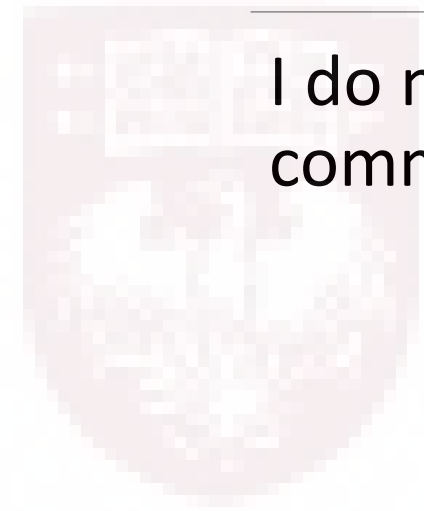


34 year-old Female with Thyroid Cancer

KATIE O'SULLIVAN, MD
FELLOW, ADULT/PEDIATRIC ENDOCRINOLOGY
UNIVERSITY OF CHICAGO ENDORAMA
THURSDAY, SEPTEMBER 15TH, 2016

Disclosures:

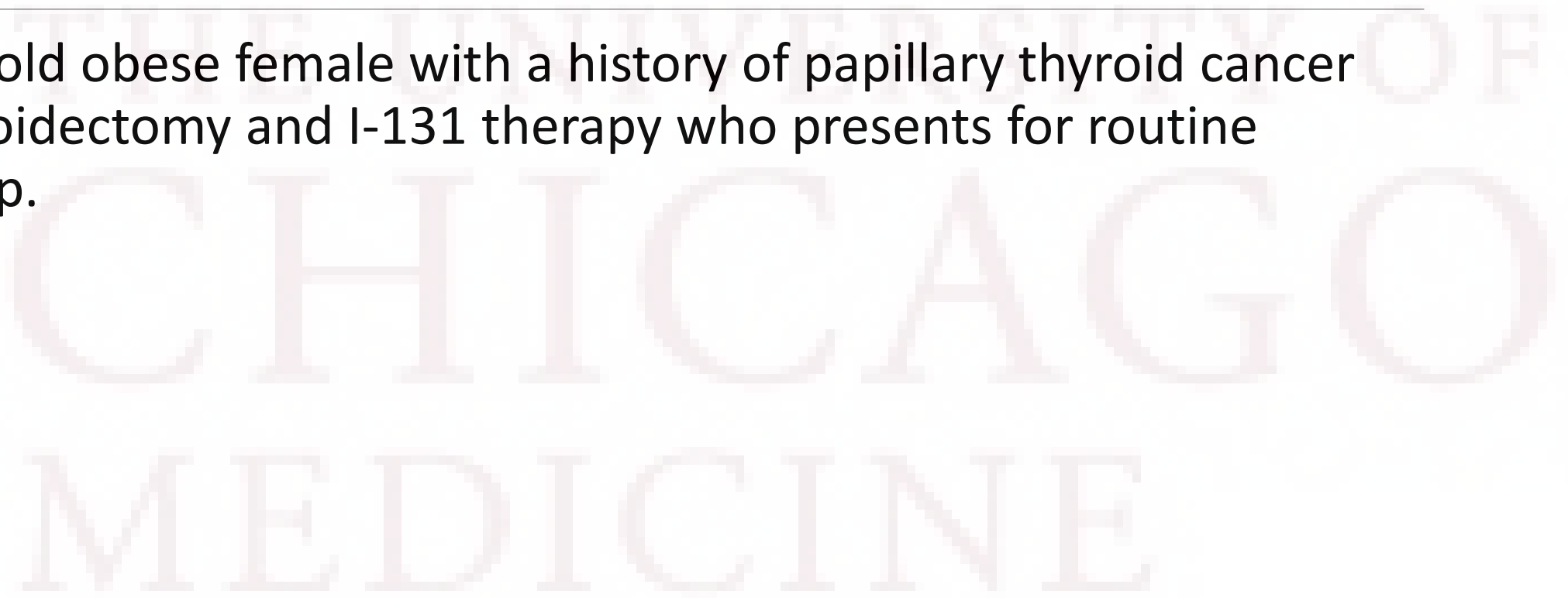
I do not have any relevant financial relationships with any commercial interests.



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Chief Complaint:

34 year-old obese female with a history of papillary thyroid cancer s/p thyroidectomy and I-131 therapy who presents for routine follow-up.



HPI: Thyroid Cancer

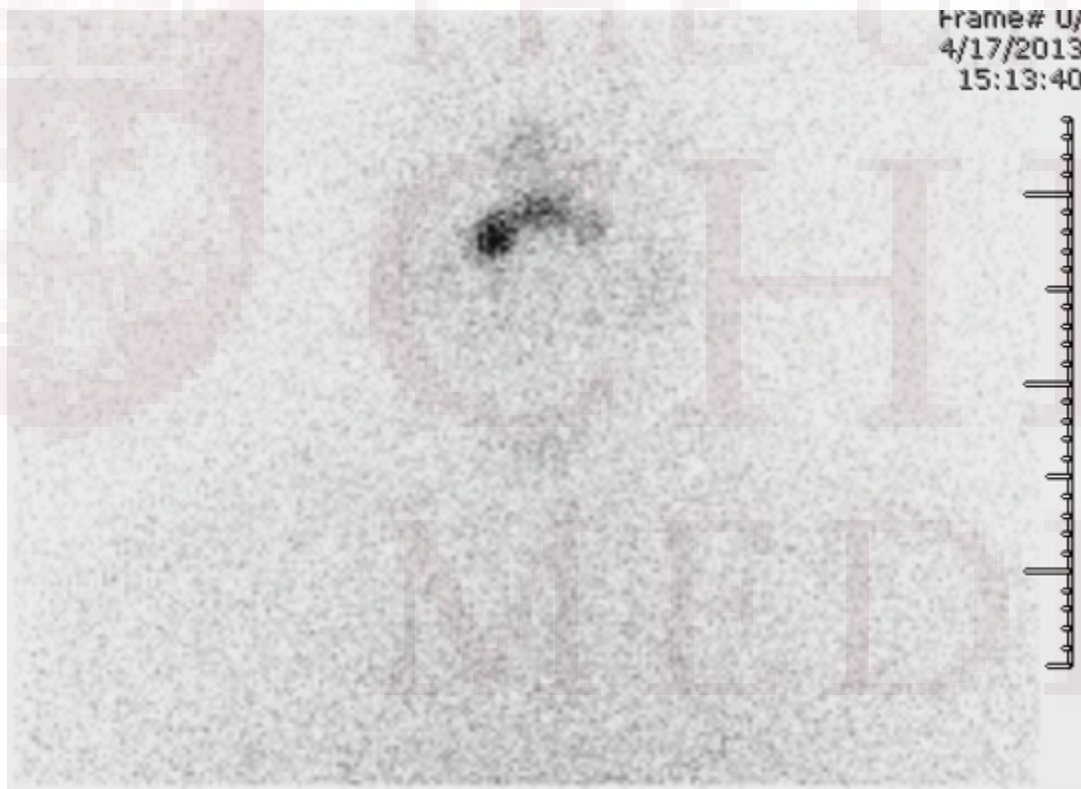
- **2012**: Found to have palpable thyroid nodule on routine exam by PCP.
 - Neck CT and **Thyroid US revealed 4.6 cm left lobe nodule** with enlarged lymph nodes.
- **12/2012**: FNA consistent with papillary thyroid carcinoma (PTC)
- **1/2013**: Thyroidectomy with central neck and left lateral neck dissection
 - Bilateral, multifocal PTC; largest lesion 6.5 cm. +Extracapsular extension. Margins clear.
 - Central neck: 3 of 9 LN positive; Left lateral neck: 4 of 9 LN positive.
 - Chronic lymphocytic thyroiditis
 - **TNM Staging: T3N1MX; AJCC: Stage 1.**

HPI: Cancer History Continued

	Ref. Range	2/19/2013	4/8/2013
TSH	0.3-4.00 mcl/mL	0.14	0.02
Free T4	0.9-1.7 ng/dL	1.88	
Thyroglobulin (Tg)	< 29 ng/mL	9	6
LT4 dose		150 daily	150 x 6 d/week 225 x 1 d/week

- 3/2013 CT Neck: No metastatic disease
- 4/10/2013: 160 mCi I-131 (s/p thyrogen)

Post-Therapy Scan – 7 days later



Head, Neck, Chest



Abdomen

What is the next step in monitoring?



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Role of Serum Thyroglobulin (Tg) in Follow-Up of Differentiated Thyroid Cancer (DTC)

- “During initial follow-up, serum **Tg on thyroxine therapy should be measured every 6-12 months**. More frequent Tg measurements may be appropriate for ATA high-risk patients. (Strong recommendation, Moderate-quality Evidence, ATA 2015 Guidelines)

Thyroglobulin (Tg)

- Glycoprotein (~ 660 kDa)
- Reaches nadir by 3-4 weeks post-operatively
- Following surgery + RAI, level ≤ 2 ng/mL
- Levels influenced by the following factors:
 - Amount of residual thyroid cancer
 - TSH level at the time of measurement
 - Sensitivity of the Tg assay
 - *Radioimmunoassay (Tg-RIA)
 - Immunometric assays (Tg-IMA)

Treatment Course

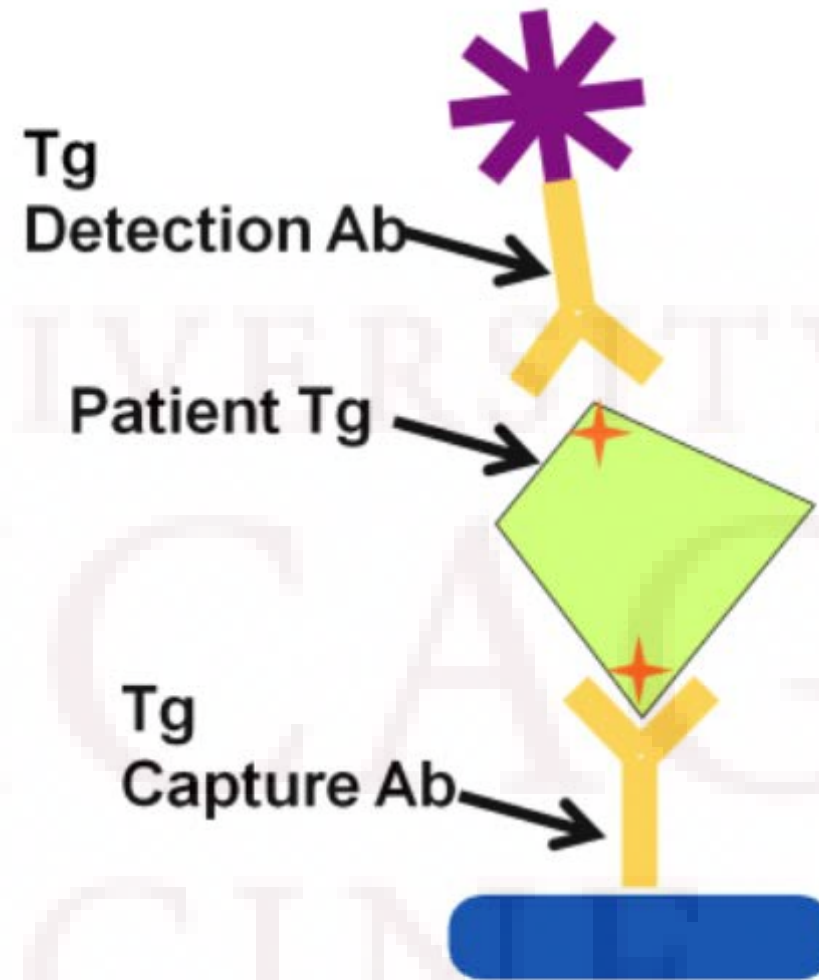
	Ref. Range	4/8/2013	7/16/2013 3 mos s/p I-131
TSH	0.3-4.00 mcl/mL	0.02	< 0.01
Free T4	0.9-1.7 ng/dL		1.67
Thyroglobulin (immunometric)	< 29 ng/mL	6	*Serum positive for Ab
LT4 dose		150 x 6 d/week 225 x 1 d/week	same

Anti-Thyroglobulin Antibodies (TgAb) and Thyroid Cancer

- Found in ~ 20-30% of patients with differentiated thyroid cancer.
- May rise after thyroidectomy or RAI
- Anti-Tg Ab disappear over median 3 years if no disease
- Increased risk of recurrence if new anti-Tg Ab or increase in titers
- Two issues in thyroid cancer pts:
 1. TgAb interferes with Tg assays making the Tg results unreliable
 - *Radioimmunoassay (Tg-RIA): ***false*** **HIGH** Tg
 - Immunometric assays (Tg-IMA): ***false*** **LOW/Undetectable** Tg
 2. Variability in sensitivity of Tg autoantibody assays

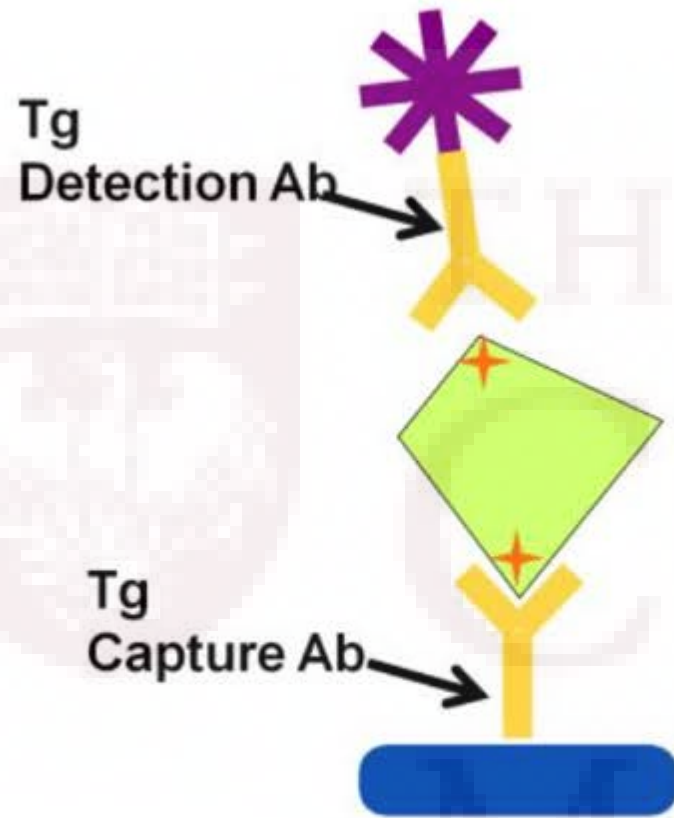
Immunometric Assays (IMA)

<http://www.mayomedicallaboratories.com/media/articles/hot-topic/2015/2015-04-01-thyroglobulin-quantitation-fulltext.pdf>



Signal generated by detection Ab is directly proportional to the concentration of Tg in the sample

In the presence of anti-Tg autoantibodies



Signal generated by detection Ab is directly proportional to the concentration of Tg in the sample



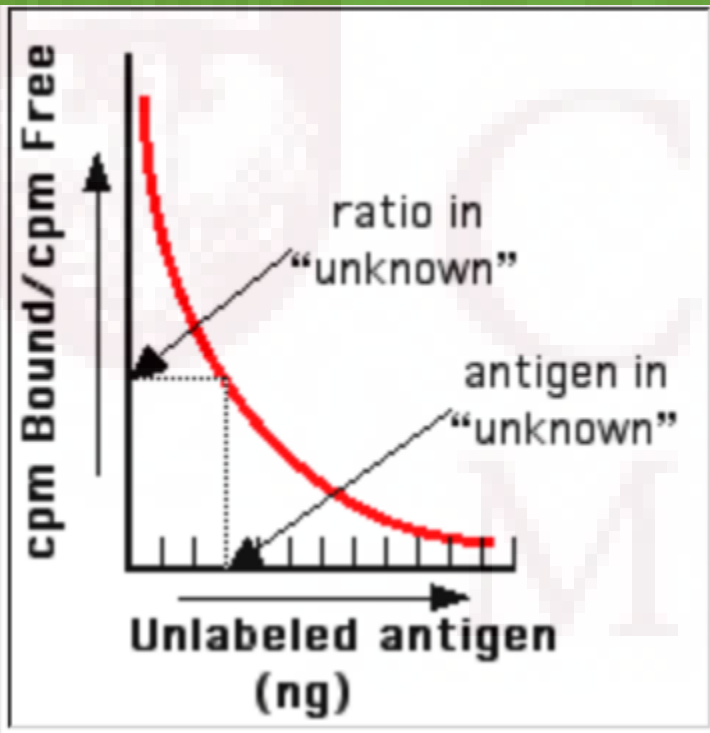
False-negative Tg

Unaffected Tg

False-negative Tg

False-negative/low Tg

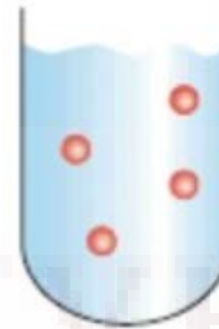
Radioimmuno- Assays (RIA)



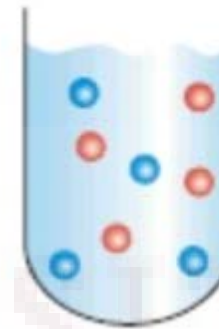
RIA Diagram



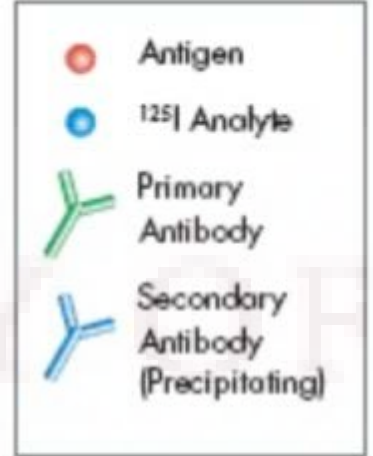
Step 1. Add buffer to the tubes.



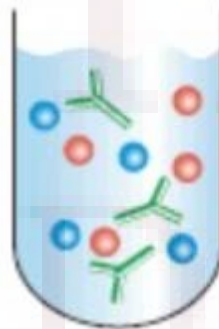
Step 2. Add known amounts of unlabeled antigen to the mixture. These compete for the binding sites of the antibodies.



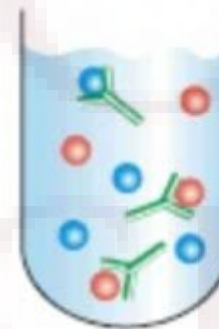
Step 3. Add radioactive antigen to the mixture.



From the data, a standard binding curve can be drawn. The samples to be assayed (the unknowns) are run in parallel. After determining the ratio of bound to free antigen in each unknown, the antigen concentrations can be read directly from the standard curve.



Step 4. Add fixed amount of antibody to the tubes.



Step 5. Radioactive antigen is displaced from the antibody molecules by the unlabeled antigen. Precipitate ag-ab complexes with PEG secondary antibody.



Step 6. The antibody-bound antigen is separated from the free antigen in the supernatant fluid and the radioactivity of each is measured.

How do you monitor thyroglobulin in a patient with positive Tg Ab?

1) Continue to trend the thyroglobulin and anti-Tg Ab – knowing that the thyroglobulin is falsely low or falsely high.

- RIA (false positive):

- If Tg negative, possibly reassured.
- If Tg positive, cannot interpret the result and cannot accurately quantify.

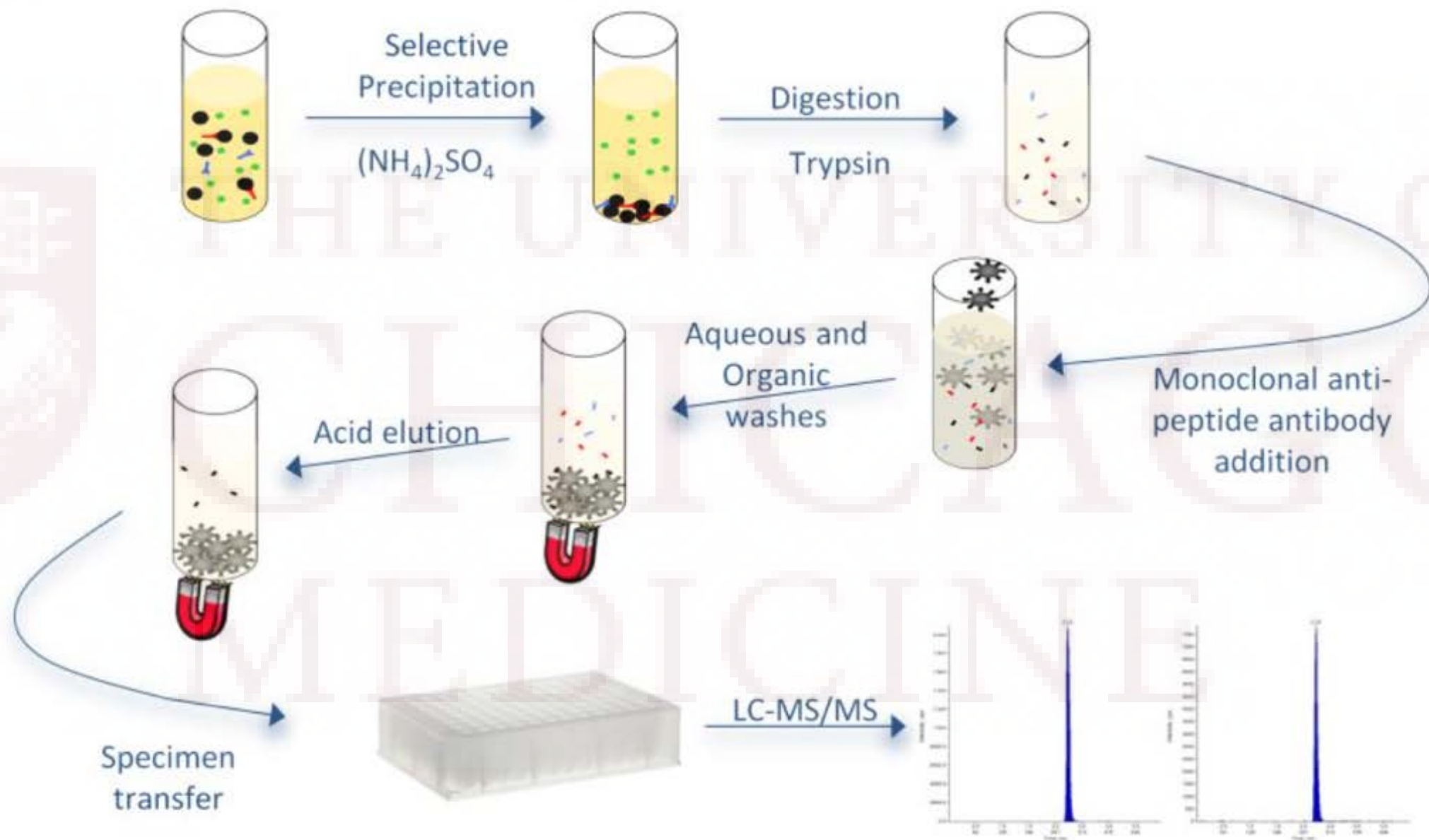
- IMA (false negative):

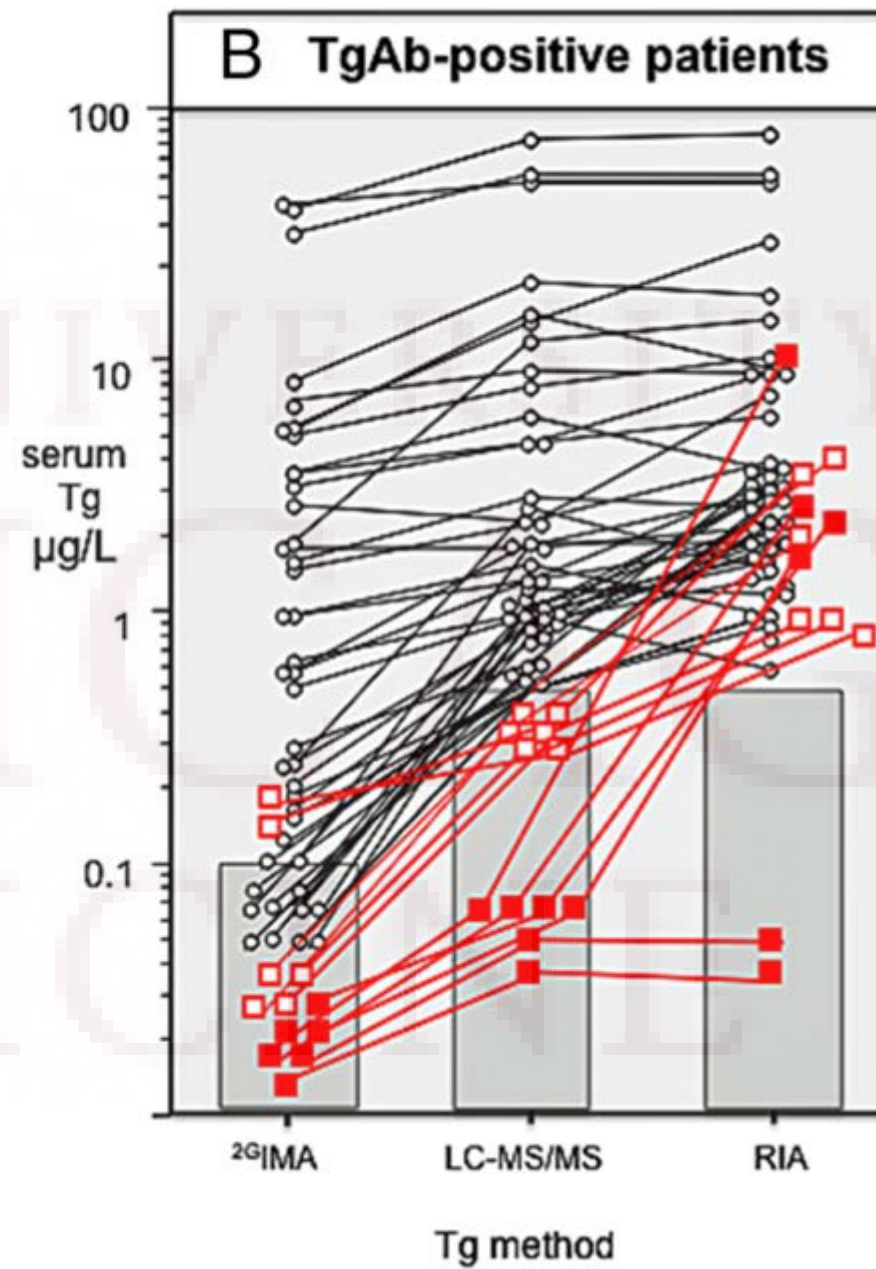
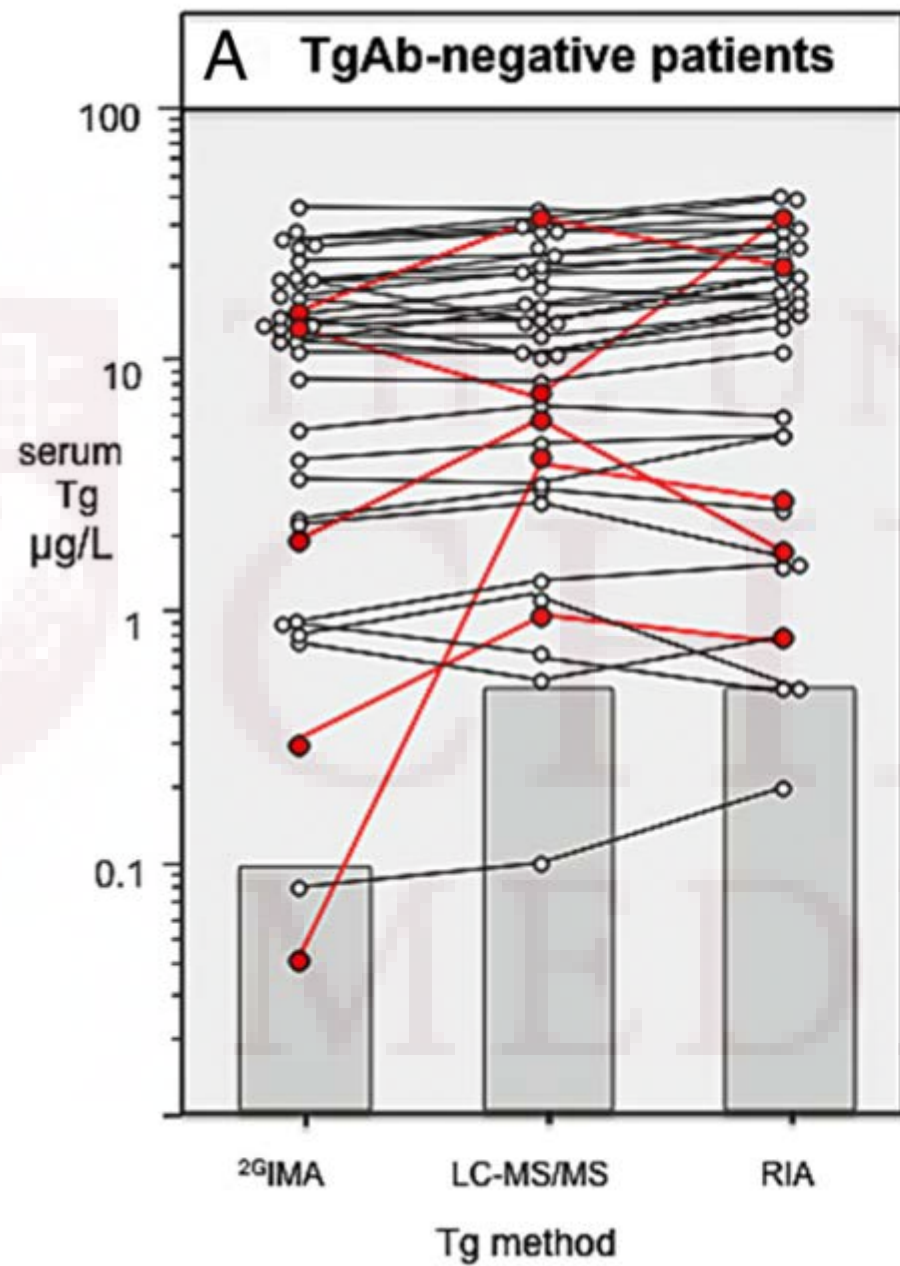
- If Tg negative, cannot interpret the result.
- If Tg positive, you know that it is there, but cannot accurately quantify.

2) Measure thyroglobulin with tandem mass-spectroscopy (Tg-MS)

Thyroglobulin measured with Tandem Mass-Spectroscopy (Tg-MS)

- Assay become recently available in last decade.
- Method:
 - Specimens are digested with trypsin
 - Everything is separated by charge and size
 - Quantification of well-conserved Tg peptides





2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force
on Thyroid Nodules and Differentiated Thyroid Cancer

Bryan R. Haugen,^{1,*} Erik K. Alexander,² Keith C. Bible,³ Gerard M. Doherty,⁴ Susan J. Mandel,⁵ Yuri E. Nikiforov,⁶ Furio Pacini,⁷ Gregory W. Randolph,⁸ Anna M. Sawka,⁹ Martin Schlumberger,¹⁰ Kathryn G. Schuff,¹¹ Steven I. Sherman,¹² Julie Ann Sosa,¹³ David L. Steward,¹⁴ R. Michael Tuttle,¹⁵ and Leonard Wartofsky¹⁶

- “The recent development of liquid chromatography-tandem mass spectroscopy assay of Tg **holds promise for accurate Tg measurement** in the presence of Tg autoantibodies.”
- “... **but further studies will be required to validate the assays** in terms of functional sensitivity, correlations with immunoassays results, and patient outcomes, reflecting either excellent response or persistent disease.”

Back to the Treatment Course

	Ref. Range	4/8/2013	7/16/13	10/8/13	3/17/14	4/27/14
TSH	0.3-4.00 mcl/mL	0.02	< 0.01	0.01	0.01	0.01
Free T4	0.9-1.7 ng/dL		1.67	1.79	1.89	
Tg	< 29 ng/mL	6	*	7 *	10 *	*

*Serum positive for Ab

5/2014: Nuclear Scan



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Back to the Treatment Course

	Ref. Range	4/28/14	1/22/15
TSH	0.3-4.00 mcl/mL	0.01	0.02
Free T4	0.9-1.7 ng/dL	--	2.08
TgAb	KU/mL	--	2.6
Tg (RIA)	< 29 ng/mL	*	5*
Tg (MS)	< 33 ng/mL	--	< 0.5

*Serum positive for Ab

-- = test not performed

Mass Spec in EPIC...



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Back to the Treatment Course

	Ref. Range	1/22/15	8/6/15	3/14/16	3/16/16
TSH	0.3-4.00 mcl/mL	0.02	0.02	0.01	99.29
Free T4	0.9-1.7 ng/dL	2.08	1.86	--	--
TgAb	KU/mL	2.6	--	--	--
Tg (RIA)	< 29 ng/mL	5*	--	--	--
Tg (MS)	< 33 ng/mL	< 0.5	0.9	0.6	11

*Serum positive for Ab

-- = test not performed

Thyroid Ultrasound 3/2016



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Back to the Treatment Course

	Ref. Range	1/22/15	8/6/15	3/14/16	3/16/16	8/4/16
TSH	0.3-4.00 mcl/mL	0.02	0.02	0.01	99.29	0.01
Free T4	0.9-1.7 ng/dL	2.08	1.86	--	--	1.96
TgAb	KU/mL	2.6	--	--	--	--
Tg (RIA)	< 29 ng/mL	5*	--	--	--	--
Tg (MS)	< 33 ng/mL	< 0.5	0.9	0.6	11	17

*Serum positive for Ab

-- = test not performed

PET Scan 8/2016



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Stimulated Thyroglobulin as a Predictor of Thyroid Cancer Recurrence

Table 3. Prognostic value of serum Tg measurements for disease-free remission and thyroid carcinoma-related death. Patients with Tg antibodies were excluded

	Outcome	Tg cut-off ($\mu\text{g/l}$)	Sensitivity \pm SE (%)	Specificity \pm SE (%)	PPV (%)	NPV (%)
Pre-ablation	Disease-free remission	27.5	84.4 \pm 2.6	88.9 \pm 5.6	97.8	49.1
	Death	21.5	66.7 \pm 9.6	81.3 \pm 2.8	30.2	95.3
Six months after initial therapy, suppressed TSH	Death	2.5	72.0 \pm 9.0	85.7 \pm 2.6	40.9	95.7
Six months after initial therapy, stimulated TSH	Death	10.0	85.0 \pm 8.0	83.5 \pm 2.9	39.5	97.8
Two years after initial therapy, suppressed TSH	Death	2.0	85.0 \pm 8.0	85.7 \pm 2.5	38.6	98.2
Five years after initial therapy, suppressed TSH	Death	2.0	82.4 \pm 9.2	92.8 \pm 2.2	58.3	97.7

PPV, positive predicted value; NVP, negative predicted value.

Results: Standardized Mixtures

- Absence of TgAb: all $r^2 > 0.99$ calibration fit
- Presence of TgAb:
 - Tg-MS: no significant effect on Tg
 - Tg-IA: (-) bias with increased [TgAb]
 - Tg-RAI: (-) bias at high [TgAb, Tg]; (+) bias at high [TgAb] and low [Tg]

Netzel et al. JCEM 2015.

Immunoassays (Mayo)	[Thyroglobulin]	% Tg Ab+ samples
Beckman Access Tg/TgAb	No difference b/n assays	41%
Siemens-Immunulite Tg/TgAb	Lower [Tg] ($p < 0.0001$)	27%
Thermo-Brahms Tg/TgAb	No difference b/n assays	39%
Roche Elecsys Tg/TgAb	No difference b/n assays	58%

Netzel et al. JCEM 2015.

Immunoassays (Mayo)	Radioimmunoassays	LC Tg Mass Spec
Beckman Access Tg/TgAb	USC-RIA	Tg-MS-1 (Mayo)
Siemens-Immunulite Tg/TgAb	UK-RIA	Tg-MS-2 (U of Washington)
Thermo-Brahms Tg/TgAb		
Roche Elecsys Tg/TgAb		