Thyroid Disorders

An update for 2017
Discussion today

• Evaluating an asymptomatic patient with incidental findings
• Pregnancy and thyroid
• Thyroid nodules: new tools in the tool kit
• Thyroid cancer: introduce the concept that “less is more”
Times are changing and so should we...

Prepared patients

Hurried Provider

Flood of information

Shanafelt TD et al, Addressing Physician Burnout: The way Forward. JAMA March 2017
RESULTS:
Persons aware of their hypothyroidism, diabetes mellitus or hypertension reported poorer self-rated health than individuals without such conditions. Women with unknown and subclinical hypothyroidism reported better self-rated health than women with normal thyroid status. In women and men, unknown and probable diabetes as well as unknown mild/moderate hypertension was not associated with poorer health. Furthermore, persons with unknown severe hypertension reported better health than normotensive persons.

CONCLUSIONS:
People with undiagnosed but prevalent hypothyroidism, diabetes mellitus and hypertension often have good self-rated health, while when aware of their diagnoses, they report reduced self-rated health. Use of screening, more sensitive tests and widened diagnostic criteria might have a negative effect on perceived health in the population.
45 yo patient, asymptomatic, presents for annual physical exam and is noted to have a 2 cm left thyroid nodule......? Needs evaluation?
## Screening for Thyroid Dysfunction: Clinical Summary of USPSTF Recommendation

<table>
<thead>
<tr>
<th>Population</th>
<th>Nonpregnant, asymptomatic adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>No recommendation.</td>
</tr>
<tr>
<td>Grade: 1 statement (insufficient evidence)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Assessment</strong></td>
<td>Risk factors for an elevated thyroid-stimulating hormone (TSH) level include female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goiter, previous hyperthyroidism, and external-beam radiation in the head and neck area. Risk factors for a low TSH level include female sex; advancing age; black race; low iodine intake; personal or family history of thyroid disease; and ingestion of iodine-containing drugs, such as amiodarone.</td>
</tr>
<tr>
<td><strong>Screening Tests</strong></td>
<td>The primary screening test for thyroid dysfunction is serum TSH testing. Multiple tests over 3 to 6 mo should be performed to confirm or rule out abnormal findings. Follow-up testing of serum thyroxine (T4) levels in persons with persistently abnormal TSH levels can differentiate between subclinical (normal T4) and &quot;overt&quot; (abnormal T4) thyroid dysfunction.</td>
</tr>
<tr>
<td><strong>Treatment and Interventions</strong></td>
<td>Hypothyroidism is treated with oral T4 monotherapy (levothyroxine sodium). Consensus is lacking on the appropriate point for clinical intervention, especially for TSH levels &lt;10.0 mIU/L. Hyperthyroidism is treated with antithyroid medications (e.g., methimazole) or nonreversible thyroid ablation therapy (e.g., radioactive iodine or surgery). Treatment is generally recommended for patients with a TSH level that is undetectable or &lt;0.1 mIU/L, particularly those with overt Graves disease or nodular thyroid disease.</td>
</tr>
<tr>
<td><strong>Balance of Benefits and Harms</strong></td>
<td>The current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant asymptomatic adults.</td>
</tr>
</tbody>
</table>

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to [http://www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org).
The USPSTF concludes with moderate certainty that screening for thyroid cancer in asymptomatic persons results in harms that outweigh the benefits.

The USPSTF found inadequate evidence to estimate the accuracy of neck palpation or ultrasound as a screening test for thyroid cancer in asymptomatic persons.

The USPSTF recommends against screening for thyroid cancer in asymptomatic adults.

It does not apply to persons who:
- experience hoarseness, pain, difficulty swallowing, or other throat symptoms or persons who have lumps, swelling, asymmetry of the neck, or other reasons for a neck examination
- persons at increased risk of thyroid cancer because of a history of exposure to ionizing radiation (eg, medical treatment or radiation fallout), particularly persons with a diet low in iodine, an inherited genetic syndrome associated with thyroid cancer (eg, familial adenomatous polyposis), or a first-degree relative with a history of thyroid cancer.

US Preventive Services Task Force, Recommendation Statement, May 9, 2017
Functional Assessment?
45 yo patient
2 cm nodule
No symptoms

? Thyroid function tests

• TSH
• Free T4
• Total T4- estrogen effect
• Free T4 Index
• Total T3
• Free T3
• Reverse T3- ? Clinical use
• ??? TPO Abs- choose your patient
Interfering substances.....

- **Biotin Treatment Mimicking Graves' Disease.**
  Kummer S, Harnsen D, Distelmaier F.
  PMID: 27532849  [Free Article]
  Similar articles

- **A caution regarding high-dose biotin therapy: misdiagnosis of hyperthyroidism in euthyroid patients.**
  Trambas CM, Sikaris KA, Lu ZX.
  PMID: 27510354  [Free Article]
  Similar articles

- **Factitious Graves' Disease Due to Biotin Immunoassay Interference: A Case and Review of the Literature.**
  Elston MS, Sehgal S, Du Toit S, Yarnley T, Conaglen JV.
  PMID: 27362288  [Free Article]
  Similar articles

- **Radiotherapeutic Effect of Epigallocatechin-3-Gallate on Salivary Gland Dysfunction After Radiodine Ablation in a Murine Model.**
  Choi JS, An HY, Park IS, Kim SK, Kim YM, Lim JY.
  PMID: 27136365  [Free PMC Article]
  Similar articles

- **Misdiagnosis of Graves' Disease with Apparent Severe Hyperthyroidism in a Patient Taking Biotin Megadoses.**
  Barbosino G.
  PMID: 27043844  [Free Article]
  Similar articles

Minkovsky et al, High Dose biotin for secondary progressive MS may interfere with thyroid assays. AACE 2016
**TSH in “Normal US Population”**

Not Gaussian curve …… Tail

Distribution of TSH values by ethnicity (NHANES III)

- Should all patients have a TSH of 2.5 mIU/L
- Simple answer: No
- Individualize
  - Age
  - Sex
  - Autoimmune thyroid disease
  - Pregnancy
  - State of health
  - Medications: amiodarone, lithium

*US Reference Population: Population without thyroid disease, goiter, or taking thyroid medication and without risk factors that include pregnancy, taking estrogen, androgens, or lithium, in the presence of thyroid antibodies and biochemical evidence of hypothyroidism or hyperthyroidism.*
Conclusions:
Changes in serum TSH are often described in elderly subjects; however, their pathophysiologic significance and the possible contributory role of both malnutrition and nonthyroidal illness are still debated. 

............the general assumption is that either hypothyroidism is increasingly prevalent among elderly, or is merely an age-related rise in TSH set point beyond any evidence of thyroid disease.

...... Factors such as lab assessment, sex, ethnicity, diet, education level, medications, socioeconomic status, BMI, and smoking may affect thyroid function resulting in elevated TSH

The controversy....is vast. It includes efforts to define more adequate serum TSH reference intervals for older adults, research into the potential contribution of decreased thyroid function to increased longevity, and the ever-present question of whether or not to treat for a dysfunction that may or may not be present.
Strengths:
- Included a sufficient number of participants to provide good statistical power
- Used validated measures of thyroid-specific quality of life as well as a range of secondary outcomes of clinical relevance

Limitations:
- TSH target of 0.40 to 4.60 mIU per liter with levothyroxine Tx,
- Some authorities have recommended a lower TSH target (e.g., 0.40 to 2.50 mIU per liter).
- Few participants had a baseline TSH level of > 10 mIU per liter, cannot address whether there are benefits in this subgroup.
- Symptom levels at trial entry were low, so cannot exclude the possibility of benefit in persons with more marked symptoms
- Did not measure thyroid antibody levels. Antibody-positive patients are more likely to have progressive hypothyroidism
- The trial was underpowered to detect any effect of LT4 on the incidence of cardiovascular events or mortality.

In conclusion, this trial indicated that treatment with levothyroxine in older persons with subclinical hypothyroidism provided no symptomatic benefits.
The percentage of subjects with an elevated TSH level by sex and decade of age. Percentages of hypothyroidism ranged from 4% to 21% in women and from 3% to 16% in men.

Canaris et al, The Colorado Thyroid Disease Prevalence Study, 2000
From: National Health and Nutrition Examination Survey III Thyroid-Stimulating Hormone (TSH)-Thyroperoxidase Antibody Relationships Demonstrate That TSH Upper Reference Limits May Be Skewed by Occult Thyroid Dysfunction

J Clin Endocrinol Metab. 2007;92(11):4236-4240. doi:10.1210/jc.2007-0287
Alterations in the serum thyroid hormone levels in the non-thyroidal illness syndrome.

Wajner et al, new insights toward the Acute Non-Thyroidal Illness Syndrome. 2012
Expert 1 wanted to Tx

Expert 2 did not want tx

Excellent discussion
2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

Erik K. Alexander,1,* Elizabeth N. Pearce,2,4 Gregory A. Brent, Rosalind S. Brown,4 Herbert Chen,5 Chrysovali Dosiou,6 William A. Grobman,7 Peter Laurberg,8–10 John H. Lazarus,9 Susan J. Mandel,10 Robin P. Peeters,11 and Scott Sullivan12
## Screening in pregnancy - controversial

<table>
<thead>
<tr>
<th>American Association of Clinical Endocrinologists</th>
<th>All women considering becoming pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Endocrine Society</td>
<td>Targeted case finding: (!)</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 30, family history, goiter, TPO +, signs/symptoms</td>
</tr>
<tr>
<td></td>
<td>Head and neck irradiation, thyroid surgery, infertility</td>
</tr>
<tr>
<td></td>
<td>h/o miscarriage or preterm delivery</td>
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<tr>
<td></td>
<td>Area of iodine deficiency</td>
</tr>
<tr>
<td>American College of Obstetrics and Gynecology</td>
<td>In symptomatic women, personal h/o thyroid disease</td>
</tr>
<tr>
<td></td>
<td>Medical conditions associated with thyroid disease (eg. TIDM)</td>
</tr>
<tr>
<td>The Cochrane Collaboration</td>
<td>Targeted screening:</td>
</tr>
<tr>
<td></td>
<td>Women at risk f thyroid disease (GDM)</td>
</tr>
<tr>
<td></td>
<td>Family h/o thyroid disease, symptomatic women</td>
</tr>
<tr>
<td></td>
<td>Personal h/o preterm birth or recurrent miscarriage</td>
</tr>
<tr>
<td>American Thyroid Association</td>
<td>Same as Endocrine Society</td>
</tr>
<tr>
<td></td>
<td>Also morbid obesity: BMI &gt; 40</td>
</tr>
<tr>
<td></td>
<td>Use of amiodarone or lithium</td>
</tr>
</tbody>
</table>
FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.
Fig. 3. Median values (rectangle) versus the range of 2.5th (ellipse, bottom) and 97.5th (ellipse, top) percentiles for each trimester of pregnancy taken from 8 studies of trimesterspecific TSH reference intervals, reported between 2004 and 2009, for women without thyroid peroxidase autoantibodies from iodine-sufficient populations. The dotted horizontal lines show the typical nonpregnant reference range (0.4–4.1 μU/mL). (From Gliñier D, Spencer CA. Serum TSH determinations in pregnancy: how, when and why? Nat Rev Endocrinol 2010;6(9):527; with permission.)
Rec # 29: Subclinical hypothyroidism in pregnancy

(a) LT4 therapy is **recommended** for
   - TPOAb- + women with a TSH greater than the pregnancy-specific reference range
   - TPOAb- - women with a TSH greater than 10.0 mU/L.

(b) LT4 therapy **may be considered** for:
   - TPOAb- + women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range.
   - TPOAb- - women with TSH concentrations greater than the pregnancy specific reference range and below 10.0 mU/L

(c) LT4 therapy is **not recommended** for
   - TPOAb- - women with a normal TSH within the pregnancy-specific reference range
### Defining Normal
- **TSH:**
  - 0.1-2.5
- **Daily iodine:**
  - 250 mcg
- **TSH:**
  - Q 4 weeks if on LT4 Tx

### Hypothyroidism
- **Subclinical**
  - No consensus
  - Except if +TPO Abs > Tx
- **Overt**
  - Treat
- **On replacement**
  - 50-85% will need dose increase
- **On replacement**
  - Q 4 weeks if on LT4 Tx

### Hyperthyroidism
- **PTU and MMI**
  - Both concerning
- **First 16 weeks**
  - PTU
- **Fetal surveillance**
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Antithyroid drugs | Effective treatment to euthyroid state within 1–2 months  
Often induces gradual remission of autoimmunity (decreasing antibody titers)  
Easily discontinued or modified. Treatment easy to take. Relatively inexpensive | Medication adverse effects (mild 5%–8%; severe 0.2%)  
Birth defects associated with use during pregnancy (MMI 3%–4%; PTU 2%–3% though less severe)  
Relapse after drug withdrawal likely in 50%–70% |
| Radioactive iodine | Easy oral administration  
Reduction in goiter size | Repeat therapy at times necessary  
Rising antibody titers following treatment may contribute to worsening orbitopathy or fetal risk | Lifelong need of levothyroxine therapy following ablation |
| Thyroidectomy | Definitive therapy of hyperthyroidism. Stable euthyroid state easily achieved on replacement levothyroxine therapy  
Post surgery, gradual remission of autoimmunity occurs  
Goiter disappears | Life-long need for levothyroxine supplementation | Surgical complications occur in 2%–5%  
Healing and recovery from surgery  
Permanent neck scar |

MMI, methimazole; PTU, propylthiouracil.
Physical Assessment
ATA Management Guidelines for adult patients with thyroid Nodules and thyroid cancer, 2015

Start with TSH

If TSH is low do a thyroid uptake and scan first

If “hot”
Risk of Ca: <1%

ATA THYROID NODULE/DTC GUIDELINES

Suspected Thyroid Nodule
TSH Normal or Elevated (R2C)

Thyroid/Neck Sonography (R6, 21)

No nodule or nodule not meeting FNA size cutoff

High Suspicion Pattern

Intermediate Suspicion Pattern

Low Suspicion Pattern

Very Low Suspicion Pattern

Benign Pattern

FNA ≥ 1 cm (R8A, B)

FNA ≥ 1.5 cm (R8C)

FNA ≥ 2 cm (R8D)

FNA not required (R8E, 8F, 23)
### Table 3. Causes of Thyrotoxicosis

Thyrotoxicosis associated with a normal or elevated RAI uptake over the neck<sup>a</sup>
- GD
- TA or TMNG
- Trophoblastic disease
- TSH-producing pituitary adenomas
- Resistance to thyroid hormone (T₃ receptor β mutation, THRB)<sup>b</sup>

Thyrotoxicosis associated with a near-absent RAI uptake over the neck
- Painless (silent) thyroiditis
- Amiodarone-induced thyroiditis
- Subacute (granulomatous, de Quervain’s) thyroiditis
- Palpation thyroiditis
- Iatrogenic thyrotoxicosis
- Factitious ingestion of thyroid hormone
- Struma ovarii
- Acute thyroiditis
- Extensive metastases from follicular thyroid cancer

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<sup>a</sup>In iodine-induced or iodine-exposed hyperthyroidism (including amiodarone type 1), the uptake may be low.

<sup>b</sup>Patients are not uniformly clinically hyperthyroid. T₃, triiodothyronine.
<table>
<thead>
<tr>
<th>Clinical situations</th>
<th>RAI</th>
<th>ATD</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy*</td>
<td>x</td>
<td>√√/!</td>
<td>√/!</td>
</tr>
<tr>
<td>Comorbidities with increased surgical risk and/or limited life expectancy</td>
<td>√/</td>
<td>√</td>
<td>x</td>
</tr>
<tr>
<td>Inactive GO</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Active GO</td>
<td></td>
<td>b</td>
<td>√</td>
</tr>
<tr>
<td>Liver disease</td>
<td>√√</td>
<td>!</td>
<td>√</td>
</tr>
<tr>
<td>Major adverse reactions to ATDs</td>
<td>√√</td>
<td>x</td>
<td>√</td>
</tr>
<tr>
<td>Patients with previously operated or externally irradiated necks</td>
<td>√√</td>
<td>√</td>
<td>!</td>
</tr>
<tr>
<td>Lack of access to a high-volume thyroid surgeon</td>
<td>√√</td>
<td>√</td>
<td>!</td>
</tr>
<tr>
<td>Patients with high likelihood of remission (especially women, with mild disease, small goiters, and negative or low-titer TRAb)</td>
<td>√</td>
<td>√√</td>
<td>√</td>
</tr>
<tr>
<td>Patients with periodic paralysis</td>
<td>√√</td>
<td>√</td>
<td>√√</td>
</tr>
<tr>
<td>Patients with right pulmonary hypertension, or congestive heart failure</td>
<td>√√</td>
<td>√</td>
<td>!</td>
</tr>
<tr>
<td>Elderly with comorbidities</td>
<td>√</td>
<td>√</td>
<td>!</td>
</tr>
<tr>
<td>Thyroid malignancy confirmed or suspected</td>
<td>x</td>
<td>-</td>
<td>√√</td>
</tr>
<tr>
<td>One of more large thyroid nodules</td>
<td>-</td>
<td>√</td>
<td>√√</td>
</tr>
<tr>
<td>Coexisting primary hyperparathyroidism requiring surgery</td>
<td>-</td>
<td>-</td>
<td>√√</td>
</tr>
</tbody>
</table>

√√ = preferred therapy; √ = acceptable therapy; ! = cautious use; - = not first-line therapy but may be acceptable depending on the clinical circumstances; X = contraindication.

*aFor women considering a pregnancy within 6 months, see discussion in Section [T2].

*bTable 14 describes the use of RAI in GO in detail, considering disease activity, severity, and other risk factors for GO progression.
Physical evaluation of thyroid

A. Palpation of the thyroid from behind
B. Palpation of the thyroid from in front

Ultrasound
CT scan
PET scan

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Features of a Benign Nodule

- Well defined nodule
- Smooth margin
- Thin walled cyst without solid component
- Chunky calcium deposition
- Colloid within nodule
- Normal blood flow
Features of a Malignant nodule

- Poorly defined nodule
- Incomplete margins
- "Microcalcification"—small calcium deposits
- Increasing size over time
- Increased blood flow
- Thick walled cyst
- Enlarged lymph nodes in neck
- Growing into muscle
- Irregular border
Observed versus Expected Changes in Age-Specific Incidence of Thyroid Cancer per 100,000 Women, 1988–2007.

- The observed rates were derived from Cancer Incidence in Five Continents, International Agency for Research on Cancer.
- The expected rates were based on the observation that before the introduction of ultrasonography and other novel diagnostic techniques, thyroid-cancer incidence increased exponentially with age in all countries with available long-term data.
- ………… We hypothesized that the progressive departure of the observed rates from the multistage model was attributable to the increased detection of asymptomatic, nonlethal disease — that is, over diagnosis.
Thyroid US

Discuss findings with patient

- size: < 1 cm
- Features:
  - < 1%
  - < 3%
- Give option of US follow-up
  - Depends on comfort
Techniques for FNA

Manual

Ultrasound-Guided
Fine Needle aspiration

- Experienced Provider
- Palpation or US guided
- Cytology/ Additional tests
Neck ultrasonography sonographic pattern

- Benign or very low suspicion
  - <3% risk of malignancy
  - Purely cystic nodules
  - Spongiform or partially cystic nodules

- Low suspicion
  - 5-10% risk of malignancy
  - Partially cystic nodules with eccentric solid areas
  - Solid isoechoic or hyperechoic nodules

- Intermediate suspicion
  - 10-20% risk of malignancy
  - Solid hypoechoic nodules with smooth margins

- High suspicion
  - >70-90% risk of malignancy
  - Solid hypoechoic nodules or solid hypoechoic component of a partially cystic nodule with one or more of the following: irregular margins, microcalcifications, taller than wide shape, rim calcifications with small extrusive soft-tissue component, extrathyroid extension, and suspicious lymph nodes

>1.5 cm

- Benign (DC 2)
  - <3% risk of malignancy
  - Surveillance

>1 cm

- Non-diagnostic (DC 3)
  - 1-4% risk of malignancy
  - Repeat FNAC

>1 cm

- AUS or FLUS (DC 4)
  - 5-25% risk of malignancy
  - Surveillance or surgery

- FN or SFN (DC 5)
  - 15-50% risk of malignancy
  - Surgery

- Suspicious (DC 6)
  - 60-75% risk of malignancy
  - Surgery

- Malignant (DC 6)
  - 70-95% risk of malignancy
  - Surgery
It is still under debate whether molecular testing should be used in routine clinical practice. Therefore, molecular testing must be always performed and interpreted within the context of the clinical, radiographic, and cytologic findings.
A Thyroid Carcinomas

- Papillary thyroid carcinoma, 84%
- Medullary thyroid carcinoma, 4%
- Follicular thyroid carcinoma, 2%
- Poorly differentiated thyroid carcinoma, 6%
- Hürthle-cell carcinoma, 2%
- Anaplastic thyroid carcinoma, 1%
- Other, 1%

B Papillary Thyroid Carcinoma

- Follicular variant, infiltrative (BRAF-V600E), 6%
- Tall cell (BRAF), 7%
- Other, <1%
- Follicular variant, encapsulated with invasion (RAS or PAX8–PPARγ), 4%
- Follicular variant, encapsulated without invasion (RAS), 17%
- Classical variant (BRAF-RET fusions), 32%
- Microcarcinoma (all variants), 33%

C NIFT-P — An Indolent Neoplasm

- Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P)

Biologic and Clinical Perspectives on Thyroid Cancer
James A. Fagin, M.D., and Samuel A. Wells, Jr., M.D.
It’s Not Cancer: Doctors Reclassify a Thyroid Tumor

By GINA KOLATA  APRIL 14, 2016
Their conclusion, and the data that led to it, was reported Thursday in the journal JAMA Oncology. The change is expected to affect about 10,000 of the nearly 65,000 thyroid cancer patients a year in the United States. It may also offer grist to those who have been arguing for the recategorization of some other kinds of cancer, including certain lesions in the breast and prostate.

The reclassified tumor is a small lump in the thyroid that is completely surrounded by a capsule of fibrous tissue. Its nucleus looks like a cancer but the cells have not broken out of their capsule, and surgery to remove the entire thyroid followed by treatment with radioactive iodine is unnecessary and harmful, the panel said. They have now renamed the tumor. Instead of calling it “encapsulated follicular variant of papillary thyroid carcinoma,” they now call it “noninvasive follicular thyroid neoplasm with papillary-like nuclear features,” or NIFTP. The word “carcinoma” is gone.
Changing management for metastatic thyroid cancer
- However clinical trials have shown limited beneficial effect on progression free survival in radioiodine refractory differentiated or medullary TC
- Still lacking convincing evidence of their impact on overall survival
- Do not have any evidence-based medicine criteria, when to start MKIs and which drug to use
- Many questions for the next year?
Conclusions

• An annual physical exam in an asymptomatic patient: include a good neck check
• Initial laboratory test: TSH, keeping in mind that it is a “screening test”
• Pregnancy is an altered physiological state and nonpregnant values should not be used
• Thyroid nodules: evaluate for functionality and malignancy
• Thyroid cancer incidence is increasing and we need better studies to define the reason
• Thyroid cancer management is now focused on “less is more”. Less surgery, less radiation, and less TSH suppression
Isn't it funny how day by day nothing changes, but when you look back, everything is different.

CS Lewis

FIG. 1. Algorithm for evaluation and management of patients with thyroid nodules based on US pattern and FNA cytology. R, recommendation in text.
Thank you