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MODERN METHODS FOR THE INVESTIGATION OF THYROID DISEASES

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Abstract. Objective: To review the main methodologies, datasets, and performance indicators of modern research approaches used in the diagnosis of thyroid diseases.

Materials and Methods: A review of the literature published between 2021 and 2026 was conducted to assess the capabilities of contemporary diagnostic methods for thyroid diseases. In all thyroid disorders, a hormonal panel is performed to determine serum levels of thyroid hormones and thyroid-stimulating hormone (TSH). In thyroiditis, autoimmune markers, including antibodies against thyroid peroxidase (TPO), thyroglobulin (Tg), and TSH receptors (TRAb), are measured. Carcinoembryonic antigen (CEA) serves as a biomarker for medullary thyroid carcinoma and carcinoid tumors. Elevated calcitonin levels are characteristic of medullary thyroid carcinoma. Increased thyroglobulin concentrations are observed in destructive thyroid processes and metastatic disease. Fine-needle aspiration biopsy (FNAB) is performed to obtain histological samples from thyroid nodules. When cytological findings are inconclusive, molecular genetic testing is carried out to identify mutations in genes such as BRAF, RAS, and RET/PTC. In addition, in silico approaches are used to identify target genes comprising 19 microRNAs whose expression profiles vary depending on the type of thyroid tumor. Ultrasonography (US), a non-invasive, relatively inexpensive, and real-time imaging technique, is widely used for the early detection and differential diagnosis of thyroid diseases. Ultrasound-guided fine-needle aspiration biopsy is recommended for deeply located thyroid nodules. Since malignant lesions are generally denser and stiffer than benign ones, ultrasound elastography (elastometry) can determine the nature of thyroid nodules with an accuracy of approximately 95–96%, often reducing the need for biopsy. Doppler ultrasonography is used to evaluate the vascularization of the thyroid gland and its nodules. Thyroid scintigraphy employs radioisotope scanning to assess the functional activity of nodular lesions. In recent years, computer-aided diagnostic systems and high-accuracy neural networks based on ultrasound images have been increasingly applied to improve diagnostic accuracy and significantly reduce the time required for clinical decision-making.

Conclusion: Compared with conventional diagnostic approaches, molecular genetic testing, advanced ultrasonographic techniques, computer-aided diagnostic systems, and high-accuracy neural networks provide superior diagnostic accuracy, sensitivity, and specificity in the investigation of thyroid diseases.

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Keywords: Thyroid Gland, Molecular Genetic Testing, Computer-Aided Diagnosis, Convolutional Neural Networks

ҚАЛҚАНША БЕЗІ АУРУЛАРЫ ЗЕРТТЕУЛЕРІНІҢ ЗАМАНАУИ ӘДІСТЕРІ

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Аңдатпа. Жұмыстың мақсаты: қалқанша безі аурулары кезіндегі заманауи зерттеулердің негізгі әдіснамаларына, деректер жиынтықтарына және өнімділік көрсеткіштеріне шолу жасау.

Материалдар мен тәсілдер: 2021-2026 жылдар аралығында жиналған әдебиеттерден қалқанша безі ауруларының заманауи зерттеулерінің мүмкіншіліктерін қарастыру. Барлық қалқанша безі ауруларында гормоналды панель – қан сарысуындағы тиреоидтық гормондары мен тиреотроптық гормонның (ТТГ) деңгейлері анықталады. Тиреодиттерде аутоиммунды маркерлер – тиреоидтық пероксидазаға, тиреоглобулинге және ТТГ рецепторларына қарсы антиденелер титрлері есептеледі. Қалқанша безінің медуллярлық обыры мен карциноидтық ісіктерінің маркері ретінде карциноэмбрионалды антиген табылады. Медуллярлық обырда кальцитонин деңгейі жоғарылайды. Тиреоглобулин деңгейінің жоғарылауы қалқанша безінің деструктивті үрдістеріңде, метастаздарында болады. Түйінді құрылымның гистологиясын көру үшін қалқанша безінің жіңішке инемен аспирациялық биопсиясы жасалады. Биопсия қорытындысы нақты нәтиже бермеген жағдайларда молекулалық-генетикалық тестілеуде BRAF, RAS, RET/PTC сияқты мутацияланған гендер ізделінеді. Қалқанша безі ісіктерінің түріне байланысты экспрессия деңгейі өзгеретін 19 микроРНҚ-дан тұратын нысаналы гендерді анықтау үшін in silico әдістері қолданылады. Безідің патологияларын ерте анықтау мен ажыратпалы диагностикасы үшін инвазивті емес, салыстырмалы түрде арзан және нақты уақыт режимінде жүргізілетін ультрадыбыстық зерттеуі (УДЗ) кеңінен қолданылады. Қалқанша безінің терең орналасқан түйіндері кезінде УДЗ бақылауымен жіңішке инемен пункциялық биопсия жасалады. Қатерлі ісіктер тығыз және қатты келетіндіктен, биопсия жасамай-ақ түйіннің сипатын 95-96% дәлдікпен анықтауға УДЗ эластографиясы (эластометрия) қолданылады. Бездің және оның ішіндегі түйіндердің қанмен қамтамасыз етілуін (васкуляризациясын) бағалауға допплерография көмек береді. Сцинтиграфия - қалқанша безін радиоизотопты қолдана отырып сканирлеу жасалып, түйінді түзілімдердің қызметтік белсендігін анықтайды. Соңғы жылдары клиникалық жұмыстардың сапасы жақсарту мен диагностикаға кететін уақытты едәуір қысқарту мақсатында ультрадыбыстық кескіндер негізінде қалқанша безі ауруларын анықтау және жіктеу үшін компьютерлік диагностика жүйелер мен жоғары дәлді нейрондық желілер қолданылады.

Қорытынды: қалқанша безі ауруларын зерттеуде дәстүрлі әдістерімен салыстырғанда молекулалық-генетикалық тесттер, заманауи ультрадыбыстық зерттеулер, компьютерлік диагностика жүйелер мен жоғары дәлді нейрондық желілер жоғары дәлдік, сезімталдық және ерекшелік көрсеткіштерін қамтамасыз етеді.

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Түйін сөздер: Қалқанша безі, молекулалық-генетикалық тесттер, компьютерлік диагностика жүйелер, жоғары дәлді нейрондық желілер

СОВРЕМЕННЫЕ МЕТОДЫ ИССЛЕДОВАНИЯ ЗАБОЛЕВАНИЙ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Аннотация. Цель исследования: провести обзор основных методологических подходов, наборов данных и показателей эффективности современных методов исследования заболеваний щитовидной железы.

Материалы и методы: проведён обзор научной литературы, опубликованной в период 2021–2026 гг., посвящённой современным возможностям исследования заболеваний щитовидной железы. При всех заболеваниях щитовидной железы проводится исследование гормонального профиля с определением уровня тиреоидных гормонов и тиреотропного гормона (ТТГ) в сыворотке крови. При тиреоидитах определяют аутоиммунные маркеры — титры антител к тиреоидной пероксидазе, тиреоглобулину и рецепторам ТТГ. Карциноэмбриональный антиген является маркером медуллярного рака щитовидной железы и карциноидных опухолей. Для медуллярного рака характерно повышение уровня кальцитонина. Повышение концентрации тиреоглобулина наблюдается при деструктивных процессах в щитовидной железе и наличии метастазов. Для гистологической оценки узловых образований выполняется тонкоигольная аспирационная биопсия. При неопределённых результатах цитологического исследования проводится молекулярно-генетическое тестирование с выявлением мутаций генов BRAF, RAS и RET/PTC. Кроме того, методы in silico используются для определения генов-мишеней, включающих 19 микроРНК, уровень экспрессии которых изменяется в зависимости от типа опухоли щитовидной железы. Для раннего выявления и дифференциальной диагностики заболеваний щитовидной железы широко применяется ультразвуковое исследование (УЗИ) — неинвазивный, относительно недорогой метод, выполняемый в режиме реального времени. При глубоко расположенных узловых образованиях проводится тонкоигольная пункционная биопсия под контролем УЗИ. Поскольку злокачественные опухоли отличаются большей плотностью и жёсткостью, ультразвуковая эластография (эластометрия) позволяет определить характер узлового образования с точностью 95–96 % без необходимости выполнения биопсии. Допплерография применяется для оценки васкуляризации щитовидной железы и её узлов. Сцинтиграфия основана на радиоизотопном сканировании щитовидной железы и позволяет определить функциональную активность узловых образований. В последние годы для повышения качества клинической диагностики и существенного сокращения времени постановки диагноза всё шире используются системы компьютерной диагностики и высокоточные нейронные сети, основанные на анализе ультразвуковых изображений.

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Заключение: по сравнению с традиционными методами исследования молекулярно-генетическое тестирование, современные ультразвуковые технологии, системы компьютерной диагностики и высокоточные нейронные сети обеспечивают более высокие показатели диагностической точности, чувствительности и специфичности при исследовании заболеваний щитовидной железы.

Ключевые слова: Щитовидная железа, молекулярно-генетические тесты, компьютерные диагностические системы, сверхточные нейронные сети

Indroduction. Thyroid diseases are among the most common disorders of the endocrine system. Hypothyroidism affects approximately 3–5% of the global population, while the prevalence of subclinical hypothyroidism reaches up to 10% in some countries. The worldwide prevalence of hyperthyroidism is estimated to range from 0.5% to 2% [1]. According to an international meta-analysis published in 2022, Hashimoto's thyroiditis is diagnosed in approximately 7.5% of the adult population [2]. Based on the GLOBOCAN 2022 database, more than 820,000 new cases of thyroid cancer are diagnosed worldwide each year [3]. In Kazakhstan, the incidence of thyroid cancer increased from 2.9 cases per 100,000 population in 2013 to 5.5 cases per 100,000 population in 2023 [4,5]. These statistics highlight the importance of early diagnosis and continuous endocrinological surveillance of thyroid diseases.

Therefore, the aim of this study is to review the anatomical and physiological characteristics of the thyroid gland and to provide a comprehensive literature review of the principal methodologies, datasets, and performance indicators used in contemporary research on thyroid diseases.

Material and methods. The literature review was conducted using open-access scientific publications published between 2021 and 2026 and retrieved from the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/), and Google Scholar databases. Relevant studies were selected to collect information on contemporary approaches to thyroid disease research, including hormonal panels, autoimmune biomarkers, molecular genetic testing, ultrasonographic techniques, computer-aided diagnostic systems, and high-accuracy convolutional neural networks. Throughout the literature search and review process, the fundamental principles of research ethics were strictly observed..

Results and Discussion. The thyroid gland is the largest endocrine gland in the human body and is located in the anterior region of the neck. It consists of two lateral lobes connected by a narrow isthmus. The gland weighs approximately 10–20 g. Its normal volume is about 18 mL in women and 25 mL in men. Each lobe measures approximately 2.5–4.0 cm in length, 1.5–2.0 cm in width, and 1.0–1.5 cm in thickness. Anatomically, the thyroid gland is closely related to the trachea, esophagus, recurrent laryngeal nerve, common carotid artery, and internal jugular vein. It is covered by the sternocleidomastoid, sternohyoid, and sternothyroid muscles. The gland receives its blood supply primarily from the superior and inferior thyroid arteries. Thyroid blood flow is approximately 5 mL/g/min under normal physiological conditions. During states of increased thyroid activity, blood flow rises markedly, making the gland palpable on physical examination and producing an audible vascular bruit ("thyroid thrill") on auscultation [6].

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The thyroid gland is composed predominantly of follicles of various sizes. The follicular lumen is filled with colloid and lined by a single layer of cuboidal epithelial cells known as thyroid follicular cells (thyrocytes). During periods of increased functional activity, these cells become columnar, whereas they flatten when thyroid activity decreases. Numerous microvilli project from the apical surface of the follicular cells into the follicular lumen. Thyrocytes synthesize the glycoprotein thyroglobulin, which is secreted into the follicular lumen by exocytosis. Thyroglobulin has a molecular weight of approximately 660 kDa, and iodine constitutes 0.1–1.0% of its molecular mass. Within the follicular lumen, thyroglobulin serves as the precursor for the synthesis of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). In addition to follicular cells, the thyroid contains parafollicular (C) cells, which synthesize and secrete calcitonin.

Iodine is an essential component required for thyroid hormone synthesis. It is obtained from food and water in the form of inorganic iodide (I^-). According to the recommendations of the World Health Organization (WHO), the daily iodine requirement for adults is 150 μg. When iodine intake falls below 50 μg/day, thyroid hormone synthesis decreases, leading initially to goiter formation and, if prolonged, to hypothyroidism.

Thyroid hormone synthesis begins with the iodination of tyrosine residues within thyroglobulin. To facilitate this process, inorganic iodide (I^-) is actively transported across the basolateral membrane of thyroid follicular cells by the sodium/iodide symporter (NIS), a process driven by the Na^+/K^+-ATPase. As a result of this active transport mechanism, the concentration of iodide within the thyroid gland becomes approximately 30–40 times higher than that in the bloodstream.

Thyroid peroxidase (TPO), located on the apical membrane of thyroid follicular cells, catalyzes the oxidation of iodide to its active form. This reaction, together with thyroid hormone synthesis, occurs within the follicular colloid. Following oxidation, TPO catalyzes the iodination of tyrosine residues, resulting in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT contains one iodine atom, whereas DIT contains two. Subsequently, two DIT molecules couple to form tetraiodothyronine (thyroxine, T4), while the coupling of one MIT and one DIT molecule produces triiodothyronine (T3).

After entering the bloodstream, thyroid hormones (T3 and T4) rapidly bind to their carrier proteins. In serum, only approximately 0.04% of thyroxine (T4) circulates in the free form, whereas 70–75% is bound to thyroxine-binding globulin (TBG), 5–10% to transthyretin (prealbumin), and 15–25% to albumin. Approximately 4% of triiodothyronine (T3) remains unbound in the circulation, while 70–75% is bound to TBG and 25–30% to albumin.

Total thyroxine (TT4) and total triiodothyronine (TT3) include both the free and protein-bound fractions of T4 and T3. However, thyroid function should be assessed primarily by measuring free T3 (FT3) and free T4 (FT4), as the concentrations of protein-bound hormones are influenced by various physiological and pathological conditions, as well as by certain medications. In some cases, increased synthesis or enhanced binding affinity of thyroid hormone-binding proteins results in elevated total T3 and T4 concentrations while free hormone levels remain within the normal range. Conversely, reduced synthesis or decreased binding capacity of these proteins may lower total T3 and T4 concentrations despite normal free hormone levels. Therefore, it is

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important to recognize clinical conditions that alter total thyroid hormone concentrations without affecting free hormone levels.

Conditions associated with increased thyroxine-binding globulin (TBG) levels include:

- Hyperestrogenemia (e.g., pregnancy or estrogen therapy);
- Acute infectious hepatitis;
- Hypothyroidism.

Conditions associated with decreased thyroxine-binding globulin (TBG) levels include:

- Androgen therapy;
- Glucocorticoid therapy;
- Malnutrition;
- Nephrotic syndrome;
- Hyperthyroidism;
- Severe systemic illnesses.

The metabolism of thyroid hormones occurs primarily in the liver, kidneys, and other peripheral tissues through the action of deiodinase enzymes. A portion of the released iodine re-enters the extracellular inorganic iodide pool via the bloodstream, while the remainder is taken up again by the thyroid gland for hormone synthesis. The non-iodinated portion of the tyrosine molecule undergoes deamination. Another major metabolic pathway involves the conversion of T4 to T3, followed by conjugation with glucuronic acid in the liver and subsequent excretion in the bile.

Thyroid function is regulated through a negative feedback mechanism. Thyroid-stimulating hormone (TSH), secreted by the anterior pituitary gland, stimulates thyroid function, whereas excessive circulating thyroxine is converted to triiodothyronine (T3) within the pituitary, thereby suppressing the synthesis and secretion of TSH.

TSH is synthesized by thyrotroph cells of the anterior pituitary and is a glycoprotein composed of α- and β-subunits. The α-subunit possesses little biological specificity, whereas the β-subunit is responsible for the biological activity and receptor specificity of TSH. TSH secretion is regulated by thyrotropin-releasing hormone (TRH), which is synthesized in the hypothalamus. TRH is a tripeptide produced primarily by neurons of the paraventricular nucleus and, to a lesser extent, the supraoptic nucleus.

Thyroid follicular cells express specific TSH receptors on their plasma membrane. Binding of TSH to these receptors stimulates virtually all aspects of thyroid function, including the uptake of inorganic iodide, activation of the sodium–potassium ATPase (Na^+/K^+-ATPase), and increased activity of the sodium/iodide symporter (NIS). TSH also promotes the synthesis of thyroglobulin, thyroid peroxidase (TPO), and lysosomal enzymes within follicular cells. Furthermore, it enhances iodide oxidation, iodination of tyrosine residues within thyroglobulin, and the synthesis of the thyroid hormones triiodothyronine (T3) and thyroxine (T4).

TSH stimulates the endocytosis of colloid vesicles containing thyroglobulin, the hydrolysis of thyroglobulin within lysosomes, and the subsequent release of T3 and T4 into the bloodstream. In addition, TSH promotes the deiodination of monoiodotyrosine (MIT) and diiodotyrosine (DIT), facilitating iodine recycling, while also stimulating thyroid growth and proliferation of thyroid follicular cells. In turn, elevated serum concentrations of T3 and T4 suppress the secretion of both TSH and TRH through a classical negative feedback mechanism. The regulation of TSH and TRH

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secretion is primarily mediated by intracellular T3 generated from the deiodination of thyroxine within the pituitary gland and hypothalamus [6].

Thyroid hormones (T3 and T4) exert diverse physiological effects and influence the function of virtually all organs and organ systems. They are essential for normal fetal growth and development, particularly for maturation of the central nervous system. In addition, thyroid hormones play critical roles in regulating the cardiovascular, respiratory, gastrointestinal, endocrine, hematopoietic, and skeletal muscular systems.

The prevalence of thyroid diseases continues to increase worldwide, and these disorders have profound effects on endocrine and metabolic homeostasis.

In recent years, substantial improvements in healthcare services have led to significant advances in laboratory diagnostics of thyroid function. Modern diagnostic technologies are highly accurate, non-invasive, and safe for patients. Contemporary diagnostic approaches enable comprehensive assessment of thyroid morphology, characterization of thyroid nodules, and evaluation of hormonal activity at the molecular level. Moreover, artificial intelligence (AI)-based technologies have significantly enhanced the accuracy of differential diagnosis.

Current diagnostic methods for thyroid diseases can be broadly classified into hormonal and immunological assays, morphological and molecular genetic investigations, as well as instrumental and imaging diagnostic techniques.

I. Hormonal and Immunological Methods

1. Hormonal panel. The hormonal panel includes the measurement of serum thyroid hormones and thyroid-stimulating hormone (TSH) concentrations (Table 1). Before interpreting the laboratory results, it is important to consider that thyroid hormone levels may be influenced by various physiological conditions, pathological states, and medications. Therefore, these factors should always be taken into account to ensure accurate assessment of thyroid function.

Table 1. **Normal Serum Concentrations of Free and Protein-Bound Thyroid Hormones (T3 and T4) and Thyroid-Stimulating Hormone (TSH)**

Hormone	**Value**	
	Free	**Total**
Triiodothyronine (T3)	3,0-8,0 pmol/l (0,2-0,52 pg/ml)	70-132 nmol/l (1,1-2,0 ng/ml)
Thyroxine (T4)	9,0-24,0 pmol/l (0,7-1,9 pg/ml)	64-154,4 nmol/l (5,0-12,0 ng/ml)
Thyroid-Stimulating Hormone (TSH)	0,5-5,0 mIU/L	

In most patients, the use of certain medications may falsely alter thyroid-stimulating hormone (TSH) levels. A list of these medications and their effects is presented in Table 2.

Table 2. **Medications Affecting TSH Levels**

Increase TSH Secretion	**Suppress TSH Secretion**
Dopamine antagonists:	Dopamine agonists:
• Metoclopramide	• L-Dopa
• Chlorpromazine	• Bromocriptine (Parlodel)
• Sulpiride	• Lisuride

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• Haloperidol	• Apomorphine
Clomiphene	Serotonin antagonists:
	• Metergoline
Lithium preparations	Somatostatin (Octreotide)
Carbamazepine	Morphine and its derivatives
Theophylline	Glucocorticoids
	Heparin

During pregnancy, circulating thyroxine-binding globulin (TBG) levels increase in response to elevated estrogen concentrations. As a result, free T4 (FT4) initially decreases, leading to a compensatory increase in thyroid-stimulating hormone (TSH) secretion. Subsequently, a new physiological equilibrium is established. Consequently, total T4 levels increase, whereas free T4 and TSH levels remain within the normal reference range. This highlights the importance of measuring only the free fraction of thyroid hormones during pregnancy.

During the first trimester, the production of human chorionic gonadotropin (hCG) increases markedly. At high concentrations, hCG may exert TSH-like stimulatory effects on the thyroid gland because the two hormones share structural similarities. Consequently, approximately 18–20% of healthy pregnant women have TSH levels below the normal reference range. During the second and third trimesters, TSH levels usually return to the normal range [7] .

2. Autoimmune markers (antithyroid antibodies) are essential diagnostic tests for autoimmune thyroiditis. Under normal conditions, antibody titers are:

- Anti-thyroid peroxidase antibodies (Anti-TPO): <1.0 IU/mL
- Anti-thyroglobulin antibodies (Anti-Tg): <1.0 IU/mL

TSH receptor antibodies (TRAb) are autoantibodies directed against receptors that regulate thyroid function. Two types of TRAb have been identified:

- Stimulating antibodies, which increase thyroid hormone production and are elevated in Graves' disease.
- Blocking antibodies, which inhibit thyroid hormone production and are associated with hypothyroidism .

Reference values may vary depending on the assay used. For the diagnosis of autoimmune thyroiditis, simultaneous measurement of Anti-Tg and Anti-TPO antibodies is recommended [8].

3. Tumor markers. Carcinoembryonic antigen (CEA) is used as a tumor marker for medullary thyroid carcinoma as well as other neuroendocrine (carcinoid) tumors.

4. Calcitonin measurement. Serum calcitonin is determined at baseline and again 2.5 minutes after intravenous administration of pentagastrin (0.5 μg/kg). Under normal conditions, serum calcitonin concentrations do not exceed 0.5 ng/mL and remain unchanged following pentagastrin stimulation. In medullary thyroid carcinoma, both elevated basal calcitonin levels and a marked increase after pentagastrin administration are observed.

5. Thyroglobulin (Tg). The normal serum thyroglobulin concentration is <40 ng/mL (40 μg/L). Elevated Tg levels are observed in destructive thyroid disorders, including subacute thyroiditis and silent thyroiditis, and may also occur in hyperthyroidism. In patients with papillary or follicular thyroid carcinoma, serum thyroglobulin measurement after total thyroidectomy is used to detect functioning metastatic disease. A serum thyroglobulin concentration >10 μg/L (10 ng/mL) is considered suggestive of metastatic disease.

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II. Morphological and Molecular Genetic Methods

1. Fine-Needle Aspiration Biopsy (FNAB) of the Thyroid Gland. Fine-needle aspiration biopsy (FNAB) is primarily used to evaluate the nature of a thyroid nodule (e.g., to differentiate between a malignant tumor and a cyst). In selected cases, it may also be performed to diagnose autoimmune thyroiditis. Under ultrasound guidance, cells are aspirated from the suspicious nodule and examined microscopically. FNAB remains the only histopathological method capable of definitively confirming thyroid malignancy.

2. Molecular Genetic Testing. Molecular genetic testing is indicated when FNAB cytology yields indeterminate or inconclusive results. In such cases, analysis is performed to detect mutations in genes such as BRAF (B-Raf proto-oncogene), RAS (membrane-associated G proteins), and RET/PTC (chromosomal rearrangements). The development of thyroid cancer is associated with genetic alterations in genes encoding cellular signaling pathways, resulting in disruption of the balance between cell proliferation and apoptosis. Certain mutations are associated with more aggressive tumor behavior, lymph node metastasis, tumor dedifferentiation, and/or reduced responsiveness to radioactive iodine therapy.

The principal genetic alterations implicated in thyroid carcinoma include:

Point mutations: BRAF, RAS, TERT, RET, and TP53.

Gene fusions/rearrangements: RET/PTC, PAX8/PPAR-γ, and NTRK [9–12] .

Therefore, molecular genetic analysis of cytological material obtained by preoperative FNAB or thyroid tissue collected after surgery has become widely used in clinical practice.

In recent years, in silico approaches have been employed to identify target genes associated with 19 microRNAs whose expression profiles differ according to the histological subtype of thyroid tumors [13] . Based on published studies, nine target genes have been identified as promising biomarkers: MCM2, RASSF2, SPAG9, SSTR2, TP53BP1, INPP4B, CCDC80, GNAS, PLK1.

Additionally, six novel potential biomarkers capable of distinguishing follicular thyroid carcinoma from follicular adenoma have been identified: CDK4, FGFR1, ERBB3, EGR1, MYLK, SRC [14].

The RET proto-oncogene is recognized as a genetic marker for Multiple Endocrine Neoplasia type 2 (MEN2) syndrome and familial medullary thyroid carcinoma.

3. HLA Typing. At present, HLA typing is not routinely used in the clinical diagnosis of thyroid diseases. However, certain HLA alleles are associated with specific thyroid disorders: HLA-B8 and HLA-DR3 are associated with diffuse toxic goiter (Graves' disease) and the atrophic form of autoimmune thyroiditis. HLA-DR5 is associated with the hypertrophic form of autoimmune thyroiditis (Hashimoto's thyroiditis). HLA-Bw35 is considered a genetic marker of subacute thyroiditis (de Quervain thyroiditis), and its presence increases the likelihood of developing this disease by approximately 30-fold.

III. Modern Instrumental and Imaging Diagnostics

1. Thyroid Ultrasonography (Ultrasound, US). Thyroid ultrasonography (US) is a non-invasive, relatively inexpensive, and real-time imaging modality that is widely used for the early detection and characterization of thyroid disorders. The examination allows assessment of the size and volume of the thyroid gland and facilitates the detection of thyroid nodules and cystic lesions.

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For non-palpable or deeply located thyroid nodules, ultrasound-guided fine-needle aspiration biopsy (US-guided FNAB) can be performed to obtain cytological specimens for diagnostic evaluation. Table 3 summarizes the ultrasonographic features of various thyroid diseases.

Table 3. **Ultrasonographic Characteristics of Various Thyroid Diseases**

Disease	**Ultrasonographic Findings**
Toxic adenoma, euthyroid nodular goiter	Hyperechoic nodule with a hypoechoic halo, or hypoechoic nodule; cystic degeneration is common.
Multifocal autonomous thyroid disease	Multiple hyperechoic nodules (their margins are not always well defined), often accompanied by cystic changes; hyperechoic structures are frequently observed.
Diffuse toxic goiter (Graves' disease), autoimmune thyroiditis	Diffuse hypoechogenicity of the thyroid parenchyma.
Subacute thyroiditis	Poorly demarcated hypoechoic areas; diffuse hypoechogenicity is less common.
Malignant tumors (thyroid carcinoma)	Hypoechoic lesions with heterogeneous echotexture and irregular nodules or focal areas.
True thyroid cyst	Anechoic lesion with a regular shape, smooth thin wall, and homogeneous fluid content.
Focal cystic degeneration of nodules	Nodules containing hypoechoic areas with no detectable blood flow on color Doppler ultrasonography.
Colloid nodules	Encapsulated lesions with variable echogenicity.
Thyroid adenomas	Well-defined, round lesions. Echogenicity is usually reduced. Color Doppler imaging typically demonstrates marked peripheral vascularization.
Adenocarcinoma	Poorly defined margins, dense solid lesion with low echogenicity; microcalcifications may be present; capsule is absent.

2. Ultrasound Elastography (Elastometry). Ultrasound elastography (elastometry) is one of the most recent and effective advances in thyroid ultrasonography. Using a specialized transducer, it measures the stiffness and elasticity of thyroid nodules. Because malignant tumors are typically denser and stiffer than benign lesions, elastography can differentiate benign from malignant nodules with an accuracy of 95–96%, thereby reducing the need for unnecessary fine-needle aspiration biopsies.

3. Color Doppler Ultrasonography. Color Doppler ultrasonography is performed during conventional ultrasound examination to assess the vascularity (blood supply) of the thyroid gland

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and its nodules. Chaotic intranodular vascularization is considered a sonographic feature suggestive of an increased risk of malignancy.

4. Thyroid Scintigraphy. Thyroid scintigraphy involves radionuclide imaging of the thyroid gland using radioactive iodine (^125I or ^131I) or technetium-99m sestamibi (99mTc-MIBI).

The procedure is used to evaluate the functional activity of thyroid nodules, classifying them as "hot," "warm," or "cold" nodules. It is particularly useful for diagnosing toxic thyroid adenoma, characterized by a hyperfunctioning autonomous ("hot") nodule with suppression of the remaining thyroid tissue.

Normal Radioactive Iodine Uptake (RAIU) Values

Normal thyroid uptake of ^125I/^131I is approximately:

- 12–20% at 2 hours
- 30% at 4 hours
- 40% at 6 hours

Conditions Associated with Increased Radioactive Iodine Uptake

- Graves' disease
- Toxic multinodular goiter
- Toxic thyroid adenoma
- TSH-dependent thyrotoxicosis

Conditions Associated with Decreased Radioactive Iodine Uptake

- Subacute thyroiditis
- Painless ("silent") thyroiditis
- Factitious (iatrogenic) thyrotoxicosis
- Hypothyroidism

Radioactive iodine uptake varies according to the body's iodine status. Reduced uptake may occur following: excessive dietary iodine intake (including iodized foods and drinking water), treatment with inorganic iodine, administration of iodinated contrast agents, treatment with amiodarone, or other iodine-containing medications [15].

Because radionuclides have short half-lives and the procedure is relatively expensive, thyroid scintigraphy is performed only for selected clinical indications.

Current Indications for Thyroid Scintigraphy

Thyroid scintigraphy is currently recommended for the following indications:

- To differentiate thyrotoxicosis associated with nodular thyroid disease (solitary nodular, multinodular, or mixed goiter), functionally autonomous thyroid nodules (toxic adenomas), and diffuse toxic goiter (Graves' disease).
- To exclude compensated (subclinical) thyroid autonomy in individuals over 45 years of age with palpable thyroid nodules and/or nodules ≥1 cm in diameter.
- Evaluation of a cervical mass suspicious for thyroid malignancy.
- Identification of retrosternal (substernal) thyroid tissue when palpation and ultrasonography are inconclusive.
- Assessment of the effectiveness of thyroidectomy performed for thyroid carcinoma, including postoperative evaluation for residual or recurrent disease.

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The clinical significance of thyroid scintigraphy using technetium-99m sestamibi ([99mTc]Tc-sestamibi, MIBI) has been variable and has somewhat declined with the rapid advancement of thyroid ultrasonography, cytological examination, molecular diagnostics, and positron emission tomography/computed tomography (PET/CT) using ^18F-fluorodeoxyglucose (^18F-FDG). However, recent studies suggest that 99mTc-sestamibi (MIBI) scintigraphy is regaining clinical importance in selected situations, particularly for the evaluation of thyroid nodules with indeterminate cytology and the diagnosis of iodine-induced thyroid dysfunction [16].

5. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT). Magnetic resonance imaging (MRI) and computed tomography (CT) are valuable imaging modalities for identifying ectopic or atypically located thyroid tissue (e.g., retrosternal or posteriorly displaced thyroid gland), detecting atypically located thyroid nodules, and determining their size and the presence of enlarged cervical lymph nodes. These techniques also facilitate the evaluation of tracheal compression caused by large goiters, local tumor invasion, the extent of thyroid carcinoma, and regional or mediastinal lymph node metastases.

At present, ultrasonography (US) is considered the primary imaging modality for the evaluation of thyroid nodules because it is safe, widely available, and cost-effective. Nevertheless, interpretation of ultrasound findings remains highly dependent on the experience and expertise of the examiner, which may result in interobserver variability and occasionally limited diagnostic accuracy.

In recent years, artificial intelligence (AI) has fundamentally transformed medical image analysis by enabling automated feature extraction, lesion classification, and clinical decision support. The application of AI—particularly machine learning (ML) and deep learning (DL) algorithms - to thyroid disease diagnosis has substantially improved diagnostic performance [17,18].

AI-based approaches provide high diagnostic accuracy, reduced interobserver variability, and more consistent clinical decision-making across diverse clinical settings. Accurate diagnosis is essential not only for identifying the specific type of thyroid disease but also for selecting the most appropriate individualized treatment strategy. Early diagnosis and timely intervention improve clinical outcomes and significantly enhance patients' quality of life.

Machine learning algorithms play an important role in the characterization of thyroid lesions, particularly in the classification of benign and malignant thyroid nodules detected by ultrasonography. Early machine learning methods - including Support Vector Machines (SVMs), k-Nearest Neighbors (k-NN), and Decision Trees - were combined with manually engineered image features such as gray-level co-occurrence matrix (GLCM) texture descriptors, wavelet transforms, and histogram-based features, yielding satisfactory diagnostic performance.

The introduction of deep learning, particularly Convolutional Neural Networks (CNNs), has significantly improved diagnostic accuracy, sensitivity, and specificity in numerous studies. By automatically learning hierarchical image features directly from data, CNN-based models outperform traditional handcrafted feature-based approaches and frequently achieve diagnostic accuracies exceeding 95%.

Furthermore, hybrid and ensemble models that combine CNN architectures with conventional classifiers (e.g., Random Forest or SVM) or incorporate attention mechanisms have

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demonstrated further improvements in model robustness, interpretability, and diagnostic performance [19–21].

Despite ongoing challenges related to dataset heterogeneity, generalizability, and model interpretability, machine learning–based diagnostic systems are increasingly regarded as scalable, non-invasive, and reproducible clinical decision-support tools that assist clinicians in the early and accurate diagnosis of thyroid diseases.

Conclusion. Compared with conventional diagnostic approaches, molecular genetic testing, advanced ultrasonographic techniques, computer-aided diagnostic systems, and high-performance neural network–based artificial intelligence models have demonstrated superior diagnostic performance in the evaluation of thyroid diseases, particularly thyroid nodules. These modern approaches provide higher diagnostic accuracy, sensitivity, and specificity, resulting in more reliable disease detection, improved diagnostic confidence, and better support for clinical decision-making.

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