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GUIDELINES

Circulating tumor markers: a guide to their appropriate clinical use

Comparative summary of recommendations from clinical practice guidelines (PART 3)

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[1] Search and selection of guidelines
[2] Appraisal of guidelines through the AGREE II tool
[3] Assessment of the rate of utilization of a subset of guidance documents in clinical practice
[4] Synthesis of recommendations and other information concerning tumor markers into summary tables
[5] Assessment of correctness and completeness of the information summarized in the tables

External validation
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ELAS-Italia (European Ligand Assay Society Italia)
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AVAPO Venezia Onlus (Associazione Volontari per l'Assistenza di Pazienti Oncologici)

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Contents

Acronyms

Abbreviations of tumor markers cited in the present article

CA125	Cancer Antigen 125
CA19.9	Cancer Antigen 19.9
CEA	CarcinoEmbryonic Antigen
Ct	Calcitonin
Cyfra 21-1	Cytokeratin 19 fragment
LDH	Lactate DeHydrogenase
NSE	Neuron-Specific Enolase
pro-GRP	pro-Gastrin-Releasing Peptide
PTH	Parathyroid Hormone
SMRP	Soluble Mesothelin-Related Peptides
Tg	Thyroglobulin
TgAb	Tg Antibodies
TSH	Thyroid-Stimulating Hormone

Introduction

This is the last part of a guide to the appropriate clinical use of circulating tumor markers (TMs). The full document was published in Italy in October 2016 by the Italian National Agency for Regional Health Services (AGENAS) on behalf of and in collaboration with 9 Italian scientific societies representative of a range of stakeholders (1). The publication of the document in English was planned in 3 parts: the first, concerning malignancies of the gastrointestinal tract, was published in December 2016 (2); the second, published in February 2017 (3), addressed urogenital tract malignancies and breast cancer; the third, appearing in the present issue, refers to head-and-neck, thyroid and thoracic malignancies and melanoma.

Rationale

The number of TM tests requested is considerably higher than expected based on the cancer prevalence, and this shows the low compliance of physicians to clinical practice guidelines (CPGs). Barriers preventing clinicians from adherence to CPG recommendations include discrepancies between the cautious position of CPGs and the encouraging results of primary studies. In fact, the evidence provided by primary studies tends to focus on the diagnostic accuracy of the tests rather than on patient outcomes, the latter being a prerequisite for good-level evidence in guideline development. While awaiting the incorporation of higher-quality evidence into comprehensive guidelines, efforts should be made to improve the adherence to existing CPGs. A project was developed to summarize recommendations on circulating TMs offered by available CPGs on solid tumors, in order to provide all possible evidence-based choices concerning TMs to anyone facing a clinical question in which the use of a TM could be considered.

The implicit goal of the present guidance document is to "stimulate discussion and promote commentaries and debate, with the ultimate ambition of improving the appropriate use of TMs but also optimizing the proposed model of comparative summary of the available evidence to facilitate extensive dissemination and consultation of the guidance provided" (4).

Methods

The structured and rigorous methodology adopted for the extraction and synthesis of relevant information from selected guidelines has been previously described in detail (2). In brief, a systematic search for CPGs was performed and a standardized set of selection criteria was used to identify potentially relevant publications. Only documents containing recommendations for clinical practice were included. A total of 1,181 potentially relevant documents were selected from 8,266 identified records. Full-text reports were obtained for 559 guidance documents concerning 20 different malignancies. The selected documents were further appraised for adherence to the standards of the Institute of Medicine (IOM), which require CPGs to be based on systematic review of existing evidence (5), and clustered into 2 groups: 127 documents in which recommendations were generated through systematic review (CPGs) and 432 guidance documents without evidence of systematic review (Other Guidance Documents – OGDs). CPGs were further assessed with the Appraisal of Guidelines for Research & Evaluation (AGREE II) tool in order to facilitate comparison of the quality of the summarized CPGs. OGDs produced by authoritative institutions or medical societies are currently used by clinicians in their daily practice. All OGDs were therefore presented to the panel members with a request to indicate those actually used in clinical practice. When 25% or more of the panel members declared that a given guidance document was used in clinical practice, it was retained. In all, 111 of 432 OGDs qualified for inclusion. Circulating biomarkers measured in body fluids (serum or plasma/urine) were considered.

Results

The tabulation of the information was structured by individual malignancies; within each malignancy, the information was clustered according to a set of clinical questions established as being common to all malignancies. All information extracted from the guidance documents was synthesized in 4 rounds (levels) of increasing simplification. The last 2 levels of synthesis are the *Take-Home Messages* and *Detailed Summary Tables*. The former are intended for use by health care providers in their clinical practice with the goal of improving the appropriateness of TM use; the latter are addressed to policy makers for potential adaptation to their own context, and to educators, allowing them to design teaching programs consistent with the available evidence.

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Take-home messages

USERS' INSTRUCTIONS

Definition and target audience

Take-Home Messages are presented in table format for every tumor type, summarizing essential information to support decision-making in clinical practice. They are intended for use by health care providers.

STRUCTURE

Total number of selected documents (number of CPGs, number of OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG (CPG acronyms)	OGD/total OGD (OGD acronyms)
The different clinical questions are reported The symbol ⚠ denotes that CPGs formulated inconsistent recommendations on TMs in the clinical question	Recommendations and information from **CPGs** that consider the clinical question are summarized The sentence "Recommendations on TMs not available" is reported when the clinical question was considered by **CPGs**, but either TMs were not addressed or no explicit recommendations on TMs were provided	The recommended TM(s) are reported When CPGs explicitly recommend against TM(s), the word "**None**" is reported The symbol ∅ is shown when the examined CPGs either do not address TMs or, if TMs are addressed, CPGs do not formulate explicit recommendations	Number of CPGs reporting the summarized information in proportion to the total number of CPGs that consider the clinical question (acronyms of the CPGs in parenthesis)	Number of ODGs reporting the summarized information in proportion to the total number of CPGs that consider the clinical question (acronyms of the OGDs in parenthesis)

AGREE evaluation

CPGs concerning every malignancy were also assessed with the Appraisal of Guidelines for Research & Evaluation (AGREE II) tool. A higher score equals a better quality of the domain. The results are reported after the *Take-Home Message* tables.

Acronym	Domain 1 Scope and purpose	Domain 2 Stakeholder involvement	Domain 3 Rigor of development	Domain 4 Clarity of presentation	Domain 5 Applicability	Domain 6 Editorial independence
Acronyms of CPGs	Scores concerning the overall aim of the guideline, the specific health questions, and the target population are reported for every CPG	Scores concerning the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users are reported for every CPG	Scores concerning the process used to gather and synthesize the evidence, and the methods to formulate the recommendations and update them are reported for every CPG	Scores concerning the language, structure, and format of the guideline are reported for every CPG	Scores concerning the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline are reported for every CPG	Scores concerning the formulation of recommendations not being unduly biased with competing interests are reported for every CPG

The scores of the 6 domains were subdivided into quartiles and marked in different colors as shown in the following table:

0-25th percentile
26th-50th percentile
51st-75th percentile
76th-100th percentile

Additional notes

- *Take-Home Messages* are reported in alphabetical order.
- Information from OGDs on a specific clinical question were only reported in the *Take-Home Messages* if the clinical question was considered by CPGs. Descriptions regarding these OGDs can, however, be found in the *Detailed Summary Tables.*
- References concerning both CPGs and OGDs are reported after the *Detailed Summary Tables*, divided by type of malignancy and cited with the acronyms used in the Tables.

Examined documents: 10 (5 CPGs, 5 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening	Recommendations on TMs not available	Ø	**2/2** (ADA 2010, USPSTF 2013)	**0/4**
Differential diagnosis	Recommendations on TMs not available	Ø	**3/3** (AHS 2013, CCO 2009, NICE 2015)	**4/4** (AIOM 2015, ESMO-EHNS-ESTRO 2010-SCC, ESMO-EHNS-ESTRO 2012-NPC, NCCN 2015)
Preoperative workup	Recommendations on TMs not available	Ø	**2/2** (AHS 2013, CCO 2009)	**1/5** (ESMO-EHNS-ESTRO 2010-SCC)
Reassessment after initial curative treatment	Recommendations on TMs not available	Ø	**1/1** (CCO 2009)	**2/4** (ESMO-EHNS-ESTRO 2010-SCC, NCCN 2015)
Early detection of recurrence or progression	Recommendations on TMs not available	Ø	**1/1** (AHS 2013)	**1/5** (ESMO-EHNS-ESTRO 2010-SCC)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	Ø	**2/2** (AHS 2013, CCO 2009)	**5/5** (AIOCC-AIRO-AIOM 2012, AIOM 2015, ESMO-EHNS-ESTRO 2010-SCC, ESMO-EHNS-ESTRO 2012-NPC, NCCN 2015)

[1] **CPG/total CPG**: CPGs reporting the summarized information/total number of CPGs that consider the clinical question.
[2] **OGD/total OGD**: OGDs reporting the summarized information/total number of OGDs that consider the clinical question.
Ø The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.

Acronyms of CPGs	**Domain 1** Scope and purpose	**Domain 2** Stakeholder involvement	**Domain 3** Rigor of development	**Domain 4** Clarity of presentation	**Domain 5** Applicability	**Domain 6** Editorial independence
ADA 2010	83	56	86	89	58	79
AHS 2013	81	44	65	75	58	79
CCO 2009	92	56	76	69	38	63
NICE 2015	89	97	91	89	71	79
USPSTF 2013	78	44	75	81	42	79

Examined documents: 29 (18 CPGs, 11 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening	Recommendations on TMs not available	∅	**2/2** (ACCP 2013, USPSTF 2014-scr)	**3/5** (AIOM 2015, NCCN 2015-scr, NCCN 2015-SCLC)
Differential diagnosis	Recommendations on TMs not available	∅	**9/9** (ACCP 2013, AHS 2014-NSCLC.s1, AHS 2014-NSCLC.s2, ASCO 2015-SCLC, BTS-SCTS 2010, CCO 2014-dia, NICE 2011, NICE 2015-dia, SIGN 2014)	**9/9** (AIOM 2015, ESMO 2013-NSCLC, ESMO 2014, ESMO 2014-NSCLC.m+, ESMO-JSMO 2013-SCLC, FS 2013, NCCN 2015-NSCLC, NCCN 2015-scr, NCCN 2015-SCLC)
Preoperative workup	Recommendations on TMs not available	∅	**8/8** (ACCP 2013, AHS 2013-NSCLC.s4, AHS 2014-NSCLC.s1, AHS 2014-NSCLC.s2, ASCO 2015-SCLC, BTS-SCTS 2010, NICE 2011, SIGN 2014)	**4/7** (AIOM 2015, ESMO 2013-NSCLC, ESMO 2014, NCCN 2015-NSCLC)
Reassessment after initial curative treatment	Post-therapy CEA normalization or significant decrease seems to be related to better survival in early-stage NSCLC treated by surgery	**CEA**	**1/1** (ELCWP 2012)	**0/2**
Early detection of recurrence or progression	For lung cancer patients treated with curative intent, it is suggested that surveillance biomarker testing not be done outside of clinical trials	**None**	**1/7** (ACCP 2013)	**1/7** (AIOM 2015)
	Recommendations on TMs not available	∅	**6/7** (AHS 2012-NSCLC.s3, AHS 2014-NSCLC.s1, AHS 2014-NSCLC.s2, CCO 2014-fu, NICE 2011, SIGN 2014)	**6/7** (ESMO 2013-NSCLC, ESMO 2014, ESMO 2014-NSCLC.m+, ESMO-JSMO 2013-SCLC, NCCN 2015-NSCLC, NCCN 2015-SCLC)
Monitoring of treatment response in advanced disease	Some circulating markers could could provide prognostic information for survival	**CEA, Cyfra 21-1, pro-GRP**	**1/10** (ELCWP 2012)	**0/8**
	Recommendations on TMs not available	∅	**9/10** (ACCP 2013, AHS 2012-SCLC.es, AHS 2012-SCLC.ls, AHS 2012-NSCLC.s3, AHS 2013-NSCLC.s4, ASCO 2015-NSCLC.s4, ASCO 2015-SCLC, CCO 2014-NSCLC.m+, SIGN 2014)	**8/8** (AIOM 2015, AIOT 2012-NSCLC, CECOG 2012-NSCLC, ESMO 2014, ESMO 2014-NSCLC.m+, ESMO-JSMO 2013-SCLC, NCCN 2015-NSCLC, NCCN 2015-SCLC)

[1] **CPG/total CPG**: CPGs reporting the summarized information/total number of CPGs that consider the clinical question.
[2] **OGD/total OGD**: OGDs reporting the summarized information/total number of OGDs that consider the clinical question.
∅ The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.
NSCLC = non-small cell lung cancer.

Examined documents: 29 (18 CPGs, 11 OGDs)

Acronyms of CPGs	Domain 1 Scope and purpose	Domain 2 Stakeholder involvement	Domain 3 Rigor of development	Domain 4 Clarity of presentation	Domain 5 Applicability	Domain 6 Editorial independence
ACCP 2013	81	67	86	83	73	75
AHS 2012-NSCLC.s3	72	44	75	72	58	79
AHS 2012-SCLC.es	69	44	64	75	58	79
AHS 2012-SCLC.ls	69	44	64	72	58	79
AHS 2013-NSCLC.s4	72	44	65	75	58	79
AHS 2014-NSCLC.s1	78	44	66	69	54	79
AHS 2014-NSCLC.s2	72	44	65	75	58	79
ASCO 2015-NSCLC.s4	86	86	76	72	58	58
ASCO 2015-SCLC	89	75	70	83	38	63
BTS-SCTS 2010	58	44	77	78	31	58
CCO 2014-dia	92	56	76	78	40	67
CCO 2014-fu	89	53	77	81	38	71
CCO 2014-NSCLC.m+	86	50	79	86	40	67
ELCWP 2012	83	44	68	78	29	50
NICE 2011	92	94	96	94	85	92
NICE 2015-dia	89	97	92	89	71	83
SIGN 2014	89	89	81	92	83	71
USPSTF 2014-scr	81	44	79	78	33	71

MELANOMA — Take-home message

Examined documents: 14 (9 CPGs, 5 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening	Recommendations on TMs not available	Ø	**3/3** (ACCC 2012, BAD 2010, USPSTF 2009)	**2/2** (AIOM 2015, SIDeMaST 2011)
Differential diagnosis	Recommendations on TMs not available	Ø	**5/5** (ACCC 2012, BAD 2010, NICE 2015-ME, NICE 2015-SC, USPSTF 2009)	**5/5** (AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, NCCN 2015, SIDeMaST 2011)
Preoperative workup	LDH is recommended in stage IV metastatic disease to determine the substage and is optional in stage III	**LDH**	**3/4** (ACCC 2012, AHS 2013-PROP, BAD 2010)	**5/5** (AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, NCCN 2015, SIDeMaST 2011)
	Recommendations on TMs not available	Ø	**1/4** (NICE 2015-ME)	**0/5**
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	It is recommended not to perform laboratory testing (or imaging) for recurrences and metastases when no suspicious findings are made during physical examination	**None**	**2/4** (ACCC 2012, AHS 2013-FU)	**1/5** (NCCN 2015)
	Recommendations on TMs not available	Ø	**2/4** (BAD 2010, NICE 2015-ME)	**4/5** (AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, SIDeMaST 2011)
Monitoring of treatment response in advanced disease	Initial laboratory analysis is performed with at least a serum LDH determination	**LDH**	**1/5** (ACCC 2012)	**1/5** (NCCN 2015)
	Recommendations on TMs not available	Ø	**4/5** (AHS 2013-IV, AHS 2015-URM, BAD 2010, NICE 2015-ME)	**4/5** (AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, SIDeMaST 2011)

[1] **CPG/total CPG**: CPGs reporting the summarized information/total number of CPGs that consider the clinical question.
[2] **OGD/total OGD**: OGDs reporting the summarized information/total number of OGDs that consider the clinical question.
Ø The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.

Examined documents: 14 (9 CPGs, 5 OGDs)

Acronyms of CPGs	**Domain 1** Scope and purpose	**Domain 2** Stakeholder involvement	**Domain 3** Rigor of development	**Domain 4** Clarity of presentation	**Domain 5** Applicability	**Domain 6** Editorial independence
ACCC 2012	81	56	68	81	67	42
AHS 2013-FU	100	44	67	67	60	79
AHS 2013-IV	80	44	64	69	60	79
AHS 2013-PROP	86	44	64	69	58	79
AHS 2015-URM	89	44	66	72	60	79
BAD 2010	67	56	65	69	46	42
NICE 2015-SC	89	97	93	86	71	88
NICE 2015-ME	94	94	92	97	92	96
USPSTF 2009	75	44	69	75	27	67

MESOTHELIOMA — Take-home message

Examined documents: 9 (6 CPGs, 3 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening of people at increased risk (asbestos-exposed subjects)	Screening of all asbestos-exposed subjects with thoracic imaging and/or biological markers cannot be presently recommended	**None**	**2/2** (ERS-ESTS 2010, NHMRC 2013)	**2/2** (imp 2013, NCCN 2015)
Differential diagnosis	Measurement of the blood SMRP level is not recommended for routine clinical diagnosis	**None**	**2/6** (BTS 2010-MPE, NHMRC 2013)	**1/3** (ESMO 2010)
	Recommendations on TMs not available	Ø	**4/6** (AHS 2012, AHS 2014-MPE, ERS-ESTS 2010, NICE 2015)	**2/3** (ESMO 2010, imp 2013)
Preoperative workup	Baseline prognostic assessment should include also markers of inflammation such as C-reactive protein, which confer an unfavorable prognosis	**C-reactive protein**	**1/3** (NHMRC 2013)	**0/3**
	Recommendations on TMs not available	Ø	**2/3** (AHS 2012, ERS-ESTS 2010)	**2/3** (ESMO 2010, imp 2013)
	Supplementary information: Increased LDH levels have been associated with poor prognosis		**3/3** (AHS 2012, ERS-ESTS 2010, NHMRC 2013)	**0/3**
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Recommendations on TMs not available	Ø	**3/3** (AHS 2012, ERS-ESTS 2010, NHMRC 2013)	**2/2** (ESMO 2010, imp 2013)
Monitoring of treatment response in advanced disease	Increasing serum SMRP levels during treatment indicate progressive disease and are an unfavorable prognostic marker	**SMRP**	**1/4** (NHMRC 2013)	**0/3**
	Recommendations on TMs not available	Ø	**3/4** (AHS 2012, AHS 2014-MPE, ERS-ESTS 2010)	**3/3** (ESMO 2010, imp 2013, NCCN 2015)

[1] **CPG/total CPG**: CPGs reporting the summarized information/total number of CPGs that consider the clinical question.
[2] **OGD/total OGD**: OGDs reporting the summarized information/total number of OGDs that consider the clinical question.
Ø The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.

Examined documents: 9 (6 CPGs, 3 OGDs)

Acronyms of CPGs	Domain 1 Scope and purpose	Domain 2 Stakeholder involvement	Domain 3 Rigor of development	Domain 4 Clarity of presentation	Domain 5 Applicability	Domain 6 Editorial independence
AHS 2012	83	44	63	78	62	79
AHS 2014-MPE	92	44	63	75	62	79
BTS 2010-MPE	78	69	72	78	33	50
ERS-ESTS 2010	69	44	69	81	33	58
NHMRC 2013	75	78	76	83	42	63
NICE 2015	89	97	92	89	73	92

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening of people at increased risk (positive family history)	Recommendations on TMs not available	∅	**3/3** (AACE-AME-ETAM 2010, ATA 2009, BTA 2014)	**2/2** (AIOCC-AIRO-AIOM 2012, NCCN 2015)
Differential diagnosis	Routine measurement of serum Tg for initial evaluation of thyroid nodules is not recommended	**None** ∅	**3/4** (AACE-AME-ETAM 2010, ATA 2009, BTA 2014	**1/3** (NCCN 2015)
	Supplementary information: Serum Tg levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer		**1/4** (ATA 2009)	**0/3**
	Recommendations on TMs not available		**1/4** (NICE 2015)	**1/3** (ESMO 2012)
Preoperative workup ⚠	Routine preoperative measurement of serum Tg is not recommended	**None** or **Tg, TgAb**	**2/3** (ATA 2009, BTA 2014)	**0/3**
	Serum Tg measurement may be useful to detect potential false-negative values due to decreased thyroglobulin immunoreactivity or heterophilic antibodies		**1/3** (AACE-AME-ETAM 2010)	**1/3** (AIOCC-AIRO-AIOM 2012)
Reassessment after initial curative treatment	Baseline postoperative serum Tg should be checked, preferably no earlier than 6 weeks after surgery or RRA (detectable serum Tg is highly suggestive of thyroid remnant, residual or recurrent tumor)	**Tg, TgAb, TSH**	**1/2** (BTA2014)	**3/3** (AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015)
	To verify the absence of residual disease, serum Tg should be measured after thyroxine withdrawal or rhTSH stimulation approximately 12 months after ablation		**2/2** (ATA 2009, BTA 2014)	**0/3**
	TgAb should be measured by a quantitative method simultaneously with measurement of serum Tg		**2/2** (ATA 2009, BTA 2014)	**0/3**
	For patients who have undergone total thyroidectomy and RRA, 9-12 months post-RRA, allocation to 1 of 3 response groups after dynamic risk stratification (based on stimulated Tg, US and [optionally] nuclear medicine imaging) is recommended		**1/2** (BTA 2014)	**1/3** (NCCN 2015)
	To ensure continuity in monitoring Tg and TgAb assays on a long-term basis, clinicians should use the same laboratory and laboratories should not change methods without prior consultation with clinical users of the service		**2/2** (ATA 2009, BTA 2014)	**0/3**
	The degree of TSH suppression to be maintained should be established on the basis of risk categories defined by dynamic risk stratification		**2/2** (ATA 2009, BTA 2014)	**1/3** (NCCN 2015)

to be continued

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Early detection of recurrence or progression	At each visit measure Tg, TgAb and TSH serum levels and perform neck US (every 6-12 months depending on the risk level of the patient)	**Tg, TgAb, TSH**	**2/2** (ATA 2009, BTA 2014)	**3/3** (AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015)
	A single elevated serum Tg should be confirmed by repeating the test before proceeding to additional investigation or therapy		**1/2** (BTA 2014)	**0/3**
	Patients in whom the basal Tg remains persistently detectable while on suppressive therapy or rises with subsequent assessments require further evaluation		**1/2** (BTA 2014)	**0/3**
	After the first WBS performed following RRA, low-risk patients with undetectable Tg during suppressive therapy with negative TgAb and negative US do not require routine WBS during follow-up		**1/2** (ATA 2009)	**0/3**
Monitoring of treatment response in advanced disease	In the presence of persistent or metastatic disease, an undetectable serum TSH level (<0.1 mU/L) should be maintained during follow-up	**TSH**	**1/2** (ATA 2009)	**1/1** (ESMO 2012)

[1] **CPG/total CPG**: CPGs reporting the summarized information/total number of CPGs that consider the clinical question.
[2] **OGD/total OGD**: OGDs reporting the summarized information/total number of OGDs that consider the clinical question.
∅ The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.
⚠: Inconsistent recommendations on TMs in the clinical question are reported by different CPGs.
rhTSH = recombinant human TSH; RRA = ^{131}I radioiodine remnant ablation; US = ultrasound; WBS = ^{131}I whole body scan.

Acronyms of CPGs	Domain 1 Scope and purpose	Domain 2 Stakeholder involvement	Domain 3 Rigor of development	Domain 4 Clarity of presentation	Domain 5 Applicability	Domain 6 Editorial independence
AACE-AME-ETAM 2010	58	44	70	92	33	75
ATA 2009	86	44	74	92	42	79
BTA 2014	81	72	80	92	50	71
NICE 2015	89	97	91	86	75	83

THYROID CANCER, MEDULLARY (MTC)

Take-home message

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening of people at increased risk (positive family history)	If there is strong presumptive evidence from the individual or family history of inherited disease, consider biochemical screening of family members at risk using stimulated Ct testing	**Ct**	**1/3** (BTA 2014)	**0/2**
	Recommendations on TMs not available	∅	**1/3** (ATA 2015)	**1/2** (AIOCC-AIRO-AIOM 2012)
Differential diagnosis	Measurement of basal serum Ct level may be useful in the initial evaluation of thyroid nodules and is mandatory in patients with a family history or clinical suspicion of MTC or MEN2	**Ct, CEA**	**1/4** (AACE-AME-ETAM 2010)	**1/3** (ESMO 2012)
	Measurement of basal plasma Ct and CEA may be useful if MTC is suspected but is not recommended routinely for all thyroid nodules		**1/4** (BTA 2014)	**1/3** (NCCN 2015)
	Physicians should decide whether measuring serum Ct levels in patients with nodular goiters may be useful in the management of patients in their clinic		**1/4** (ATA 2015)	**0/3**
	If the Ct level is increased, the test should be repeated in basal conditions and, if confirmed in the absence of modifiers, a stimulation test could increase the diagnostic accuracy	∅	**2/4** (AACE-AME-ETAM 2010, BTA 2014)	**0/3**
	Supplementary information: Ct can be increased for causes different from MTC. Serum Ct levels in patients with nonthyroid malignancies do not increase in response to stimulation		**2/4** (AACE-AME-ETAM 2010, ATA 2015)	**0/3**
	Recommendations on TMs not available		**1/4** (NICE 2015)	**1/3** (AIOCC-AIRO-AIOM 2012)
Preoperative workup	Patients presenting with a thyroid nodule and a cytological or histological diagnosis of MTC should have determination of serum levels of Ct and CEA, and genetic testing for a RET germline mutation	**Ct, CEA**	**1/3** (ATA 2015)	**3/3** (AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015)
	Before surgery, all patients with suspected MTC should undergo a staging workup including basal serum calcium and plasma or 24-h urine metanephrines and normetanephrines to exclude pheochromocytoma and hyperparathyroidism	**Metanephrines, normetanephrines serum calcium**	**2/3** (ATA 2015, BTA 2014)	**3/3** (AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015)
Reassessment after initial curative treatment	Postoperatively, Ct and CEA should be measured at 3 months (no earlier than 15 days after thyroidectomy) and at 6 months to predict outcome and plan long-term follow-up	**Ct, CEA**	**2/2** (ATA 2015, BTA 2014)	**2/3** (ESMO 2012, NCCN 2015)

to be continued

THYROID CANCER, MEDULLARY (MTC)

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
	Patients with postoperative Ct levels <150 pg/mL should have a physical examination and US of the neck. If these are negative, patients should be followed with measurement of serum levels of Ct and CEA, and US every 6 months. Patients with postoperative Ct >150 pg/mL should be evaluated by imaging procedures (neck, skeleton, liver)		**1/2** (ATA 2015)	**1/3** (ESMO 2012)
Early detection of recurrence or progression	Serum levels of Ct and CEA should be regularly assessed during follow-up (at least every 6 months in patients with detectable serum levels of Ct and/or CEA to determine their doubling times)	**Ct, CEA**	**2/2** (ATA 2015, BTA 2014)	**3/3** (AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015)
	The presence of an elevated but stable Ct level postoperatively may be managed conservatively (active surveillance), provided treatable disease has been excluded radiologically. Progressively rising Ct concentrations should trigger imaging for further staging		**1/2** (BTA 2014)	**1/3** (NCCN 2015)
	Supplementary information: Ct and CEA doubling times correlate with tumor progression and are useful prognostic indicators for MTC recurrence and survival		**1/2** (BTA 2014)	**2/3** (ESMO 2012, NCCN 2015)
Monitoring of treatment response in advanced disease	Basal levels of serum Ct and CEA should be measured concurrently in patients with advanced MTC	**Ct, CEA** Ø	**1/2** (ATA 2015)	**0/3**
	Systemic therapy should not be administered to patients who have increasing serum Ct and CEA levels but no documented metastatic disease nor to patients with stable low-volume metastatic disease and Ct and CEA doubling times greater than 2 years		**1/2** (ATA 2015)	**0/3**
	Recommendations on TMs not available		**1/2** (BTA 2014)	**3/3** (AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015)

[1] **CPG/total CPG**: CPGs reporting the summarized information/total number of CPGs that consider the clinical question.
[2] **OGD/total OGD**: OGDs reporting the summarized information/total number of OGDs that consider the clinical question.
Ø The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.
MEN2 = multiple endocrine neoplasia type 2; RET gene = REarranged during Transfection gene; US = ultrasound.

Acronyms of CPGs	Domain 1 Scope and purpose	Domain 2 Stakeholder involvement	Domain 3 Rigor of development	Domain 4 Clarity of presentation	Domain 5 Applicability	Domain 6 Editorial independence
AACE-AME-ETAM 2010	58	44	70	92	33	75
ATA 2015	75	44	72	92	42	79
BTA 2014	81	72	80	92	50	71
NICE 2015	89	97	91	86	75	83

Detailed summary tables

USERS' INSTRUCTIONS

Definition and target audience

Take-Home Messages are presented in table format for every tumor type, summarizing essential information to support decision-making in clinical practice. They are intended for use by health care providers.

STRUCTURE

Total number of selected documents (number of CPGs, number of OGDs)

Clinical question	CPG	OGD	Summary of recommendations	Supplementary information
The different clinical questions are reported	Number of CPGs addressing the clinical question	Number of OGDs addressing the clinical question	Recommendations from **CPGs** and from OGDs that are consistent with those of **CPGs** Only those parts of the text explicitly defined as recommendations and clearly recognizable as such were considered Similar recommendations and supplementary information from different guidance documents are reported once, followed by the acronyms of the guidance documents by which they are provided Acronyms of **CPGs** are printed in bold blue type, those of OGDs are printed in regular type	Useful supplementary information for the clinical application of TMs from both **CPGs** and OGDs are summarized (e.g., suggested cutoff points, timing of serial sample monitoring, causes of false positive or false negative TM results) Recommendations from OGDs that are inconsistent with those of **CPGs** are reported Advice for clinical practice not declared or not recognizable as recommendation in the document is reported Acronyms of **CPGs** are printed in bold blue type, those of OGDs are printed in regular type

Examined documents: 10 (5 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	2	0	Clinical question considered, no explicit recommendations on TMs provided (**ADA 2010**) Clinical question considered, but TMs not addressed (**USPSTF 2013**)	
Differential diagnosis	3	4	Clinical question considered, but TMs not addressed (**AHS 2013**, **CCO 2009**, **NICE 2015**, AIOM 2015, ESMO-EHNS-ESTRO 2012-NPC, ESMO-EHNS-ESTRO 2010-SCC, NCCN 2015)	
Preoperative workup	2	5	Clinical question considered, but TMs not addressed (**AHS 2013**, **CCO 2009**, ESMO-EHNS-ESTRO 2010-SCC)	The pre-treatment plasma/serum load of Epstein-Barr viral DNA has been shown to be of prognostic value in nasopharyngeal cancer (AIOCC-AIRO-AIOM 2012, AIOM 2015, ESMO-EHNS-ESTRO 2012-NPC, NCCN 2015)
Reassessment after initial curative treatment	1	4	Clinical question considered, but TMs not addressed (**CCO 2009**, ESMO-EHNS-ESTRO 2010-SCC, NCCN 2015)	The determination of plasma/serum Epstein-Barr viral DNA 2 months after the initial treatment can be considered in nasopharyngeal cancer (AIOCC-AIRO-AIOM 2012, AIOM 2015)
Early detection of recurrence or progression	1	5	Clinical question considered, but TMs not addressed (**AHS 2013**, ESMO-EHNS-ESTRO 2010-SCC)	Regular post-treatment determination of plasma/serum Epstein-Barr viral DNA can be considered as it has been shown to be of prognostic value in nasopharyngeal cancer (AIOCC-AIRO-AIOM 2012, AIOM 2015, ESMO-EHNS-ESTRO 2012-NPC, NCCN 2015) TMs are not recommended in the absence of clinical indications (AIOM 2015)
Monitoring of treatment response in advanced disease	2	5	Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2013**, **CCO 2009**, AIOCC-AIRO-AIOM 2012, AIOM 2015, ESMO-EHNS-ESTRO 2012-NPC, ESMO-EHNS-ESTRO 2010-SCC, NCCN 2015)	

[1] Recommendations from **CPGs** and from **OGDs**, if consistent with those of **CPGs**.
[2] Supplementary information from both **CPGs** and **OGDs**, and recommendations from **OGDs** that are inconsistent with those of **CPGs**.

Examined documents: 29 (18 CPGs, 11 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	2	5	Clinical question considered, but TMs not addressed (**ACCP 2013**, **USPSTF 2014-scr**, AIOM 2015, NCCN 2015-SCLC, NCCN 2015-scr)	The role of biomarkers needs to be determined (**ACCP 2013**, **USPSTF 2014-scr**) Other screening methods, such as biomarkers, are not recommended for clinical use (ESMO 2013-NSCLC, ESMO 2014)
Differential diagnosis	9	9	Clinical question considered, no explicit recommendations on TMs provided (**ACCP 2013, SIGN 2014**) Clinical question considered, but TMs not addressed (**AHS 2014-NSCLC.s1**, **AHS 2014-NSCLC.s2**, **ASCO 2015-SCLC**, **BTS-SCTS 2010**, **CCO 2014-dia**, **NICE 2011**, **NICE 2015-dia**, AIOM 2015, ESMO 2013-NSCLC, ESMO 2014, ESMO 2014-NSCLC.m+, ESMO-JSMO 2013-SCLC, FS 2013, NCCN 2015-NSCLC, NCCN 2015-scr, NCCN 2015-SCLC)	No evidence was identified supporting the use of TMs in the diagnosis of lung cancer (**ACCP 2013, SIGN 2014**)
Preoperative workup	8	7	Clinical question considered, but TMs not addressed (**ACCP 2013**, **AHS 2013-NSCLC.s4**, **AHS 2014-NSCLC.s1**, **AHS 2014-NSCLC.s2**, **ASCO 2015-SCLC**, **BTS-SCTS 2010**, **NICE 2011**, **SIGN 2014**, AIOM 2015, ESMO 2013-NSCLC, ESMO 2014, NCCN 2015-NSCLC)	In NSCLC routine use of serum markers (such as CEA) is not recommended (ESMO 2014-NSCLC.M+) In SCLC initial assessment should include LDH since it is associated with excessive bulk of disease (ESMO-JSMO 2013-SCLC, NCCN 2015-SCLC)
Reassessment after initial curative treatment	1	2	Postoperative CEA determination could provide additional prognostic information (**ELCWP 2012**)	Post-therapy CEA normalization or significant decrease seems to be related to better survival in early-stage NSCLC treated with surgery (**ELCWP 2012**) Clinical question considered, but TMs not addressed (ESMO 2014-NSCLC.M+, NCCN 2015-SCLC)
Early detection of recurrence or progression	7	7	For lung cancer patients treated with curative intent, it is suggested that surveillance biomarker testing not be done outside of clinical trials (**ACCP 2013,** AIOM 2015) Clinical question considered, but TMs not addressed (**AHS 2012-NSCLC.s3**, **AHS 2014-NSCLC.s1**, **AHS 2014-NSCLC.s2**, **CCO 2014-fu**, **NICE 2011**, **SIGN 2014**, ESMO 2013-NSCLC, ESMO 2014, ESMO 2014-NSCLC.m+, ESMO-JSMO 2013-SCLC, NCCN 2015-NSCLC, NCCN 2015-SCLC)	
Monitoring of treatment response in advanced disease	10	8	Some circulating markers (CEA, Cyfra 21-1 and pro-GRP, and to a lesser extent NSE, CA125 and CA19.9) could provide prognostic information for survival (**ELCWP 2012**) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**ACCP 2013**, **AHS 2012-NSCLC.s3, AHS 2012-SCLC.es, AHS 2012-SCLC.ls**, **AHS 2013-NSCLC.s4**, **ASCO 2015-NSCLC.s4**, **ASCO 2015-SCLC**, **CCO 2014-NSCLC.m+**, **SIGN 2014**, AIOM 2015, AIOT 2012-NSCLC, CECOG 2012-NSCLC, ESMO 2014, ESMO 2014-NSCLC.m+, ESMO-JSMO 2013-SCLC, NCCN 2015-NSCLC, NCCN 2015-SCLC)	Post-therapy CEA normalization or significant decrease seems to be related to better survival in advanced NSCLC treated with chemotherapy and after salvage gefitinib in relapsing NSCLC (**ELCWP 2012**)

[1] Recommendations from **CPGs** and from **OGDs**, if consistent with those of **CPGs**.
[2] Supplementary information from both **CPGs** and **OGDs**, and recommendations from **OGDs** that are inconsistent with those of **CPGs**.
NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

Examined documents: 14 (9 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	3	2	Clinical question considered, but TMs not addressed (**ACCC 2012**, **BAD 2010**, **USPSTF 2009**, AIOM 2015, SIDeMaST 2011)	
Differential diagnosis	5	5	Clinical question considered, but TMs not addressed (**ACCC 2012**, **BAD 2010**, **NICE 2015-ME**, **NICE 2015-SC**, **USPSTF 2009**, AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, NCCN 2015, SIDeMaST 2011)	
Preoperative workup	4	5	LDH is recommended to determine substage in stage IV metastatic disease (**ACCC 2012**, **AHS 2013-PROP**, **BAD 2010**, AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, NCCN 2015, SIDeMaST 2011) LDH determination is optional in stage III (**AHS 2013-PROP**) Clinical question considered, but TMs not addressed (**NICE 2015-ME**)	
Reassessment after initial curative treatment	0	0	Clinical question not addressed by **CPGs**	
Early detection of recurrence or progression	4	5	It is recommended not to perform laboratory testing (or imaging) for recurrences and metastases when no suspicious findings are made during physical examination (**ACCC 2012**, **AHS 2013-FU**, NCCN 2015) Clinical question considered, but TMs not addressed (**BAD 2010**, **NICE 2015-ME**, AIOM 2015, SIDeMaST 2011)	Clinical question considered, no explicit recommendations on TMs provided (EDF-EADO-EORTC 2012, ESMO 2012)
Monitoring of treatment response in advanced disease	5	5	Initial laboratory analysis is performed with at least a serum LDH determination (**ACCC 2012**, NCCN 2015) Clinical question considered, no explicit recommendations on TMs provided (**BAD 2010**) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2013-IV**, **AHS 2015-URM**, **NICE 2015-ME**, AIOM 2015, EDF-EADO-EORTC 2012, ESMO 2012, SIDeMaST 2011)	Patients with elevated LDH have a reduced likelihood of benefiting from currently available systemic treatment (**BAD 2010**)

[1] Recommendations from **CPGs** and from **OGDs**, if consistent with those of **CPGs**.
[2] Supplementary information from both **CPGs** and **OGDs**, and recommendations from **OGDs** that are inconsistent with those of **CPGs**.

MESOTHELIOMA — Detailed summary tables

Examined documents: 9 (6 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk (asbestos-exposed subjects)	2	2	Screening of all asbestos-exposed subjects with thoracic imaging and/or biological markers cannot be presently recommended (**ERS-ESTS 2010**, **NHMRC 2013**, NCCN 2015)	Given the prevalence of the disease, the sensitivity and specificity of the available biological markers (such as SMRP and osteopontin) are not adequate for screening purposes (**ERS-ESTS 2010**, **NHMRC 2013**, imp 2013) There is no evidence that screening procedures for malignant mesothelioma affect clinical outcomes (e.g., decrease mortality) (**NHMRC 2013**, imp 2013, NCCN 2015)
Differential diagnosis	6	3	Measurement of the blood SMRP level is not recommended for routine clinical diagnosis (**BTS 2010-MPE**, **NHMRC 2013**) Pleural fluid and serum TMs do not currently have a role in the routine investigation of pleural effusions (**BTS 2010-MPE**) Clinical question considered, but TMs not addressed (**AHS 2012**, **AHS 2014-MPE**, **ERS-ESTS 2010**, **NICE 2015**)	To date, no serum biomarker has shown sufficient positive predictive value for a diagnosis of malignant mesothelioma that would allow it to replace existing imaging-cytology-biopsy requirements (**NHMRC 2013**) A positive serum or pleural fluid mesothelin level is highly suggestive of pleural malignancy and might be used to expedite a tissue diagnosis, but a negative result cannot be considered reassuring (**BTS 2010-MPE**) Clinical question considered, no explicit recommendations on TMs provided (ESMO 2010, imp 2013) The precise role of SMRP and osteopontin is yet to be defined (ESMO 2010) SMRP and osteopontin require further validation before clinical application (imp 2013) SMRP determination is optional; osteopontin does not appear to be useful for diagnosis (NCCN 2015)
Preoperative workup	3	3	Baseline prognostic assessment should include also markers of inflammation such as C-reactive protein (**NHMRC 2013**) Clinical question considered, no explicit recommendations on TMs provided (**AHS 2012**, **ERS-ESTS 2010**, imp 2013)	SMRP serum levels appear to be predictive of reduced mean survival in the epithelioid subtype. Their predictive power is removed in multivariate models which include FDG-PET. Serum osteopontin levels add no more prognostic information than SMRP (**NHMRC 2013**) Increased LDH levels have been associated with a poor prognosis (**AHS 2012**, **ERS-ESTS 2010**, **NHMRC 2013**) New serum biomarkers with potential prognostic significance (e.g., SMRP and osteopontin) are currently under investigation (**ERS-ESTS 2010**, imp 2013) SMRP levels may also be assessed and may correlate with disease status (NCCN 2015) Clinical question considered, but TMs not addressed (ESMO 2010)
Reassessment after initial curative treatment	0	0	Clinical question not addressed by **CPGs**	

to be continued

Examined documents: 9 (6 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Early detection of recurrence or progression	3	2	Clinical question considered, but TMs not addressed (**AHS 2012**, **ERS-ESTS 2010**, **NHMRC 2013**, ESMO 2010, imp 2013)	
Monitoring of treatment response in advanced disease	4	3	Increasing serum SMRP levels during treatment are an unfavorable prognostic marker (**NHMRC 2013**) Clinical question considered, no explicit recommendations on TMs provided (**ERS-ESTS 2010**, imp 2013) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2012, AHS 2014-MPE**, ESMO 2010, NCCN 2015)	Rising SMRP is indicative of progressive disease. SMRP response correlates with radiological response and TGV on FDG-PET (**NHMRC 2013**) PET scan and biological markers are still under investigation for the evaluation of response to treatment (**ERS-ESTS 2010**) SMRP and osteopontin require further validation before clinical application (imp 2013)

[1] Recommendations from **CPGs** and from **OGDs**, if consistent with those of **CPGs**.
[2] Supplementary information from both **CPGs** and **OGDs**, and recommendations from **OGDs** that are inconsistent with those of **CPGs**.
FDG-PET = positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose; TGV = total glycolytic volume.

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk (positive family history)	3	2	Clinical question considered, but TMs not addressed (**AACE-AME-ETAM 2010**, **ATA 2009**, **BTA 2014**, AIOCC-AIRO-AIOM 2012)	Major risk factors for differentiated thyroid cancer are: neck irradiation in childhood; endemic goiter; family or personal history of thyroid adenoma; familial thyroid cancer (**BTA 2014**) Clinical question considered, no explicit recommendations on TMs provided (NCCN 2015)
Differential diagnosis	4	3	Routine measurement of serum Tg for initial evaluation of thyroid nodules is not recommended (**AACE-AME-ETAM 2010**, **ATA 2009**, **BTA 2014**, NCCN 2015) Determinaton of serum calcium or/and PTH are recommendend if a nodular lesion is suggestive of intrathyroidal parathyroid adenoma on US examination (**AACE-AME-ETAM 2010**, AIOCC-AIRO-AIOM 2012) Clinical question considered, but TMs not addressed (**NICE 2015**, ESMO 2012)	Serum Tg levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer (**ATA 2009**)
Preoperative workup	3	3	Routine preoperative measurement of serum Tg is not recommended (**ATA 2009**, **BTA 2014**) Serum Tg measurement may be useful to detect potential false-negative values due to decreased Tg immunoreactivity or heterophilic antibodies (**AACE-AME-ETAM 2010**) In case of suspicious US features of a lymph node, the metastatic nature of the node may be confirmed with measurement of Tg in the washout of the needle used for UGFNA biopsy (**AACE-AME-ETAM 2010**)	There is limited evidence that high preoperative concentrations of serum Tg may predict a higher sensitivity for postoperative surveillance with serum Tg (**ATA 2009**) Markers indicated for differentiated thyroid carcinoma: Tg, TgAb (AIOCC-AIRO-AIOM 2012) Clinical question considered, but TMs not addressed (ESMO 2012, NCCN 2015)

to be continued

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Reassessment after initial curative treatment	2	3	Baseline postoperative serum Tg should be checked, preferably no earlier than 6 weeks after surgery or RRA (**BTA 2014**, AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015) To verify the absence of residual disease, serum Tg should be measured after thyroxine withdrawal or rhTSH stimulation approximately 12 months after ablation (**ATA 2009, BTA 2014**) Following total thyroidectomy and RRA, and before evaluation of the patient's response to treatment after 9-12 months, TSH should be suppressed to below 0.1 mU/L (**BTA 2014**) In patients who have not undergone RRA who are clinically free of disease and have undetectable suppressed serum Tg and normal neck US, the serum TSH may be allowed to rise to the low normal range (0.3-2 mU/L) (**BTA 2014**) TgAb should be measured by a quantitative method simultaneously with measurement of serum Tg. If TgAb are detectable, measurement should be repeated at regular (~6-monthly) intervals (**BTA 2014**) TgAb, even if negative, should be measured at follow-up when Tg is measured (**ATA 2009, BTA 2014**) For patients who have undergone total thyroidectomy and RRA, 9-12 months post-RRA, allocation to 1 of 3 response groups after dynamic risk stratification (based on stimulated Tg, US and [optionally] nuclear medicine imaging) is recommended (**BTA 2014**, NCCN 2015) The degree of TSH suppression to be maintained should be established on the basis of risk categories defined by dynamic risk stratification (**ATA 2009**, **BTA 2014**, NCCN 2015) - Low risk: TSH may be allowed to rise to the low-normal range (0.3-2 mU/L) - Intermediate risk: TSH should be maintained between 0.1 and 0.5 mU/L for 5-10 years (then reexamine) - High risk: TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications	Detectable serum Tg is highly suggestive of thyroid remnant, residual or recurrent tumor (**BTA 2014**) Stimulated Tg should be measured on day 5 following the first injection of rhTSH (**BTA 2014**) A serum TSH concentration >30 mU/L should be achieved to assess stimulated Tg (**BTA 2014**) To ensure continuity in monitoring Tg and TgAb assays on a long-term basis, clinicians should use the same laboratory and laboratories should not change methods without prior consultation with clinical users of the service (**ATA 2009, BTA 2014**) Tg should be measured by an immunometric assay that is calibrated against the CRM-457 standard (**ATA 2009**) *Dynamic Risk Stratification* - Excellent response (low risk): all the following: (i) suppressed and stimulated Tg <1 µg/L*, (ii) neck US without evidence of disease, (iii) cross-sectional and/or nuclear medicine imaging negative (if performed) - Intermediate response (intermediate risk): any of the following: (i) suppressed Tg 1 µg/L* and stimulated Tg ≥1 and <10 µg/L*, (ii) neck US with nonspecific changes or stable sub-centimeter lymph nodes, (iii) cross-sectional and/or nuclear medicine imaging with nonspecific changes, although not completely normal - Incomplete response (high risk): any of the following: (i) suppressed Tg ≥1 µg/L* or stimulated Tg ≥10 µg/L*, (ii) rising Tg values, (iii) persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging (NB. *Assumes absence of interference in the Tg assay) (**BTA 2014**)

to be continued

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Early detection of recurrence or progression	2	3	At each visit the following tasks should be completed: determination of Tg and TgAb serum levels; adequacy of TSH suppression; neck US (**ATA 2009**, **BTA 2014**, AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015) For low-risk patients with no evidence of biochemical or structural disease, annual measurement of serum Tg while on suppressive treatment is adequate (**ATA 2009, BTA 2014**, AIOCC-AIRO-AIOM 2012) There is normally no need to measure serum Tg more frequently than 3-monthly during routine follow-up **(BTA 2014)** Patients in whom basal Tg remains persistently detectable while on suppressive therapy or rises with subsequent assessments require further evaluation **(BTA 2014)** After the first WBS performed following RRA, low-risk patients with undetectable Tg during suppressive therapy with negative TgAb and negative US do not require routine WBS during follow-up (**ATA 2009**) A single elevated serum Tg result should be confirmed by repeating the test before proceeding to additional investigation or therapy (**BTA 2014**) An elevated serum Tg level should lead to a detailed neck US (**BTA 2014**)	Serum Tg should be measured every 6-12 months depending on the risk level of the patient (**ATA 2009, BTA 2014**, AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015) TgAb should be measured by a quantitative method simultaneously with measurement of serum Tg. If TgAb are detectable, measurement should be repeated at regular (~6-monthly) intervals (**BTA 2014**) TgAb, even if negative, should be measured at follow-up when Tg is measured **(ATA 2009, BTA 2014)** Serum TSH concentration should be determined concurrently to aid interpretation **(BTA 2014)** To ensure continuity in monitoring, clinicians should use the same laboratory, Tg and TgAb assays on a long-term basis. Laboratories should not change methods without prior consultation with clinical users of the service (**ATA 2009, BTA 2014**) Tg should be measured by an immunometric assay that is calibrated against the CRM-457 standard (**ATA 2009**)
Monitoring of treatment response in advanced disease	2	1	In the presence of persistent or metastatic disease, an undetectable serum TSH level (<0.1 mU/L) should be maintained during follow-up (**ATA 2009**, ESMO 2012)	It is uncertain whether empirical ^{131}I treatment is beneficial in patients with raised serum Tg, compared to active surveillance (**BTA 2014**)

[1] Recommendations from **CPGs** and from **OGDs**, if consistent with those of **CPGs**.
[2] Supplementary information from both **CPGs** and **OGDs**, and recommendations from **OGDs** that are inconsistent with those of **CPGs**.
rhTSH = recombinant human TSH; RRA = ^{131}I radioiodine remnant ablation; UGFNA = ultrasound-guided fine-needle aspiration; US = ultrasound; WBS = ^{131}I whole body scan.

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk (positive family history)	3	2	If there is strong presumptive evidence from the individual or family history of inherited disease, consider biochemical screening of family members at risk using stimulated (intravenous calcium/pentagastrin) Ct testing from age 5 years (**BTA 2014**) Clinical question considered, but TMs not addressed (**ATA 2015**, AIOCC-AIRO-AIOM 2012)	Genetic counseling and genetic testing for specific germline mutations should be offered to first-degree relatives of patients with proven hereditary MTC (**AACE-AME-ETAM 2010**, **ATA 2015**, **BTA 2014**, AIOCC-AIRO-AIOM 2012, NCCN 2015) The traditional approach of stimulating secretion of Ct by either pentagastrin or calcium infusion to identify patients with MTC is no longer recommended, because elevated Ct is not a specific or adequately sensitive marker for MTC (NCCN 2015)
Differential diagnosis	4	3	Measurement of basal serum Ct level may be useful in the initial evaluation of thyroid nodules (**AACE-AME-ETAM 2010**, ESMO 2012) Measurement of basal plasma Ct and CEA may be useful if MTC is suspected but is not recommended routinely for all thyroid nodules (**BTA 2014,** NCCN 2015) Measurement is mandatory in patients with a family history or clinical suspicion of MTC or MEN2 (**AACE-AME-ETAM 2010)** Physicians should decide whether measuring serum Ct levels in patients with nodular goiters may be useful in the management of patients in their clinic (**ATA 2015**) If the Ct level is increased, the test should be repeated in basal conditions and, if confirmed in the absence of modifiers, a pentagastrin- or calcium-stimulation test will increase the diagnostic accuracy (**AACE-AME-ETAM 2010**, **BTA 2014**) FNA findings that are inconclusive or suggestive of MTC should have Ct measured in the FNA washout fluid to detect the presence of markers such as Ct, chromogranin and CEA and the absence of Tg (**ATA 2015**) Clinical question considered, but TMs not addressed (**NICE 2015**, AIOCC-AIRO-AIOM 2012)	Ct can be increased for causes different from MTC (**AACE-AME-ETAM 2010, ATA 2015)** - other malignancies: pulmonary or pancreatic endocrine tumors, prostate cancer, small cell and large cell lung cancer - benign conditions: kidney failure, autoimmune thyroid disease, sepsis, hypergastrinemia (resulting from proton-pump inhibitor therapy), hyperparathyroidism - miscellanea: sex, age, weight, increased calcium levels, alcohol consumption, smoking, heterophilic anticalcitonin antibodies Serum Ct levels in patients with various nonthyroid malignancies do not increase in response to calcium or pentagastrin stimulation (**ATA 2015**)

to be continued

THYROID CANCER, MEDULLARY (MTC) — Detailed summary tables

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Preoperative workup	3	3	Patients presenting with a thyroid nodule and a cytological or histological diagnosis of MTC should have determination of serum levels of Ct and CEA, and genetic testing for a RET germline mutation (**ATA 2015**, AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015) Before surgery, all patients with suspected MTC should undergo a staging workup including basal serum calcium and plasma or 24-h urine metanephrines and normetanephrines to exclude pheochromocytoma and hyperparathyroidism (**ATA 2015**, **BTA 2014**, AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015) even in the absence of a positive family history or symptoms (**BTA 2014**)	Clinicians should consider falsely high or low serum Ct levels when serum Ct levels are disproportionate to the expected clinical findings (**ATA 2015**) Preoperative systemic staging is indicated in node-positive patients with Ct levels >400 pg/mL (**BTA 2014**) In patients with advanced MTC, marked elevation of the serum CEA level disproportionate to a lower serum Ct level or normal or low levels of both serum Ct and CEA indicate poorly differentiated MTC (**ATA 2015**) In case of suspicious US features, the metastatic nature of a lymph node may be confirmed with measurement of Ct (and/or Tg) in the washout of the needle used for UGFNA biopsy (**AACE-AME-ETAM 2010**)
Reassessment after initial curative treatment	2	3	Clinicians should consider … postoperative serum Ct levels in predicting outcome and planning long-term follow-up of patients treated by thyroidectomy (**ATA 2015**, **BTA 2014**, ESMO 2012, NCCN 2015) Postoperatively, Ct and CEA should be measured at 3 months (no earlier than 15 days after thyroidectomy) and at 6 months (**ATA 2015**, **BTA 2014**, NCCN 2015)	Patients with elevated postoperative serum Ct levels less than 150 pg/mL should have a physical examination and US of the neck. If these are negative, patients should be followed with measurement of serum levels of Ct and CEA, and US every 6 months (**ATA 2015**, ESMO 2012) If the postoperative serum Ct is >150 pg/mL, patients should be evaluated by imaging procedures (neck, skeleton, liver) (**ATA 2015**, ESMO 2012) Following unilateral thyroidectomy, completion thyroidectomy is recommended in patients with a RET germline mutation, an elevated postoperative serum Ct level, or imaging studies indicating residual MTC (**ATA 2015**) Clinical question considered, but TMs not addressed (AIOCC-AIRO-AIOM 2012)

to be continued

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Early detection of recurrence or progression	2	3	Serum levels of Ct and CEA should be should be regularly assessed (**ATA 2015**, **BTA 2014**, AIOCC-AIRO-AIOM 2012, ESMO 2012, NCCN 2015) Ct and CEA doubling times correlate with tumor progression and are useful prognostic indicators for MTC recurrence and survival (**BTA 2014**, ESMO 2012, NCCN 2015)	Reported schedule(s) of CEA and Ct determination: - every 6 months for 1 year and yearly thereafter in patients with undetectable basal Ct and CEA within reference range (**ATA 2015**, NCCN 2015) - at least every 6 months in patients with detectable serum levels of Ct and/or CEA to determine their doubling times (**ATA 2015**, **BTA 2014**, NCCN 2015) Increasing serum CEA levels associated with stable or declining serum Ct levels are considered an indication of poorly differentiated MTC (**ATA 2015**) At least 4 Ct/CEA values are required to calculate the doubling time. An online calculator is available (**BTA 2014**) Doubling time <6 months is a poor prognostic factor (**BTA 2014**) Distant metastases exceeded 50% at Ct levels of 5,000 pg/mL and were virtually always present when Ct levels exceeded 20,000 pg/mL (**ATA 2015**) The presence of an elevated but stable Ct level postoperatively may be managed conservatively (active surveillance), provided treatable disease has been excluded radiologically. Progressively rising Ct concentrations should trigger imaging for further staging (**BTA 2014**, NCCN 2015)
Monitoring of treatment response in advanced disease	2	3	Basal levels of serum Ct and CEA should be measured concurrently in patients with advanced MTC (**ATA 2015**) Systemic therapy should not be administered to patients who have increasing serum Ct and CEA levels but no documented metastatic disease nor to patients with stable low-volume metastatic disease and Ct and CEA doubling times greater than 2 years (**ATA 2015**) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**BTA 2014**, AIOCC-AIRO-AIOM 2012, ESMO 2012)	Clinical question considered, but TMs not addressed (NCCN 2015)

[1] Recommendations from **CPGs** and from **OGDs**, if consistent with those of **CPGs**.
[2] Supplementary information from both **CPGs** and **OGDs**, and recommendations from **OGDs** that are inconsistent with those of **CPGs**.
FNA = fine-needle aspiration; MEN2 = multiple endocrine neoplasia type 2; RET gene = REarranged during Transfection gene; UGFNA = ultrasound-guided fine-needle aspiration; US = ultrasound.

Selected guidelines (by cancer site)

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