THYROGLOBULIN AND THYROGLOBULIN ANTIBODY: GUIDELINES FOR USE IN THYROID CANCER MONITORING

Version:	1.0
Ratified by:	Clinical Biochemistry Senior Staff meeting
Date ratified:	23-7-2020
Name of originator/author:	Elizabeth Hall
Director responsible for implementation:	Edmund Lamb
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Target audience:	Clinical staff (medical, nursing and scientific) Trust wide

Version Control Schedule

Version	Date	Author	Status	Comment
1.0				

Contents

1. Policy Summary

This policy gives guidance on requesting thyroglobulin (Tg) and thyroglobulin antibodies (TgAb) for the monitoring of thyroid cancer patients. It also gives guidance on the interpretation of Tg results in the presence of TgAb using the assays provided by East Kent Hospitals University NHS Foundation Trust (EKHUFT) and comparison of results with previous methods.

2. Purpose and Scope

This policy outlines Tg and TgAb testing for patients within the Trust.

3. Definitions

T4	thyroxine
T3	triiodothyronine
TSH	Thyroid stimulating hormone
Tg	Thyroglobulin
TgAb	Anti-thyroglobulin antibodies
HAMA	human anti-mouse antibodies
RIA	radioimmunoassay
IMA	immunometric assay

4. Introduction

Tg is a large glycoprotein synthesised by thyroid follicular cells. It acts as a scaffold protein for the synthesis of thyroid hormones, triiodothyronine (T3) and thyroxine (T4), and also as the storage form of T3 and T4. When thyroid hormone secretion is stimulated by thyroid stimulating hormone (TSH) the Tg is endocytosed and digested to release the thyroid hormones.

Serum Tg is a specific marker for thyroid tissue and the circulating concentration is roughly proportional to thyroid gland mass. Its usefulness as a tumour marker for differentiated papillary or follicular thyroid carcinoma is greatest after total thyroid ablation (surgery and radioiodine treatment) and when patients are on suppressive doses of L-thyroxine.

Tg measurement is affected by the presence of endogenous TgAb in patient samples. The effect of this interference is dependent on the type of Tg assay used. Previously the different Trusts in Kent and Medway have sent samples for Tg and TgAb to several different laboratories, using assays with varying detection limits and subject to differing effects from antibody interference. Measurement of Tg and TgAb has recently been introduced using Abbott Architect assays in EKHUFT to enable a unified approach to patient management for all Kent and Medway patients.

4.1 Assay limitations

Tg assays use antibodies to detect Tg in patient serum. There are several limitations to these assays that should be considered when interpreting results. Some tumours may lose the ability to synthesise or secrete Tg. All assays were developed using a Tg reference preparation derived from normal thyroid tissue; this may not be representative of the Tg expressed by every cancer type. Endogenous antibodies to the reagent antibodies or to thyroglobulin may interfere in Tg measurement.

Endogenous TgAb interfere by reducing the binding of the reagent antibodies to the Tg in the patient sample.

The EKHUFT Abbott Tg assay is an immunometric assay (IMA); if present, TgAb may give falsely low Tg results.

Previously samples were analysed at Birmingham using a radioimmunoassay (RIA). In this assay, if present TgAb may give falsely high Tg results.

Patients who have received mouse monoclonal antibodies as diagnostic or therapeutic agents may develop endogenous human anti-mouse antibodies (HAMA). The presence of HAMA in a sample may cause falsely high or falsely low Tg or TgAb results.

5. Guidelines for requesting thyroglobulin and thyroglobulin antibodies

As with any other laboratory investigation full and explicit clinical details should be provided. All requests will be reviewed before analysis and inappropriate requests will not be processed. TgAb should not be requested in the routine investigation and management of non-malignant thyroid disease.

5.1 Sample requirements

Blood collected into plain 4 mL tubes without gel (red top). Serum must be separated within 8 hours. Separated serum may be stored at 4^{o}C for 3 days and at -20^{o}C for 30 days. At least 1.0 mL is required for measurement of Tg and TgAb at EKHUFT and to provide sufficient sample to send to Birmingham for dual reporting or confirmation of Tg results.

TSH must be measured at the same time using a separate yellow-top serum gel tube.

5.2 When to measure Tg and TgAb

Tg measurement is used as a tumour marker in the follow-up of patients who have been treated for thyroid cancer. Frequency of measurement will depend on the clinical situation. Annual Tg measurement is adequate for low risk patients with no evidence of biochemical or structural disease. Tg should not normally be measured more frequently than 3-monthly.

Assessment of Tg status should not be performed within 6 weeks of thyroid ablation (to clear Tg released during treatment).

TgAb will be measured with every Tg request.

6. Guidelines for interpretation of thyroglobulin and thyroglobulin antibody results

6.1 Interpretation of Tg results

Tg is useful as a tumour marker for differentiated thyroid cancer after thyroid ablation. Tg concentrations in individuals with an intact thyroid are usually in the range 3.7 – 64 µg/L using the Abbott assay. Detectable Tg in serum following total thyroidectomy and radioiodine ablation is highly suggestive of thyroid remnant, residual tumour or tumour recurrence. Rising Tg concentrations in patients on TSH-suppressing doses of L-thyroxine indicate tumour recurrence or progression. However the assay used in EKHUFT is a sensitive assay and there may be patients with very low detectable concentrations of Tg. The clinical significance of such low concentrations is unclear and it is recommended that a rising trend with serial measurements is used to indicate recurrence.

Trends in Tg concentration may have some value for monitoring low risk surveillance hemithyroidectomy patients.

Tg results are reported in µg/L. Results below the limit of quantitation of the Abbott assay are reported as <0.14 µg/L.

6.2 Stimulated Tg results

Dynamic Risk Stratification to assess the need for continued TSH suppression is determined 9–12 months following total thyroidectomy and radioiodine remnant ablation by performing a stimulated Tg test and neck ultrasound scan. Patients attend clinic C at Kent and Canterbury Hospital for pre-booked Thyrogen 900 mg IM injections on a Monday (day 1) and a Tuesday (day 2) and then have Tg, TgAb and TFT blood tests on the Friday of the same week (day 5).

6.3 Interpretation of TgAb results

TgAb is reported in kU/L to whole numbers. Some assays used in the past, or from other laboratories, may be reported with a reference range derived from a healthy population with intact thyroid glands. Such a population may have TgAb concentrations up to 4 kU/L in the Abbott assay. For the purposes of potential interference in Tg measurement the decision limit on the TgAb reports from EKHUFT is the detection limit of the Abbott assay. Negative TgAb results are reported as <2 kU/L. Results ≥2 kU/L are considered positive.

Serial measurements of TgAb have been recommended in the long-term monitoring of patients with differentiated thyroid cancer. Successful removal of the all thyroglobulin-producing tissue should lead to a decline in TgAb concentrations (median 3 years). A new occurrence of TgAb (using the same assay) is a risk factor for recurrent disease.

6.4 Interpretation of Tg results in the presence of TgAb

Endogenous antibodies to Tg may interfere in its measurement. If TgAb are present, the EKHUFT Tg level may be unreliable and give a false negative (low) result. Tg results in TgAb positive samples must be interpreted with caution. If TgAb is detectable the Tg result by any method is likely to be unreliable, especially if the Tg results obtained with different methods are discordant.

Any Tg results that do not fit with the clinical picture can be discussed with the duty biochemist. Such results could be due to other assay interferences such as HAMA.

Long term monitoring, comparison with previous methods and plans for double reporting

Detection of disease recurrence depends on changes in Tg or TgAb results with time as well as on absolute concentrations. Ideally patients are always monitored using the same analytical method to enable identification of trends.

Any sample with detectable TgAb will be sent to Birmingham for Tg measurement by RIA. Other samples may be sent to Birmingham after discussion with the Duty Biochemist for investigation of unexpected results.

7. Duties

All staff involved in the requesting of Tg and TgAb, whether clinical or laboratory, must adhere to this policy.

8. Key Stakeholders, Consultation, Approval and Ratification Process

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff, K&M Thyroid TSSG, Mr Alistair Balfour. Records are kept on the S drive (S:\Path\SnrStaff\Comms with users\Clinical guidelines).

9. Review and Revision Arrangements

Two years from implementation date, by author.

10 Dissemination and Implementation

TrustNet, by proactive implementation through the Care Groups by appropriate clinical leads.

Links on reports

11. Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

12. Monitoring Compliance

Within the Trust, compliance with this policy must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

13. References

1. Peros P et al. Clin Endocrinol. 2014; 81 (s1): 1-122. British Thyroid Association guidelines for the management of thyroid cancer.

2. Pickett AJ, Jones M, Evans C. Ann Clin Biochem 2012; 49: 463-7. Causes of discordance between thyroglobulin antibody assays

3. Abbott insert for Architect Thyroglobulin assay. 2018

4. Abbott insert for Architect Thyroglobulin Antibody assay. 2015

5. Spencer C et al. Curr Opin Endocrinol Diabetes Obes 2014; 21: 394-404. How sensitive (second generation) thyroglobulin measurement is changing paradigms for monitoring patients with differentiated thyroid cancer, in the absence or presence of thyroglobulin antibodies.

14. Associated Documentation

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Thyroglobulin and thyroglobulin antibody: Guidelines for requesting

Details of person completing the EHRIA	
Name	Miss Elizabeth Hall
Job Title	Principal Clinical Scientist
Department/Specialty	Laboratory Medicine/Clinical Biochemistry
Telephone Number	ext 722-2868

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate requesting and interpretation of thyroglobulin and thyroglobulin antibodies across the health service in Kent and Medway.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Miss Elizabeth Hall, Principal Clinical Scientist, EKHUFT

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr Edmund Lamb, Clinical Director, Pathology, EKHUFT

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	