

# A 2023 International Survey of Clinical Practice Patterns in the Management of Graves Disease: A Decade of Change

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## Abstract

**Context:** Over the past several decades, there have been indications of potential shifts in the diagnostic strategies, treatment, and monitoring of patients with Graves disease (GD).

**Objective:** To evaluate current practices in managing GD and compare them to previous surveys

**Methods:** We used a global online survey of endocrinologists to assess shifts in the diagnosis, monitoring, and treatment in a typical patient with GD, as well as treatment variation in 5 different clinical scenarios.

**Results:** A total of 1252 respondents from 85 countries completed the survey. Methods used to diagnose an uncomplicated GD case have changed over the past decade, reflecting increased use of thyrotropin receptor antibody (TRAb) and reciprocal decreases in nuclear medicine studies. The preferred mode of therapy for uncomplicated GD was antithyroid drugs (ATDs) by 91.5% of respondents, radioactive iodine (RAI) therapy by 7%, and thyroidectomy by 1.5%. Compared with previous surveys, the use of RAI as a first-line choice decreased in all geographic regions. The United States had the sharpest decline in the selection of initial therapy with RAI, decreasing from 69% in 1990 to 11.1% in 2023. In patients with persistent TRAb positivity after 18 months, 68.7% of respondents would continue the use of ATDs. After a relapse of GD, resumption of ATDs was selected by 59.9% of respondents. In patients with active thyroid eye disease or planning pregnancy, ATDs were the first choice (67.5% and 72.8%, respectively), and thyroidectomy emerged as the second choice (22.9% and 15.6%, respectively).

**Conclusion:** Paradigm shifts have occurred in the management of uncomplicated GD and its variants, as well as the response to persistent and recurrent hyperthyroidism.

**Key Words:** Graves disease, hyperthyroidism, thyroid eye disease, antithyroid drug therapy, radioiodine therapy, pregnancy

**Abbreviations:** AACE, Association of Clinical Endocrinology; ATA, American Thyroid Association; ATD, antithyroid drug; CBM, carbimazole; ESA, Endocrine Society of Australia; ETA, European Thyroid Association; GD, Graves disease; KTA, Korea Thyroid Association; LATS, Latin America Thyroid Society; MMI, methimazole; PTU, propylthiouracil; RAI, radioactive iodine; RAIU, radioactive iodine uptake; SBEM, Brazilian Society of Endocrinology and Metabolism; T4, thyroxine; TED, thyroid eye disease; TRAb, thyrotropin receptor antibody; TSH, thyrotropin (thyroid stimulating hormone); TSI, thyroid stimulating immunoglobulin.

Graves disease (GD) is an autoimmune disease and is the most common form of hyperthyroidism (1), with an annual incidence of 30 to 50 per 100 000, and a decidedly female predominance. The treatment of GD has evolved over the last century, especially after the introduction of radioactive iodine (RAI) therapy in the 1940s and antithyroid drug (ATD) therapy in the 1940s and 1950s. Over that period of time, treatment preferences have changed in the United States as well as the rest of the world, as reflected in surveys conducted among endocrinologists (2–7). In general, international surveys have shown that physicians living in the United States are traditionally more apt to prescribe RAI as the initial therapy for GD compared with their international colleagues.

Over the past several decades, there have been indications of potential shifts in the utilization of RAI vs ATD to treat

GD in the United States, based on serial clinical practice surveys (4, 7) and insurance claims data (8). In addition, perceptions about the relationship between long-term ATD therapy and the chances of remission have changed, with recent randomized controlled trial data (9) and case series data (10) suggesting that the likelihood of remission increases after many years of continuous treatment.

Concern over a possible increased risk of solid tumors in patients treated with RAI for hyperthyroidism has been another factor potentially impacting therapeutic decision-making (11, 12), as is the potential risk of new or worsened thyroid eye disease (TED) observed following RAI therapy (13–15). The relative importance of these various patient and provider-specific contributors to changes in treatment preference for GD is unknown.

Recent data pertaining to the management of GD in pregnancy and in older persons have presented new questions about optimal management in these subgroups. The recognition of teratogenic effects of both methimazole (MMI) and propylthiouracil (PTU) (16, 17) have led to changes in clinical practice guidelines related to the use of ATDs during pregnancy (18, 19), but it is unclear to what extent this guidance has affected actual clinical practice. The management of GD patients with TED has also changed dramatically in the past 5 years with the introduction of new therapeutic agents, although current global availability and affordability of these agents remains severely limited (20).

To further define the changing landscape in the management of GD, we conducted an international survey of endocrinologists and allied specialists in order to 1) examine current management practices in typical GD; 2) evaluate practice modifications in response to TED, pregnancy, older age, and persistent or relapsing GD; 3) examine trends in the management of GD compared to prior surveys over the past 30 years; 4) explore factors influencing current patient and provider preferences for the treatment of GD; and 5) assess international differences in the selection of primary therapy for GD.

## Methods

### Survey Methodology

The study was conducted using a web-based survey management service (SurveyMonkey, Palo Alto, California; [www.SurveyMonkey.com](http://www.SurveyMonkey.com)), and consisted of 31 questions involving the management of an index case of GD (Table 1), including preferred diagnostics, treatment choices, and monitoring. Five variants of the index case were then presented, including active TED, pregnancy, older age, persistent disease after ATDs, and recurrent GD. Respondent demographics were collected including age, gender, years of practice, world region of practice, and professional association affiliations.

### Question Design Strategy

When feasible, survey questions were similar or identical to those used in our earlier survey (7) in order to assess interval change. Most questions required selection of one best answer among multiple choices. Questions pertaining to diagnostic testing or specific therapies among multiple available options permitted multiple selections. A question dealing with patient and provider preference requested a ranking of several potential influences in order of importance. Survey questions were carefully constructed to avoid phrasing that could potentially bias responses and included a wide range of answers, also to avoid bias. The total time of the survey was beta tested to be approximately 10 minutes. The complete survey in PDF form is available in the Supplement section (21).

### Outreach to Potential Respondents

The target groups for the survey were clinically active international members of the American Association of Clinical Endocrinology (AACE), Endocrine Society (TES), American Thyroid Association (ATA), European Thyroid Association (ETA), European Society of Endocrinology (ESE), British Thyroid Association (BTA), Latin America Thyroid Society (LATS), Brazilian Society of Endocrinology and Metabolism (SBEM), Asia and Oceania Thyroid Association (AOTA), Japan Thyroid Association (JTA), Korea Thyroid Association

**Table 1. Graves disease index case**

A 42-year-old woman presents with moderate hyperthyroid symptoms of 2 months duration. She is otherwise healthy, takes no medications, and does not smoke cigarettes. She has 2 children, the youngest of whom is 10 years old, and does not plan on being pregnant again. This is her first episode of hyperthyroidism. She has a diffuse goiter, approximately 2 to 3 times normal size, pulse rate of 105 beats per minute, and has a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal (free T4 = 3.6 ng/dL, normal range = 1.01-1.79 ng/dL [46.33 pmol/L; normal range = 12.99-23.03 pmol/L]), with an undetectable thyrotropin level (TSH < 0.01 mIU/liter).

(KTA), Endocrine Society of Australia (ESA), New Zealand Society of Endocrinology (NZSE), Iranian Endocrine Society (IES), Society for Endocrinology Metabolism and Diabetes of South Africa (SEMDSA). Respondents were contacted according to the current bylaws and philosophies of each society. Most societies agreed to send the survey link directly to members by email, including AACE, ATA, ETA, EES, LATS, SBEM, KTA, ESA, New Zealand Society of Endocrinology, Iranian Endocrine Society, and Society for Endocrinology Metabolism and Diabetes of South Africa. The Endocrine Society permitted posting of the survey link on 2 occasions on their community webpage, specifically targeting individuals interested in thyroid disease. Outreach to Chinese endocrinologists was facilitated by Haixia Guan, MD, PhD, who kindly forwarded the survey link to 110 practicing endocrinologists across all 31 provinces within China, including members of the Chinese Endocrine Society (CSE).

### Collection and Summary of Responses

The survey was open from May 1 to August 31, 2023. Only one response from the same IP address was permitted. All responses were anonymous and stored electronically on the SurveyMonkey server.

### Geographical Region of Respondents

Respondents were grouped according to the United Nations country grouping into the following geographical regions: Africa, Asia, Europe, Latin America, the Middle East, North America, and Oceania.

### Statistical Analysis

Summary statistics were prepared for responses to each question. Since not every participant responded to every question, the response to each question was presented as a percentage (the number of respondents giving any specific response was divided by the total number of responses for that question). Statistical analysis explored the relationship between the categorical variables of respondent age, gender, geographical location, and society affiliation with the choices of diagnostic testing, primary therapy of the index case and variants, preferred ATD, dose and duration of ATD therapy, and the adjunctive use of ATDs. When necessary, the chi-square test or Fisher exact test were applied to compare gender, age grouping, and geographical region proportions. The Cramer V test indicated the degree of association between categorical variables. Data were analyzed using SAS System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc, 2002-2012, Cary, NC, USA.

## Results

### Response Rate and Society Membership

Among 1429 respondents who began the survey, 1252 (87.6%) completed the full survey. Respondents who provided society membership data (n = 1239) consisted of 48.5% (602/1239) Endocrine Society members, 20.9% (260/1239) AACE members, 20.5% (254/1239) ATA members, 12.1% (151/1239) ETA members, 10.5% (131/1239) SBEM members, 9.6% (119/1239) Asia and Oceania Thyroid Association members, 9.4% (117/1239) LATS members, 3.3% (42/1239) ESA members, 2.3% (29/1239) European Society of Endocrinology members, 1.9% (24/1239) KTA members, 1.6% (20/1239) CSE members, and fewer than 20 respondents from several additional professional societies. Membership in more than one society was noted by 38.1% (473/1239) respondents; 15.7% (195/1239) respondents did not specify society memberships. Individual society response rates, calculated as the number of respondents divided by the published number of society members is shown for the top responding societies in Supplementary Table S1 (21).

### Respondent Demographics

Respondents (Table 2) were 58.1% (728/1252) women, 40.6% men (508/1252); 1.3% (16/1252) declined to answer. Respondent age groupings were ≤ 35 years (13.2% [165/1244]), 36 to 50 years (45.0% [560/1244]), 51 to 65 years (27.6% [344/1244]), and > 65 years (14.1% [175/1244]). Responses to the survey were submitted from 85 different countries. The geographical regions of the respondents' practices by United Nations categories included Latin America (25.9% [323/1248]), Asia (24.6% [(307/1248)], North America (21.1% [263/1248]), Europe (13.6% [170/1248]), Oceania (6.8% [85/1248]), the Middle East (5.7% [71/1248]), and Africa (2.3% [29/1248]). Responses from Africa and the Middle East were pooled for summary statistics, given the low number of responses from Africa. The type of medical practice was reported by 1248 respondents, including 92.7% (1157/1248) adult endocrinologists, 3.0% (37/1248) general surgeons or head and neck surgeons, 1.8% (23/1248) general internists, 1.4% (17/1248) pediatric endocrinologists, and 1.1% (14/1248) nuclear medicine physicians. Most respondents 65.2% (815/1250) reported seeing between 1 and 5 new GD patients per month.

### Diagnostic Evaluation of the Index Case

Figure 1A shows the percentage of respondents ordering the specified laboratory tests. Among 1429 respondents completing this section, repeat confirmatory measurement of free thyroxine (T4) was requested by 49.4% (706/1429), repeat thyrotropin (TSH) by 48.6% (694/1429), measurement of total T3 was requested by 27.4%, (392/1429), and free T3 by 31.8% (454/1429). For antibody testing, 77.4% (1106/1429) requested thyrotropin receptor antibody (TRAb) testing, 35.5% (507/1429) requested thyroid stimulating immunoglobulin (TSI) measurement, 48.4% (692/1429) requested thyroid peroxidase antibody (TPO-Ab) testing, and 33.0% (472/1429) requested thyroglobulin antibody (TgAb) testing. At least one test of TSH-receptor (TSH-R) antibodies was requested by 94.2% (1346/1429) of respondents. Interestingly, 21% of the responders selected both TRAb

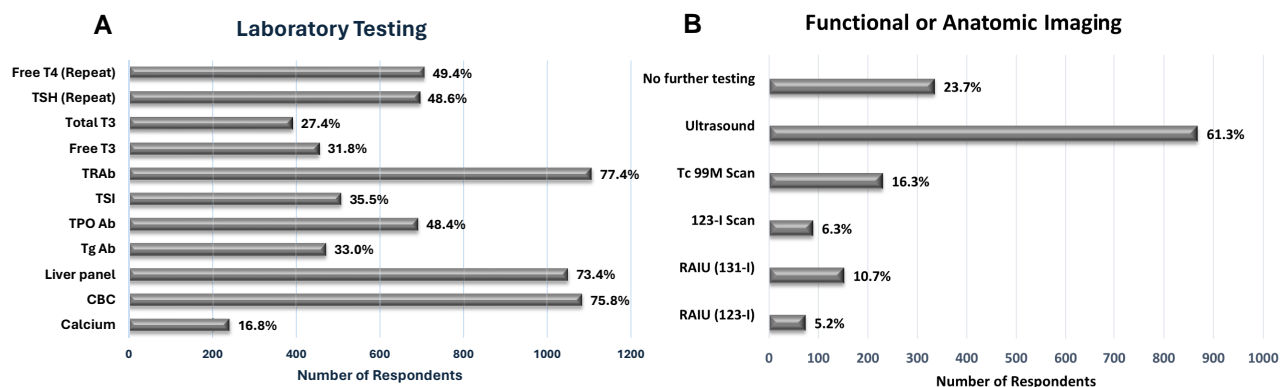
**Table 2. Survey respondent characteristics**

Characteristic	
<b>Gender</b>	
Male	40.6% (508)
Female	58.1% (728)
Prefer not to state	1.3% (16)
<b>Age</b>	
Under 35 years	13.1% (164)
36-50 years	44.6% (559)
51-65 years	27.4% (343)
More than 65 years	14.0% (175)
Prefer not to state	0.9% (11)
<b>Region</b>	
Latin America	25.9% (323)
Asia	24.6% (307)
North America	21.1% (263)
Europe	13.6% (170)
Oceania	6.8% (85)
Middle East	5.7% (71)
Africa	2.3% (25)
<b>Specialty</b>	
Adult Endocrinology	92.7% (1157)
Endocrine Surgery	1.7% (21)
Head and Neck Surgery	1.4% (17)
General Internal Medicine	1.8% (22)
Pediatric Endocrinology	1.4% (17)
Nuclear Medicine	1.1% (14)
<b>Professional associations affiliation</b>	
The Endocrine Society	48.5% (602)
American Association of Clinical Endocrinology	20.9% (260)
American Thyroid Association	20.5% (254)
European Thyroid Association	12.1% (151)
Brazilian Society of Endocrinology and Metabolism	10.5% (131)
Asia and Oceania Thyroid Association	9.6% (119)
Latin America Thyroid Association	8.6% (117)
Other or None	23.3% (333)

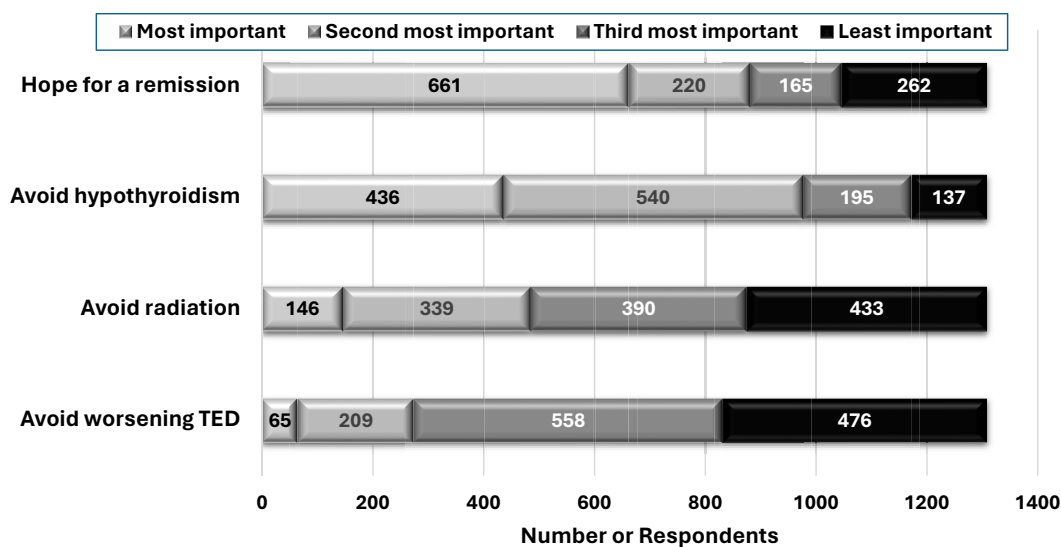
Missing data: gender (177), age (177), region (185), specialty (181), professional associations affiliations (90).

and TSI. Analyzing the data on choice of thyroid antibodies (TRAb and TSI), there was no significant association between age, gender, and geographical localization. Baseline liver panels and complete blood count would be requested by 73.4% (1049/1429) and 75.8% (1083/1429), respectively, and calcium testing by 16.8% (240/1429). No variable (gender, age, geographical localization, professional organization) was significantly related to these laboratory testing choices.

Figure 1B shows anatomic and functional testing preferences for the index case. Among 1415 respondents completing this section of the survey, 61.3% (868/1415) would obtain a thyroid ultrasound, and 15.9% (225/1415) would obtain radioactive iodine uptake (RAIU), two-thirds of whom preferred <sup>131</sup>I RAIU, and one-third <sup>123</sup>I RAIU. A thyroid scan would be obtained by 23.6% (334/1415) respondents, 16.3% (231/1415) selecting only Tc-99m, 6.3% (89/1415)



**Figure 1.** Percentage of participants who would obtain the listed laboratory test (A) or functional and anatomic study (B) in a patient with uncomplicated GD. Abbreviations: RAIU radioactive iodine uptake; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; TSI, thyroid stimulating immunoglobulins.



**Figure 2.** The relative importance of factors impacting the selection of primary therapy in uncomplicated GD. Respondents were asked to rank 4 possibilities by level of importance, from most important to least important. The choices are shown in order of the number of respondents indicating that a listed rationale is the most important determining factor.

selecting only <sup>123</sup>I, and 1.0% (14/1415) selecting both type of scan. Among respondents not requesting a thyroid scan, 59.9% (659/1101) requested a thyroid ultrasound. Younger aged respondents (26-45 years) would obtain a thyroid ultrasound more frequently compared to older respondents (age 66-80 years) (chi-square *P* = .0001, Cramer V test strong association). Also, respondents from Oceania were less likely to perform ultrasound compared to other regions (chi-square *P* = .0011, Cramer V test weak association). The “no additional imaging” response was selected by 23.7% (335/1415) of respondents; however, 9 of these also selected thyroid ultrasound and several noted in free-text comments that a scan would only be obtained if TSH-R antibodies were negative.

## Therapy

### Preferred Primary Treatment Modality in the Index Case

Among 1353 respondents, ATD therapy was the preferred primary mode of therapy in 91.5% (1238/1353), RAI therapy in 7.0% (95/1353), and thyroidectomy in 1.5% (20/1353).

Geographical differences were noted (Supplementary Fig. S1A-S1H (21)), related to the selection of ATDs or radioiodine, with a consistently low selection of thyroidectomy across all regions. The selection of RAI as primary therapy ranged from a low of 1.8% (3/170) of European respondents to a high of 13.1% (13/99) from pooled Africa and the Middle East respondents, with Asia at 5% (14/306), Oceania 5.9% (5/85), Latin America 7.5% (24/320), and North America at 11.1% (29/261). Female gender and younger age (26-45) were both associated with ATD use in the index case (chi-square < 0.001, Cramer V test weak association). There was no significant association between choice of primary therapy and respondent professional association affiliation.

### Rationale for Selection of Primary Therapy

Among 1308 respondents ranking 4 possible reasons for patients and their providers preferring ATD therapy over RAI, the 2 reasons ranked with the highest importance were 1) a desire to avoid hypothyroidism and 2) a desire to achieve a remission (Fig. 2). The third most frequently cited reason for

selecting ATD therapy was to avoid exposure to RAI, and the reason ranked of least importance was the avoidance of worsening TED related to RAI therapy.

### Preferred Drug and Dosing for ATD Therapy

Among 1344 respondents indicating a specific ATD, MMI was preferred by 84.2% (1132/1344), carbimazole (CBM) by 14.9% (200/1344), and PTU by 0.9% (121/1344). There were no age or gender-related differences in choice of ATD, but regional differences were noted with greater use of CBM among respondents from Oceania and Africa ( $P < .0001$ , Cramer V strong association). Among 1325 respondents selecting an ATD and a starting dose from the range of selections available in the survey, MMI 20 mg once daily was selected by 28.9% (383/1325), followed by MMI 10 mg once daily 14.3%, (189/1325), MMI 30 mg once daily 13.4% (178/1325), and MMI 10 mg twice daily 12.2% (162/1325). Grouping responses by total daily dose of antithyroid drug, a daily dosing of 20 mg of MMI was selected by 40.7% (545/1340) of respondents who provided a preferred dosing regimen either from the survey selection or in free-text comments, followed by MMI 30 mg daily 17.2% (230/1340), and MMI 10 mg daily 14.2% (190/1340). There were no differences in ATD dosing strategies when analyzed by age, gender, or geographical location. Supplementary Tables S2A and S2B list all dose selections by survey respondents (21).

### Monitoring ATD Therapy

Among respondents completing the section on monitoring of ATD therapy, the first check of thyroid hormone levels after starting ATDs would be at 4 weeks by 49.4% (668/1352), 6 weeks by 23.5% (318/1352), 2 weeks by 9.1% (123/1352), and 3 weeks by 5.9% (78/1352). Fewer than 10% of respondents would first check thyroid function tests at 8 weeks or beyond. Once biochemical euthyroidism is attained, thyroid function tests would generally be monitored at 3-month intervals by 56.9% (744/1307) of respondents, every 2 months by 27.1% (354/1307), at 4-month intervals by 9.7% (127/1307), and monthly by 6.3% (82/1307). Routine laboratory monitoring in patients being treated with ATDs included obtaining of a liver panel by 74.4% (1006/1352) of respondents, and complete blood count by 67.1% (906/1351).

Respondents were asked about their approach to a patient taking ATDs who develops a pruritic macular rash that fails to improve with antihistamines. Among 1351 respondents, 61.8% (835/1351) would switch to an alternate ATD, 32.8% (443/1351) would consider an alternate mode of primary therapy, and 5.4% (73/1351) would refer the patient to an allergist for desensitization therapy.

### Adjunctive Therapy With ATDs in Patients Selecting Radioiodine or Thyroidectomy

Respondents were asked about adjunctive use of ATDs before or after RAI therapy. Among 1350 respondents, 54.0% (729/1350) routinely pretreat patients with ATDs prior to RAI therapy, 37.2% (502/1350) only pretreat selected patients, and 8.8% (119/1350) do not pretreat at all before RAI therapy. Regarding the use of ATDs immediately after RAI therapy, among 1348 respondents, 22.8% (307/1348) routinely restart ATDs after RAI, 61.6% (830/1348) use ATDs selectively after RAI, and 15.6% (210/1348) do not restart ATDs

after RAI therapy. Finally, respondents were asked whether they routinely use ATDs to render patients euthyroid before thyroidectomy and 95.9% (1297/1352) replied affirmatively.

## Variations on the Index Case

### Thyroid Eye Disease

The index case was modified to include current tobacco smoking and active TED, consisting of pain with eye movement, moderate scleral injection, eyelid edema (clinical activity score 3), proptosis to 23 mm bilaterally, and normal visual acuity. Respondents were asked about further testing and consultation in the presence of active moderate-severe TED. Among 1306 respondents, orbital computed tomography and/or orbital magnetic resonance imaging would be requested by 47.6% (622/1306), visual field testing would be obtained by 23.4% (306/1306), and referral to an ophthalmologist with TED expertise would be requested by 90.2% (1178/1306). Only 3.8% (50/1306) of respondents would request no further testing or consultation in this circumstance.

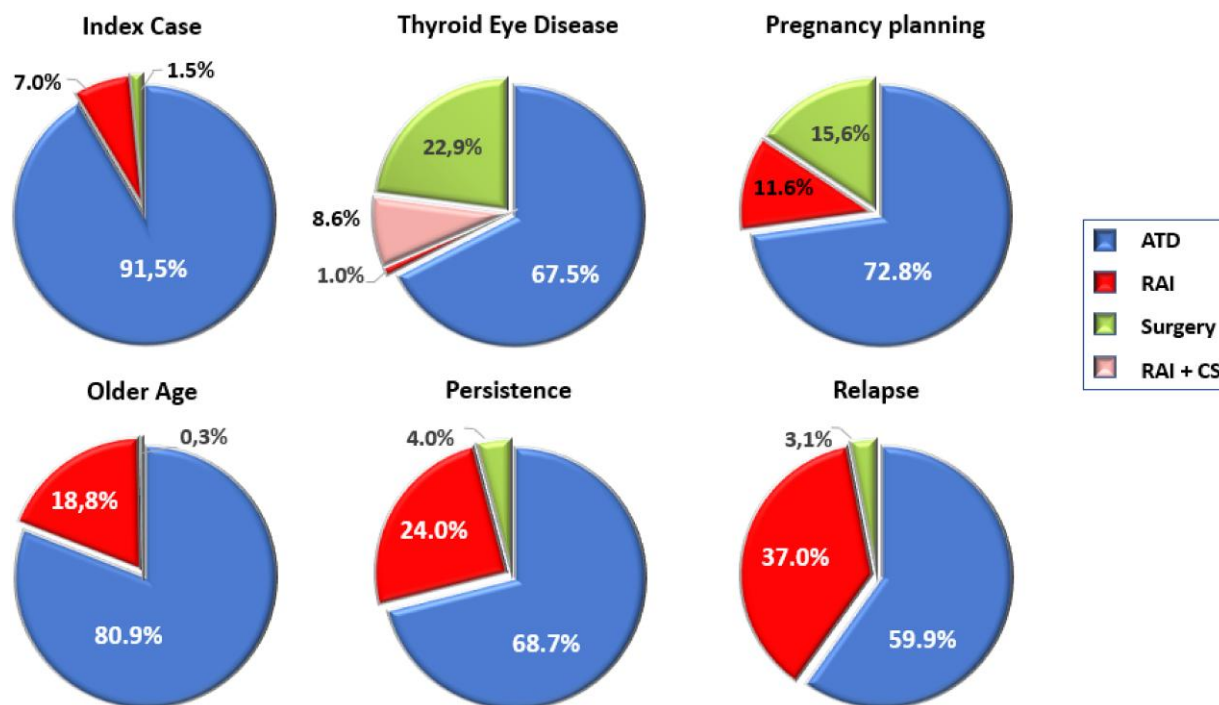
The respondents were next asked about their preferred primary treatment modality for hyperthyroidism in the presence of active TED. Among 1302 respondents, 67.5% (879/1302) would utilize prolonged treatment with ATDs, 22.9% (298/1302) would now utilize thyroidectomy, 8.6% (112/1302) would utilize radioiodine therapy with prophylactic corticosteroids, and 1.0% (13/1302) would treat with radioiodine therapy alone (Fig. 3). Compared to the index case, in the presence of TED, a significantly higher percentage of respondents would use thyroidectomy, and fewer would use ATD or RAI (without corticosteroids) ( $P < .0001$ ).

Treatment choices for TED were next probed. Among 1306 respondents, 95.6% (1249/1306) would advise smoking cessation and 86.4% (1128/1306) would advise use of lubricant eye drops. Selenium therapy would be prescribed by 41.7% (545/1306) of respondents, glucocorticoid therapy by 58.1% (759/1306), and teprotumumab by 16.1% (210/1306) of respondents. More than one answer was permitted for this question. Regional differences in the treatment of TED and the other survey variants are being reported separately. Additional medical therapies were suggested by between 1 and 10 (<1%) respondents in free text and included mycophenolate, rituximab, tocilizumab, statins, cyclosporine, azathioprine, rapamycin, and external radiation therapy.

Finally, we explored which type of provider is responsible for prescribing medical therapy for TED. Among 1306 respondents, 50.6% (661/1306) noted that endocrinologists at their center prescribe the medical therapy used for TED, 45.9% (600/1306) noted ophthalmologists had primary responsibility, 2.7% (35/1306) provided other free-text responses (mostly noting shared prescribing responsibilities between endocrinology and ophthalmology), and 0.8% (10/1306) noted that primary care physicians write for these medications.

### Pregnancy

The survey next explored the management of hyperthyroidism in women with GD who are planning to become pregnant in the next 6 to 12 months, as well as management after conception. ATDs were selected by 72.8% (923/1269) respondents for the woman planning pregnancy in the near future, and compared to the index case, there was a shift toward greater



**Figure 3.** The impact of patient variation on choice of primary therapy for GD. Changes in choice of primary therapy are shown for TED, pregnancy, older age, persistence after a course of ATDs, and relapse in GD patients previously attaining drug-free euthyroidism during a course of ATDs. Statistical analyses of differences in variant primary management from the index case are provided in the text.

use of thyroidectomy 15.6% (198/1269) and RAI therapy 11.6% (147/1269) (Fig. 3). Compared with the index case, in the women planning pregnancy, a significantly higher percentage of respondents would use thyroidectomy or RAI, and fewer would use ATD ( $P < .0003$ ).

When ATDs are recommended to a woman with GD who is planning pregnancy in the next 6 to 12 months, MMI or CBM would be advised by 50.6% (641/1267) respondents, and PTU by 49.4% (626/1267). For women being treated with MMI who become pregnant, 91.9% (1166/1269) respondents would recommend switching to PTU and 8.1% (103/1269) would continue MMI into pregnancy. For women entering the second trimester who were treated with PTU in the first trimester, 69.7% (885/1270) respondents would recommend switching the patient back to MMI, whereas 30.3% (385/1270) would continue with PTU for as long as an ATD was needed during pregnancy.

### Older Age

We sought to determine changes in management of new onset GD in an older patient. We described a 72-year-old woman with hyperthyroid symptoms of 2 months duration and no history of cardiovascular disease or tobacco usage. She was described as having a pulse of 105, a small goiter, and free T4 approximately twice the upper limit of normal, with an undetectable TSH. In this setting, among 1266 respondents 80.9% (1024/1266) would utilize ATDs, 18.8% (238/1266) would select RAI therapy, and 0.3% (4/1266) respondents would utilize thyroidectomy (Fig. 3). Compared with the index case, in the older patient, a significantly higher percentage of respondents would use RAI, and fewer would use ATD or thyroidectomy ( $P < .0001$ ). Female gender and younger age (26-45) were associated with the selection of ATD use as

preferred therapy in this variant (chi-square  $< 0.001$ , Cramer V test weak association).

### Persistence

Respondents were queried as to their general recommendation to patients who fail to achieve a remission and still have positive TSH-R antibodies after 12 to 18 months of continuous ATD therapy. Among 1347 respondents to this question, 68.7% (926/1347) would continue ATDs as long as required to either achieve a remission or maintain euthyroidism, 24.0% (323/1347) would now refer for RAI therapy, 4.0% (54/1347) would refer for thyroidectomy, and 3.3% (44/1347) would increase the ATD dose and add levothyroxine (Fig. 3). Compared to the index case, in the patient with persistent hyperthyroidism after a course of ATDs, a significantly higher percentage of respondents would now utilize thyroidectomy or RAI therapy, and fewer would utilize ATD therapy ( $P < .0001$ ).

### Recurrence

In the last variation, we described a 42-year-old woman who received ATDs for 18 months and this treatment was tapered and successfully stopped when TRAb levels became undetectable, but 8 months later is seen with recurrent overt thyrotoxicosis. Regarding selection of primary therapy for this patient, 59.9% (755/1261) of respondents would restart ATDs as primary treatment, 37.0% (467/1261) would refer the patient for RAI therapy, and 3.1% (39/1261) would now recommend thyroidectomy (Fig. 3). Compared to the index case, in the patient with recurrent hyperthyroidism, a significantly higher percentage of respondents would now utilize thyroidectomy or RAI therapy, and fewer would utilize ATD therapy ( $P < .0001$ ). When asked about the planned duration of

ATD therapy for the patient with recurrent GD before moving on to alternative measures such as RAI therapy or surgery, 43.1% (540/1253) of respondents would use ATDs for 6 to 12 months, 29.1% (365/1253) for 18 to 24 months, and 16.4% (205/1253) would use ATDs indefinitely.

## Discussion

The current study, with more than 1400 respondents from 85 countries, represents the largest and most geographically diverse GD management survey published to date. The study, which was designed to mirror a prior survey (7) published by our group just over one decade ago, allows a determination of clinical practice changes during this time. By including 15 professional societies across the globe, we were able to ensure representation of endocrinologists and allied specialists in Latin America, Asia, Oceania, the Middle East, and Africa to a greater extent than all prior surveys, in addition to continued representation of specialists across North America and Europe. We report remarkable changes in the way GD is diagnosed, the choice of primary therapy in uncomplicated GD and its variants, and the response to persistent and recurrent hyperthyroidism in patients with GD.

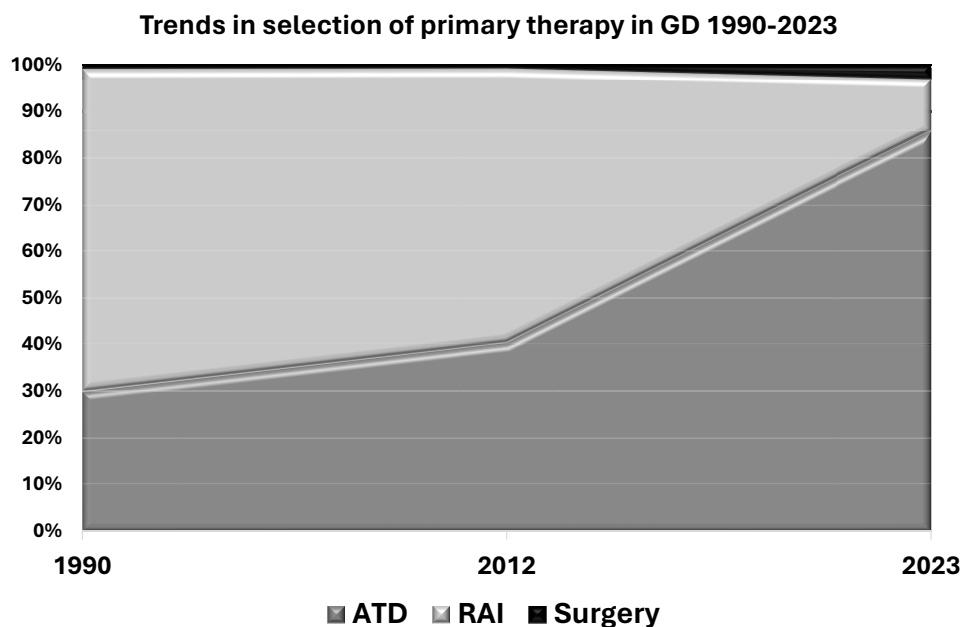
Methods used to make the diagnosis of GD have undergone dramatic shifts over the past decade, reflecting an increased use of laboratory testing and decreased use of nuclear medicine studies. In 2012, 58.1% of respondents would obtain at least one test of TSH-receptor antibodies, and this has increased to 94.2% in the current survey. Conversely, in 2012, a radioactive iodine uptake (RAIU) would be obtained by 47.0% of respondents but this decreased to 15.9% in the current study. Likewise, in 2012 41.9% of respondents would request a thyroid scan (either  $^{123}\text{I}$  or Tc-99m), and this rate fell to 23.6% in the current survey. Finally, in 2012, 25.8% of respondents would obtain a thyroid ultrasound and this has more than doubled to the current rate of 61.3%. Thyroid ultrasound use was more frequent in younger responders than older responders. It is likely that younger respondents have had ultrasonography more fully incorporated into their training and practices, while older endocrinologists are more likely to rely on palpation alone in patients with GD. The TRAb assay was twice as commonly selected as TSI, probably reflecting greater availability and lower costs.

The stark decline in the use of radioiodine in North America both diagnostically and therapeutically in patients with GD is perhaps the most striking change evident from the current study (Fig. 4). This continues a trend from baseline surveys more than 3 decades ago, but the rapid pace of this decline is particularly noteworthy. The 1990 survey found that 69% of US members of the ATA preferred to use RAI therapy in a case of uncomplicated GD (4). In our prior survey published in 2012, we found that 59.7% of US members of the ATA, Endocrine Society, and AACE would prefer RAI therapy as the first-line treatment in patients with GD (7). In 2016, Brito and colleagues published a report of primary treatment selection in 8217 patients with GD based on private insurance and Medicare Advantage claims and found that only 35% of patients had been treated with RAI, 6% with surgery, and the remaining majority with ATDs (8). Our current finding that only 11.1% of North American respondents would recommend RAI therapy in uncomplicated GD demonstrates a rapid acceleration in the rate of decline in RAI therapy selection in North America, as well as further declines

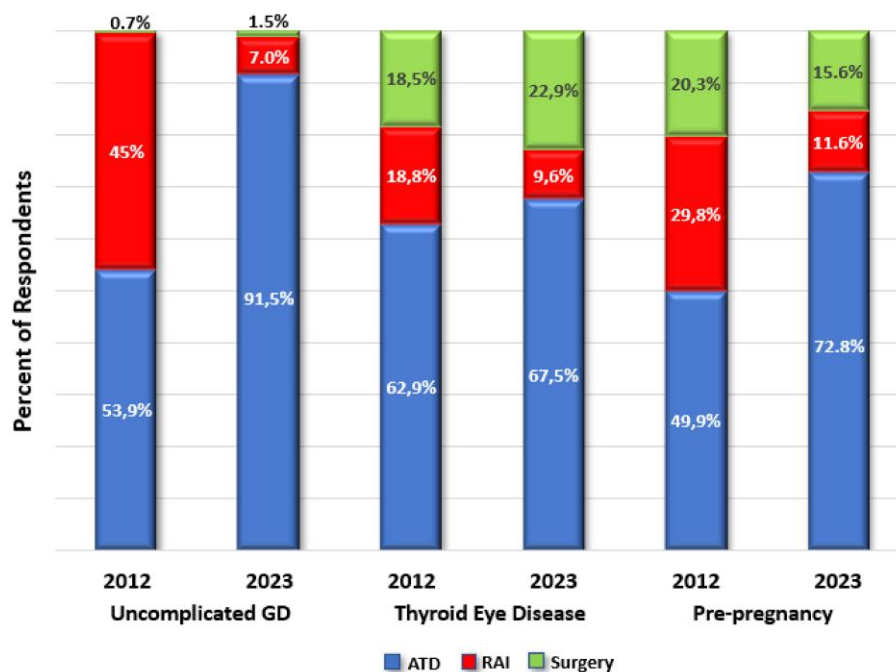
in already lower rates of utilization in all other regions studied. Our finding that younger and female respondents are more likely to choose medical over ablative therapy suggests that the paradigm shifts in the management of GD are at least in part related to changing demographics among practicing endocrinologists (22).

We explored potential motivations for the observed changes in primary treatment preferences. When asked to indicate respondents' reasons for recommending, and their patients' reasons for selecting antithyroid drugs over RAI therapy, the chance of achieving a remission from GD and a desire to avoid permanent hypothyroidism were both cited as the key factors in selecting ATDs (Fig. 2). These results are consistent with a 2021 study from the Netherlands in which patients with GD and their providers were presented with treatment options and potential adverse effects, as well as estimates of the likelihood of remission from GD (including remissions after successful RAI therapy or surgery). Both patients and their physicians indicated that the chance of remission was the most important determining factor, with a preference for ATDs over either surgery or RAI therapy (23). Recent studies have in fact demonstrated that a prolonged duration of ATD therapy is associated with higher rates of remission from GD. A randomized controlled trial found a remission rate of 85% in GD patients treated with MMI for a total of 4.5 to 11 years (9). Another study found that the remission rate of 57.6% after 1 year of ATDs improved progressively with longer durations of therapy to as high as 80.9% if ATDs were continued more than 6 years (10). Patients and providers electing to use primary treatment with ATDs in 2023 should be made aware of the potential need for many years of ATD use if a remission is the ultimate goal. In terms of the avoidance of hypothyroidism as a rationale for avoiding RAI therapy, this expectation may not be consistent with the actual outcomes (24). A long-term follow-up report for a large cohort of GD patients found that only 40% of patients initially treated with ATDs were euthyroid without thyroid medications 6 to 10 years later (25). Another combined series of patients with GD treated to an initial remission from hyperthyroidism found an estimated "cure" rate of approximately 27% (26). Finally, a recent report of outcomes in patients with GD after a 25-year follow-up found that only 34% had normal thyroid function without the need for thyroid medication (27), since many of these patients had eventually been treated with RAI or surgery. In the present report, the index case did not have major risk factors for developing TED; this is a potential reason that concern for worsening TED was not as prominent a factor in the selection of ATD therapy.

The ramifications of the paradigm shift away from RAI therapy are substantial. If one assumes an annual incidence of GD of as high as 50 cases per 100 000 persons and a US adult population of 258 million persons, then a decrease from 60% to 11% utilization of RAI therapy translates to approximately 63 200 fewer patients treated with RAI each year in the United States, and a proportionate increase in the number of patients treated with ATDs. Since our survey shows that 50% to 60% of patients treated with RAI therapy are pretreated with ATDs, the additional exposure to ATDs in the United States is approximately 25 000 to 32 000 patients annually. If serious adverse effects associated related to ATD use are considered, the trend in primary management should lead to an additional 50 to 160 cases of agranulocytosis, and 25 to 65 additional cases of ATD-associated liver injury per year in the United States alone, assuming the incidence of agranulocytosis



**Figure 4.** Changes in selection of primary therapy for GD in North America 1990-2023. The dates shown reflect the publication dates for the prior surveys (4, 7) as well as the current study. Abbreviations: ATD, antithyroid drugs; RAI, radioactive iodine therapy.



**Figure 5.** Changes in primary therapy selections from 2012-2023 in uncomplicated GD, GD complicated by TED, and in women planning pregnancy over the next 6-12 months. Abbreviations: ATD, antithyroid drugs; RAI, radioactive iodine therapy; TED, thyroid eye disease.

and liver injury related to ATD therapy to be 0.2% to 0.5% and 0.1% to 0.2%, respectively (28). Real-world data are needed to examine this potential change in overall risk related to the management of GD in the United States and elsewhere. Potential cardiovascular consequences related to the increased ATD use for GD in the elderly are discussed later.

Additional shifts in the management of uncomplicated GD over the past decade are notable from the current study. A higher percentage of respondents report routinely monitoring a liver panel (74.4% vs 53.8% in 2012) or a complete blood

count (67.1% vs 40.2% in 2012) during ATD therapy. The use of adjunctive ATDs before or after RAI therapy has also changed, with a higher percentage of respondents now routinely pretreating with ATDs (54.0% vs 37.7% in 2012), and inversely fewer respondents reserving pretreatment for selected higher risk patients (37.2% vs 49.6% in 2012). It is possible that this more cautious approach reflects a greater percentage of higher risk patients among the minority of patients currently selected for RAI therapy, but this is not discernable from currently available data.



The presence of active TED impacted respondents' selection for primary management of hyperthyroidism, with a 15-fold increased use of thyroidectomy compared to the index case, largely at the expense of ATDs. The selective use of thyroidectomy in the setting of active TED could be justified as an effective treatment for hyperthyroidism with no impact on the clinical course of TED. Similarly low percentages of respondents would use RAI in the presence of TED, and most of these would recommend concurrent prophylactic corticosteroids to prevent worsening of TED. In comparison to 2012, there is a reduction in the use of RAI in patients with TED by nearly 50%, even with prophylactic glucocorticoids, with a reciprocal and nearly equal increases in the use of ATDs and thyroidectomy, respectively (Fig. 5). Shared management of TED by endocrinologists and ophthalmologists was evident in responses to the survey, with primary responsibility for medical management nearly evenly shared. In the patient described in the variant with moderate active TED, the majority of respondents would treat with glucocorticoid therapy, with fewer than 1 in 5 selecting teprotumumab therapy. The 2022 ATA-ETA Consensus Statement on the Management of TED recommended the use of teprotumumab as a preferred therapy, when available, in patients with active moderate to severe TED with significant proptosis and/or diplopia (29). The relatively modest selection of teprotumumab in the current survey likely reflects limited availability outside of the United States and the high cost of this therapy, which is approximately 2000 times more expensive than IV-glucocorticoids (29). Similar regional differences in the relative preferences of glucocorticoids and teprotumumab were noted in another recent survey and cost was the most important barrier to the use of teprotumumab among North American respondents (30). More than 40% of respondents chose sodium selenite as a treatment option. Although there was a predominance among European respondents, 30% to 40% of responders from other regions also selected selenium. Despite the scant evidence of improvement in cases of moderate to severe TED with selenium, especially in North America where there is dietary selenium sufficiency, its low cost, negligible side effects, and easy access may influence the decision to recommend it.

The optimal management of a woman with GD planning pregnancy in the near future or already pregnant remains controversial. Clinical practice guidelines recommend avoiding MMI in the first trimester of pregnancy due to a higher risk of embryopathy from that seen with PTU (18, 19). In order to avoid MMI exposure during early pregnancy, it has been suggested that women take one of several courses, including 1) electing to receive definitive therapy before pregnancy; 2) switching MMI to PTU before pregnancy; 3) switching MMI to PTU as soon as pregnancy is diagnosed; or 4) attempting to stop ATDs all together when pregnancy is diagnosed if hyperthyroidism is mild and well controlled (18, 19). Guidelines have suggested that women requiring ATDs during the first trimester be maintained on PTU for the first 16 weeks, and then either switched back to MMI or continued on PTU (18, 19). Recent meta-analyses have confirmed that the risk of embryopathy is higher with MMI than PTU and interestingly, infants born to women exposed to both ATDs during the first trimester appear to have a higher rate of malformations than those exposed to either ATD alone (31, 32). As these analyses reflect retrospective data and are subject to potential confounders, it is not possible to assign causality between the process of ATD switching in early pregnancy and

the higher incidence of embryopathy in women exposed to both ATDs in early pregnancy. In a recent cohort including 4712 pregnant patients with a history of current or prior hyperthyroidism, those managed before conception with thyroidectomy or RAI therapy experienced inadequately controlled thyroid function during pregnancy more frequently than those maintained on ATDs (33). Another study examined the effect of stopping ATDs in early pregnancy and found that rebound hyperthyroidism occurred in nearly one-third and was associated with adverse pregnancy outcomes (34). Respondents to the current survey would recommend thyroidectomy in the pre-pregnant woman at an approximately 10-fold higher rate than in the index case, although this rate is still low at 15.6%, and lower than in the 2012 survey, which was 20.2%. Also, compared to the 2012 survey, more women would be maintained on ATDs before pregnancy (73% vs 50% in 2012) and fewer patients would be referred for RAI therapy (12% vs 30% in 2012) (Fig. 4). Half of respondents to the current survey would preemptively switch a woman from MMI or CBM to PTU in the pre-pregnancy period, which was similar to the rate in 2012. For those women taking MMI upon entering pregnancy, more than 90% would be switched to PTU in the first trimester, which was greater than the switch rate of 76% in 2012.

In the case of the older patient with GD, respondents generally continued to favor ATDs but were more than twice as likely to recommend RAI therapy than in the index case. While this possibly relates to a greater urgency to restore euthyroidism in the elderly, our survey did not explore the rationale for this choice. Data from 2 recent large cohorts of patients with GD have suggested higher rates of cardiovascular morbidity in patients treated with long-term ATDs compared to successful therapy with RAI (35, 36). The adverse events appeared related to inadequate control of hyperthyroidism, as worse cardiovascular outcomes were also seen in patients treated unsuccessfully with RAI therapy. In the second cohort, an association was found between the duration of ATD therapy and the risk of developing heart failure (36). While both studies involved patients across the age spectrum, it can be expected that older patients would be particularly susceptible to cardiovascular effects related to inadequate control of hyperthyroidism.

The willingness to use long-term therapy with ATDs is apparent from the current survey and represents another major paradigm shift in GD management over the past decade. In the 2012 survey, more than 90% of respondents would treat with ATDs for 24 months or less and few respondents selected the survey choice of 36 months before turning to alternate therapies. In the current survey more than two-thirds of respondents would use ATDs as long as it takes to achieve a remission or maintain euthyroidism. The 2016 ATA Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis recommended chronic ATD therapy in patients failing to achieve a remission after 12 to 18 months, but mainly in patients who refuse radioiodine or surgery (18).

Our study has both strengths and limitations. The large number of respondents from a geographically diverse population of endocrinologists and allied specialties surpasses all prior surveys on the management of GD. As opposed to our 2012 survey, in which international respondents were exclusively members of US-based associations, which could potentially introduce bias, in the present study we approached

international associations of thyroidologists and endocrinologists from across the globe in addition to US-based professional societies. Although the percentage of respondents from North America represented was less than in our previous survey, the actual number of respondents from North America was similar (7). In terms of weaknesses, the percentage of members from individual associations participating in the survey was low, representing 4% to 25% of society membership. Secondly, it is not clear to what extent responses to surveys are reflected in real-world practice, although we advised respondents to consider their management of recent patient cases when formulating their responses. Inherent in that directive is the incorporation of recent patient choices in management of their own disease. The trends in management identified in the current survey mirror and extend those seen in earlier insurance claims analysis (37) as well as clinical surveys of patients and their providers (23). In addition, the international nature of the survey and heterogeneous admixture of the respondent health care systems prevented consideration of the influence of practice setting on specific survey responses. Finally, it is not known with certainty what percentage of patients selecting ATD as primary therapy for GD ultimately elect to undergo ablative therapy, which was approximately 50% in 2 recent GD cohorts with long-term follow-up (25, 27).

In summary, in 2024, a typical patient with uncomplicated GD will undergo laboratory testing without nuclear medicine studies to confirm the diagnosis and will have a thyroid ultrasound performed to assess thyroid anatomy. She will most commonly be treated with MMI/CBM until a remission is obtained. Thyroid labs will generally be repeated 4 weeks after starting ATDs and then serial monitoring of thyroid hormone levels will be performed at 3-month intervals, with routine monitoring of a liver panel and complete blood count. If the patient experiences a relapse of GD following attainment of a remission, she will be 6 times more likely to be treated with RAI than at initial presentation, but still more likely to be restarted on ATDs. If a woman taking MMI/CBM is planning a pregnancy in the next 12 to 18 months, she will be 10 times more likely to be referred for thyroidectomy prior to pregnancy, although most will still be managed with ATDs. A woman taking MMI prior to pregnancy will often (50% likelihood) be switched to PTU in advance of the pregnancy. If taking MMI/CBM at the time of pregnancy, she will likely be switched to PTU for the first trimester and then switched back to MMI in the second trimester. If a patient with GD has or develops TED, there is a 15-fold higher likelihood that they will be referred for thyroidectomy but still most TED patients with hyperthyroidism will be managed with antithyroid drugs. If RAI is used in the setting of TED, concurrent prophylactic corticosteroids will nearly always be given. The patient with moderate to severe TED worldwide is more likely to be treated with glucocorticoids than with an IGF-1 receptor antagonist such as teprotumumab, as the latter is not currently widely available and/or affordable.

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## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

## Note

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