscopy is the diagnostic and therapeutic modality of choice for parotid obstructive sialadenitis.[33, 34]

Fine needle aspiration cytology (FNAC)

Due to its numerous advantages, fine-needle aspiration cytology has become a standard method for assessing salivary gland masses in the preoperative evaluation of head and neck neoplasms. FNAC is a safe and minimally invasive procedure that provides valuable insights, allowing for an accurate diagnosis and appropriate management of these conditions. While FNAC is generally associated with low rates of complications and morbidity, it is essential to be aware of the potential rare instances of adverse effects. Complications such as bleeding, facial nerve damage, and fibrosis have been reported in rare cases, although they occur infrequently. Fine-needle aspiration cytology is highly recommended for assessing salivary gland masses. Its numerous advantages include its safety, minimally invasive nature, and the ability to provide valuable insights for accurate diagnosis and appropriate management.[12, 35, 36]

Surgical biopsy

A biopsy removes tissue from a living patient for macroscopic examination, microscopic analysis, chemical analysis, or a combination of the above.[37] The surgical biopsy will be the definitive diagnostic method for diagnosing salivary gland lesions. It will be considered the second clinical step procedure to roll out any suspected tumor that can be found. Histopathological examinations are the most definitive methods in diagnosing the type, characteristics, and prognosis of a pathologic lesion.[37, 38] The histomorphological examination is the gold standard for classifying slivery lesions. Despite advances in immunohistochemistry and molecular pathology, the WHO still uses histomorphology as the primary basis for classification. However, morphological similarities can make diagnosis difficult without the assistance of ancillary techniques. In this short review, we describe these changes in the latest WHO classification, discuss particular areas of diagnostic difficulty, and suggest some valuable antibodies that can be used to diagnose.[39]

A recent study by Al sanie *et al*. (2022) investigated about the epidemiological data, including demographic, anatomical location and histological diagnoses of SGT from multiple centers across the world.[38] The analysis reports the most considerable multicenter investigation of SGT, showing that the majority are benign (65%), with a slight preference for females (54%). Approximately 69% of SGT occurs in patients between the fourth and seventh decade of life, with a significant difference between the average age for benign and malignant tumors. Pleomorphic adenoma was the most common benign, and mucoepidermoid carcinoma was the most common malignant tumor. The majority of SGT presented in the major glands (68%), with the parotid gland being the most common location (70%) for benign and minor glands (47%) for malignant tumors.

Advanced molecular and biological testing

Antibody Tests Detect the presence of antibodies associated with autoimmune salivary gland diseases like Sjögren's syndrome. Thus, the Proteomic Analysis investigates the protein content of saliva to identify specific markers associated with salivary gland diseases. In addition, Biomarker Detection identifies specific molecules in saliva that can indicate the presence of diseases such as Sjögren's syndrome or oral cancer. PCR (Polymerase Chain Reaction): it's about detecting the presence of specific genetic material, helping diagnose infections, or identifying genetic mutations linked to salivary gland diseases. FISH (Fluorescence in Situ Hybridization): Identifies and locates specific genes or chromosomes through fluorescent labeling, aiding in diagnosing certain tumors.[40, 41]

Biological markers (biomarkers) are descriptors or measures of biological systems. Biomarkers should reflect biological effects caused by a disease/ therapeutic medication. Biomarkers can be presented as the state of the patient's nutritional health and wellness, predicting and diagnosing diseases.[42, 43] Some biomarkers are easily measured, like a patient's blood pressure or heart rate, or less apparent measures like the cell cycle stages, life, or death.[44] Biomarkers are crucial to the balanced development of medical diagnostics and therapeutics.[42, 45]

The biomarkers were found to be a diagnostic tool in the salivary gland, to be used as a supplement with other investigations, especially in cases that have overlap in the final diagnosis; up to this date, there are about 100 types of salivary biological markers currently existing, ranging from non-organic compound biomarkers, protein biomarkers, and DNA-, RNA-, and microRNA-related biomarkers to metabolomics biomarkers and miscellaneous biomarkers. Salivary-based biomarkers gained their importance through evaluating the risk of malignant diseases.[46] A worthy biomarker must be measurable with little to no variability (lack of consistency).[47] Optimal combinations of biomarkers appear essential [48] to contribute to the diagnostic process and improve the prognosis.[49, 50]

Saliva analysis

Saliva is an exocrine secretion composed predominantly of water, accounting for 99% of its content. It also contains diverse electrolytes such as sodium, potassium, calcium, chloride, magnesium, bicarbonate, and phosphate. Furthermore, it harbors proteins encompassing enzymes with catalytic properties that facilitate chemical reactions within the oral cavity. Immunoglobulins and other antimicrobial factors are present in saliva to protect against various pathogens. Additionally, mucosal glycoproteins play a role in maintaining oral health by creating a protective barrier on the surface epithelium. Minor constituents can be detected in saliva's composition, including traces of albumin, polypeptides, and oligopeptides that have significant implications for oral health.[51-53] Using saliva as a diagnostic tool requires careful consideration of various factors. These factors include individual variation in saliva flow and composition, which can be influenced by age, diet, medication, pathologies, and sensory stimulation during food consumption. Saliva analysis offers a potential means of diagnosing various diseases and monitoring treatment outcomes.[3] One of the most promising advancements in oral cancer diagnosis is the use of salivary biomarkers. The specific molecules present in saliva can indicate the presence of early oral squamous cell carcinoma. These biomarkers include mRNA, miRNA, DUSP100, s100P, IL-8, IL-1B, TNF-a, and MMP-9. A screening protocol was developed to evaluate the potential of these salivary biomarkers in diagnosing early OSCC.

Blood screenings

The "blood test" for diagnosing salivary gland disorders is not recommended without a literature review. The blood test is typically requested during the initial investigations to assess markers of inflammation, infection, or autoimmune conditions that may affect the salivary glands. The first study to look into pretreatment differential leukocyte counts and percentages in patients with benign and malignant Salivary Gland Tumors (SGT) was done in a case series analysis on 182 SGT patients treated between January 2010 and May 2015; individuals with malignant SGTs had lower lymphocyte counts and percentages, greater NLRs, and neutrophil percentages than individuals with benign SGTs. The data indicate that the combination of NLR and lymphocyte percentage may be used as a potential inflammatory marker in patients to distinguish low- to high-grade malignant parotid gland. These measurements are affordable and frequently tested in clinics for patients with SGT tumors.[54] A recent study published in June 2023, demonstrated using a nomogram for distinguishing benign and malignant parotid gland tumors. The study used a nomogram with four features: current smoking status, pain/tenderness, peripheral facial paralysis, and lymphocyte-to-monocyte ratio (LMR). It showed that the nomogram based on clinical characteristics and preoperative blood markers was reliable for discriminating BPGTs from MPGTs preoperatively.[55]

Conclusion

A wide range of advanced diagnostic methods are available to detect diseases associated with the salivary glands. We recommended establishing clinical guidelines in patients suffering from salivary gland diseases, either lesions or neoplastic. The Radiological investigations will be the first line if there is no history of neoplastic lesions, and according to the review literature, the ultrasound is an ideal option for initial imaging of major salivary gland disorders, especially when combined with FNA. It produces more accurate results. CT and MRI are better options to determine the degree and nature of the disease, primarily when we investigate SGTs. Positron emission tomography (PET) can be employed in blend with CT or MRI for early detection of any metastasis or secondary tumor of the SGs, followed by Sialography, where the patient has a history of recurrent lesions affecting the gland or neoplastic. The second recommendation is the surgical interventions to obtain histological diagnosis, which is the gold diagnostic for salivary glands by focusing on the IHC that shows accuracy in the final diagnosis. Lastly, a diagnostic biomarker is a new diagnostic method discussed in a study by Freiberger *et al*. 2021, a SalvGlandDx panel used in diagnosing salivary gland neoplasms by a custom Next Generation Sequencing (NGS).[56] It requires a single test, and it's the first to be validated to include all relevant genes to detect specific alternations, mutations, fusion, and gene expression. Finally, using genetic mapping from the Saudi Human Genome Program and these extracted data as early diagnosis, the gene analysis shows the gold diagnostics methods after histologists in diagnosing salivary gland diseases.

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Conflict of interest

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Ethics statement

None.

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