European Journal of Endocrinology, 2025, **193**, ii117–ii127
https://doi.org/10.1093/ejendo/lvaf010

Review Article

EndoCompass project: research roadmap for thyroid endocrinology

Agnieszka Piekiełko-Witkowska,[1] Rossella Elisei,[2,*] Juliane Leger,[3] Běla Bendlová,[4] Barbora Bulanová Pekova,[4] Philippe Caron,[5] Cosimo Durante,[6] Martin Fassnacht,[7,8] Ulla Feldt-Rasmussen,[9,10] Helena Filipsson Nyström,[11,12,13] Heleen Jansen,[14] Josef Köhrle,[15] Aleksander Kuś,[16] Marian Ludgate,[17] Jonathan Mertens,[18] Małgorzata Oczko-Wojciechowska,[19] Catherine Peters,[20] Nadia Schoenmakers,[21] Athanasia Stoupa,[22] Hanneke van Santen,[23] Pierpaolo Trimboli,[24,25] Paul van Trotsenburg,[26,27] and W. Edward Visser[28]

[1]Department of Biochemistry and Molecular Biology, Centre of Postgraduate Medical Education, Centre of Translational Research, ul. Marymoncka 99/103, 01-818 Warsaw, Poland
[2]Unit of Endocrinology, Department of Clinical and Experimental Medicine, Pisa University Hospital, 56124 Pisa, Italy
[3]AP-HP, Nord Université Paris Cité, Service d'Endocrinologie et Diabétologie Pédiatrique, Centre de Référence Maladies Endocriniennes Rares de la Croissance et du Développement, Inserm U1141 NeuroDiderot, Hôpital Universitaire Robert-Debré, Paris 75019, France
[4]Department of Molecular Endocrinology, Institute of Endocrinology, Národní 8, 110 00 Praha 1, Czech Republic
[5]Department of Endocrinology, Metabolic Diseases and Nutrition, Cardiovascular and Metabolic Unit, Larrey University Hospital, 24 Chemin de Pouvourville, TSA 30030, 31059 Toulouse, France
[6]Department of Translational and Precision Medicine, Sapienza University of Rome, 00161 Rome, Italy
[7]Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany
[8]Comprehensive Cancer Center Mainfranken, University of Würzburg, Würzburg, Germany
[9]Department of Endocrinology and Metabolism, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[10]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[11]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[12]Wallenberg's Centre of Molecular and Translational Medicine, Region Västra Götaland, Sweden
[13]Department of Endocrinology, Sahlgrenska University Hospital, Gothenburg, Sweden
[14]Endocrine Laboratory, Department of Laboratory Medicine, Amsterdam UMC location Vrije Universiteit Amsterdam and University of Amsterdam, Amsterdam Gastroenterology, Endocrinology and Metabolism, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
[15]Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institut für Experimentelle Endokrinologie, Berlin, Germany
[16]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, 02-097 Warsaw, Poland
[17]School of Medicine, Cardiff University, Cardiff CF14 4XN, UK
[18]Laboratory of Experimental Medicine and Paediatrics, Universiteit Antwerpen, Antwerp, Flanders, Belgium
[19]Department of Clinical and Molecular Genetics, Maria Skłodowska-Curie National Research Institute of Oncology Gliwice Branch, 44-102 Gliwice, Poland
[20]Department of Paediatric Endocrinology, Great Ormond Street Hospital for Children, London, UK
[21]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK
[22]Pediatric Endocrinology, Gynecology and Diabetology Department, Hôpital Universitaire Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Paris, France; Cochin Institute, Paris, and IMAGINE Institute affiliate, Paris, Université Paris Cité, France
[23]Department of Pediatric Endocrinology and Supportive Care, Wilhelmina Children's Hospital and Princess Máxima Center, 3508 AB Utrecht, The Netherlands
[24]Clinic for Endocrinology and Diabetology, Lugano Regional Hospital, Ente Ospedaliero Cantonale, 6500 Bellinzona, Switzerland
[25]Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), 6900 Luganoo, Switzerland
[26]Amsterdam Gastroenterology Endocrinology and Metabolism Research Institute, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
[27]Department of Pediatric Endocrinology, Emma Children's Hospital, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
[28]Department of Internal Medicine, Erasmus MC Academic Center for Thyroid Diseases, 3015 GE Rotterdam, The Netherlands

*Corresponding author: Unit of Endocrinology, Department of Clinical and Experimental Medicine, Pisa University Hospital, 56124 Pisa, Italy.
Email: rossella.elisei@med.unipi.it

Received: January 19, 2025. **Editorial Decision:** January 22, 2025. **Accepted:** May 9, 2025

Abstract

Background: Endocrine science remains underrepresented in European Union research programs despite the fundamental role of hormone health in human well-being. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At national funding level, endocrine societies report limited or little attention of national research funding toward endocrinology. The EndoCompass project—a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges.

Methods: Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014-2020). Expert consultation in thyroid endocrinology was conducted to identify key research priorities, followed by broader stakeholder engagement including society members and patient advocacy groups.

Results: For thyroid disorders, research priorities encompass neoplastic and nonneoplastic conditions, focusing on disease mechanisms, improved diagnostics and treatments, and the impact of environmental and metabolic factors. Key areas include personalized medicine approaches, artificial intelligence applications, and the establishment of pan-European registries to advance understanding of rare thyroid conditions.

Conclusions: The thyroid component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into thyroid disease pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of thyroid disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact in endocrine health.

Keywords: thyroid, thyroid cancer, medullary thyroid cancer, autoimmune thyroid disease, Hashimoto's thyroiditis, Graves' disease, subclinical thyroid disease, congenital hypothyroidism, microbiome, endocrine-disrupting chemicals

Introduction

The thyroid is a bilobed gland located in close proximity to the trachea. The endocrine function of the thyroid depends on the follicular cells (the thyrocytes) and the parafollicular cells (C cells).

The thyrocytes are polarized cells that form follicles surrounding a colloid niche. These highly specialized follicular units enable biosynthesis and monocarboxylate transporter 8 (MCT8)–mediated export of thyroid hormones (THs): 3,5,3′ 5′-tetraiodothyronine (thyroxine, T4) and 3,5,3′-tri-iodothyronine (T3).[1] In the circulation, THs are rapidly bound by plasma proteins, so <0.5% of THs circulate in a free form (FT4, FT3). While 100% of T4 is synthesized in the thyroid, most T3 (80%) is generated in extrathyroidal tissues, due to the activity of iodothyronine deiodinases that catalyze T4 deiodination. Thyroid hormones enter and leave target cells through plasma membrane transporters (eg, MCT8). Due to deiodinases and plasma membrane transporters, intracellular TH concentrations can be independent of their serum/plasma levels.[2]

Parafollicular C cells are distributed throughout the thyroid. They synthesize and secrete calcitonin, thereby regulating calcium homeostasis.

Thyroid hormones affect all human tissues, regulating key developmental and metabolic processes. Both TH excess (hyperthyroidism) and deficiency (hypothyroidism) may adversely affect quality of life (QoL), as well as causing significant pediatric and adult morbidities, including marked fetal and childhood developmental impairment (predominantly hypothyroidism), and severe adult and childhood cardiovascular, ophthalmological, and metabolic dysfunction. A successful pan-European implementation of neonatal screening for congenital hypothyroidism has prevented severe motor and intellectual disabilities in many children in recent decades.

Thyroid diseases affect 200 million patients worldwide.[3] They pose a heavy burden on patients, their families, societies, health systems, and EU economies. Hence, development of efficient diagnostic and therapeutic strategies for thyroid dysfunction is crucial for European public health.

Thyroid neoplastic disorders

Epidemiology, societal impact, and research state of the art

Palpable nodules affect ~5% of the population, while up to 68% of patients have nodules detectable by ultrasound techniques. The Thyroid Imaging Reporting and Data System™ based on ultrasound imaging and Bethesda cytological microscopy examination scores support therapeutic decisions.[4] Although most nodules are benign and have a favorable prognosis, both approaches are insufficient to identify aggressive tumors leading to clinically persistent/metastatic disease. In this regard, the use of molecular markers is coming to the fore in preoperative diagnosis.

Thyroid cancer (TC) affects both sexes. It is the fifth most commonly diagnosed cancer in women worldwide and the second most common in women older than 50 years. The incidence of TC, including early onset TC, is rising. Although this may be due to increased use of better imaging techniques[5,6] (eg, ultrasound), other factors may be involved, including obesity or microbiota changes.[7,8] Furthermore, the growing environmental burden and polluting factors (EDC, nitrate, fine particulate matter [PM], and other toxicants) may also contribute to increased TC incidence.[9–11] Finally, studies suggest that frequent dental X-ray examinations may possibly increase the risk of TC.[12–15] The exact impact of all these factors to the increasing TC incidence requires careful clinical and experimental evaluation. In 2020, TC incidence rates were 10.1/100 000 women and 3.1/100 000 men, with mortality at 0.5/100 000 women and 0.3/100 000 men, reaching >87 000 diagnoses in Europe.[5]

Differentiated thyroid carcinoma (DTC), the most common type of TC, includes papillary thyroid carcinoma, follicular thyroid carcinoma, and rare oncocytic carcinoma of the thyroid (OCA). The other, rare types of TC include anaplastic thyroid carcinoma (ATC) and medullary thyroid carcinoma (MTC), the last representing a biologically distinct TC type originating from the C cells, with features closer to neuroendocrine tumors[16] and with hereditary inheritance in about 25% of cases. At the time of diagnosis, 10%-20% of patients with MTC and >40% of patients with ATC have distant metastatic disease. In almost 40% of these patients, metastases emerge during follow-up.[17,18]

In children, TC is a rare disease. However, the incidence of, mainly papillary, pediatric TC is rising.[19] There are some major differences between adult and pediatric differentiated TC regarding clinical, molecular, and pathological characteristics. Compared with adults, pediatric patients present more often with advanced disease at diagnosis, with more frequent lymph node involvement, distant metastasis, and multifocal disease.[20]

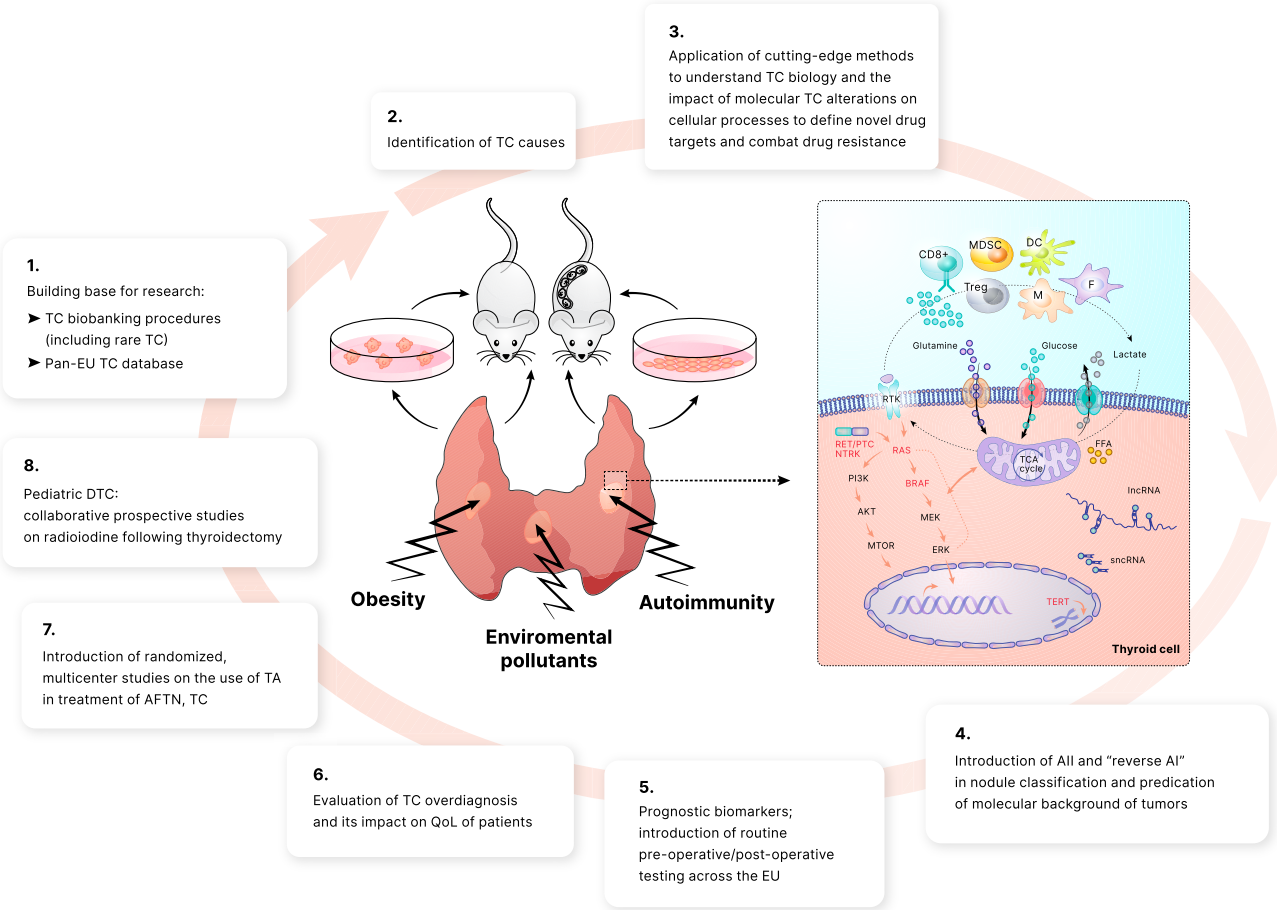

Figure 1. Unmeet needs in thyroid cancer research: suggestions for possible future research that should lead to clinical application (please see text for details).

Interestingly, despite presentation at a more advanced stage, pediatric DTC has an excellent prognosis.

Thyroid carcinomas are driven by various genetic changes, knowledge of which benefits the preoperative and postoperative diagnosis and prognosis of the disease. In adults, the most common pathogenic gene variants in TC are *BRAF*, *RAS*, and *RET* mutations that affect MAPK and PI3K/mTOR/Akt signaling pathways. The rare (~10%) coexistence of *BRAF* V600E mutation and *TERT* promoter variants defines a very small, high-risk patient group.[21]

The knowledge of the molecular background of TC facilitated introduction of tyrosine kinase inhibitors. Although great progress has been made recently in the development of targeted tyrosine kinase inhibitors, new therapies for specific genetic changes still need to be introduced. In pediatric DTC, the most common genetic alterations are *RET/PTC* and *NTRK* fusions.[22,23] Alterations of epigenetic modifications, including DNA hypermethylation, microRNAs, and long noncoding RNAs, play crucial roles in malignant transformation and have already provided therapeutic and diagnostic opportunities in other cancers.[24–26] However, their role in TC is largely underexplored.

The apparent and widespread overdiagnosis of TC places a heavy burden on patients' QoL by exposing them to unnecessary diagnostics and/or treatments. It also increases the financial costs of healthcare systems, thereby limiting the resources that are necessary for patients who indeed are affected by malignant disease.

Future research priorities

The key future research areas in thyroid neoplasms include the following (Figure 1):

- Identification of the causes of TC, in particular the causes of the increasing incidence of TC.
- Development of personalized medicine–oriented strategies regarding (1) malignant nodules, (2) aggressive tumors or metastatic disease, and (3) novel treatment options and combatting drug resistance.
- In patients with chronic forms of TC (eg, metastatic MTC), development of web-based patient decision aids, providing tailored support over time and addressing specific needs, QoL, realistic expectations, and impact on patient's partner and family.
- Developing multidisciplinary expert programs for transition of care from childhood to adulthood in patients with hereditary forms of TC.

Specific aims, to achieve these goals, include the following.

Building the base for research

1. Establishing biobanking procedures for TC and normal thyroid tissues (including liquid biopsies): it is important

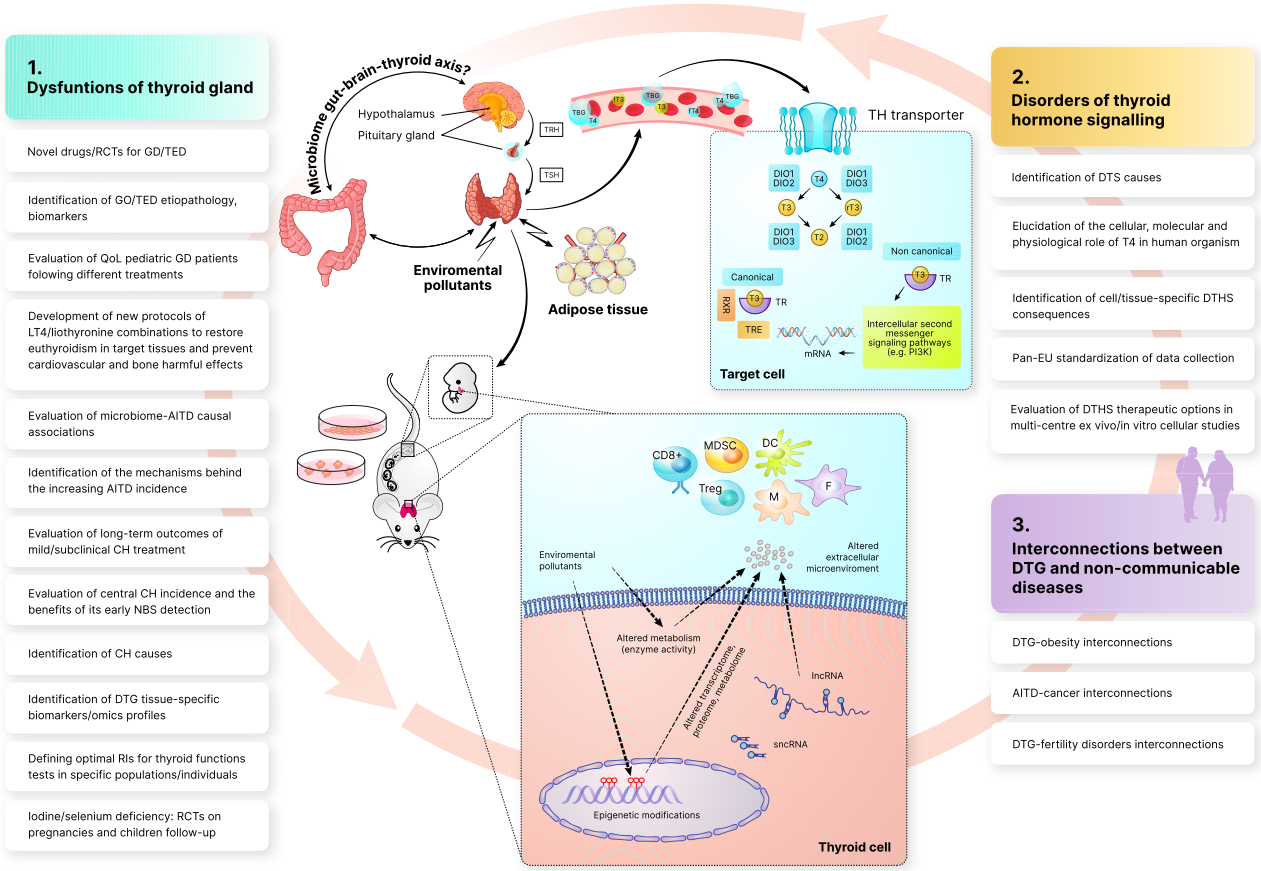

Figure 2. Unmeet needs in thyroid benign disease research: suggestions for possible future research that should lead to clinical application (see text for details). Part of the figure was adapted from Jansen et al.[27]

to focus strongly on rare types of TC and metastatic nodes and tumors.

2. Creation of a pan-European database (involving adult and pediatric cohorts) comprehensively describing individual TC tissue phenotypes, including clinical data and detailed molecular characterization using omics methods.

Identifying causes of increased TC incidence

Knowledge of the key gene mutations that drive carcinogenic processes in the thyroid does not give information about the ultimate causes of these molecular alterations (apart from the small subgroup of TCs directly caused by radiation exposure or genetic predisposition to hereditary TC). The incidence of TC is growing, while the reasons for this increase are unknown. Some debatable causes include obesity, microbiota changes, lifestyle, environmental factors, endocrine-disrupting chemicals (EDCs), or chemicals with mechanisms of action different from EDCs. However, detailed studies are needed to identify the exact triggers of carcinogenic processes in the thyroid. Functional studies involving in vitro/ex vivo/in vivo models and large-scale omics technologies are needed to verify the following.

Autoimmunity. The previously suggested causative associations between autoimmune thyroid disease (AITD) and increased risk of TC and other cancers[28–30] should be evaluated by large-scale clinical trials combined with molecular analyses.

Obesity. The role of obesity/fat tissue in TC development and progression should be examined, including the role of immunomodulatory and proinflammatory functions of fat tissue.

Environmental pollution. The role of environmental polluting factors should be also explored, including dose-dependent studies using TC models of in vitro, ex vivo, in utero, and in vivo exposures, with special focus on epigenetic modifications as mediators of environmental pollution effects.

Applying cutting-edge methods to understand TC biology

Single-cell/spatial omics, long-read Seq, and large-scale epigenetics methods should be involved to analyze TC, particularly in aggressive and rare types of TC (ATC, MTC, OCA). This requires establishment of a pan-European multicenter expert group for molecular characterization of rare TC using multiomics methods. The project should combine biobanking, wet lab, and bioinformatic analysis including artificial intelligence (AI), which should be validated in various European centers. The studies should be aimed at delineation of the impact of molecular TC alterations on cellular processes. In particular, the research should be targeted toward signaling pathways, metabolic alterations, noncoding RNAs (including

small and long noncoding RNAs), cancer immunology, and microenvironment, using experimental in vitro/ex vivo/in vivo models to define novel drug targets and combat drug resistance.

Applying AI

1. Use of AI in nodule classification/diagnosis should reduce unnecessary fine-needle aspiration biopsy and facilitate TC diagnosis.
2. "Reverse AI"-based analysis of the imaging data to predict tumor molecular background based on image features should facilitate cost-effective decisions about the appropriate treatment.

Identifying new prognostic biomarkers

Biomarker identification and translation into clinics by the introduction of routine preoperative/postoperative testing across the Europe are required, based on uniform optimal diagnostic and therapeutic strategies specified for children, adults, and the elderly.

Thoroughly evaluating the issue of possible overdiagnosis

The impact on mental health and QoL of patients with thyroid nodules requires evaluation, due to their high rate and challenges in determining tumor aggressiveness.

Examining the use of thermal ablation

Introduction and validation of randomized, multicenter studies on the use of thermal ablation in the treatment of autonomously functioning thyroid nodules and TC should be undertaken.

Studying radioactive iodine after thyroidectomy in pediatric DTC

Collaborative prospective studies should be introduced on the role of radioactive iodine following thyroidectomy in children with DTC.

Anticipated impact of future research

Despite multiple studies on the molecular background of TC, the ultimate causes of the increasing incidence of TC are still unknown. Discovery of the exact stimuli that trigger molecular alterations in TC will help to establish procedures and guidelines that assist in avoiding cancerogenic exposures across the Europe. This will also help to introduce closer monitoring of individuals at risk of TC development.

Establishing biobanking procedures and a pan-European database for TC (in particular for rare TC subtypes), as well as application of cutting-edge methods (omics, AI) and detailed modeling of TC cellular processes, will facilitate research to increase knowledge about the pathogenesis of TC. This will lead to the identification of diagnostic, prognostic, and predictive biomarkers, development of efficient novel drugs, and increased effectiveness of the existing therapies.

Introduction of routine preoperative/postoperative testing across the Europe, inclusion of AI-based predictive methods, and establishing the utility of thermal ablation in the treatment of autonomously functioning thyroid nodules and TC will facilitate cost-effective decisions on the appropriate treatment. Elucidation of the impact on the QoL of patients with thyroid nodules will help to introduce proper procedures, preventing deterioration of mental health and high societal and public costs.

Because pediatric DTC has such an excellent survival rate, research must mainly be aimed at decreasing the adverse effects of treatment while maintaining the numbers cured. For this reason, studies should focus on determining which children need higher-intensity treatment and those in whom lower-intensity treatment will suffice. Comparable to the current "trend" in adult TC, children may currently be overtreated, and low-risk patients may not need adjuvant radioactive iodine for survival.

Consequently, future studies must aim to develop a dynamic prediction model for tumor behavior based on genetic, pathological, and imaging findings. To develop such a model, we need a large prospective multicenter study, randomized and correcting for other determinants, such as thyroidectomy and prophylactic central lymph node dissection. It may be very challenging to conduct a prospective collaborative study within Europe, with a long enough follow-up time. Combining current European and American cohorts to create a large cohort of patients may provide an alternative way of gathering more evidence on outcomes, in relation to a given treatment in pediatric DTC, with sufficient patient numbers. With such a dynamic prediction model, children would have the same survival rates but with improved outcomes and reduced adverse effects of (over)treatment.

Thyroid nonneoplastic disorders

Epidemiology, societal impact, and research state of the art

Nonneoplastic thyroid disorders are defined by improper TH actions (due either to impaired extrathyroidal activation and intracellular availability of TH or impaired TH receptor activation) and/or abnormal TH concentrations in serum/plasma or tissues (eg, due to excess or deficient TH synthesis). Their causes include genetic, autoimmune, and environmental factors (eg, micronutrient deficiency, EDCs).

Nonneoplastic thyroid disorders arise from dysfunctions of the thyroid gland (DTGs) and disorders of TH signaling (DTHSs) and can be manifested as hypothyroidism or thyrotoxicosis, with important developmental or metabolic consequences.

Micronutrients (eg, iodine, selenium, iron) are essential for TH biosynthesis and metabolism. Their proper supply is crucial for adequate thyroid function and TH homeostasis. Moderate to severe iodine deficiency in pregnant women results in goiter and mild to severe fetal brain impairment (cretinism). In many countries, iodine fortification helps prevent moderate to severe iodine deficiency. Mild iodine deficiency still remains worldwide during pregnancy, with >70% of European countries having insufficient iodine intake during pregnancy.[31]

Dysfunctions of the thyroid gland

The DTGs include (but are not limited to) congenital hypothyroidism and AITDs, comprising Graves' disease (GD) and Hashimoto's thyroiditis. Acquired DTGs are common, related to the country's iodine status and the patients' age and sex, with an estimated prevalence of 3.8% in Europe.[32] Graves' disease prevails in iodine sufficiency (incidence of 21/100 000 individuals/year), while autonomous thyroid hyperfunction is more common in iodine deficiency.[33,34] Hyperthyroidism has a prevalence of 0.2-1.3/100, and hypothyroidism has a

prevalence of 1-2/100, which increases with age and is 8-10 times more prevalent in women.[34] Primary congenital hypothyroidism detected by newborn screening (NBS) has an prevalence of between 1/2000 and 1/3000.[35,36] Diagnosis of DTGs is based on thyrotrophin (TSH) and FT4 testing, sometimes combined with FT3 evaluation. Newborn screening for congenital hypothyroidism facilitates early treatment, preventing neurocognitive defects.

Levothyroxine (LT4) monotherapy is a standard treatment for primary hypothyroidism, but about 15%-20% of biochemically euthyroid patients on standard therapy with LT4 report impaired QoL (fatigue, depressed mood)[37] and are offered different treatments (eg, increased LT4 dosage, liothyronine alone or associated with LT4, desiccated thyroid extracts).[38–40] Treatments for GD include antithyroid drugs (carbimazole, methimazole, propylthiouracil), total thyroidectomy, radioactive iodine, and new immune-modulating treatments. Approximately 40% of patients with GD develop Graves' orbitopathy/thyroid eye disease (TED) that affects QoL and requires specific therapy.[41,42] Active, moderate to severe TED is usually treated with glucocorticoids. Alternative TED therapies (ie, teprotumumab, tocilizumab, rituximab) were recently proposed.[43] In moderate severe cases of TED, surgery has a central role. In the active state, orbital decompression may be necessary to preserve visual acuity, and in the chronic noninflammatory state, correction of proptosis, double vision, and eye lids may be necessary.

Autoimmune thyroid disease is associated with changes in microbiome. Animal studies indicated that the gut microbiome is altered in GD/TED; antibiotics ameliorated but human GD/TED fecal transplantation exacerbated induced disease.[44,45] In human patients with GD, microbiota may affect the functioning of the immune system[46] while particular species of bacteria correlate with the presence of thyroid autoantibodies.[47] It is currently unclear whether modulating the microbiota is useful in the treatment of human AITD.

Disorders of TH signaling

The DTHSs include defects in TH transport (eg, mutations in MCT8 causing Allan–Herndon–Dudley syndrome), RTH alpha/beta resistance due to mutations in the respective TH receptors (THRA/THRB), and deiodination defects (eg, selenoprotein deficiencies due to SBP2 and $tRNA^{[Ser]Sec}$ mutations). The DTHSs are rare (1/10 000 individuals), but the associated multisystem manifestations may be devastating, posing a heavy burden on patients and society.[48] Understanding the mechanisms of DTHSs and the therapeutic and diagnostic options are limited due to the lack of systematic collection of clinical and functional data.

Interconnections between DTGs and noncommunicable diseases

Thyroid hormone status affects fertility and the functioning of the reproductive hormone system (in both females and males). There is a global decrease in fertility (at least in countries of higher socioeconomic status/"global north"); the causes of which are largely unclear. European countries display among the highest global prevalence of lifetime infertility.[49] Studies suggest that AITD may adversely affect birth outcomes.[50,51] However, it is unclear to what extent the high prevalence of DTGs is responsible for the increasing problem of infertility in the European Union.

Obesity affects DTGs in children and adults[52–54] while DTGs impair the functioning of adipose tissue[55–57] increasing the risk of dyslipidemia and obesity comorbidities. The European population is heavily affected by obesity epidemics[58] which may have a large impact on the functioning of the thyroid gland. Studies in pediatric cohorts suggest that obesity may lead to misdiagnosis of thyroid disease.[52] Thus, neglecting the role of fat tissue in DTG management may lead to misdiagnosis and inadequate treatment. Furthermore, THs affect the functioning of cancer cells and TH receptors have been shown to act as tumor suppressors.[59] However, studies on associations between DTGs and cancer provided conflicting results[59] and whether DTGs affect cancer risk and should be used as a prognostic factor in cancer monitoring needs to be clarified.

Future research priorities

Research priorities in DTGs (Figure 2)

Iodine deficiency. Observations suggest that mild iodine deficiency during pregnancy is associated with lower offspring IQ[60,61] or attention deficit hyperactivity disorder.[62] However, adequate randomized controlled trials during pregnancy with follow-up of children's cognition are lacking. The link between iodine deficiency and the risk of developing neuropsychiatric disorders is also unclear.[63] Human trials should be accompanied by studies using human models based on induced pluripotent stem cells and animal models to explore in utero effects of mild iodine deficiency on brain structure, neuronal signaling, and neuron–glia interactions. Spatial omics studies should be involved to analyze 3D molecular changes. Special focus should be placed on the role of epigenetics and noncoding RNAs as mediators of the effects of mild iodine deficiency.

DTG diagnostics.

- High interindividual, but limited intraindividual, variation in TSH/TH concentrations leads to wide population-based reference intervals (RIs).[64] Optimal individual RIs might be much narrower and genetically determined[64–66] and may also vary depending on assay, age, pregnancy, or LT4 treatment.[67–69] Future studies should define optimal RIs for thyroid function tests in specific populations/individuals (pregnancy, elderly, LT4-treated patients), based on clinical/genetic profiles. Reference intervals for newly identified TH biomarkers are also required. Personalized treatment dosing by development of algorithms and use of AI is a future area of research avoiding overdosing or underdosing despite guidelines especially in young children.[70]
- Serum TSH/FT4 concentrations do not always reflect TH function in peripheral tissues.[71] Tissue-specific biomarkers/omics profiles and their clinical application may support personalized nonneoplastic thyroid disorder treatment.

Congenital hypothyroidism.

- Thyrotrophin-only screening detects primary, but misses central, congenital hypothyroidism and some DTHSs (MCT8 deficiency, THRA/THRB mutations). Early

central congenital hypothyroidism detection by NBS may be associated with better neurocognitive outcomes. The incidence of central congenital hypothyroidism and the benefits of its early detection by NBS need to be clarified in pan-European, multicenter studies on childhood cognition and QoL, along with analyses of the cost-effectiveness of NBS-based testing.

- Genetic NBS was suggested as an alternative to metabolite-/hormone-based NBS.[36] However, only ~20% of cases of congenital hypothyroidism have genetic explanations. The causes of congenital hypothyroidism, especially thyroid/pituitary maldevelopment, require clarification.
- Detailed human, animal, and in vitro studies are needed to improve understanding of the developmental biology and physiology of the human thyroid (including at the single-cell level), its perturbations, and the determinants of goitrogenesis.
- Compared with mild disease, severe primary congenital hypothyroidism requires considerably higher serum FT4 for TSH normalization. Questions remain around the cause(s) of this phenomenon, and whether the serum TSH or the FT4 concentration needs to be normalized.
- Lowering of NBS TSH thresholds increased the number of newborns with mild/subclinical congenital hypothyroidism and even transient congenital hypothyroidism. Questions concern the etiology and benefits of treatment of this group of children with respect to growth and long-term neurocognitive outcomes and metabolic effects (eg, cardiovascular disease).

Autoimmune thyroid disease.

- The mechanisms underlying AITD should be explored, including interactions between the immune system and thyrocytes/thyroidal microenvironment in AITD, and mechanisms underlying primary and secondary immune dysfunction implicated in AITD. Such studies should include evaluation of germline and somatic genomics using cutting-edge technologies, spatial and single-cell transcriptomics, proteomics, and metabolomics in addition to functional studies
- The mechanisms behind the increasing incidence of AITD should be explored, including the micronutrient supply and the role of environmental polluting factors. The research should involve dose-dependence studies performed in vitro/ex vivo/in utero/in vivo models, with a special focus on large-scale epigenetic studies to verify the role of epigenetic modifications as mediators of the impact of environmental pollution. The impact of the analyzed compounds on thyroid cells, thyroid gland microenvironment, and immune system should be analyzed by cutting-edge technologies, such as spatial and single-cell transcriptomics, proteomics, and metabolomics.
- The causal associations between the microbiome and AITD (including pediatric GD) require elucidation. Future human microbiome studies should apply standardized protocols[72] preferably using shotgun sequencing and include reference reagents[73] to enable comparison of data from disease cohorts in different countries and to facilitate meaningful meta-analyses. With regard to the QoL of patients with AITD, the impact of the microbiome–brain axis should be also explored, by means of in vitro and in vivo models of AITD. The potential anti-inflammatory and microbiome-modifying effects of specific diets (eg, gluten-free, vegan) on thyroid disease occurrence and outcomes are not clear and require detailed, large cohort well-controlled studies. These studies should also focus on identification of pre- and probiotic supplements that may help to alleviate persisting symptoms of AITD despite normal TH concentrations.
- There is a need for independent investigator studies in GD and TED, comparing new immunomodulatory and disease-modifying drugs in TED with the cheaper currently available treatments such as intravenous glucocorticoids and immunosuppressants.
- International/pan-European registries of GD/TED patients treated with biologics agents are needed to facilitate studies on treatment efficacy and long-term patients' outcomes.
- New therapies, including studies of LT4/liothyronine combinations and regenerative approaches, are needed to restore euthyroidism in target tissues and prevent harmful cardiovascular and bone effects. Furthermore, the QoL of treated patients with GD requires evaluation, along with studies aimed at identifying the means to prevent excess weight gain following restoration of euthyroidism. This should involve a pan-European study research on GD to understand long-term outcome data including treatment complications and QoL that will provide patients with sufficient data for the informed choice of therapy.
- Immunological remission in pediatric GD may be improved by prolonged antithyroid drug treatment and immune-modulating therapy (rituximab, Ki70 monoclonal antibody, other immune-modulating drugs).[74,75] The QoL of patients after such treatments, when compared with thyroidectomy/radioactive iodine (that need lifelong LT4 supplementation), requires evaluation.
- Future GD/TED research should reveal the etiopathology, diagnostic/prognostic/treatment response biomarkers, and novel drugs targeting immune dysregulation and persistent mental syndromes, along with randomized controlled trials for optimal therapies.

Research priorities in DTHSs (Figure 2)

- Improving understanding of the genetic and acquired etiologies of DTHS pathologies by evaluating and phenotyping affected humans with appropriate parallel ex vivo/in vitro experiments.
- Elucidating the cellular, molecular, and physiological role of TH metabolism, in particular to verify biological/thyromimetic activity of T4 and TH metabolites other than T3. The studies should involve careful analysis of the physiological effects at the level of cells, tissues, and the organism as a whole, with detailed analysis of the possible molecular effects on cellular signaling pathways. This should be done using careful evaluation of ex vivo/in vitro and in vivo models with cutting-edge, large-scale, multi-omics methodology, as well as validation with the help of the traditional methods of molecular biology.
- Cell- and tissue-specific consequences of DTHSs and their mechanisms require analysis using human-relevant

models (eg, patient-derived cells, setting up in vitro cocultures or organoid models, and using induced pluripotent stem cells) to develop diagnostic and therapeutic strategies. This includes identification of biomarkers of cell-/tissue-specific TH signaling alterations in the context of DTHS genetic variants. The ultimate goal should be identification of the mechanisms by which THs contribute to the intercellular/intertissue interaction and communication to maintain organism homeostasis.
- Pan-European projects systemically collecting real-world, standardized data (including genetics, diagnosis, and clinical outcomes) are needed to fully characterize the short- and long-term health consequences of DTHSs.
- There is need to develop tools for early DTHS diagnosis (including prenatal and neonatal test based on genetic and/or biochemical screening) and adequate treatment programs (including in utero treatments) of DTHS (such as RTHalpha/beta resistance as well as TH transport and deiodination defects).
- Therapeutic options should be investigated using multicenter trials supported by ex vivo/in vitro cellular studies designed appropriately for rare disorders.

Research priorities in interconnections between DTGs and noncommunicable diseases (Figure 2)

Interdisciplinary clinical and basic/molecular studies are needed to reveal the associations between DTGs and (1) obesity, (2) cancer, and (3) fertility disorders, and to translate them into clinical practice.

Subclinical hypothyroidism and subclinical hyperthyroidism affect >5% of the population.[76–78] Despite associated adverse outcomes (eg, increased incidence of cardiovascular conditions), no clear evidence currently supports treatment. Multicenter, international therapeutic trials are recommended as future research, with a focus on ameliorating CVD.

Recent studies provided hints for the causative associations between AITD and cancer, including TC.[28–30] However, the results of these studies provide conflicting data on the impact of AITD having cancer promoting/attenuating effects or no influence on cancer development. Detailed studies on well-defined patient cohorts supported with careful basic in vitro, ex vivo, and in vivo studies are needed to clarify this issue.

Specific questions related to DTG-associated fertility disorders include the following:

1. Studies to investigate the mechanisms underpinning associations of thyroid autoimmunity with adverse pregnancy outcomes and whether autoimmunity can be modulated to improve outcomes.
2. Management of pregnancy in patients with rare thyroid diseases or conditions (eg, central hypothyroidism) in which TSH is not an appropriate biomarker of TH status.
3. Relative roles of maternal T4 and T3 in fetal physiology and placental TH transport.
4. Long-term outcome data of babies born to mothers with GD or thyrotoxicosis.
5. Large-scale prospective studies on causal links between subclinical hypothyroidism and infertility, as well as the efficacy of assisted reproductive techniques (ARTs).
6. Clarification of the influence of hypothyroidism and AITD on male fertility and ARTs.

Regarding the role of AITD in infertility treatments, the significance of thyroglobulin antibodies requires evaluation.[51]

The research should include in vitro/ex vivo/in vivo DTG models, involving both sexes (DTG phenotypes are sex specific)[59] and omics technologies (eg, single-cell RNA-seq, spatial omics, multicolor flow cytometry, multicolor immunofluorescence analysis). Subcellular effects of TH alterations need to be explored using cutting-edge methods such as super-resolution confocal microscopy to complement the molecular data. Paracrine and endocrine interactions between fat tissue and the thyroid, as well as the immune system, should be explored to find how the secretory functions of the adipocytes affect the signaling pathways and the functioning of thyrocytes, the thyroid gland microenvironment, and the immune cells. Conversely, the role of hypo- and hyperthyroidism in cancer development should be mechanistically explored to reveal the impact of changes in TH/TSH on signaling pathways and the functioning of target tissues such as breast glands.

Anticipated impact of future research

Due to their prevalence, DTGs considerably influence public health. The proposed research directions will significantly improve health of European populations:

1. Defining the effects of mild iodine deficiency/selenium deficiency and etiopathology of primary and central congenital hypothyroidism, as well as central congenital hypothyroidism screening, will help to better understand these disorders and avoid their consequences for neurocognitive and metabolic outcomes. Intelligence/IQ largely influences educational success, occupational status, the use of health services, lifestyle and recreational choices, or crime. A lower average IQ increases the percentage of intellectually disabled children, limiting their potential and increasing healthcare and societal costs. To introduce nutrient supplementation at the population level, treatment studies are essential due to iodine's narrow therapeutic window. This research will help to harmonize international practice during pregnancy. Another gap of knowledge is to decide when supplementation with LT4 is needed during pregnancy. Is LT4 therapy necessary in women with TSH >2.5, >4 mU/L, or 10 mU/L in order to reduce the consequences of primary hypothyroidism during gestation on intelligence and IQ of the neonates and infants?
2. Defining reliable TSH/TH RIs and tissue-specific biomarkers of TH action will support personalized treatments for DTGs, preventing application of inefficient/nonoptimal therapies. This will result in high cost-effectiveness, since LT4 is one of the most commonly prescribed drugs worldwide.[79]
3. Alternative treatment regimens for hypothyroidism will improve patients' QoL while remaining euthyroid. New LT4 formulations are needed in order to treat patients with abnormal absorption of present TH formulations.
4. Novel diagnostic/treatment options for GD/TED will improve patients' QoL and provide cost-effectiveness by avoiding cardiovascular and bone-affecting comorbidities.
5. Robust AITD-linked microbiome data will define lifestyle changes to reduce disease risk.[8]
6. New data regarding DTHSs will (1) improve disease awareness, permitting timely diagnosis and limiting

devastating outcomes, (2) yield appropriate diagnostic tools, (3) generate new therapies which may significantly alleviate the negative outcomes of DTHS and have the potential for use across other DTGs, and (4) inform guidelines. Disorders of TH signaling are rare, but gene variants in similar pathways with a milder impact may be more frequent in the general population and modulate the outcomes of common nonneoplastic thyroid disorders.

7. Delineation of associations between DTGs and noncommunicable diseases will (1) help to discover efficient and cost-effective obesity treatments and (2) clarify whether patients with DTGs should be monitored for cancer risks.

Funding

None declared.

Authors' contributions

Agnieszka Piekiełko-Witkowska (Conceptualization [equal], Investigation [equal], Methodology [equal], Project administration [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Rossella Elisei (Formal analysis [equal], Investigation [equal], Project administration [equal], Writing—original draft [equal], Writing—review & editing [equal]), Juliane Leger (Investigation [equal], Writing—original draft [equal]), Běla Bendlova (Investigation [equal], Writing—original draft [equal]), Barbora Bulanová Pekova (Investigation [equal], Writing—original draft [equal]), Philippe Caron (Investigation [equal], Writing—original draft [equal]), Cosimos Durante (Investigation [equal], Writing—original draft [equal]), Martin Fassnacht (Writing—review & editing [equal]), Ulla Feldt-Rasmussen (Investigation [equal], Writing—original draft [equal]), Helena Filipsson Nyström (Investigation [equal], Writing—original draft [equal]), Heleen Jansen (Investigation [equal], Visualization [equal], Writing—original draft [equal]), Josef Köhrle (Investigation [equal], Writing—original draft [equal]), Aleksander Kus (Investigation [equal], Writing—original draft [equal]), Marian Ludgate (Investigation [equal], Writing—original draft [equal]), Jonathan Mertens (Writing—review & editing [equal]), Małgorzata Oczko-Wojciechowska (Investigation [equal], Writing—original draft [equal]), Catherine Peters (Investigation [equal], Writing—original draft [equal]), Nadia Schoenmakers (Investigation [equal], Writing—original draft [equal]), Athanasia Stoupa (Investigation [equal], Writing—original draft [equal]), Hanneke van Santen (Investigation [equal], Writing—original draft [equal]), Pierpaolo Trimboli (Investigation [equal], Writing—original draft [equal]), A S van Trotsenburg (Investigation [equal], Writing—original draft [equal]), and W. Edward Visser (Investigation [equal], Writing—original draft [equal])

Conflict of interest: None declared.

References

1. Bogusławska J, Godlewska M, Gajda E, Piekiełko-Witkowska A. Cellular and molecular basis of thyroid autoimmunity. *Eur Thyroid J*. 2022;11(1):e210024. https://doi.org/10.1530/ETJ-21-0024
2. Köhrle J, Frädrich C. Deiodinases control local cellular and systemic thyroid hormone availability. *Free Radic Biol Med*. 2022;193(1):59-79. https://doi.org/10.1016/j.freeradbiomed.2022.09.024
3. The untapped potential of the thyroid axis. *Lancet Diabetes Endocrinol*. 2013;1(3):163. https://doi.org/10.1016/S2213-8587(13)70166-9
4. Chen P, Feng C, Huang L, Chen H, Feng Y, Chang S. Exploring the research landscape of the past, present and future of thyroid nodules. *Front Med (Lausanne)*. 2023;9:831346. https://doi.org/10.3389/fmed.2022.831346
5. Pizzato M, Li M, Vignat J, *et al.* The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. *Lancet Diabetes Endocrinol*. 2022;10(4):264-272. https://doi.org/10.1016/S2213-8587(22)00035-3
6. Demuru E, Rossi S, Ventura L, *et al.* Estimating complete cancer prevalence in Europe: validity of alternative vs standard completeness indexes. *Front Oncol*. 2023;13:1114701. https://doi.org/10.3389/fonc.2023.1114701
7. Franchini F, Palatucci G, Colao A, Ungaro P, Macchia PE, Nettore IC. Obesity and thyroid cancer risk: an update. *Int J Environ Res Public Health*. 2022;19(3):1116. https://doi.org/10.3390/ijerph19031116
8. Ludgate ME, Masetti G, Soares P. The relationship between the gut microbiota and thyroid disorders. *Nat Rev Endocrinol*. 2024;20(9):511-525. https://doi.org/10.1038/s41574-024-01003-w
9. Yang K, Zhang G, Li Y. Association between air pollutants, thyroid disorders, and thyroid hormone levels: a scoping review of epidemiological evidence. *Front Endocrinol*. 2024;15:1398272. https://doi.org/10.3389/fendo.2024.1398272
10. Paz-Ibarra J, Concepcion-Zavaleta MJ, Quiroz-Aldave JE. Environmental factors related to the origin and evolution of differentiated thyroid cancer: a narrative review. *Expert Rev Endocrinol Metab*. 2024;19(6):469-477. https://doi.org/10.1080/17446651.2024.2377687
11. Neira M. The Minderoo-Monaco commission on plastics and human health. *Ann Glob Health*. 2023;89(1):23. https://doi.org/10.5334/aogh.4056
12. Tamam N, Almuqrin AH, Mansour S, *et al.* Occupational and patients effective radiation doses in dental imaging. *Appl Radiat Isot*. 2021;177:109899. https://doi.org/10.1016/j.apradiso.2021.109899
13. Memon A, Rogers I, Paudyal P, Sundin J. Dental X-rays and the risk of thyroid cancer and meningioma: a systematic review and meta-analysis of current epidemiological evidence. *Thyroid*. 2019;29(11):1572-1593. https://doi.org/10.1089/thy.2019.0105
14. Neta G, Rajaraman P, Berrington de Gonzalez A, *et al.* A prospective study of medical diagnostic radiography and risk of thyroid cancer. *Am J Epidemiol*. 2013;177(8):800-809. https://doi.org/10.1093/aje/kws315
15. Memon A, Godward S, Williams D, Siddique I, Al-Saleh K. Dental x-rays and the risk of thyroid cancer: a case control study. *Acta Oncol*. 2010;49(4):447-453. https://doi.org/10.3109/02841860003705778
16. Wells SA Jr, Asa SL, Dralle H, *et al.* Revised American Thyroid Association Guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567-596. https://doi.org/10.1089/thy.2014.0335
17. Filetti S, Durante C, Hartl D, *et al.* Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(12):1856-1883. https://doi.org/10.1093/annonc/mdz400
18. Angelousi A, Hayes AR, Chatzellis E, Kaltsas GA, Grossman AB. Metastatic medullary thyroid carcinoma: a new way forward. *Endocr Relat Cancer*. 2022;29(7):85-103. https://doi.org/10.1530/ERC-21-0368
19. Lebbink CA, van den Broek MFM, Kwast ABG, *et al.* Opposite incidence trends for differentiated and medullary thyroid cancer in young Dutch patients over a 30-year time span. *Cancers (Basel)*. 2022;14(20):5104. https://doi.org/10.3390/cancers13205104
20. Lebbink CA, Links TP, Czarniecka A, *et al.* 2022 European Thyroid Association Guidelines for the management of pediatric thyroid nodules and differentiated thyroid carcinoma. *Eur Thyroid J*. 2022;11(6):e220146. https://doi.org/10.1530/ETJ-22-0146

21. Liu X, Qu S, Liu R, *et al.* TERT promoter mutations and their association with BRAF V600E mutation and aggressive clinicopathological characteristics of thyroid cancer. *J Clin Endocrinol Metab*. 2014;99(6):1130-1136. https://doi.org/10.1210/jc.2013-4048
22. Zhao X, Kotch C, Fox E, *et al.* NTRK fusions identified in pediatric tumors: the frequency, fusion partners, and clinical outcome. *JCO Precis Oncol*. 2021;1:PO.20.00250. https://doi.org/10.1200/PO.20.00250
23. Pekova B, Sykorova V, Dvorakova S, *et al.* RET, NTRK, ALK, BRAF, and *MET* fusions in a large cohort of pediatric papillary thyroid carcinomas. *Thyroid*. 2020;30(12):1771-1780. https://doi.org/10.1089/thy.2019.0802
24. Rodriguez J, Frigola J, Vendrell E, *et al.* Chromosomal instability correlates with genome-wide DNA demethylation in human primary colorectal cancers. *Cancer Res*. 2006;66(17):8462-9468. https://doi.org/10.1158/0008-5472.CAN-06-0293
25. Martelli MP, Martino G, Cardinali V, Falini B, Martinelli G, Cerchione C. Enasidenib and ivosidenib in AML. *Minerva Med*. 2020;111(5):411-426. https://doi.org/10.23736/S0026–4806.20.07024-X
26. Straining R, Eighmy W. Tazemetostat: EZH2 inhibitor. *J Adv Pract Oncol*. 2022;13(2):158-163. https://doi.org/10.6004/jadpro.2022.13.2.7
27. Jansen HI, Bruinstroop E, Heijboer AC, Boelen A, Biomarkers indicating tissue thyroid hormone status: ready to be implemented yet? *J Endocrinol* 2022;253(2):R21-R45. https://doi.org/10.1530/JOE-21-0364
28. Hu X, Wang X, Liang Y, *et al.* Cancer risk in Hashimoto's thyroiditis: a systematic review and meta-analysis. *Front Endocrinol*. 2022;13:937871. https://doi.org/10.3389/fendo.2022.937871
29. Chen YK, Lin CL, Cheng FT, Sung FC, Kao CH. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. *Br J Cancer*. 2013;109(9):2496-2501. https://doi.org/10.1038/bjc.2013.597
30. Resende de Paiva C, Grønhøj C, Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto's thyroiditis and thyroid cancer in 64,628 patients. *Front Oncol*. 2017;7:53. https://doi.org/10.3389/fonc.2017.00053
31. Ittermann T, Albrecht D, Arohonka P, *et al.* Standardized map of iodine status in Europe. *Thyroid*. 2020;30(9):1346-1354. https://doi.org/10.1089/thy.2019.0353
32. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99(3):923-931. https://doi.org/10.1210/jc.2013-2409
33. Abraham-Nordling M, Byström K, Törring O, *et al.* Incidence of hyperthyroidism in Sweden. *Eur J Endocrinol*. 2011;165(6):899-905. https://doi.org/10.1530/EJE-11-0548
34. Taylor PN, Albrecht D, Scholz A, *et al.* Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;14(5):301-316. https://doi.org/10.1038/nrendo.2018.18
35. Léger J, Olivieri A, Donaldson M, *et al.* European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *J Clin Endocrinol Metab*. 2014;99(2):363-384. https://doi.org/10.1210/jc.2013-1891
36. van Trotsenburg P, Stoupa A, Léger J, *et al.* Congenital hypothyroidism: a 2020–2021 Consensus Guidelines update—an ENDO-European Reference Network initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid*. 2021;31(3):387-419. https://doi.org/10.1089/thy.2020.0333
37. Hegedüs L, Bianco AC, Jonklaas J, Pearce SH, Weetman AP, Perros P. Primary hypothyroidism and quality of life. *Nat Rev Endocrinol*. 2022;18(4):230-242. https://doi.org/10.1038/s41574-021-00625-8
38. Jonklaas J, Bianco AC, Cappola AR, *et al.* Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. *Eur Thyroid J*. 2021;10(1):10-38. https://doi.org/10.1089/thy.2020.0720
39. Biondi B, Celi FS, McAninch EA. Critical approach to hypothyroid patients with persistent symptoms. *J Clin Endocrinol Metab*. 2023;108(10):2708-2716. https://doi.org/10.1210/clinem/dgad224
40. Caron P. Key data from the 2022 European Thyroid Association congress: treatment of primary hypothyroidism: levothyroxine alone or a combination of levothyroxine and liothyronine? *Ann Endocrinol*. 2023;84(6):751-753. https://doi.org/10.1016/j.ando.2023.05.005
41. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362(8):726-738. https://doi.org/10.1056/NEJMra0905750
42. Chin YH, Ng CH, Lee MH, *et al.* Prevalence of thyroid eye disease in Graves' disease: a meta-analysis and systematic review. *Clin Endocrinol (Oxf)*. 2020;93(4):363-374. https://doi.org/10.1111/cen.14296
43. Taylor PN, Zhang L, Lee RWJ, *et al.* New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. *Nat Rev Endocrinol*. 2020;16(2):104-116. https://doi.org/10.1038/s41574-019-0305-4
44. Masetti G, Moshkelgosha S, Köhling HL, *et al.* Gut microbiota in experimental murine model of Graves' orbitopathy established in different environments may modulate clinical presentation of disease. *Microbiome*. 2018;6(1):97. https://doi.org/10.1186/s40168-018-0478-4
45. Moshkelgosha S, Verhasselt HL, Masetti G, *et al.* Modulating gut microbiota in a mouse model of Graves' orbitopathy and its impact on induced disease. *Microbiome*. 2021;9(1):45. https://doi.org/10.1186/s40168-020-00952-4
46. Su X, Yin X, Liu Y, *et al.* Gut dysbiosis contributes to the imbalance of Treg and Th17 cells in Graves' disease patients by propionic acid. *J Clin Endocrinol Metab*. 2020;105(11):dgaa511. https://doi.org/10.1210/clinem/dgaa511
47. Biscarini F, Masetti G, Muller I, *et al.* Gut microbiome associated with Graves disease and graves orbitopathy: the INDIGO multicenter European study. *J Clin Endocrinol Metab*. 2023;108(8):2065-2077. https://doi.org/10.1210/clinem/dgad030
48. Moran C, Schoenmakers N, Visser WE, Schoenmakers E, Agostini M, Chatterjee K. Genetic disorders of thyroid development, hormone biosynthesis and signalling. *Clin Endocrinol (Oxf)*. 2022;97(4):502-514. https://doi.org/10.1111/cen.14817
49. World Health Organization. *Infertility Prevalence Estimates, 1990–2021*. Geneva, Switzerland: World Health Organization; 2023. ISBN: 978-92-4-006831-5.
50. Karakosta P, Alegakis D, Georgiou V, *et al.* Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J Clin Endocrinol Metab*. 2012;97(12):4464-4472. https://doi.org/10.1210/jc.2012-2540
51. Hubalewska-Dydejczyk A, Gietka-Czernel M, Trofimiuk-Müldner M, *et al.* Thyroid diseases and fertility disorders—Guidelines of the Polish Society of Endocrinology [Choroby tarczycy a zaburzenia płodności—rekomendacje Polskiego Towarzystwa Endokrynologicznego]. *Endokrynol Pol*. 2022;73(4):645-679. https://doi.org/10.5603/EP.a2022.0069
52. Licenziati MR, Valerio G, Vetrani I, De Maria G, Liotta F, Radetti G. Altered thyroid function and structure in children and adolescents who are overweight and obese: reversal after weight loss. *J Clin Endocrinol Metab*. 2019;104(7):2757-2765. https://doi.org/10.1210/jc.2018-02399
53. Yang H, Xia Q, Shen Y, Chen TL, Wang J, Lu YY. Gender-specific impact of metabolic obesity phenotypes on the risk of Hashimoto's thyroiditis: a retrospective data analysis using a health check-up database. *J Inflamm Res*. 2022;15:827-837. https://doi.org/10.2147/JIR.S353384
54. Richardson TG, Crouch DJM, Power GM, *et al.* Childhood body size directly increases type 1 diabetes risk based on a lifecourse Mendelian randomization approach. *Nat Commun*. 2022;13(1):2337. https://doi.org/10.1038/s41467-022-29932-y
55. Lahesmaa M, Orava J, Schalin-Jäntti C, *et al.* Hyperthyroidism increases brown fat metabolism in humans. *J Clin Endocrinol Metab*. 2014;99(1):28-35. https://doi.org/10.1210/jc.2013-2312

56. Weiner J, Kranz M, Klöting N, *et al*. Thyroid hormone status defines brown adipose tissue activity and browning of white adipose tissues in mice. *Sci Rep*. 2016;6(1):38124. https://doi.org/10.1038/srep38124
57. Guilherme A, Yenilmez B, Bedard AH, *et al*. Control of adipocyte thermogenesis and lipogenesis through β3-adrenergic and thyroid hormone signal integration. *Cell Rep*. 2020;31(5):107598. https://doi.org/10.1016/j.celrep.2020.107598
58. World Health Organization. *WHO European Regional Obesity Report 2022*. Geneva, Switzerland: World Health Organization; 2022. ISBN: 9789289057738.
59. Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid hormones and cancer: a comprehensive review of preclinical and clinical studies. *Front Endocrinol (Lausanne)*. 2019;10:59. https://doi.org/10.3389/fendo.2019.00059
60. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet*. 2013;382(9889):331-337. https://doi.org/10.1016/S0140-6736(13)60436-5
61. Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab*. 2013;98(5):1954-1962. https://doi.org/10.1210/jc.2012-4249
62. Mulder TA, Korevaar TIM, Peeters RP, *et al*. Urinary iodine concentrations in pregnant women and offspring brain morphology. *Thyroid*. 2021;31(6):964-972. https://doi.org/10.1089/thy.2020.0582
63. Greenwood DC, Webster J, Keeble C, Taylor E, Hardie LJ. Maternal iodine status and birth outcomes: a systematic literature review and meta-analysis. *Nutrients*. 2023;15(2):387. https://doi.org/10.3390/nu15020387
64. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab*. 2002;87(3):1068-1072. https://doi.org/10.1210/jcem.87.3.8165
65. Hansen PS, Brix TH, Sørensen TI, Kyvik KO, Hegedüs L. Major genetic influence on the regulation of the pituitary-thyroid axis: a study of healthy Danish twins. *J Clin Endocrinol Metab*. 2004;89(3):1181-1187. https://doi.org/10.1210/jc.2003-031641
66. Kuś A, Chaker L, Teumer A, Peeters RP, Medici M. The genetic basis of thyroid function: novel findings and new approaches. *J Clin Endocrinol Metab*. 2020;105(6):dgz225. https://doi.org/10.1210/clinem/dgz225
67. Osinga JAJ, Derakhshan A, Palomaki GE, *et al*. TSH and FT4 reference intervals in pregnancy: a systematic review and individual participant data meta-analysis. *J Clin Endocrinol Metab*. 2022;107(10):2925-2933. https://doi.org/10.1210/clinem/dgac425
68. Raverot V, Bonjour M, Abeillon du Payrat J, *et al*. Age- and sex-specific TSH upper-limit reference intervals in the general French population: there is a need to adjust our actual practices. *J Clin Med*. 2020;9(3):792. https://doi.org/10.3390/jcm9030792
69. Jansen HI, Bult MM, Bisschop PH, Boelen A, Heijboer AC, Hillebrand JJ. Increased fT4 concentrations in patients using levothyroxine without complete suppression of TSH. *Endocr Connect*. 2023;12(4):220538. https://doi.org/10.1530/EC-22-0538
70. Bachmann F, Koch G, Pfister M, Szinnai G, Schropp J. OptiDose: computing the individualized optimal drug dosing regimen using optimal control. *J Optim Theory Appl*. 2021;189(1):46-65. https://doi.org/10.1007/s10957-021-01819-w
71. Friesema EC, Kuiper GG, Jansen J, Visser TJ, Kester MH. Thyroid hormone transport by the human monocarboxylate transporter 8 and its rate-limiting role in intracellular metabolism. *Mol Endocrinol*. 2006;20(11):2761-2772. https://doi.org/10.1210/me.2005-0256
72. Tourlousse DM, Narita K, Miura T, *et al*. Validation and standardization of DNA extraction and library construction methods for metagenomics-based human fecal microbiome measurements. *Microbiome*. 2021;9(1):95. https://doi.org/10.1186/s40168-021-01048-3
73. Amos GCA, Logan A, Anwar S, *et al*. Developing standards for the microbiome field. *Microbiome*. 2020;8(1):98. https://doi.org/10.1186/s40168-020-00856-3
74. Mooij CF, Cheetham TD, Verburg FA, *et al*. 2022 European Thyroid Association Guideline for the management of pediatric Graves' disease. *Eur Thyroid J*. 2022;11(1):210073. https://doi.org/10.1530/ETJ-21-0073
75. Cheetham TD, Cole M, Abinun M, *et al*. Adjuvant rituximab-exploratory trial in young people with Graves disease. *J Clin Endocrinol Metab*. 2022;107(3):743-754. https://doi.org/10.1210/clinem/dgab763
76. Razvi S, Weaver JU, Pearce SH. Subclinical thyroid disorders: significance and clinical impact. *J Clin Pathol*. 2010;63(5):379-386. https://doi.org/10.1136/jcp.2008.057414
77. Ursem SR, Boelen A, Bruinstroop E, *et al*. A systematic review of subclinical hyperthyroidism guidelines: a remarkable range of recommendations. *Eur Thyroid J*. 2024;13(3):240036. https://doi.org/10.1530/ETJ-24-0036
78. Mendes D, Alves C, Silverio N, Batel Marques F. Prevalence of undiagnosed hypothyroidism in Europe: a systematic review and meta-analysis. *Eur Thyroid J*. 2019;8(3):130-143. https://doi.org/10.1159/000499751
79. Liu H, Li W, Zhang W, Sun S, Chen C. Levothyroxine: conventional and novel drug delivery formulations. *Endocr Rev*. 2023;44(3):393-416. https://doi.org/10.1210/endrev/bnac030