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GUIDELINES

Circulating tumor markers: a guide to their appropriate clinical use

Comparative summary of recommendations from clinical practice guidelines (PART 1)

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Contents

Introduction

Some studies have recently shown that the number of tumor markers (TMs) requested is considerably higher than expected based on cancer prevalence (1,2), and that many factors may contribute to overordering of laboratory tests (3). These findings are in agreement with studies performed in case series showing that TMs are frequently requested inappropriately (4). The high rate of overutilization is related to an increased risk of both overdiagnosis and false positive results, with significant repercussions both on individual patients and health care systems (5).

The pathway of knowledge translation of TM research results to clinical practice has changed over the years. Until a couple of decades ago, primary studies were considered the major source of information for clinical practice; studies reporting promising results were frequently advocated to sustain the utilization of the marker. Over the last 2 decades – also because of a progressive shrinkage of resources allotted to the health care sector – clinical practice guidelines (CPGs) have been more and more frequently considered the reference evidence to support clinical choices. However, it should be noted that the primary studies concerning TMs frequently lack design requirements needed to provide good-level evidence according to criteria set for therapeutic intervention trials. Randomization and blinding methods are applied in only few studies where a TM is used as a predictive marker to select patients for a given therapy. The majority of studies on TMs evaluate the diagnostic or prognostic information provided by the markers in a nonrandomized manner; in the case of determination of circulating tumor markers, whichever the result may be, it has no immediate impact on clinical decision-making. As a result, panels preparing CPGs typically lack high-level evidence on TMs according to standard requirements for intervention trials; they frequently either do not produce recommendations, or opt for formulating negative recommendations.

Nevertheless, in spite of either available negative recommendations or the absence of recommendations, TM overordering persists and tends to increase over time, demonstrating the poor adherence of clinicians to CPGs. Many barriers may prevent clinicians from following guideline recommendations, including discrepancies between promising results of primary studies and the cautious position of CPGs, and the frequent poor consistency between recommendations prepared by different CPGs on the same clinical question.

Diagnostic randomized controlled trials are still infrequently performed, and although the number of comparative diagnostic test accuracy studies is increasing, the vast majority of the available evidence comes from single test evaluation studies. The latter studies do not measure patient-relevant outcomes directly, and cannot be equated to pharmacological clinical trials due to intrinsic differences in both design and endpoints. Although a framework of "linked evidence" has been in place for years, which strives to use evidence on true positive, true negative, false positive and false negative test results to deduct therapeutic and other patient-relevant consequences of testing, the application of this framework has been shown to be challenging (6). While awaiting the distillation of higher quality evidence into comprehensive guidelines with possibly an application of the linked-evidence or related frameworks (7), efforts should be made to improve the adherence to existing guidelines.

Harmonization of different CPGs is a current strategy to handle uncertainties or discrepancies between different CPGs in settings where the clinical questions are complex, e.g., screening programs or disease prevention campaigns. Studies on the harmonization of recommendations for circulating cancer biomarkers have not been published so far.

The aim of the present research project is to develop a tool to summarize the recommendations and supplementary information on circulating TMs offered by available CPGs on solid tumors. The tool is intended to provide all possible evidence-based choices concerning TMs for people facing a clinical question in which the use of a TM could be contemplated.

Diligence was adopted to develop the tool according to a structured and rigorous methodology in order to guarantee the accurate extraction of relevant information including recommendations from selected guidelines as well as the validity of the synthesis of information from different sources.

Recommendations and supplementary information extracted from CPGs were clustered and summarized applying 4 increasing levels of synthesis, summarizing and simplifying the information to make it explicit, verifiable, valid and reproducible. The first 2 levels of clustering and synthesis are available for consultation upon request. The last 2 levels of synthesis are reported in the present article. They are the Detailed Summary Tables and Take-Home Messages, which represent the levels of synthesis suitable for practical use. The Take-Home Messages are intended for use by health care providers in clinical practice with the goal of improving the appropriateness of TM use. The Detailed Summary Tables can be used by policy makers for potential adaptation to their own context and by educators to design teaching programs consistent with the available evidence.

The tabulation of the information has been structured by individual malignancies. Within each malignancy, we clustered the information according to a set of clinical questions established as being common to all malignancies. A parallel assessment of the quality of the included CPGs has been performed and the results are shown alongside the Take-Home Messages in order to inform the reader about the quality of the source (CPGs) from which the recommendations were distilled.

The purpose of this project was to provide an accurate and synthetic reproduction of the available evidence on the clinical use of circulating TMs. We endeavored to avoid any interpretation of the content of CPGs and used verbatim reporting of the original sentences whenever possible.

Likewise, the expert panel intentionally avoided expressing its own opinion in cases where different CPGs showed discrepant positions on a clinical question. Dissimilar recommendations of diverse CPGs may be due to different causes; in fact, CPG panels have to interpret the primary TM evidence in different local contexts with possibly dissimilar available resources or patient preferences. Our panel deemed that the complete presentation of clinical questions in which the consistency between guidelines seemed poor represents a

strength of the present project for 2 reasons; firstly, it provides an inventory of all possible recommendations after the application of evidence synthesis frameworks; secondly, it should help identify areas in which primary studies are especially needed to answer clinical questions concerning TMs.

References

1. Gion M, Peloso L, Trevisiol C, et al. An epidemiology-based model as a tool to monitor the outbreak of inappropriateness in tumor marker requests: a national scale study. Clin Chem Lab Med. 2016;54:473-482.
2. Franceschini R, Trevisiol C, Dittadi R, et al. Tumour markers requesting pattern with regards to different organizational settings in Italy: a survey of hospital laboratories. Ann Clin Biochem. 2009;46:316-321.
3. Sood R, Sood A, Ghosh AK. Non-evidence-based variables affecting physicians' test-ordering tendencies: a systematic review. Neth J Med. 2007;65:167-177.
4. Zhi M, Ding EL, Theisen-Toupal J, et al. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. PLoS One. 2013;8:e78962. doi: 10.1371/journal.pone.0078962
5. Moynihan R, Henry D, Moons KG. Using evidence to combat overdiagnosis and overtreatment: evaluating treatments, tests, and disease definitions in the time of too much. PLoS Med. 2014;11:e1001655. doi: 10.1371/journal. pmed.1001655.
6. Merlin T, Lehman S, Hiller JE, Ryan P. The "linked evidence approach" to assess medical tests: a critical analysis. Int J Technol Assess Health Care. 2013;29:343-350.
7. Schünemann HJ, Mustafa R, Brozek J, et al; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76:89-98.

Methodology

Scope

CPGs are critical for translating evidence to application in medical decision-making. Trustworthy guidelines are based on a systematic review of the clinical evidence (1, 2). The number of CPGs has grown considerably and their quality is often heterogeneous. The objective of the project was to provide an easy-to-use but complete synthesis of TM recommendations distilled from evidence-based CPGs. The ultimate aim was to improve the appropriate use of TMs in clinical practice.

For the synthesis document to be useful it had to have the following characteristics:

- to be developed with sound and structured methodology
- to include all recommendations and information on circulating biomarkers reported in CPGs on solid tumors
- to synthesize recommendations and information in easy-to-use tables at 2 decreasing levels of complexity
- to be useful for the following target audience: (i) health care providers, (ii) policy makers for potential adaptation to specific settings, and (iii) staff developing educational material informed by available evidence.

Panel composition and project planning

The participating institutions and scientific societies suggested 74 delegates to be enrolled in the expert panel. The panel comprised a multidisciplinary group of medical oncologists, radiation oncologists, clinical pathologists, general practitioners, internists, gynecologists, urologists, and experts in evidence-based methodology.

The project was organized in work packages (WPs) with dedicated tasks and milestones:

WP1 – Definition of the primary objectives of the project and management strategies
WP2 – Search and selection of guidelines
WP3 – Appraisal of guidelines through the AGREE II tool
WP4 – Assessment of the rate of utilization of a subset of guidance documents in clinical practice
WP5 – Synthesis into "Detailed Summary Tables" and "Take-Home Messages" regarding the recommended use of TMs
WP6 – Assessment of the correctness and completeness of the information summarized in the summary tables by our expert panel (n=74)
WP7 – External and independent verification of the correctness and completeness of the information summarized in the tables by an independent external committee (n=18).

WP1 was jointly managed by the Steering Committee and the Scientific Committee of the project. The activities of WPs 2 to 6 were carried out by working groups composed of members of the expert panel, in which oncologists and other clinicians, laboratory staff, methodologists and other research staff participated (see p. e364-e367). WP7 was realized by the members of the Interregional Biomarkers Working Group, instituted by the Health Commission of the Italian Permanent Conference for Relations between State, Regions and the Autonomous Provinces of Trento and Bolzano.

Search and selection process

We performed a systematic search for CPGs in the following databases: PubMed, the National Guidelines Clearinghouse and the GIN library. The search for guidance documents included the following search terms, their synonyms, and associated MESH terms: "guideline OR recommendation OR consensus OR consensus development conference" AND "neoplasms OR carcinoma OR cancer OR tumor". We included guidance documents published from January 2009 to July 2015 in English or Italian. The search identified a total of 8,266 citations. In addition to searching bibliographic databases, we searched 11 websites of state or local government agencies and 61 websites of pertinent professional organizations in Italy.

We used a standardized set of selection criteria to identify potentially relevant publications. The identified documents were assessed for pertinence according to shared criteria established by a selected group of 4 members of the expert panel to select guidelines that fit the objectives of the project.

Only documents containing recommendations for clinical practice were included. Reviews, technology assessments, commentaries to CPGs, and service documents were ex-

cluded. The types of biomarker considered were circulating biomarkers measured in body fluids (blood derivatives of serum or plasma/urine) with commercially available assay methods. Fecal blood tests, laboratory tests aimed at monitoring metabolism, organ damage and blood cell counts were not considered, as these do not present a direct relationship with the tumor. Circulating tumor cells, cell-free circulating DNA, and microRNA were also excluded from the assessment. Guidance papers limited to rare tumors, sarcomas, hematological malignancies, the pediatric population, pregnant women, and specific aspects of specialized topics (i.e., imaging techniques, radiotherapy procedures, drug administration modalities) were excluded. We did not consider health care procedures established by the Italian National Health Service at the national and regional level (i.e., hereditary tumors other than those of the ovary and thyroid), nor did we consider screening programs currently provided by the Italian National Health Service (i.e., screening for colorectal cancer, uterine cervix cancer and breast cancer), as the latter do not include circulating TMs. Details on the search strategy and selection criteria will be described in a dedicated report on the systematic review process (in preparation and available from the corresponding author of the present article).

Selection of CPGs was independently performed by 3 examiners on the basis of the titles and abstracts of the 8,266 identified documents. A guidance document was considered potentially relevant when 2 of the 3 examiners opted for inclusion. Documents included by a single examiner were discussed until consensus for inclusion or exclusion was reached.

A total of 1,181 potentially relevant documents were selected, for which full-text reports were obtained. The resulting set was then screened for inclusion and the included reports were grouped by guideline, allowing multiple reports on a single guideline. If several versions of a specific guideline were found, we included the most recently updated version.

We included a final set of 559 CPGs concerning 20 different malignancies: carcinomas of the breast, biliary tract, colon-rectum, endometrium, esophagus, head and neck, kidney, liver, lung, stomach, ovary, pancreas, prostate, uterine cervix, urinary bladder, differentiated and medullary thyroid cancer, germ cell testicular cancer, melanoma, mesothelioma and neuroendocrine tumors.

Quality appraisal of guidelines

The selected guidance documents were further appraised to determine their adherence to the IOM standards, which require CPGs to be based on systematic reviews of existing evidence (1). The 559 guidance documents were clustered into 2 groups: 127 documents in which systematic reviews were essential to generate recommendations (CPGs) and 432 guidance documents without evidence of systematic review methodology (other guidance documents – OGDs). However, authoritative institutions or medical societies typically produce guidance documents without applying systematic review methods. We also knew up front that these documents are currently used by clinicians in their daily practice. The Steering Committee therefore decided to provide all guidance documents to the panel members with a request to judge which of the OGDs were used by our target audience. Whenever 25% or more of the panel members declared that a given guidance document was used in clinical practice, the guidance document was retained. In all, 111 of 432 OGDs qualified for inclusion.

The development process

The detailed process of document development was agreed upon by the Steering Committee and the Scientific Committee (report in preparation and available from the corresponding author of the present article). The basic steps in the process are summarized below:

– classifying the clinical questions (e.g., screening, diagnosis, therapy)
– choosing the biomarkers of interest
– developing the specific queries on TM use within the clinical questions
– retrieving and tagging information concerning every clinical question
– data extraction from both types of guidance documents, with quality assessment of CPGs and assessment of clinical use of OGDs
– clustering and synthesizing information at decreasing levels of complexity
– final write-up.

Classifying the clinical question

Given that the role of TMs may differ widely in the different clinical phases of the disease, we decided to consider the clinical questions separately: (i) screening, (ii) differential diagnosis, (iii) preoperative workup, (iv) reassessment after curative treatment, (v) early detection of recurrence or progression, and (ii) monitoring of treatment response in advanced disease. Details of the considered clinical questions are reported elsewhere (in preparation and available from the corresponding author of the present article).

Developing specific queries within the clinical questions

The information related to the following specific queries were found in the selected guidance documents:

1. Is the use of TM(s) explicitly recommended or not recommended?
2. Which TM(s) is/are recommended or not recommended?
3. In which type of patients is/are TM(s) recommended or not recommended?
4. Can TM(s) be used autonomously or should they be used in association with other tests?
5. Are rules to interpret the result of TM determination provided?
6. Do the TM results have an impact on treatment decisions or, more broadly, on the clinical management of the patient?
7. Is information on possible causes of false positive and false negative results provided?
8. Is information on preanalytical or analytical issues that can influence the reliability of the TM result provided?

Retrieving and tagging information concerning every clinical question

For every malignancy, all information concerning TMs in the different clinical questions was identified in the selected guidance documents. For each guidance document, the relevant information was tagged, extracted (whenever possible as a verbatim transcription) and classified as follows:

– *Recommendation:* part of text explicitly defined and clearly recognizable as recommendation
– *Supplementary information:* (i) implicit advice for clinical practice not recognizable as explicit recommendation; (ii) additional information concerning the application and interpretation of TMs
– *Supporting evidence:* reporting and conclusions of the evidence used by the author team that developed the published guidance document to draw up recommendations.

All information extracted from guidance documents was clustered and synthesized in 4 rounds (levels) of increasing simplification as described elsewhere (report in preparation and available from the corresponding author of the present article) and briefly summarized below.

– Level 1: The parts pertaining to TMs were retrieved from every guidance document and transcribed verbatim, preserving the textual structure – e.g., paragraph, complete clause – in which they were included, in a *Master table* (first-level tabulation)
– Level 2: Portions of text strictly referring to TMs were extracted, clustered as recommendations and supplementary information, and transcribed verbatim in a table (second-level tabulation). Information from different guidelines was summarized separately
– Level 3: Similar recommendations and supplementary information from different guidelines were summarized as a single entry, followed by the acronyms of the CPGs and/or ODGs formulating them (third-level tabulation: *Detailed Summary Table*)
– Level 4: Essential information to support decision-making in clinical practice was distilled and summarized in a further simplified table (fourth-level tabulation: *Take-Home Message*).

The present article reports the *Detailed Summary Tables* and *Take-Home Messages*, which represent the levels of synthesis suitable for practical use.

Managing information of CPGs and OGDs

Recommendations provided by CPGs are displayed in *Detailed Summary Tables* and *Take-Home Messages.* Recommendations from OGDs are embedded in both tables whenever they were consistent with those of CPGs. Recommendations reported exclusively by OGDs are not included in the *Take-Home Messages*, but are provided as supplementary information in the *Detailed Summary Tables.* CPGs and OGDs are labeled as such in all tables in order to allow the reader to track the source of the reported information.

Wording

The terms used to formulate recommendations were found to be highly heterogeneous among the included guidelines, reflecting (i) the variable quality of the supporting evidence, (ii) the different weight given to the trade-off between the benefits and harms of an intervention in different contexts, and (iii) the uneven methodological rigor used to develop the guidance documents. In agreement with the scope of the project, the Scientific Committee settled on maintaining the original terms used by different CPGs, thus avoiding any attempt towards harmonization of the terms. When the same recommendation was provided by more than one CPG, the less stringent term (e.g., *should* rather than *have to*) was chosen in the synthesis.

Indications concerning TMs can be grouped into 3 categories: positive recommendation (CPG recommends to use TM), negative recommendation (CPG recommends not to use the marker), and no explicit recommendation available. The third category (no explicit recommendation available) encompasses different circumstances in relation to either the availability and quality of evidence or the assessment of benefit and harms, or both.

The following sentences were used in the synthesis to represent the different circumstances in which no recommendations were provided:

1. *Clinical question considered, but TMs not addressed:* The clinical question (screening, differential diagnosis, initial workup, etc.) is comprehensively considered by the CPG, but circulating TMs are not mentioned.
2. *Clinical question considered, no explicit recommendations on TMs provided:* TMs are mentioned and discussed with reference to the clinical question, but the panel that developed the CPG deemed the available evidence or the assessment of benefit and harms, or both, not adequate to support a positive or negative recommendation.
3. *Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed:* Response rates to different therapeutic regimens and survival benefits are the most frequently addressed topics by guidance documents in the clinical question "Monitoring of treatment response in advanced disease". If the guidance document does not mention criteria to monitor the response, it cannot be assumed that a systematic search of the primary literature on TMs in this setting was performed. Therefore, a sentence different from the first one was used since it could not be appraised whether the clinical question had been *comprehensively* considered.

These 3 sentences are used in the *Detailed Summary Tables* to provide comprehensive information on how different guidelines considered TMs in different clinical questions. In the *Take-Home Messages* a more general sentence indicating that there are no recommendations on TMs was preferred (*Recommendations on TMs not available*), given the practical purpose of this level of synthesis.

Agreeing on the synthesis process and results

The process of synthesis was agreed upon within the Scientific Committee. The *Detailed Summary Tables* and *Take-Home Messages* were submitted to the expert panel for evaluation (internal evaluation) and approval of the synthesis, or for suggestions. Comments and suggestions were discussed and accepted when appropriate. The *Detailed Summary Tables* and *Take-Home Messages* were then submitted to the members of the Interregional Biomarkers Working Group, instituted by the Health Commission of the Italian Permanent Conference for Relations between State, Regions and the Autonomous Provinces of Trento and Bolzano for external and independent verification of the correctness and completeness of the information summarized in the tables.

Assessment of CPGs with the AGREE II instrument

CPGs were assessed with the Appraisal of Guidelines for Research & Evaluation (AGREE II) tool, in order to facilitate comparison of the quality of the summarized CPGs on the basis of an objective, standardized method (3). The instrument comprises 23 key items organized into 6 domains. Each domain captures a distinct dimension of guideline quality: 1. Scope and purpose; 2. Stakeholder involvement; 3. Rigor of development; 4. Clarity of presentation; 5. Applicability; 6. Editorial independence. An AGREE quality score is calculated for each of the 6 AGREE domains using a 7-point scoring system. A higher score indicates a better quality of the domain. The 6 domain scores are independent and should not be combined into a single score.

Each CPG was rated by 2 evaluators independently. If the CPG addressed multiple diseases, the evaluators considered the documents as many times as the number of diseases addressed. The evaluators achieved high interrater reliability. The scores of the 6 domains were subdivided into quartiles and marked in different colors for easier comprehension of the score (4).

References

1. IOM (Institute of Medicine). Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press, 2011.
2. Qaseem A, Forland F, Macbeth F, et al; Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. Ann Intern Med. 2012;156:525-531.
3. Brouwers M, Kho ME, Browman GP, et al; for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Can Med Assoc J. 2010;182:E839-842.
4. http://www.snlg-iss.it/banca_dati_comparativa. (Accessed November 24, 2016).

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.

BILIARY CANCER — Take-home message

Examined documents: 7 (2 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 of people at increased risk (sclerosing cholangitis)	Recommendations on TMs not available	∅	**1/1** (ACG 2014)	**1/2** (AASLD 2010)
Differential diagnosis	Recommendations on TMs not available	∅	**2/2** (ACG 2014, NICE 2015)	**4/5** (AIRO 2012, ESMO 2011, NCCN 2015, SIGE 2010)
Preoperative workup	Recommendations on TMs not available	∅	**1/1** (ACG 2014)	**1/3** (SIGE 2010)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Clinical question not addressed by **CPGs**	---	---	---
Monitoring of treatment response in advanced disease	Clinical question not addressed by **CPGs**	---	---	---

[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.

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
ACG 2014	58	36	67	92	25	88
NICE 2015	93	88	96	93	72	81

Examined documents: 19 (10 CPGs, 9 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	Recommendations on TMs not available	Ø	**4/4** (AGA 2010, NICE 2011-SU, SIGN 2011, USMSTF 2012)	**3/3** (AIOM 2015, ESMO 2013-C, NCCN 2015-C)
Differential diagnosis	Recommendations on TMs not available	Ø	**5/5** (ASCRS 2012-C, CCO 2014-CRC, NICE 2014, NICE 2015, SIGN 2011)	**4/4** (AIOM 2015, ESMO 2012-CRC, ESMO 2013-C,ESMO 2013-R)
Preoperative workup	CEA should be assessed before elective surgery for the establishment of baseline values	**CEA**	**3/6** (ASCRS 2012-C, ASCRS 2013-R, CCO 2014-R)	**7/7** (AIOM 2015, EGTM 2013, ESMO 2012-CRC, ESMO 2013-C, ESMO 2013-R, NCCN 2015-C, NCCN 2015-R)
	At present there is insufficient evidence to support the routine use of other TMs such as CA19.9 in addition to CEA	Ø	**2/6** (ASCRS 2012-C, ASCRS 2013-R)	**1/7** (AIOM 2015)
	Recommendations on TMs not available	Ø	**3/6** (AGA 2010, NICE 2014, SIGN 2011)	**0/7**
Reassessment after initial curative treatment	Recommendations on TMs not available	Ø	**1/1** (SIGN 2011)	**2/3** (ESMO 2013-C, ESMO 2013-R)
Early detection of recurrence or progression	CEA should be regularly assessed at least in the first 3-5 years during follow-up to monitor for signs of recurrence	**CEA**	**4/4** (ASCRS 2012-C, ASCRS 2013-R, NICE 2014, SIGN 2011)	**7/8** (AIOM 2015, ASCO 2013, EGTM 2013, ESMO 2012-CRC, ESMO 2013-C, NCCN 2015-C, NCCN 2015-R)
	A confirmed rise in postoperative CEA levels during surveillance should prompt further investigation for recurrent disease		**2/4** (ASCRS 2012-C, ASCRS 2013-R)	**5/8** (AIOM 2015, EGTM 2013, ESMO 2013-C, NCCN 2015-C, NCCN 2015-R)
	At present there is insufficient evidence to support the routine use of other TMs such as CA19.9 in addition to CEA		**2/4** (ASCRS 2012-C, ASCRS 2013-R)	**1/8** (ESMO 2013-C)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	Ø	**3/3** (ASCRS 2012-C, NICE 2014, SIGN 2011)	**3/7** (AIOM 2015, ESMO 2012-CRC, ESMO 2013-R)

[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: 19 (10 CPGs, 9 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
AGA 2010	72	33	49	78	21	54
ASCRS 2012-C	58	33	67	83	25	33
ASCRS 2013-R	53	36	59	81	19	38
CCO 2014-CRC	94	53	77	75	35	100
CCO 2014-R	97	50	83	81	38	67
NICE 2011-SU	97	92	93	97	79	88
NICE 2014	100	94	97	94	88	92
NICE 2015	94	92	95	94	88	83
SIGN 2011	86	81	78	89	73	63
USMSTF 2012	67	36	67	69	19	50

Examined documents: 9 (5 CPGs, 4 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 (Barrett's esophagus)	Recommendations on TMs not available	Ø	**3/3** (AHS 2014, mep 2012, NHMRC 2014)	**0/0**
Differential diagnosis	Recommendations on TMs not available	Ø	**5/5** (AHS 2014, mep 2012, NHMRC 2014, NICE 2015, STS 2013)	**3/3** (AIOM 2015, ESMO 2013, NCCN 2015)
Preoperative workup	Recommendations on TMs not available	Ø	**3/3** (AHS 2014, NHMRC 2014, STS 2013)	**4/4** (AIOM 2015, AIRO 2012, ESMO 2013, NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Recommendations on TMs not available	Ø	**1/1** (AHS 2014)	**4/4** (AIOM 2015, AIRO 2012, ESMO 2013, NCCN 2015)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	Ø	**1/1** (STS 2013)	**4/4** (AIOM 2015, AIRO 2012, ESMO 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.

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 2014	92	44	68	67	58	79
mep 2012	72	67	65	75	33	67
NHMRC 2014	83	67	68	81	44	75
NICE 2015	89	97	90	92	73	79
STS 2013	58	44	69	69	25	50

GASTRIC CANCER — Take-home message

Examined documents: 8 (3 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 of people at increased risk	Recommendations on TMs not available	∅	**1/1** (ACCC 2009)	**1/1** (NCCN 2015)
Differential diagnosis	Recommendations on TMs not available	∅	**1/1** (NICE 2015)	**2/2** (AIOM 2015, ESMO 2013)
Preoperative workup	Recommendations on TMs not available	∅	**1/1** (ACCC 2009)	**4/5** (AIOM 2015, EGTM 2013, ESMO 2013, NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Determining TMs for the follow-up of patients operated on for gastric carcinoma is not worthwhile because it does not lead to clinical benefit	**None**	**1/1** (ACCC 2009)	**0/4**
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	∅	**2/2** (ACCC 2009, CCO 2014)	**4/4** (AIOM 2015, AIRO 2012, ESMO 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.
∅ 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
ACCC 2009	**83**	**61**	**71**	**75**	**33**	**50**
CCO 2014	**83**	**56**	**81**	**75**	**42**	**71**
NICE 2015	**89**	**97**	**91**	**89**	**71**	**83**

HEPATOCELLULAR CARCINOMA (HCC) — Take-home message

Examined documents: 12 (6 CPGs, 6 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 	Surveillance of patients in the high-risk group is based on periodic ultrasonography combined with measurement of AFP	**AFP**	**2/3** (JSH 2013, NICE 2013-HBV)	**1/6** (NCCN 2015)
	Recommendations on TMs not available		**1/3** (MCC 2011)	**1/6** (ESMO 2012)
	Supplementary information: Screening for HCC should use ultrasonography alone. AFP (and other TMs) not indicated for surveillance strategy because of low sensitivity (lower than ultrasonography) and low specificity	Ø	**1/3** (MCC 2011)	**5/6** (AIOM 2015, AIRO 2012, AISF 2013, EASL-EORTC 2012, ESMO 2012)
Differential diagnosis 	Recommendations on TMs not available	Ø	**4/4** (ACG 2014-FLL, JSH 2013, MCC 2011, NICE 2015)	**3/6** (AIOM 2015, AIRO 2012, EASL-EORTC 2012)
	Supplementary information n. 1: The diagnostic workup of a patient with suspected HCC includes serum AFP measurement		**1/4** (ACG 2014-FLL)	**2/6** (AIOM 2015, ESMO 2012)
	Supplementary information n. 2: No primary care evidence was identified pertaining to the diagnostic accuracy of AFP in patients with suspected liver cancer where the clinical responsibility was retained by primary care		**1/4** (NICE 2015)	**0/6**
Preoperative workup	Recommendations on TMs not available	Ø	**2/2** (JSH 2013, MCC 2011)	**3/6** (AIRO 2012, EASL-EORTC 2012, ESMO 2012)
Liver transplant priority and delisting policies	Periodic waiting-list monitoring should be performed by imaging and AFP measurement	**AFP**	**1/3** (OLT4HCG 2012)	**2/4** (AISF 2013, EASL-EORTC 2012)
	Increased AFP levels and/or changes in serum AFP over time may predict the risk of dropout from liver transplant waiting list	Ø	**1/3** (OLT4HCG 2012)	**2/4** (AISF 2013, EASL-EORTC 2012)
	Recommendations on TMs not available		**2/3** (JSH 2013, MCC 2011)	**2/4** (AIOM 2015, NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Monitoring after liver transplant and palliative treatments may include periodic AFP measurements	**AFP**	**1/1** (OLT4HCG 2012)	**3/5** (AISF 2013, ESMO 2012, NCCN 2015)

to be continued

HEPATOCELLULAR CARCINOMA (HCC)

Take-home message

Examined documents: 12 (6 CPGs, 6 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	∅	**2/2** (JSH 2013, MCC 2011)	**5/6** (AIOM 2015, AIRO 2012, AISF 2013, EASL-EORTC 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.
∅ 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.

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
ACG 2014-FLL	58	42	70	89	33	88
JSH 2013	75	44	60	81	40	29
MCC 2011	56	44	63	72	33	58
NICE 2013-HBV	94	89	97	97	81	88
NICE 2015	89	97	91	86	73	83
OLT4HCG 2012	56	61	68	75	31	50

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	Clinical question not addressed by **CPGs**	---	---	---
Differential diagnosis	Recommendations on TMs not available	Ø	**2/2** (ISGPS 2014-A, NICE 2015)	**3/3** (AIOM 2015, ESMO 2012, NCCN 2015)
	Supplementary information: CA 19.9 may be falsely positive in cases of biliary obstruction (regardless of etiology) and in cases of infection or inflammation of the biliary tract (NCCN 2015)		**1/2** (ISGPS 2014-A)	**3/3** (AIOM 2015, ESMO 2012, NCCN 2015)
Preoperative workup	CA19.9 may be included in standard preoperative diagnostics for patients with *borderline resectable pancreatic cancer*	**CA19.9** Ø	**1/3** (ISGPS 2014-B)	**0/3**
	Supplementary information: Elevated preoperative CA19.9 may have negative prognostic value		**2/3** (ISGPS 2014-B, S3 2014)	**3/3** (AIOM 2015, ESMO 2012, NCCN 2015)
	Recommendations on TMs not available		**2/3** (ISGPS 2014-A, S3 2014)	**1/3** (ESMO 2012)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Clinical question not addressed by **CPGs**	---	---	---
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	Ø	**1/1** (S3 2014)	**2/3** (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.

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
ISGPS 2014-A	**81**	**44**	**58**	**67**	**27**	**42**
ISGPS 2014-B	**81**	**44**	**59**	**67**	**27**	**42**
NICE 2015	**89**	**97**	**91**	**89**	**73**	**88**
S3 2014	**58**	**44**	**60**	**69**	**27**	**63**

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: 7 (2 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk	1	2	Clinical question considered, but TMs not addressed (**ACG 2014**)	The current evidence does not support routine screening for cholangiocarcinoma in asymptomatic patients with underlying primary sclerosing cholangitis (**ACG 2014,** AASLD 2010, SIGE 2010) Patients with primary sclerosing cholangitis should undergo careful surveillance for cholangiocarcinoma development mainly during the first 2 years of follow-up (SIGE 2010) Surveillance with CA19.9 and one imaging technique (CT or MRI) is at present the suggested approach (SIGE 2010) No study has demonstrated any value for the serum CA19.9 test as a screening modality in asymptomatic primary sclerosing cholangitis (AASLD 2010, SIGE 2010)
Differential diagnosis	2	5	Clinical question considered, no explicit recommendations on TMs provided (**ACG 2014**, **NICE 2015**, AIRO 2012, NCCN 2015, SIGE 2010)	CA19.9 is a serum marker that can be measured to identify cases with intrahepatic cholangiocarcinoma in patients with focal liver lesions, but it has low specificity and sensitivity (**ACG 2014**, AASLD 2010, AIRO 2012, SIGE 2010) No primary care evidence was identified pertaining to the diagnostic accuracy of … CA19.9 in patients with suspected gallbladder cancer where the clinical responsibility was retained by primary care (**NICE 2015**) CA19.9 can be elevated in patients with diseases other than biliary cancer (AASLD 2010, AIRO 2012, NCCN 2015): - other malignancies (e.g., gastric or pancreatic cancer) - benign conditions (bacterial cholangitis, cholestatic jaundice, gallbladder lithiasis) Patients negative for the Lewis antigen will not have an elevated serum CA19.9 level despite having cholangiocarcinoma (AASLD 2010) Clinical question considered, but TMs not addressed (ESMO 2011)
Preoperative workup	1	3	Clinical question considered, but TMs not addressed (**ACG 2014**)	CEA and CA19.9 could be considered as part of the initial workup (in conjunction with imaging studies) (AIRO 2012, NCCN 2015) Clinical question considered, no explicit recommendations on TMs provided (SIGE 2010)
Reassessment after initial curative treatment	0	1	Clinical question not addressed by **CPGs**	Clinical question considered, but TMs not addressed (ESMO 2011)
Early detection of recurrence or progression	0	3	Clinical question not addressed by **CPGs**	Clinical question considered, no explicit recommendations on TMs provided (AIRO 2012, NCCN 2015) Clinical question considered, but TMs not addressed (ESMO 2011)

to be continued

Examined documents: 7 (2 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Monitoring of treatment response in advanced disease	0	3	Clinical question not addressed by CPGs	Clinical question considered, but TMs not addressed (ESMO 2011) In the event of disease relapse or progression CEA and CA19.9 could be considered as part of the initial workup … in conjunction with imaging studies (NCCN 2015) CA19.9 testing can be considered after biliary decompression (NCCN 2015) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (SIGE 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**.

Examined documents: 19 (10 CPGs, 9 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk	4	3	Clinical question considered, but TMs not addressed (**AGA 2010**, **NICE 2011-SU**, **SIGN 2011**, **USMSTF 2012**, AIOM 2015, ESMO 2013-C, NCCN 2015-C)	
Differential diagnosis	5	4	Clinical question considered, but TMs not addressed (**ASCRS 2012-C**, **CCO 2014-CRC**, **NICE 2014**, **NICE 2015**, **SIGN 2011**, AIOM 2015, ESMO 2012-CRC, ESMO 2013-R)	Clinical question considered, no explicit recommendations on TMs provided (ESMO 2012-C) CEA has low predictive value for diagnosis in asymptomatic patients due to its relatively low sensitivity and specificity (ESMO 2013-C)
Preoperative workup	6	7	CEA should be assessed before elective surgery for the establishment of baseline values (**ASCRS 2012-C**, **ASCRS 2013-R**, **CCO 2014-R**, AIOM 2015, EGTM 2013, ESMO 2012-CRC, ESMO 2013-C, ESMO 2013-R, NCCN 2015-C, NCCN 2015-R) At present there is insufficient evidence to support the routine use of other TMs such as CA19.9 (**ASCRS 2012-C**, **ASCRS 2013-R**, AIOM 2015) Clinical question considered, but TMs not addressed (**AGA 2010**, **NICE 2014**, **SIGN 2011**)	Increased levels of CEA have been correlated with poorer prognosis (**ASCRS 2012-C**, **ASCRS 2013-R**, AIOM 2015, EGTM 2013, ESMO 2013-C) Data are insufficient to justify the use of a high preoperative CEA level as an indication for adjuvant therapy (**ASCRS 2012-C**, **ASCRS 2013-R**, AIOM 2015, EGTM 2013)
Reassessment after initial curative treatment	1	3	Clinical question considered, but TMs not addressed (**SIGN 2011**, ESMO 2013-R)	An increased preoperative value not normalized after 1 month following surgical resection may indicate persistent disease (AIOM 2015, ESMO 2013-C) Clinical question considered, no explicit recommendations on TMs provided (ESMO 2013-C)

to be continued

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Early detection of recurrence or progression	4	8	CEA should be regularly assessed during follow-up to monitor for signs of recurrence (**ASCRS 2012-C**, **ASCRS 2013-R**, **NICE 2014**, **SIGN 2011**, AIOM 2015, ASCO 2013, EGTM 2013, ESMO 2012-CRC, ESMO 2013-C, NCCN 2015-C, NCCN 2015-R) A confirmed rise in the postoperative CEA during surveillance should prompt further investigation for recurrent disease (**ASCRS 2012-C**, **ASCRS 2013-R**, AIOM 2015, EGTM 2013, ESMO 2013-C, NCCN 2015-C, NCCN 2015-R) At present there is insufficient evidence to support the routine use of other TMs such as CA19.9 (**ASCRS 2012-C**, **ASCRS 2013-R,** ESMO 2013-C)	Reported schedule(s) of CEA determination: - at least every 6 months in the first 3 years (**NICE 2014**) - every 2-3 months in the first 3 years, every 6 months at years 4 and 5 (EGTM 2013) - every 3 months in the first 3 years, every 6 months at years 4 and 5 (ESMO 2012-CRC) - every 3-4 months in the first 3 years, every 6 months at years 4 and 5 (AIOM 2015) - every 3-6 months for 5 years. Patients at higher risk of recurrence should be considered for testing in the more frequent end of the range (ASCO 2013) - every 3-6 months in the first 2 years, every 6 months at years 4 and 5 (NCCN 2015-C, NCCN 2015-R) - every 3-6 months in the first 3 years, every 6-12 months at years 4 and 5 (ESMO 2013-C) - evidence does not consent to recommend one specific protocol, but a pragmatic protocol of follow-up is recommended (**NICE 2014**, **SIGN 2011**) Caution should be exercised in interpreting CEA levels, as both false-positive rates of CEA elevation (7%-16%) and false-negative rates (up to 40%) have been reported (EGTM 2013, ESMO 2013-C) In rectal cancer, clinical, laboratory (including CEA) and radiological examinations are of unproven benefit and should be restricted to patients with suspicious symptoms (ESMO 2013-R)

to be continued

Examined documents: 19 (10 CPGs, 9 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Monitoring of treatment response in advanced disease	3	7	Clinical question considered, but TMs not addressed (**NICE 2014**) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**ASCRS 2012-C**, **SIGN 2011**, AIOM 2015, ESMO 2013-R)	Clinical question considered, no explicit recommendations on TMs provided (ESMO 2012-CRC) CEA >50 ng/mL is an established poor prognostic factors in advanced CRC (ESMO 2012-CRC) CEA flare and drop are predictive factors of response to treatment in advanced CRC (ESMO 2012-CRC) CEA – if initially elevated – should be measured before and periodically during chemotherapy for metastatic disease (EGTM 2013, ESMO 2014-mCRC) CEA should be included in the initial workup of suspected or proven metastatic disease (NCCN 2015-C, NCCN 2015-R) Use of CEA is as accurate as CT imaging for assessing the response of colorectal cancer liver metastasis to chemotherapy (EGTM 2013) Reported schedule of patient re-evaluation: - patients should be re-evaluated every 2-3 months if chemotherapy is continued (ESMO 2014-mCRC)

[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: 9 (5 CPGs, 4 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk (Barrett's esophagus)	3	0	Clinical question considered, but TMs not addressed (**AHS 2014**, **mep 2012**, **NHMRC 2014**)	
Differential diagnosis	5	3	Clinical question considered, but TMs not addressed (**AHS 2014**, **mep 2012**, **NHMRC 2014**, **NICE 2015**, **STS 2013**, AIOM 2015, ESMO 2013, NCCN 2015)	
Preoperative workup	3	4	Clinical question considered, but TMs not addressed (**AHS 2014**, **NHMRC 2014**, **STS 2013**, AIOM 2015, AIRO 2012, ESMO 2013, NCCN 2015)	
Reassessment after initial curative treatment	0	4	Clinical question not addressed by **CPGs**	Clinical question considered, but TMs not addressed (AIOM 2015, AIRO 2012, ESMO 2013, NCCN 2015)
Early detection of recurrence or progression	1	4	Clinical question considered, but TMs not addressed (**AHS 2014**, AIOM 2015, AIRO 2012, ESMO 2013, NCCN 2015)	
Monitoring of treatment response in advanced disease	1	4	Clinical question considered, but TMs not addressed (**STS 2013**, AIOM 2015, AIRO 2012, ESMO 2013, 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: 8 (3 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk	1	1	Clinical question considered, but TMs not addressed (**ACCC 2009**, NCCN 2015)	
Differential diagnosis	1	2	Clinical question considered, but TMs not addressed (**NICE 2015**, AIOM 2015, ESMO 2013)	
Preoperative workup	1	5	Clinical question considered, but TMs not addressed (**ACCC 2009**, AIOM 2015, ESMO 2013, NCCN 2015)	CEA and CA19.9 may be considered (AIRO 2012) Clinical question considered, no explicit recommendations on TMs provided (EGTM 2013)
Reassessment after initial curative treatment	0	1	Clinical question not addressed by **CPGs**	Clinical question considered, but TMs not addressed (NCCN 2015)
Early detection of recurrence or progression	1	4	Determining TMs for the follow-up of patients operated on for gastric carcinoma is not worthwhile because it does not lead to clinical benefit (**ACCC 2009**)	CEA and CA19.9 may be considered (AIOM 2015, AIRO 2012) TMs contribute to the earlier detection of recurrences after surgery with curative intent; however, this is without therapeutic consequences (**ACCC 2009**, AIOM 2015) Clinical question considered, but TMs not addressed (ESMO 2013, NCCN 2015)
Monitoring of treatment response in advanced disease	2	4	Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**ACCC 2009**, **CCO 2014**, AIOM 2015, AIRO 2012, ESMO 2013, 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: 12 (6 CPGs, 6 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening of people at increased risk	3	6	Surveillance of patients in the high-risk group is based on periodic ultrasonography combined with measurement of AFP (**JSH 2013**, **NICE 2013-HBV**, NCCN 2015) Do not offer surveillance for HCC in people with low risk (**NICE 2013-HBV**) Clinical question considered, no explicit recommendations on TMs provided (**MCC 2011**, ESMO 2012)	Risk categories for surveillance strategy: cirrhosis associated with hepatitis B or alcohol, genetic hemochromatosis, autoimmune hepatitis, nonalcoholic steatohepatitis, primary biliary cirrhosis, alpha-1 antitrypsin deficiency; individuals without cirrhosis who are HBV carriers or have other risk factors (e.g., active viral replication, high HBV DNA concentration, family history of HCC); patients with chronic HCV infection and severe liver fibrosis (**NICE 2013-HBV**, AIRO 2012, NCCN 2015) AFP (and other TMs) not indicated for surveillance strategy because of low sensitivity (lower than ultrasonography) and low specificity (**MCC 2011**, AIOM 2015, AIRO 2012, AISF 2013, EASL-EORTC 2012, ESMO 2012) Screening for HCC should use ultrasonography alone (**MCC 2011**, AIOM 2015, AISF 2013, EASL-EORTC 2012, ESMO 2012) Combination of AFP and other markers (AFP-L3, DCP) is suggested (**JSH 2013**) The use of other markers (DCP, AFP-L3) in combination with AFP is not suggested (**MCC 2011**, AIRO 2012, EASL-EORTC 2012, NCCN 2015) AFP should be used only in combination with ultrasonography (AIRO 2012) AFP can be used autonomously only if ultrasonography is not feasible (AIOM 2015) Reported surveillance schedule(s) of ultrasonography and AFP determination: - every 3-4 months in people at extremely high risk; every 6 months in those at high risk (**JSH 2013**) - every 6 months in people at high and intermediate risk (**NICE 2013-HBV**) - every 6-12 months (NCCN 2015) Elevated AFP found during surveillance is not necessary related to cancer (**MCC 2011**) AFP can also be elevated in intrahepatic cholangiocarcinoma and in some cases of metastasis from colon cancer (NCCN 2015)
Differential diagnosis	4	6	Clinical question considered, no explicit recommendations on TMs provided (**ACG 2014-FLL**, **NICE 2015**, AIOM 2015, EASL-EORTC 2012) Clinical question considered, but TMs not addressed (**JSH 2013**, **MCC 2011**, AIRO 2012)	The diagnostic workup of a patient with suspected HCC includes serum AFP measurement (**ACG 2014-FLL**, AIOM 2015, ESMO 2012) AFP measurement should not be considered a diagnostic test for HCC in the assessment of focal liver lesions (AISF 2013) No primary care evidence was identified pertaining to the diagnostic accuracy of ultrasound, CT, MRI or AFP in patients with suspected liver cancer where the clinical responsibility was retained by primary care (**NICE 2015**) AFP has low diagnostic sensitivity and specificity (AIOM 2015, AISF 2013, NCCN 2015) AFP may also be elevated in intrahepatic cholangiocarcinoma, some metastases from colon cancer, and germ cell tumors (AIOM 2015, AISF 2013, NCCN 2015)

to be continued

Examined documents: 12 (6 CPGs, 6 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Preoperative workup	2	6	Clinical question considered, no explicit recommendations on TMs provided (**MCC 2011**, EASL-EORTC 2012) Clinical question considered, but TMs not addressed (**JSH 2013**, AIRO 2012, ESMO 2012)	Elevated AFP levels, possibly integrated into prognostic algorithms, may offer prognostic information (e.g., CLIP score) (**MCC 2011**, AIOM 2015, AISF 2013, EASL-EORTC 2012, NCCN 2015) AFP cannot be used to guide therapeutic decisions based on the best scientific evidence currently available (AISF 2013)
Liver transplant priority and delisting policies	3	4	Periodic waiting-list monitoring should be performed by imaging and AFP measurement (**OLT4HCG 2012**) AFP concentrations add prognostic information (**OLT4HCG 2012**) Clinical question considered, but criteria to assess dropout (including TMs) not addressed (**JSH 2013**, **MCC 2011**, AIOM 2015, NCCN 2015)	The presence of high AFP concentrations seem to predict a higher risk of dropout (**OLT4HCG 2012**, AISF 2013, EASL-EORTC 2012) Increased AFP levels (see cutoff values below) and/or changes in serum AFP over time may be useful to evaluate the risk of dropout from liver transplant waiting list (AISF 2013, EASL-EORTC 2012) - higher than 200 ng/mL (EASL-EORTC 2012) - higher than 400 ng/mL (**OLT4HCG 2012**) Biomarkers other than AFP cannot yet be used for clinical decision-making regarding liver transplant for HCC (**OLT4HCG 2012**)
Reassessment after initial curative treatment	0	5	Clinical question not addressed by **CPGs**	In patients with markedly elevated (>200-400 ng/mL) or progressively increasing levels, AFP may provide useful prognostic information to assess the response to locoregional and systemic treatments (AISF 2013, EASL-EORTC 2012, NCCN 2015) AFP levels may be helpful, particularly in the case of not easily measurable disease, but should not be used as the only determinant for treatment decisions (ESMO 2012) Clinical question considered, no explicit recommendations on TMs provided (AIRO 2012, EASL-EORTC 2012, NCCN 2015)
Early detection of recurrence or progression	1	5	Monitoring after liver transplant and palliative treatments may include periodic AFP measurements (**OLT4HCG 2012**, ESMO 2012, NCCN 2015)	An increase in AFP during follow-up may suggest HCC recurrence. Nevertheless, AFP assessment cannot replace radiological surveillance follow-up (AISF 2013) AFP levels may be helpful but should not be used as the only determinant for treatment decisions (ESMO 2012) Clinical question considered, no explicit recommendations on TMs provided (AIRO 2012, AISF 2013) Clinical question considered, but TMs not addressed (AIOM 2015)
Monitoring of treatment response in advanced disease	2	6	Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**JSH 2013**, **MCC 2011**, AIOM 2015, AIRO 2012, AISF 2013)	AFP determination may be helpful for assessment of response, particularly in the case of not easily measurable disease, but should not be used as the only determinant for treatment decisions (EASL-EORTC 2012, ESMO 2012, NCCN 2015) Clinical question considered, no explicit recommendations on TMs provided (EASL-EORTC 2012, 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: 7 (4 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	0	2	Clinical question not addressed by **CPGs**	Clinical question considered, but TMs not addressed (ESMO 2012) Clinical question considered, no explicit recommendations on TMs provided (NCCN 2015)
Differential diagnosis	2	3	Clinical question considered, no explicit recommendations on TMs provided (**ISGPS 2014-A**, **NICE 2015**, AIOM 2015, ESMO 2012, NCCN 2015)	No primary care evidence was identified pertaining to the diagnostic accuracy of TMs (CA19.9 and CA72-4) in patients with suspected pancreatic cancer where the clinical responsibility was retained by primary care (**NICE 2015**) Serum TMs (CA19.9, CEA) … are useful only when they are positive. When negative, they do not aid in determining the nature of the suspicious lesion and therefore have little influence on the decision to proceed with exploration/resection or not (**ISGPS 2014-A**) CA19.9 is of limited diagnostic value since it is not specific for pancreatic cancer (ESMO 2012) CA19.9 has good diagnostic sensitivity and specificity in symptomatic patients (NCCN 2015) and in those with advanced disease (AIOM 2015) CA19.9 may be falsely positive in cases of biliary obstruction (regardless of etiology) (**ISGPS 2014-A**, AIOM 2015, ESMO 2012, NCCN 2015) and in cases of biliary infection (cholangitis) or inflammation (NCCN 2015) CA19.9 may be undetectable in Lewis antigen-negative patients with pancreatic cancer, who are unable to synthesize CA19.9 (ESMO 2012, NCCN 2015)
Preoperative workup	3	3	Clinical question considered, no explicit recommendations on TMs provided (**ISGPS 2014-A**, **S3 2014**, ESMO 2012) CA19.9 may be included in standard preoperative diagnostics for patients with *borderline resectable pancreatic cancer* to assess potential benefits in survival with surgery but not for prediction of resectability (**ISGPS 2014-B**)	Serum CA19.9 level alone is not advocated for determining operability in pancreatic cancer (**ISGPS 2014-A**) Elevated preoperative CA19.9 has negative prognostic value (**ISGPS 2014-B**, AIOM 2015, NCCN 2015) but must be evaluated with caution because the evidence is based on retrospective cohort analyses (**ISGPS 2014-B**) Elevated preoperative CA19.9 levels correlate with advanced stage (ESMO 2012, NCCN 2015) including peritoneal carcinosis (**S3 2014**) CA19.9 may be falsely positive in cases of biliary obstruction (regardless of etiology) and in cases of biliary infection (cholangitis) or inflammation (NCCN 2015) CA19.9 may be undetectable in Lewis antigen-negative patients with pancreatic cancer, who are unable to synthesize CA19.9 (ESMO 2012, NCCN 2015) Preoperative measurement of CA19.9 is therefore best performed when biliary decompression is complete and bilirubin is normal. If biliary decompression is not performed in a jaundiced patient, CA19.9 levels can be assessed but do not represent an accurate baseline (NCCN 2015) CA19.9 should be measured before surgery (AIOM 2015, NCCN 2015)

to be continued

Examined documents: 7 (4 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Reassessment after initial curative treatment	0	2	Clinical question not addressed by **CPGs**	CA19.9 should be measured following surgery immediately prior to administration of adjuvant therapy (AIOM 2015, NCCN 2015) Low postoperative serum CA19.9 levels or a serial decrease in CA19.9 levels following surgery have been found to be prognostic for survival (AIOM 2015, NCCN 2015)
Early detection of recurrence or progression	0	3	Clinical question not addressed by **CPGs**	Assessment of CA19.9 could be performed periodically during follow-up (AIOM 2015, ESMO 2012, NCCN 2015) Reported schedule(s) of CA19.9 measurement: - every 3 months for 2 years if preoperative levels were elevated (ESMO 2012) - every 3-6 months for 2 years (NCCN 2015) - every 6 months for 3 years (AIOM 2015) No data are available to show that earlier treatment of recurrences following detection by increased TM levels or CT scan leads to better patient outcomes (NCCN 2015)
Monitoring of treatment response in advanced disease	1	3	Clinical question considered, but criteria to monitor therapy response (including TMs) not addressed (**S3 2014**)	CA19.9 can be periodically measured during the treatment of advanced disease (AIOM 2015) Clinical question considered, no explicit recommendations on TMs provided (NCCN 2015) Change in CA19.9 levels during chemotherapy in patients with advanced disease has been shown to be useful for evaluating the benefit of treatment, although the data are not entirely consistent (NCCN 2015) Clinical question considered, but TMs not addressed (ESMO 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**.

Selected guidelines (by cancer site)

Biliary cancer

AASLD 2010. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010; 51(2):660-78. doi:10.1002/hep.23294.

ACG 2014. Marrero JA, Ahn J, Rajender Reddy K; American College of Gastroenterology. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014; 109(9):1328-47. doi: 10.1038/ajg.2014.213.

AIRO 2012. Gruppo di studio AIRO per i tumori gastrointestinali. La Radioterapia dei Tumori Gastrointestinali: Indicazioni e Criteri Guida. Roma, IT: Associazione Italiana di Radioterapia Oncologica (AIRO); 2012.

ESMO 2011. Eckel F, Brunner T, Jelic S; ESMO Guidelines Working Group. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011; 22(Suppl 6):vi40-4. doi: 10.1093/annonc/mdr375.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatobiliary cancers, version 1.2016. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng12.

SIGE 2010. Alvaro D, Cannizzaro R, Labianca R, et al. Cholangiocarcinoma: A position paper by the Italian Society of Gastroenterology (SIGE), the Italian Association of Hospital Gastroenterology (AIGO), the Italian Association of Medical Oncology (AIOM) and the Italian Association of Oncological Radiotherapy (AIRO). Dig Liver Dis. 2010; 42(12):831-8. doi: 10.1016/j.dld.2010.06.005.

Colorectal cancer

AGA 2010. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010 ;138(2):738-45. doi: 10.1053/j.gastro.2009.12.037.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Tumori del colon retto. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

ASCO 2013. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2013; 31(35):4465-70. doi: 10.1200/JCO.2013.50.7442.

ASCRS 2012-C. Chang GJ, Kaiser AM, Mills S, Rafferty JF, Buie WD; Practice parameters for the management of colon cancer. Dis Colon Rectum. 2012; 55(8):831-43. doi: 10.1097/DCR.0b013e3182567e13.

ASCRS 2013-R. Monson JR, Weiser MR, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum. 2013; 56(5):535-50. doi: 10.1097/DCR.0b013e31828cb66c.

CCO 2014-CRC. Del Giudice L, Vella E, Hey A, et al. Referral of patients with suspected colorectal cancer by family physicians and other primary care providers. Toronto, ON: Cancer Care Ontario; 2011. Validity verification: 2014.

CCO 2014-R. Kennedy E, Vella E, MacDonald DB, et al. Optimization of preoperative assessment in patients diagnosed with rectal cancer. Toronto, ON: Cancer Care Ontario; 2014.

EGTM 2013. Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. Int J Cancer. 2014; 134(11):2513-22. doi: 10.1002/ijc.28384.

ESMO 2012-CRC. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol. 2012; 23(10):2479-516.

ESMO 2013-C. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi64-72. doi: 10.1093/annonc/mdt354.

ESMO 2013-R. Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi81-8. doi: 10.1093/annonc/mdt240.

ESMO 2014-mCRC. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D; ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 (Suppl 3):iii1-9. doi: 10.1093/annonc/mdu260. Erratum in: Ann Oncol. 2015; 26 (Suppl 5):v174-7.

NCCN 2015-C. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colon cancer, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NCCN 2015-R. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Rectal cancer, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2011-SU. National Institute for Health and Clinical Excellence (NICE). Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. London, UK: National Institute for Health and Clinical Excellence (NICE); 2011. URL: https://www.nice.org.uk/guidance/CG118.

NICE 2014. National Collaborating Centre for Cancer. Colorectal cancer. The diagnosis and management of colorectal cancer. London, UK: National Institute for Health and Care Excellence (NICE); 2011. URL: https://www.nice.org.uk/guid-

ance/cg131. Validity verification: 2014.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng12.

SIGN 2011. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer. A national clinical guideline. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network (SIGN); 2011.

USMSTF 2012. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012; 143(3):844-57. doi: 10.1053/j.gastro.2012.06.001.

Esophageal cancer

AHS 2014. Alberta Provincial Gastrointestinal Tumour Team. Management of patients with early esophageal cancer, dysplastic and non-dysplastic Barrett's esophagus. Edmonton, Alberta: CancerControl Alberta; 2014.

AIOM 2015. Associazione Italiana di Oncologia Medica. Tumori dell'esofago e della giunzione gastroesofagea. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

AIRO 2012. Gruppo di studio AIRO per i tumori gastrointestinali. La Radioterapia dei Tumori Gastrointestinali: Indicazioni e Criteri Guida. Roma, IT: Associazione Italiana di Radioterapia Oncologica (AIRO); 2012.

ESMO 2013. Stahl M, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi51-6. doi: 10.1093/annonc/mdt342.

mep 2012. Bennett C, Vakil N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology. 2012;143(2):336-46. doi: 10.1053/j.gastro.2012.04.032.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Esophageal and esophagogastric junction cancers, version 3.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NHMRC 2014. Cancer Council Australia Barrett's Oesophagus Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and Early Oesophageal Adenocarcinoma. Sydney: Cancer Council Australia. [VersionURL: http://wiki.cancer.org.au/australiawiki/index.php?oldid=113682, cited 2016 May 19]. Available from: http://wiki.cancer.org.au/australia/Guidelines:Barrett%27s.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng12.

STS 2013. Varghese TK Jr, Hofstetter WL, Rizk NP, et al. The society of thoracic surgeons guidelines on the diagnosis and staging of patients with esophageal cancer. Ann Thorac Surg. 2013; 96(1):346-56. doi: 10.1016/j.athoracsur.2013.02.069.

Gastric cancer

ACCC 2009. National Working Group on Gastrointestinal Cancers. Gastric carcinoma. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres; 2009.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Neoplasie dello stomaco. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

AIRO 2012. Gruppo di studio AIRO per i tumori gastrointestinali. La Radioterapia dei Tumori Gastrointestinali: Indicazioni e Criteri Guida. Roma, IT: Associazione Italiana di Radioterapia Oncologica (AIRO); 2012.

CCO 2014. MacKenzie M, Spithoff K, Jonker D, Gastrointestinal Cancer Disease Site Group. Systemic therapy for advanced gastric cancer. Jonker D, Poon R, reviewers. Toronto, ON: Cancer Care Ontario; 2010. Validity verification: 2014.

EGTM 2013. Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014 guidelines update. Int J Cancer. 2014; 134(11):2513-22. doi: 10.1002/ijc.28384.

ESMO 2013. Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi57-63. doi: 10.1093/annonc/mdt344.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Gastric cancer, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng12.

Hepatocellular carcinoma

ACG 2014. Marrero JA, Ahn J, Rajender Reddy K; American College of Gastroenterology. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014; 109(9):1328-47. doi: 10.1038/ajg.2014.213.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Epatocarcinoma. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

AIRO 2012. Gruppo di studio AIRO per i tumori gastrointestinali. La Radioterapia dei Tumori Gastrointestinali: Indicazioni e Criteri Guida. Roma, IT: Associazione Italiana di Radioterapia Oncologica (AIRO); 2012.

AISF 2013. Italian Association for the Study of the Liver (AISF); Bolondi L, Cillo U, Colombo M, et al. Position paper of the Italian Association for the Study of the Liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma. Dig Liver Dis. 2013; 45(9):712-23. doi: 10.1016/j.dld.2013.01.012.

EASL-EORTC 2012. European Association for Study of Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer. 2012; 48(5):599-641. doi:10.1016/j.ejca.2011.12.021.

ESMO 2012. Verslype C, Rosmorduc O, Rougier P; ESMO

Guidelines Working Group. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 (Suppl 7):vii41-8.

JSH 2013. Committee for Revision of the Clinical Practice Guidelines for Hepatocellular Carcinoma. Evidence-Based Clinical Practice Guidelines for Hepatocellular Carcinoma, 2013. Tokyo, Japan: The Japan Society of Hepatology; 2013.

MCC 2011. Sherman M, Burak K, Maroun J, et al. Multidisciplinary Canadian consensus recommendations for the management and treatment of hepatocellular carcinoma. Curr Oncol. 2011; 18(5):228-40.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatobiliary cancers, version 1.2016. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2013-HBV. National Clinical Guideline Centre. Hepatitis B (chronic). Diagnosis and management of chronic hepatitis B in children, young people and adults. London, UK: National Institute for Health and Care Excellence (NICE); 2013. URL: http://www.nice.org.uk/guidance/cg165.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng12.

OLT4HCG 2012. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012;13(1):e11-22. doi: 10.1016/S1470-2045(11)70175-9.

Pancreatic cancer

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Carcinoma del pancreas esocrino. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

ESMO 2012. Seufferlein T, Bachet JB, Van Cutsem E, Rougier P; ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 (Suppl 7):vii33-40.

ISGPS 2014-A. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014; 155(6):977-88. doi: 10.1016/j.surg.2014.02.001.

ISGPS 2014-B. Asbun HJ, Conlon K, Fernandez-Cruz Let al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014; 155(5):887-92. doi: 10.1016/j.surg.2013.12.032.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ng12.

S3 2014. Seufferlein T, Porzner M, Heinemann V, Tannapfel A, Stuschke M, Uhl W. Ductal pancreatic adenocarcinoma. Dtsch Arztebl Int. 2014; 111(22):396-402. doi:10.3238/arztebl.2014.0396.

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GUIDELINES

Circulating tumor markers: a guide to their appropriate clinical use

Comparative summary of recommendations from clinical practice guidelines (PART 2)

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Contributions of panel members
[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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Contents

Acronyms

Abbreviations of tumor markers cited in the present article

AFP	Alpha- FetoProtein
CA125	Cancer Antigen 125
CA15.3	Cancer Antigen 15.3
CA19.9	Cancer Antigen 19.9
CA27.29	Cancer Antigen 27-29
CEA	CarcinoEmbryonic Antigen
hCG	human Chorionic Gonadotropin
HE4	Human Epididymis protein 4
LDH	Lactate DeHydrogenase
MCM5	MiniChromosome Maintenance 5
NMP22	Nuclear Matrix Protein number 22
PCA3	Prostate Cancer Associated 3
PHI	Prostate Health Index
PSA	Prostate-Specific Antigen
PSADT	Prostate-Specific Antigen Doubling Time
SCC	Squamous Cell Carcinoma antigen

Introduction

This is the second of 3 parts 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, appearing in the present issue, refers to urogenital tract malignancies and breast cancer.

Rationale

The number of TMs requested is considerably higher than expected based on the cancer prevalence, and this shows the low compliance of clinicians 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 distillation 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 for anyone facing a clinical question in which the use of a TM could be considered.

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 guidelines concerning 20 different malignancies. The selected documents were further appraised for adherence to the standards of the Institute of Medicine (IOM), which require guidelines to be based on systematic review of existing evidence (3), 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 Detailed Summary Tables are addressed to both policy makers for potential adaptation to their own context and educators to design teaching programs consistent with the available evidence.

The implicit goal of the present guidance document is to "stimulate extensive 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).

References

1. Gion M, Trevisiol C, Rainato G, Fabricio ASC. Marcatori circolanti in oncologia: guida all'uso clinico appropriato. I Quaderni di Monitor. Roma: AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali 2016.
2. Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Circulating tumor markers: a guide to their appropriate clinical use. Comparative summary of recommendations from clinical practice guidelines (Part 1). Int J Biol Markers. 2016;31:e332-e367.
3. IOM (Institute of Medicine). Clinical practice guidelines we can trust. Washington, DC: The National Academies Press 2011.
4. Gion M. Need for knowledge translation to improve tumor marker application. Int J Biol Markers. 2016;31:e331.

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: 15 (7 CPGs, 8 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	∅	**1/1** (USPSTF 2011)	**4/4** (AIOM 2015, EAU 2015-NM, EAU 2015-UT, ESMO 2014)
Differential diagnosis	Urinary biomarkers (e.g., NMP22) can be used as an adjunct to cystoscopy to detect invisible tumor in secondary care	**NMP22** ∅	**1/2** (NICE 2015-BC)	**1/8** (EAU 2015-NM)
	In primary care do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer		**1/2** (NICE 2015-BC)	**2/8** (AURO 2010, EAU 2015-NM)
	Recommendations on TMs not available		**1/2** (NICE 2015-SC)	**6/8** (AIOM 2015, EAU 2015-MI, EAU 2015-UR, EAU 2015-UT, ESMO 2014, NCCN 2015)
	Supplementary information: No primary care evidence was identified pertaining to the diagnostic accuracy of urine markers (NMP22 and MCM5) in patients with suspected bladder cancer where the clinical responsibility was retained by primary care		**1/2** (NICE 2015-SC)	**0/8**
Preoperative workup	Recommendations on TMs not available	∅	**4/4** (AHS 2013-MI, AHS 2013-NM, AHS 2013-UT, NICE 2015-BC)	**8/8** (AIOM 2015, AURO 2010, EAU 2015-MI, EAU 2015-NM, EAU 2015-UR, EAU 2015-UT, ESMO 2014, NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	Do not substitute urinary biomarkers for cystoscopy for follow-up after treatment for bladder cancer	**None**	**1/5** (NICE 2015 BC)	**3/8** (AIOM 2015, EAU 2015-NM, ESMO 2014)
	Recommendations on TMs not available	∅	**4/5** (AHS 2013-MI, AHS 2013-NM, AHS 2013-UT, CUA 2013)	**4/8** (AURO 2010, EAU 2015-MI, EAU 2015-UR, EAU 2015-UT)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	∅	**3/3** (AHS 2013-MI, AHS 2013-UT, NICE 2015-BC)	**4/5** (AIOM 2015, AURO 2010, ESMO 2014, 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.
∅ The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.

to be continued

BLADDER CANCER

Take-home message

Examined documents: 15 (7 CPGs, 8 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 2013-MI	92	42	67	67	67	58
AHS 2013-NM	86	42	66	69	58	79
AHS 2013-UT	83	42	65	67	58	79
CUA 2013	44	28	58	56	23	58
NICE 2015-SC	89	98	92	89	72	78
NICE 2015-BC	97	89	90	94	85	83
USPSTF 2011	92	47	79	78	44	79

Examined documents: 15 (9 CPGs, 6 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Differential diagnosis	Recommendations on TMs not available	∅	**2/2** (NICE 2012-EarlyBC, NICE 2015-SC)	**5/5** (AIOM 2015, ESMO 2013-EarlyBC, EUSOMA 2014-Young, NCCN 2014-Diagn, NCCN 2015)
Preoperative workup	Recommendations on TMs not available	∅	**2/2** (AHS 2012-BB, NICE 2012-EarlyBC)	**3/4** (AIOM 2015, EUSOMA 2014-Young, NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	The use of CA15.3 or CA27.29 or CEA is not recommended for routine surveillance of breast cancer after primary therapy in an otherwise asymptomatic patient with no specific findings on clinical examination	**None**	**3/4** (AHS 2013-FU, ASCO 2012-FU, NHMRC 2010)	**3/4** (AIOM 2015, ESMO 2013-EarlyBC, EUSOMA 2014-Young)
	TMs are recommended only if clinically indicated	**CA15.3, CEA**	**1/4** (NHMRC 2010)	**1/4** (ESMO 2013-EarlyBC)
	Recommendations on TMs not available	∅	**1/4** (NICE 2012-EarlyBC)	**1/4** (NCCN 2015)
Monitoring of treatment response in advanced disease	TMs may be used as adjunctive assessment to contribute to decisions regarding therapy for metastatic breast cancer	**CA15.3, CEA**	**1/3** (ASCO 2015-M+)	**2/4** (ESMO 2014-ABC, EUSOMA 2014-Young, NCCN 2015)
	Data are insufficient to recommend use of TMs alone for monitoring response to treatment	∅	**1/3** (ASCO 2015-M+)	**3/4** (ESMO 2014-ABC, EUSOMA 2014-Young, NCCN 2015)
	Recommendations on TMs not available		**2/3** (CECOG 2009, NICE 2014-M+)	**1/4** (AIOM 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.
∅ The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.

to be continued

BREAST CANCER — Take-home message

Examined documents: 15 (9 CPGs, 6 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-BB	83	38	65	81	67	92
AHS 2013-FU	41	55	62	78	65	86
ASCO 2012-FU	87	83	83	83	64	61
ASCO 2015-M+	94	70	80	85	61	94
CECOG 2009	72	56	68	69	23	33
NHMRC 2010	81	78	78	78	57	69
NICE 2014-M+	96	91	90	94	92	89
NICE 2012-EarlyBC	94	89	88	94	89	83
NICE 2015-SC	94	96	90	87	94	89

Examined documents: 7 (3 CPGs, 4 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Differential diagnosis	Recommendations on TMs not available	∅	**1/1** (NICE 2015)	**3/4** (AIOM 2015, ESMO 2012, NCCN 2015)
Preoperative workup	Recommendations on TMs not available	∅	**1/1** (AHS 2013)	**3/4** (AIOM 2015, ESMO 2012, NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	---	---	---
Early detection of recurrence or progression	The use of TMs (including SCC) in asymptomatic patients cannot be recommended because the impact of asymptomatic recurrence detection on survival rates is not known	**None**	**1/2** (CCO 2015)	**2/4** (AIOM 2015, NACB 2010)
	Recommendations on TMs not available	∅	**1/2** (AHS 2013)	**2/4** (ESMO 2012, NCCN 2015)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	∅	**1/1** (AHS 2013)	**3/3** (AIOM 2015, 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.
∅ 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
AHS 2013	97	47	58	69	50	75
CCO 2015	72	50	58	75	40	71
NICE 2015	89	97	91	89	67	83

ENDOMETRIAL CANCER — Take-home message

Examined documents: 7 (3 CPGs, 4 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening	Clinical question not addressed by **CPGs**	**---**	---	---
Differential diagnosis	Recommendations on TMs not available	Ø	**1/1** (NICE 2015)	**4/4** (AIOM 2015, ESMO 2013, NCCN 2015, SGO 2014)
Preoperative workup	In case of increased serum CA125 levels preoperative imaging is advisable to rule out metastatic spread	**CA125**	**1/1** (ACN 2011)	**1/3** (NCCN 2015)
Reassessment after initial curative treatment	Clinical question not addressed by **CPGs**	**---**	---	---
Early detection of recurrence or progression	Recommendations on TMs not available	Ø	**1/1** (AHS 2013)	**1/4** (ESMO 2013)
Monitoring of treatment response in advanced disease	Recommendations on TMs not available	Ø	**1/1** (AHS 2013)	**4/4** (AIOM 2015, ESMO 2013, NCCN 2015, SGO 2014)

[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
ACN 2011	**78**	**42**	**71**	**89**	**54**	**67**
AHS 2013	**86**	**44**	**65**	**72**	**58**	**100**
NICE 2015	**89**	**97**	**92**	**89**	**71**	**79**

Examined documents: 22 (12 CPGs, 10 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Screening general polulation	Screening for ovarian cancer in the general population is not recommended	**None**	**2/2** (SIGN 2013-EC, USPSTF 2012)	**3/3** (ACOG 2011-EC, AIOM 2015, NCCN 2015)
Screening of people at increased risk (positive family history)	Screening for ovarian cancer in high-risk groups should only be offered in the context of a research study	**None**	**3/3** (AHS 2011-HR, NHMRC 2011-HR, SIGN 2013-EC)	**2/5** (ACOG 2011-EC, NCCN 2015)
Differential diagnosis	CA125 measurement in conjunction with pelvic ultrasound should be carried out in women with suspicious symptoms of ovarian cancer or an adnexal mass	**CA125**	**5/6** (BSGE 2011, CCO 2011-AM, NICE 2011-EC, NICE 2015, SIGN 2013-EC)	**5/7** (ACOG 2011-EC, ACOG 2013-AM, AIOM 2015, ESMO 2013-EC, NCCN 2015)
	An estimation of the risk of malignancy should be carried out for the assessment of an ovarian mass		**4/6** (BSGE 2011, CCO 2011-AM, NICE 2011-EC, SIGN 2013-EC)	**1/7** (ESMO 2013-EC)
	Supplementary information: CA125 can be elevated for reasons other than ovarian cancer, such as other malignancies, physiological causes and benign conditions		**3/6** (BSGE 2011, CCO 2011-AM, SIGN 2013-EC)	**3/7** (ACOG 2011-EC, ACOG 2013-AM, ESMO 2013-EC)
	LDH, AFP and βhCG should be measured in all women under age 40 with a complex ovarian mass because of the possibility of germ cell tumors	**AFP, βhCG, LDH**	**3/6** (AHS 2013-GCT, BSGE 2011, NICE 2011-EC)	**3/7** (ACOG 2013-AM, ESMO 2012-GCT, NCCN 2015)
Preoperative workup	Recommendations on TMs not available for epithelial ovarian cancer	∅	**2/3** (AHS 2013-EC, SIGN 2013-EC)	**3/4** (AIOM 2015, ESMO 2013-EC, ESMO 2012-GCT)
	Tumor histology-specific TMs should be used in association with clinical findings to determine the prognosis and class risk of nonepithelial ovarian cancer	**AFP, βhCG, LDH**	**1/3** (AHS 2013-GCT)	**1/4** (NCCN 2015)
Reassessment after initial curative treatment	Recommendations on TMs not available	∅	**1/1** (AHS 2013-EC)	**0/4**

to be continued

OVARIAN CANCER — Take-home message

Examined documents: 22 (12 CPGs, 10 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 ⚠	In the absence of symptoms, routine measurement of CA125 during follow-up is not mandatory	**None** or **CA125**	**1/4** (SIGN 2013-EC)	**0/6**
	CA125 is not recommended for routine follow-up		**1/4** (AHS 2013-EC)	**0/6**
	Some women may benefit from routine measurement of CA125, including those who are eligible for secondary cytoreductive surgery		**1/4** (NHMRC 2012)	**5/6** (AIOM 2015, ESGO 2011, ESGO 2012-FU, ESMO 2013-EC, NCCN 2015)
	Radiological imaging should be performed if there is CA125 evidence of recurrence		**1/4** (NHMRC 2012)	**3/6** (AIOM 2015, ESGO 2012-FU, ESMO 2013-EC)
	Women should be fully informed of the pros and cons of routine measurement of CA125 during follow-up		**1/4** (NHMRC 2012)	**3/6** (AIOM 2015, ESGO 2012-FU, NCCN 2015)
	It is recommended to continue histology-specific TM measurement in the routine follow-up of patients with nonepithelial ovarian cancer	**AFP, βhCG, LDH, inhibin**	**1/4** (AHS 2013-GCT)	**2/6** (ESGO 2011, NCCN 2015)
Monitoring of treatment response in advanced disease	Serial measurement of CA125 is useful to assess the response to chemotherapy	**CA125**	**1/5** (CCO 2011)	**2/4** (ESMO 2013-EC, NCCN 2015)
	Recommendations on TMs not available	∅	**4/5** (AHS 2013-EC, AHS 2013-GCT, NICE 2011-EC, SIGN 2013-EC)	**1/4** (AIOM 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.
∅ 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.

to be continued

Examined documents: 22 (12 CPGs, 10 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 2011-HR	92	44	67	75	58	87
AHS 2013-EC	80	39	70	69	58	83
AHS 2013-GCT	86	30	64	69	56	83
BSGE 2011	83	67	76	78	50	58
CCO 2011	86	44	74	69	31	58
CCO 2011-AM	92	56	78	75	35	58
NHMRC 2011-HR	78	69	70	69	25	58
NHMRC 2012	69	67	74	69	29	58
NICE 2011-EC	100	89	92	94	85	86
NICE 2015	94	89	91	89	81	83
SIGN 2013-EC	86	86	80	86	75	75
USPSTF 2012	83	39	65	86	27	75

PROSTATE CANCER — Take-home message

Examined documents: 33 (24 CPGs, 9 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Organized screening programs	PSA-based mass screening for prostate cancer is not recommended	**None**	**2/2** (EAU 2015, USPSTF 2012)	**2/2** (AIOM 2015, ESMO 2013)
Spontaneous screening ⚠	Screening for prostate cancer of asymptomatic men with the PSA test is not recommended	**None** or **PSA**	**2/9** (CTFPHC 2014, USPSTF 2012)	**0/3**
	For men aged less than 55 years or older than 70-75, or with a life expectancy <10 years screening for prostate cancer with the PSA test is not recommended		**4/9** (ASCO 2012, AUA 2013-ED, SIOG 2014, UMHS 2012)	**1/3** (AIOM 2015)
	An individualized, risk-adapted strategy for early detection might be offered to a well-informed man with a good performance status and life expectancy of at least 10-15 years		**4/9** (AHS 2013, CUA 2011, EAU 2015, UMHS 2012)	**2/3** (AIOM 2015, NCCN 2014)
	If there is a higher risk of prostate cancer (e.g., positive family history or African-American descent), PSA-based screening should be offered at age 40 years		**5/9** (AUA 2013-ED, CUA 2011, EAU 2015, UMHS 2012, USPSTF 2012)	**1/3** (AIOM 2015)
	If prostate cancer screening is considered, men should be informed of the potential benefits and risks of early detection		**4/9** (AHS 2013, ASCO 2012, AUA 2013-ED, USPSTF 2012)	**3/3** (AIOM 2015, ESMO 2013, NCCN 2014)
	No evidence has demonstrated that age-adjusted PSA cutoffs; free PSA; and PSA density, velocity, slope, and doubling-time testing improve health outcomes when used for screening purposes		**5/9** (ASCO 2012, CTFPHC 2014, EAU 2015, UMHS 2012, USPSTF 2012)	**0/3**

to be continued

Examined documents: 33 (24 CPGs, 9 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Differential diagnosis	Indications for biopsies include a clinical suspicion of prostate cancer based on PSA and DRE findings, considering also clinical history and risk factors	**PSA**	**3/8** (AHS 2013, EAU 2015, NICE 2015)	**4/6** (AIOM 2015, GEC-ESTRO 2013, ESMO 2013, NCCN 2015)
	Limited PSA elevation alone should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardized conditions		**2/8** (EAU 2015, NICE 2014)	**2/6** (AIOM 2015, NCCN 2014)
	Consider PSA to assess for prostate cancer in men with any lower urinary tract symptoms or any unexplained symptoms suggestive of metastatic prostate cancer		**2/8** (CCO 2015, NICE 2015)	**0/6**
	Supplementary information n. 1: Elevated PSA and/or abnormal DRE are not diagnostic of prostate cancer; they do serve to risk stratify patients		**1/8** (AHS 2013)	**0/6**
	Supplementary information n. 2: Many conditions other than prostate cancer may increase PSA		**2/8** (CUA 2011, EAU 2015)	**1/6** (NCCN 2014)
	Supplementary information n. 3: There is no level of PSA below which the risk of prostate cancer can be eliminated		**1/8** (EAU 2015)	**1/6** (NCCN 2014)
	Supplementary information n. 4: Other tests (PSA density, PSA velocity, PSA free-to-total ratio, PHI, PCA3) may improve the PSA sensitivity and specificity but have limited clinical impact given the slight net benefit provided for clinical decision-making		**3/8** (CUA 2011, EGAPP 2014, EAU 2015)	**3/6** (AIOM 2015, NCCN 2014, SIURO 2013)
Rebiopsy ⚠	The indications for a repeat biopsy are: rising and/or persistently elevated PSA	only **PSA** or **PSA, PCA3**	**2/4** (EAU 2015, NICE 2014)	**3/4** (AIOM 2015, ESMO 2013, SIURO 2013)
	Currently, the main indication for PCA3 is to determine whether repeat biopsy is needed after an initially negative biopsy		**1/4** (EAU 2015)	**1/4** (NCCN 2014)
	Evidence is insufficient to recommend PCA3 or PHI to inform decisions as to when to rebiopsy previously biopsy-negative patients		**2/4** (EGAPP 2014, NICE 2015-PCA3)	**0/4**
	Supplementary information: Very low quality evidence is available for age, PSA free-to-total ratio, PSA velocity, PCA3 score, and PSA density in the indication for a repeat biopsy.		**4/4** (EGAPP 2014, EAU 2015, NICE 2014, NICE 2015-PCA3)	**0/4**

to be continued

PROSTATE CANCER — Take-home message

Examined documents: 33 (24 CPGs, 9 OGDs)

Clinical question	Summary of recommendations	Recommended tumor marker(s)	CPG/total CPG [1] (CPG acronyms)	OGD/total OGD [2] (OGD acronyms)
Preoperative workup	PSA, combined with clinical stage and Gleason score, is used as risk stratification to discuss with the patient the choice of therapy options	**PSA**	**7/8** (AHS 2013, AUA 2011, CCO 2010, CCO 2012-BT, EAU 2015, NICE 2014, SIOG 2014)	**4/5** (AIOM 2015, AUA 2013, ESMO 2013, NCCN 2015)
	Radiographic staging (CT and bone scan) is recommended for patients with a PSA level >10 ng/mL prior to treatment		**2/8** (AUA 2011, EAU 2015)	**3/5** (AIOM 2015, AUA 2013, GEC-ESTRO 2013)
	Supplementary information: Evidence is insufficient to recommend PCA3 to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan		**1/8** (EGAPP 2014)	**1/5** (AIOM 2015)
Active surveillance	PSA <10 ng/mL is one of the criteria to identify patients eligible for active surveillance	**PSA**	**3/10** (CCO 2014-AS, EAU 2015, SIOG 2014)	**1/2** (AIOM 2015)
	Monitoring of patients on active surveillance should include PSA testing (every 3-6 months)		**6/10** (ACS 2014, AHS 2013, ASCO 2015, CCO 2014-AS, EAU 2015, NICE 2014)	**2/2** (AIOM 2015, NCCN 2015)
	Accelerated elevation of the PSA level (PSA doubling time) is one of the criteria considered to start active therapy		**3/10** (CUA 2011, AHS 2013, EAU 2015)	**1/2** (AIOM 2015)
	Supplementary information: Evidence is not sufficient to recommend PCA3 testing to determine if the disease is indolent or aggressive		**2/10** (CCO 2014-AS, EGAPP 2014)	**1/2** (AIOM 2015)
Reassessment after initial curative treatment (RP and RT)	First postoperative PSA measurement should be done 4-12 weeks after surgery and PSA should be undetectable	**PSA**	**4/4** (ACS 2014, AHS 2013, EAU 2015, NICE 2014)	**3/3** (AIOM 2015, AUA 2013, NCCN 2015)
	PSA level should progressively decrease after RT, reaching the nadir after 6-12 months (interval before PSA nadir is reached can be up to 3 years)		**2/2** (EAU 2015, NICE 2014)	**2/2** (AIOM 2015, AUA 2013)

to be continued

Examined documents: 33 (24 CPGs, 9 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 (RP)	Periodic PSA measurement should be offered to detect disease recurrence	**PSA**	**6/6** (ACS 2014, AHS 2013, ASCO 2014, ASCO 2015, EAU 2015, NICE 2014)	**4/5** (AIOM 2015, AUA 2013, ESMO 2013, NCCN 2015)
	After RP biochemical recurrence is defined by 2 consecutive PSA values >0.2 ng/mL		**3/6** (AHS 2013, ASCO 2014, EAU 2015)	**3/5** (AIOM 2015, AUA-ASTRO 2013, NCCN 2015)
	It is recommended that the finding of a single elevated serum PSA level be reconfirmed before starting therapy		**2/6** (EAU 2015, NICE 2014)	**0/5**
	Accelerated PSA doubling time is a negative prognostic factor after a biochemical relapse		**2/6** (AHS 2013, EAU 2015)	**1/5** (NCCN 2015)
	Bone scan and CT should only be considered in asymptomatic patients with biochemical failure after RP who have high baseline PSA (>10 ng/mL) or high PSA kinetics (PSA doubling time <6 months or PSA velocity >0.5 ng/mL/month)		**1/6** (EAU 2015)	**0/5**
Early detection of recurrence or progression (RT)	Periodic PSA measurement should be offered to detect disease recurrence	**PSA**	**3/3** (AHS 2013, EAU 2015, NICE 2014)	**1/1** (AIOM 2015)
	Biochemical recurrence after RT is defined as a rise ≥2 ng/mL above the nadir (defined as the lowest PSA level reached)		**3/3** (AHS 2013, EAU 2015, NICE 2014)	**1/1** (AIOM 2015)
	Accelerated PSA doubling time is a negative prognostic factor after biochemical relapse		**2/6** (AHS 2013, EAU 2015)	**1/5** (NCCN 2015)
Monitoring of treatment response in advanced disease	Patients with stage M1 disease showing a good treatment response should be evaluated at 3 and 6 months with PSA and testosterone measurement during hormonal treatment	**PSA**	**4/6** (AHS 2013, ASCO-CCO 2014, AUA 2015, EAU 2015)	**3/3** (AIOM 2015, APC 2015, NCCN 2015)
	Castration-resistant prostate cancer (CRPC) is defined as serum testosterone <50 ng/dL plus 3 consecutive rises in PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL		**3/6** (AUA 2015, EAU 2015, SOGUG 2012)	**1/3** (APC 2015)
	In patients undergoing intermittent androgen deprivation, PSA and testosterone should be monitored at set intervals during the treatment pause (1 or 3 months) and intermittent hormone therapy should be stopped when PSA is >10 ng/mL		**2/6** (EAU 2015, NICE 2014)	**0/3**

[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.
CT = computed tomography; DRE = digital rectal examination; RP = radical prostatectomy; RT = radiotherapy.

PROSTATE CANCER — Take-home message

Examined documents: 33 (24 CPGs, 9 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
ACS 2014	58	39	66	69	33	67
AHS 2013	43	24	38	43	36	47
ASCO 2012	92	47	58	81	33	63
ASCO 2014	89	69	74	81	33	63
ASCO 2015	83	78	65	86	33	63
ASCO-CCO 2014	86	83	81	78	63	75
AUA 2011	61	42	73	86	42	75
AUA 2013-ED	58	44	72	89	42	83
AUA 2015	64	42	75	92	42	88
CCO 2010	89	50	75	83	42	63
CCO 2012-BT	89	56	82	78	42	71
CCO 2014-AS	94	56	76	83	42	67
CCO 2015	97	56	77	81	42	58
CTFPHC 2014	89	58	80	81	73	67
CUA 2011	61	44	68	81	31	42
EAU 2015	64	78	68	83	33	88
EGAPP 2014	86	47	76	75	42	42
NICE 2014	92	94	93	92	83	83
NICE 2015	89	97	91	86	73	83
NICE 2015-PCA3	92	89	88	97	85	92
SIOG 2014	67	72	61	81	46	67
SOGUG 2012	67	42	68	83	27	67
UMHS 2012	58	42	50	75	31	50
USPSTF 2012	83	44	83	89	33	83

Examined documents: 10 (7 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	Recommendations on TMs not available	∅	**2/2** (ACCC 2012, ICUD-EAU 2011)	**0/0**
Differential diagnosis	LDH may also be determined at the moment of presentation for all nonmetastatic patients, given that it is not always immediately clear if a patient has metastatic disease	**LDH**	**1/5** (ACCC 2012)	**1/3** (ESMO 2014)
	Recommendations on TMs not available	∅	**4/5** (AHS 2012, EAU 2015, ICUD-EAU 2011, NICE 2015)	**2/3** (AIOM 2015, NCCN 2015)
Preoperative workup	Recommendations on TMs not available	∅	**4/4** (ACCC 2012, AHS 2012, EAU 2015, ICUD-EAU 2011)	**3/3** (AIOM 2015, ESMO 2014, NCCN 2015)
Reassessment after initial curative treatment	Recommendations on TMs not available	∅	**1/1** (AUA 2013)	**0/0**
Early detection of recurrence or progression	LDH determination may be used at the discretion of the clinician	**LDH**	**1/5** (AUA 2013)	**0/3**
	Recommendations on TMs not available	∅	**4/5** (ACCC 2012, AHS 2012, EAU 2015, ICUD-EAU 2011)	**2/3** (ESMO 2014, NCCN 2015)
Monitoring of treatment response in advanced disease	LDH may be used as a prognostic factor (incorporated in the Memorial Sloan-Kettering Cancer Center [MSKCC] or Motzer score) in patients with advanced/metastatic disease treated with some types of systemic therapy	**LDH**	**3/5** (ACCC 2012, EAU 2015, ICUD-EAU 2011)	**3/3** (AIOM 2015, ESMO 2014, NCCN 2015)
	Recommendations on TMs not available	∅	**2/5** (AHS 2012, SOGUG 2014)	**0/3**

[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.

to be continued

RENAL CANCER — Take-home message

Examined documents: 10 (7 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
ACCC 2012	75	78	64	67	29	50
AHS 2012	80	44	66	67	58	75
AUA 2013	72	44	78	80	33	75
EAU 2015	64	72	64	72	33	83
ICUD-EAU 2011	72	44	66	69	33	50
NICE 2015	89	97	91	89	73	88
SOGUG 2014	56	36	61	81	21	42

Examined documents: 12 (7 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	Serum TMs or any other blood tests are not recommended to screen for germ cell tumors in asymptomatic men	**None**	**1/2** (ASCO 2010)	**0/1**
	Recommendations on TMs not available	Ø	**1/2** (USPSTF 2011)	**1/1** (EAU 2015)
Differential diagnosis	Serum TMs are recommended before orchiectomy for all patients suspected of having a testicular germ cell tumor to help establish the diagnosis and interpret post-orchiectomy levels	**AFP, βhCG, LDH**	**2/3** (ASCO 2010, SIGN 2011)	**5/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015)
	The use of serum TM results is not recommended to guide decision-making on the need for orchiectomy because concentrations in the normal range do not rule out testicular cancer or the need for diagnostic orchiectomy		**1/3** (ASCO 2010)	**0/5**
	Supplementary information n. 1: When using TM results for clinical decisions one should consider the possible occurrence of false positive results (other malignancies, benign conditions, physiological causes)	Ø	**1/3** (ASCO 2010)	**0/5**
	Supplementary information n. 2: For hCG determination the use of assay methods that measure total hCG (intact α/β dimer plus free β monomer) is recommended		**1/3** (ASCO 2010)	**0/5**
	Recommendations on TMs not available		**1/3** (NICE 2015)	**0/5**
Preoperative workup (before and after orchiectomy, and before chemotherapy and/or additional surgery)	Serum AFP, βhCG and LDH are recommended pre-orchiectomy, shortly after orchiectomy, and weekly thereafter until normalization or plateau	**AFP, βhCG, LDH**	**4/4** (AHS 2013, ASCO 2010, SIGN 2011, SIU-ICUD-UICC 2011)	**5/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015)
	Marker concentrations should be used along with imaging techniques to allocate patients to prognostic groups (UICC, 2009, 7th ed.)		**3/4** (AHS 2013, ASCO 2010, SIGN 2011)	**4/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013)
	Supplementary information: The persistence of elevated serum TMs after orchiectomy might indicate the presence of metastatic disease (macro- or microscopic) and classify patients into the substage S1		**3/4** (AHS 2013, ASCO 2010, SIU-ICUD-UICC 2011)	**4/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013)

to be continued

TESTICULAR CANCER — Take-home message

Examined documents: 12 (7 CPGs, 5 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	Periodic determination of TMs is recommended. Duration of follow-up after therapy is completed should be at least 10 years in NSGCTs and at least 5 years in seminomas; evaluation should be more frequent in the first 2 years and in patients under active surveillance	**AFP, βhCG, LDH**	**4/5** (AHS 2013, ASCO 2010, SIGN 2011, SIU-ICUD-UICC 2011)	**5/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015)
	Supplementary information n. 1: Frequency of TM determination during follow-up should be scheduled with reference to initial stage, histological type and post-orchiectomy treatments		**2/5** (AHS 2013, ASCO 2010)	**2/5** (EAU 2015, NCCN 2015)
	Supplementary information n. 2: LDH has not been shown to be helpful in the follow-up of patients with germ cell tumors	∅	**1/5** (SIGN 2011)	**0/5**
	Recommendations on TMs not available		**1/5** (CCO 2014)	**0/5**
Monitoring of treatment response in advanced disease	In NSGCT determination of TMs is recommended at the start of each chemotherapy cycle and again when chemotherapy is completed	**AFP, βhCG, LDH**	**2/2** (AHS 2013, ASCO 2010)	**5/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015)
	In metastatic patients, TM levels before the start of chemotherapy should be used for the correct allocation to the IGCCC prognostic category into good-, intermediate- or poor-risk groups		**2/2** (AHS 2013, ASCO 2010)	**5/5** (AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 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.
∅ The examined **CPGs** that consider the clinical question either do not address TMs or, if TMs are addressed, CPGs do not present explicit recommendations.
IGCCC = International Germ Cell Consensus Classification; NSGCT = non-seminomatous germ cell tumor.

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 2013	75	44	66	72	60	79
ASCO 2010	92	81	83	86	33	67
CCO 2014	94	72	83	75	54	71
NICE 2015	89	97	91	86	73	83
SIGN 2011	92	89	80	94	73	58
SIU-ICUD-UICC 2011	72	44	69	81	33	33
USPSTF 2011	81	33	73	81	29	67

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

BLADDER CANCER — Detailed summary tables

Examined documents: 15 (7 CPGs, 8 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	1	4	Clinical question considered, no explicit recommendations on TMs provided (**USPSTF 2011**, EAU 2015-NM)	Current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults (**USPSTF 2011**, EAU 2015-NM) Routine application of screening is not recommended (EAU 2015-NM, ESMO 2014) Clinical question considered, but TMs not addressed (AIOM 2015, EAU 2015-UT, ESMO 2014)
Differential diagnosis	2	8	In primary care do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer, except in the context of a clinical research study (**NICE 2015-BC**, AURO 2010, EAU 2015-NM) Urinary biomarkers (e.g., NMP22) can be used as an adjunct to cystoscopy to detect invisible tumor in secondary care (**NICE 2015-BC**, EAU 2015-NM) Clinical question considered, no explicit recommendations on TMs provided (**NICE 2015-SC**, AIOM 2015, EAU 2015-MI, ESMO 2014)	No primary care evidence was identified pertaining to the diagnostic accuracy of urine markers (NMP22 and MCM5) in patients with suspected bladder cancer where the clinical responsibility was retained by primary care (**NICE 2015-SC**) No bladder TM test has yet been shown to be superior to urine cytology and cystoscopy (AIOM 2015, AURO 2010, EAU 2015-MI, EAU 2015-NM, ESMO 2014) Clinical question considered, but TMs not addressed (EAU 2015-UR, EAU 2015-UT, NCCN 2015)
Preoperative workup	4	8	Clinical question considered, no explicit recommendations on TMs provided (**NICE 2015-BC**) Clinical question considered, but TMs not addressed (**AHS 2013-MI, AHS 2013-NM, AHS 2013-UT**, AIOM 2015, AURO 2010, EAU 2015-MI, EAU 2015-NM, EAU 2015-UR, EAU-2015 UT, ESMO 2014, NCCN 2015)	
Reassessment after initial curative treatment	0	0	Clinical question not addressed by **CPGs**	
Early detection of recurrence or progression	5	8	Do not substitute urinary biomarkers for cystoscopy for follow-up after treatment for bladder cancer (**NICE 2015-BC**, AIOM 2015, EAU 2015-NM, ESMO 2014) Do not use urinary biomarkers or cytology in addition to cystoscopy for follow-up after treatment for low-risk bladder cancer (**NICE 2015-BC**, AIOM 2015) Clinical question considered, but TMs not addressed (**AHS 2013-MI, AHS 2013-NM, AHS 2013-UT, CUA 2013**, EAU 2015-MI, EAU 2015-UR, EAU 2015-UT)	No bladder TM test has yet been shown to be superior to urine cytology and cystoscopy (AIOM 2015, AURO 2010, ESMO 2014, NCCN 2015) Urinary urothelial TM measurement is considered an optional investigation (NCCN 2015) Clinical question considered, no explicit recommendations on TMs provided (AURO 2010)

to be continued

Examined documents: 15 (7 CPGs, 8 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Monitoring of treatment response in advanced disease	3	5	Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2013-MI, AHS 2013-UT, NICE 2015-BC**, AURO 2010, ESMO 2014, NCCN 2015)	Currently, no biomarkers can be recommended in daily clinical practice because they have no impact on outcome prediction, treatment decisions, or therapy monitoring in muscle-invasive bladder cancer (EAU 2015-MI) Clinical question considered, but TMs not addressed (AIOM 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: 15 (9 CPGs, 6 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Differential diagnosis	2	5	Clinical question considered, but TMs not addressed (**NICE 2012-EarlyBC**, **NICE 2015-SC**, AIOM 2015, ESMO 2013-EarlyBC, EUSOMA 2014-Young, NCCN 2014-Diagn, NCCN 2015)	
Preoperative workup	2	4	Clinical question considered, but no explicit recommendations on TMs provided (**AHS 2012-BB**) Clinical question considered, but TMs not addressed (**NICE 2012-EarlyBC**, AIOM 2015, EUSOMA 2014-Young, NCCN 2015)	Patients do not benefit from TM staging (ESMO 2013-EarlyBC)
Reassessment after initial curative treatment	0	0	Clinical question not addressed by **CPGs**	
Early detection of recurrence or progression	4	4	The use of CA15.3, CA27.29 or CEA is not recommended for routine surveillance of breast cancer after primary therapy in an otherwise asymptomatic patient with no specific findings on clinical examination (**AHS 2013-FU**, **ASCO 2012-FU**, **NHMRC 2010**, AIOM 2015, ESMO 2013-EarlyBC, EUSOMA 2014-Young) TMs are recommended only if clinically indicated (**NHMRC 2010**, ESMO 2013-EarlyBC) Clinical question considered, but TMs not addressed (**NICE 2012-EarlyBC**)	In asymptomatic patients, there are no data to indicate that any TMs (such as CA15.3 or CEA) produce a survival benefit (**NHMRC 2010**, ESMO 2013-EarlyBC, NCCN 2015) Clinical question considered, but no explicit recommendations on TMs provided (NCCN 2015)
Monitoring of treatment response in advanced disease	3	4	CEA, CA15.3 and CA27.29 may be used as adjunctive assessments to contribute to decisions regarding therapy for metastatic breast cancer (**ASCO 2015-M+**, ESMO 2014-ABC, EUSOMA 2014-Young, NCCN 2015) Data are insufficient to recommend use of CEA, CA15.3 and CA27.29 alone for monitoring response to treatment (**ASCO 2015-M+**, ESMO 2014-ABC, EUSOMA 2014-Young, NCCN 2015) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**CECOG 2009**, AIOM 2015) Clinical question considered, but no explicit recommendations on TMs provided (**NICE 2014-M+**)	Caution should be used when interpreting increasing CEA, CA15.3 or CA27.29 levels during the first 4 to 6 weeks of administration of a new therapy, given that spurious early increases may occur (**ASCO 2015-M+**) In the absence of readily measurable disease, a 20% to 30% increase in CEA, CA15.3 or CA27.29 may be used to indicate treatment failure, along with supporting clinical evidence, before considering discontinuation of therapy (**ASCO 2015-M+**) Serum TM levels in association with patient symptoms may be indicative of disease progression in patients with bone-dominant metastatic disease (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: 7 (3 CPGs, 4 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Differential diagnosis	1	4	Clinical question considered, but TMs not addressed (**NICE 2015**, AIOM 2015, ESMO 2012, NCCN 2015)	Currently available serum TMs, including SCC, are not recommended for use in screening or diagnosis of cervical cancer (NACB 2010)
Preoperative workup	1	4	Clinical question considered, but TMs not addressed (**AHS 2013**, ESMO 2012, NCCN 2015)	Pretreatment SCC concentrations are not recommended for routine use. In fact, an elevated pretreatment SCC concentration has been found to be an independent risk factor for poor prognosis in several studies, but the clinical usefulness in treatment planning is uncertain (NACB 2010) Elevated concentrations have been found in conditions other than cervical cancer (NACB 2010): - other malignancies (squamous cell carcinomas of the vulva, vagina, head and neck, esophagus, and lung) - benign conditions of the skin (e.g., psoriasis, eczema), lung (e.g., sarcoidosis), liver, and kidney. Very high values have been found in patients with renal failure or lung disease Clinical question considered, but no explicit recommendations on TMs provided (AIOM 2015)
Reassessment after initial curative treatment	0	1	Clinical question not addressed by **CPGs**	Clinical question considered, but no explicit recommendations on TMs provided (NACB 2010) Persistently elevated serum SCC concentrations after treatment suggest tumor persistence (NACB 2010)
Early detection of recurrence or progression	2	4	The use of TMs (including SCC) in asymptomatic patients cannot be recommended because the impact of asymptomatic recurrence detection on on survival rates is not known (**CCO 2015,** AIOM 2015, NACB 2010) Clinical question considered, but TMs not addressed (**AHS 2013**, ESMO 2012, NCCN 2015)	SCC monitoring after primary treatment strongly correlates with clinical course of disease in patients with squamous cell cervical cancer but there is as yet no clear evidence that earlier detection improves outcome (**CCO 2015**, NACB 2010) TMs may be considered in high-risk patients with locally advanced disease in whom clinical evaluation is impaired as a consequence of treatment (AIOM 2015)
Monitoring of treatment response in advanced disease	1	3	Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2013**, AIOM 2015, NCCN 2015) Clinical question considered, but TMs not addressed (ESMO 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**.

ENDOMETRIAL CANCER — Detailed summary tables

Examined documents: 7 (3 CPGs, 4 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	0	1	Clinical question not addressed by **CPGs**	Clinical question considered, but TMs not addressed (NCCN 2015)
Differential diagnosis	1	4	Clinical question considered, no explicit recommendations on TMs provided (**NICE 2015**)	No evidence was identified pertaining to the diagnostic accuracy of CA125 in patients with suspected endometrial cancer where the clinical responsibility was retained by primary care (**NICE 2015**) Clinical question considered, but TMs not addressed (AIOM 2015, ESMO 2013, NCCN 2015, SGO 2014)
Preoperative workup	1	3	Preoperative abdominopelvic CT scan may be useful in cases with increased serum CA125 levels (**ACN 2011**)	CA125 is not recommended for routine preoperative workup, though it may be useful in selected cases (NCCN 2015) CA125 may be indicated as an optional test in patients in whom metastatic disease is suspected (NCCN 2015) Clinical question considered, but TMs not addressed (AIOM 2015, ESMO 2013)
Reassessment after initial curative treatment	0	0	Clinical question not addressed by **CPGs**	
Early detection of recurrence or progression	1	4	Clinical question considered, but TMs not addressed (**AHS 2013**, ESMO 2013)	Do not measure TMs (CEA, CA125, CA19.9, AFP, etc.) if there are no suspicious symptoms of recurrence (AIOM 2015) The utility of serum CA125 assessment remains controversial (SGO 2014) CA125 is optional (NCCN 2015)
Monitoring of treatment response in advanced disease	1	4	Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2013**, AIOM 2015, ESMO 2013, NCCN 2015, SGO 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**.

Examined documents: 22 (12 CPGs, 10 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening general polulation	2	3	In asymptomatic women without known genetic mutations that increase the risk of ovarian cancer, do not screen for ovarian cancer (**USPSTF 2012**, ACOG 2011-EC, NCCN 2015) Screening for ovarian cancer in the general population should not be performed outside the research setting (**SIGN 2013-EC**)	No clear benefit of screening (serum CA125 level combined with transvaginal ultrasound or transvaginal ultrasound alone) has been demonstrated (**SIGN 2013-EC, USPSTF 2012**, ACOG 2011-EC, AIOM 2015) Clinical question considered, no explicit recommendations on TMs provided (AIOM 2015)
Screening of people at increased risk (positive family history)	3	5	Ovarian cancer surveillance should not be recommended for women at high or potentially high risk (**AHS 2011-HR, NHMRC 2011-HR**, ACOG 2011-EC) Screening for ovarian cancer in high-risk groups should only be offered in the context of a research study (**SIGN 2013-EC**)	Individuals should be counseled on the limitations of the currently available surveillance methods and the symptoms/signs of ovarian cancer (**AHS 2011-HR**) No clear evidence was identified as to whether screening in high-risk groups has an impact on mortality from ovarian cancer (**SIGN 2013-EC**, ACOG 2011-EC, NCCN 2015) For those patients who have not elected risk-reducing salpingo-oophorectomy, there may be circumstances where clinicians find screening helpful (NCCN 2015-HR) The low prevalence of ovarian cancer and the high likelihood of a positive screening test result necessitating further invasive surgical evaluation are obstacles in ovarian cancer screening programs among women at inherited risk (ACOG 2009-HR) Clinical question considered, no explicit recommendations on TMs provided (ACOG 2009-HR, AIOM 2015)

to be continued

Examined documents: 22 (12 CPGs, 10 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Differential diagnosis	6	7	CA125 in conjunction with transvaginal pelvic ultrasound should be carried out in women with suspicious symptoms of ovarian cancer or an adnexal mass (**NICE 2011-EC, NICE 2015, SIGN 2013-EC,** ACOG 2011-EC, ACOG 2013-AM, AIOM 2015, ESMO 2013-EC, NCCN 2015) An estimation of the risk of malignancy should be carried out for the assessment of an ovarian mass (**BSGE 2011, CCO 2011-AM, NICE 2011-EC, SIGN 2013-EC**, ESMO 2013-EC) As a standalone modality, serum CA125 is not recommended for distinguishing between benign and malignant adnexal masses (**CCO 2011-AM**) CA125 assay does not need to be undertaken in premenopausal women when an ultrasonographic diagnosis of a simple ovarian cyst has been made (**BSGE 2011**) LDH, AFP and hCG should be measured in all women under age 40 with a complex ovarian mass because of the possibility of germ cell tumors: - CA125 (**AHS 2013-GCT, NICE 2011-EC**, NCCN 2015) - AFP (**AHS 2013-GCT, BSGE 2011, NICE 2011-EC**, ACOG 2013-AM, ESMO 2012-GCT, NCCN 2015) - βhCG (**AHS 2013-GCT, BSGE 2011, NICE 2011-EC**, ACOG 2013-AM, ESMO 2012-GCT, NCCN 2015) - LDH (**AHS 2013-GCT, BSGE 2011**, ACOG 2013-AM, ESMO 2012-GCT) - inhibin (ESMO 2012-GCT, NCCN 2015)	RMI I (*Risk of Malignancy Index I*) is the most accurate scoring system for women with suspected ovarian cancer (**BSGE 2011, NICE 2011-EC, SIGN 2013-EC**) The choice of scoring system may be made based on clinician preference (**CCO 2011-AM**) Serum CA125 is elevated in only 50% of early-stage ovarian cancers (**BSGE 2011, CCO 2011-AM**, ACOG 2011-EC, ESMO 2013-EC) Measuring the CA125 level may predict cancer more accurately in postmenopausal than premenopausal women (**CCO 2011-AM**, ACOG 2011-EC, ACOG 2013-AM) CA125 can be elevated for reasons other than ovarian cancer (**BSGE 2011, CCO 2011-AM, SIGN 2013-EC**, ACOG 2011-EC, ACOG 2013-AM, ESMO 2013-EC): - other malignancies (tumors of the pancreas, breast, lung, colon) - benign conditions (endometriosis, pelvic inflammatory disease and liver disease, uterine leiomyomata, systemic lupus erythematosus, inflammatory bowel disease, ascites of any etiology, pleural or pericardial effusions, a recent laparotomy) - physiological causes (menstruation, pregnancy) CA125 is likely to be raised to several hundreds or thousands of units/mL in stage III-IV endometriosis (**BSGE 2011**, ACOG 2013-AM) Other TMs have not been proved to improve early detection and survival rates (**NICE 2011-EC**, ACOG 2011-EC, NCCN 2015) Preliminary data on HE4 showed it to have relatively high sensitivity and specificity, but data on HE4 are not yet substantial enough to enable it to be recommended instead of serum CA125 (**NICE 2011-EC**) Clinical question considered, but TMs not addressed (ESGO 2011)
Preoperative workup	3	4	AFP, βhCG and LDH in association with clinical findings are used to determine prognosis for dysgerminomas and non-dysgerminomas (**AHS 2013-GCT**) Clinical question considered, but TMs not addressed (**AHS 2013-EC, SIGN 2013-EC**, ESMO 2012-GCT, ESMO 2013-EC)	Risk class definition (in association with clinical findings) (**AHS 2013-GCT**): Dysgerminoma - Good: any LDH, βhCG, normal AFP. Intermediate: any LDH, βhCG, normal AFP Non-dysgerminoma - Good: LDH <1.5 times N, AND βhCG <5,000, AND AFP <1,000. Intermediate: LDH 1.5-10 times N, OR βhCG 5,000-50,000, OR AFP 1,000-10,000. Poor: LDH >10 times N, OR βhCG >50,000, OR AFP >10,000 (N: upper limit of the reference interval) TMs (including CA125, inhibin and βhCG) can be measured if clinically indicated (NCCN 2015) Clinical question considered, no explicit recommendations on TMs provided (AIOM 2015)

to be continued

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Reassessment after initial curative treatment	1	4	Clinical question considered, but TMs not addressed (**AHS 2013-EC**)	Serial measurement of CA125 is a useful marker to assess the response to chemotherapy in epithelial ovarian cancer (AIOM 2015, ESMO 2013-EC, NCCN 2015) If the CA125 level does not reach the normal range before the end of chemotherapy, the disease status would be regarded as a partial response to frontline treatment (ESMO 2013-EC) If the CA125 level does not reach the normal range approximately 20 days after radical surgery, it should be considered as a negative prognostic factor (AIOM 2015) Serum TMs (CA125 and inhibin, AFP, βhCG, LDH) can correlate with tumor response during chemotherapy (ESMO 2012-GCT, NCCN 2015)
Early detection of recurrence or progression	4	6	CA125 blood test has not been proven to be beneficial and is therefore not recommended for routine follow-up (**AHS 2013-EC**) In the absence of symptoms, routine measurement of CA125 during follow-up is not mandatory (**SIGN 2013-EC**) It is recommended to continue histology-specific TM measurement in the routine follow-up of patients with nonepithelial ovarian cancer (**AHS 2013-EC**, ESGO 2011, NCCN 2015) A rising CA125 level should trigger further imaging (**NHMRC2012**, AIOM 2015, ESGO 2012-FU, NCCN 2015) Women should be fully informed of the pros and cons of routine measurement of CA125 during follow-up (**NHMRC2012**, AIOM 2015, ESGO 2012-FU, NCCN 2015) Some women may benefit from routine measurement of CA125, including those who are eligible for secondary cytoreductive surgery (**NHMRC2012**)	Follow-up may include CA125 (ESGO 2011, ESGO 2012-FU, NCCN 2015) A rising CA125 level does not directly lead to a change in treatment (AIOM 2015, ESMO 2013-EC, NCCN 2015) Elevated values must be confirmed by 2 separate measurements obtained at least 1 week apart (ESMO 2013-EC) There is no evidence of a survival benefit for women who commenced early chemotherapy for first relapse based on raised CA125 level alone (**NHMRC2012**, NCCN 2015) There is no recommended frequency of follow-up consultations. Different guidelines report partially different schemes, which are summarized as follows: - there is no recommended frequency of follow-up consultations (**NHMRC2012**) - observe TMs every 3 months if levels are initially elevated; observe for 2 years. After 2 years from completing treatment, visits every 6 months (**AHS 2013-EC**) - measurement of CA125 is often carried out every 3 months for 2 years, then every 6 months during years 4 and 5 or until progression (ESMO 2012-GCT, ESMO 2013-EC) - every 3 months for the first 2 years, then every 6 months during the third, fourth and fifth years (AIOM 2015) - at least every 3/4 months during the first 3 years after initial treatment and every year thereafter (ESGO 2011) Prolonged follow-up is required in women with borderline ovarian tumors because late recurrences have been reported (after 20 years) (ESGO 2011)

to be continued

Examined documents: 22 (12 CPGs, 10 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Monitoring of treatment response in advanced disease	5	4	Serial measurement of CA125 is useful to assess the response to chemotherapy (**CCO 2011**, ESMO 2013-EC, NCCN 2015) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2013-EC, AHS 2013-GCT, SIGN 2013 EC, NICE 2011 EC**, AIOM 2015)	Progression or recurrence based on serum CA125 level is defined according to Gynecologic Cancer InterGroup (GCIG) criteria (ESMO 2013-EC) GCIG response criteria: CA125 response is defined as at least a 50% reduction in CA125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment Serum TMs (βhCG, AFP, LDH, CA125 and inhibin) can be measured during chemotherapy in nonepithelial ovarian cancer (ESMO 2012-GCT)

[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: 33 (24 CPGs, 9 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Organized screening programs	2	2	Do not use PSA-based mass screening for prostate cancer (**EAU 2015**, **USPSTF 2012**, AIOM 2015, ESMO 2013)	The benefits of PSA-based screening for prostate cancer do not outweigh the harms (mainly due to high overdiagnosis and overtreatment rates) (**USPSTF 2012,** ESMO 2013)
Spontaneous screening	9	3	Screening for prostate cancer with the PSA test is not recommended (**CTFPHC 2014**) PSA screening for average-risk men of all ages is not recommended (**USPSTF 2012**) Evidence is sufficient to recommend against PSA screening in men older that 75 or with a life expectancy <10 years (**ASCO 2012**) For men aged less than 55 years or older that 70 screening for prostate cancer with PSA is not recommended (**AUA 2013-ED**, **SIOG 2014,** AIOM 2015) Prostate cancer screening should be offered to all men 50 years of age with at least a 10-year life expectancy (**AHS 2013, CUA 2011, UMHS 2012**) An individualized risk-adapted strategy for early detection might be offered to a well-informed man with a good performance status and at least 10-15 years of life expectancy (**EAU 2015**, AIOM 2015, NCCN 2014) If there is a higher risk of prostate cancer (e.g., positive family history or African-American descent), PSA-based screening should be offered at age 40 years (**AUA 2013-ED**, **CUA 2011, EAU 2015**, **UMHS 2012, USPSTF 2012**, AIOM 2015) If prostate cancer screening is considered, men should be informed of the potential benefits and risks of early detection (**AHS 2013**, **ASCO 2012, AUA 2013-ED**, **USPSTF 2012**, AIOM 2015, ESMO 2013, NCCN 2014)	Men at elevated risk of prostate cancer: men over 50 years of age, men over 45 years of age and a family history of prostate cancer, African-Americans, men with a PSA level >1 ng/mL at 40 years of age, men with a PSA level >2 ng/mL at 60 years of age (**EAU 2015**) No evidence has demonstrated that age-adjusted PSA cutoffs; free PSA; and PSA density, velocity, slope, and doubling-time testing improve health outcomes when used for screening purposes **(ASCO 2012, CTFPHC 2014, EAU 2015, UMHS 2012, USPSTF 2012)** When used for screening, annual PSA determination has been the standard; however, 2 screening studies found that screening is beneficial every 2 to 4 years (**CUA 2011**, **USPSTF 2012**) When a risk-adapted screening strategy is considered, PSA may be repeated every 2 years for men initially at risk (**EAU 2015**, NCCN 2014)

to be continued

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Differential diagnosis	8	6	Indications for biopsies include a clinical suspicion of prostate cancer based on PSA and DRE findings, considering also clinical history and risk factors. Do not automatically offer a prostate biopsy on the basis of serum PSA level alone (**AHS 2013**, **EAU 2015, NICE 2015**, AIOM 2015, ESMO 2013, GEC-ESTRO 2013, NCCN 2015) Consider PSA to assess for prostate cancer in men with any lower urinary tract symptoms or any unexplained symptoms suggestive of metastatic prostate cancer (**CCO 2015**, **NICE 2015**) Limited PSA elevation alone should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardized conditions **(EAU 2015**, **NICE 2014**, AIOM 2015, NCCN 2014) Evidence is not sufficient to recommend PCA3 to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (increased PSA or suspicious DRE) (**EGAPP 2014, EAU 2015,** AIOM 2015)	Elevated PSA and/or abnormal DRE are not diagnostic of prostate cancer; they do serve to risk stratify patients **(AHS 2013)** Many conditions may increase PSA (including BPH, prostatitis, urethral instrumentation, prostate biopsy, a vigorous DRE and recent ejaculation) (**CUA 2011**, **EAU 2015**, NCCN 2014) There is no level of PSA below which the risk of prostate cancer can be eliminated (**EAU 2015**, NCCN 2014) 5-alpha reductase inhibitors (5αRIs) reduce the PSA level by about 50% at 6 months and are non-dose-dependent (**CUA 2011**, NCCN 2014) Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken (**EAU 2015**, NCCN 2014) PSA velocity, PSA density and PSA free-to-total ratio may improve PSA sensitivity and specificity (**CUA 2011**, NCCN 2014, SIURO 2013) PSA velocity and PSA density have limited diagnostic use and do not provide additional information compared with PSA alone (**EAU 2015**) The use of age-adjusted PSA ranges may improve PSA specificity (**CCO 2015**, SIURO 2013) The role of age-adjusted PSA ranges is still under debate (**USPSTF 2012**) The PHI test has as yet undetermined clinical impact given the slight net benefit provided for clinical decision-making (**EAU 2015**)
Rebiopsy	4	4	The indications for a repeat biopsy are: rising and/or persistently elevated PSA (**EAU 2015**, AIOM 2015, ESMO 2013, SIURO 2013) Evidence is insufficient to recommend PCA3 to inform decisions for when to rebiopsy previously biopsy-negative patients (**EGAPP 2014**, **NICE 2015-PCA3**) PHI is not recommended for use in people who have had a negative or inconclusive prostate biopsy (**NICE 2015-PCA3**) A man with risk factors whose multiparametric MRI was negative should not necessarily have rebiopsy but should be monitored in secondary care and rebiopsied and reimaged based on PSA kinetics or patient choice (**NICE 2014**) Currently, the main indication for PCA3 is to determine whether repeat biopsy is needed after an initially negative biopsy (**EAU 2015**, NCCN 2014)	Very low quality evidence is available for age, PSA free-to-total ratio, PSA velocity, PCA3 score, and PSA density in the indication for a repeat biopsy (**NICE 2014**)

to be continued

Examined documents: 33 (24 CPGs, 9 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Preoperative workup	8	5	PSA, combined with clinical stage and Gleason score, is used as risk stratification to discuss therapy options with the patient (**AHS 2013**, **AUA 2011, CCO 2010, CCO 2012-BT, EAU 2015**, **NICE 2014**, **SIOG 2014**, AIOM 2015, AUA 2013, ESMO 2013, NCCN 2015) Radiographic staging (CT and bone scan) is recommended for patients with a PSA level >20 ng/mL (**AUA 2011,** AUA 2013, GEC-ESTRO 2013) or >10 ng/mL prior to treatment (**EAU 2015**, AIOM 2015) Evidence is insufficient to recommend PCA3 testing to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan (**EGAPP 2014,** AIOM 2015)	Risk groups (endorsed by: **AHS 2013**, **AUA 2011, CCO 2010, CCO 2012-BT, EAU 2015**, **NICE 2014**, **SIOG 2014**, AIOM 2015, ESMO 2013, NCCN 2015): - Low risk: PSA <10 and Gleason ≤6 and clinical stage ≤T2a - Intermediate risk: PSA 10-20 or Gleason 7 - High risk: PSA >20 or Gleason ≥8 or clinical stage ≥T3 Measurement of PSA level alone has limited ability to predict final pathological stage accurately (**EAU 2015**, AIOM 2015)
Active surveillance	10	2	PSA <10 ng/mL is one of the criteria to identify patients eligible for active surveillance (**CCO 2014-AS, EAU 2015, SIOG 2014**, AIOM 2015) Monitoring of patients on active surveillance should include PSA testing (every 3-6 months) **(AHS 2013, ACS 2014, ASCO 2015, CCO 2014-AS, EAU 2015**, **NICE 2014,** AIOM 2015, NCCN 2015) Accelerated elevation of PSA level (i.e., a PSADT <3 years according to **AHS 2013, EAU 2015**) is one of the criteria to start active therapy **(CUA 2011,** AIOM 2015) Evidence is not sufficient to recommend PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan **(CCO 2014-AS, EGAPP 2014,** AIOM 2015)	The optimal timing for follow-up is still unclear **(ACS 2014, AUA 2011, EAU 2015, NICE 2014**, AIOM 2015)
Reassessment after initial curative treatment (RP)	4	3	First postoperative PSA measurement should be done 4-12 weeks after surgery (RP) (**ACS 2014, AHS 2013, EAU 2015, NICE 2014**) PSA should decrease and remain at undetectable levels 4-12 weeks after RP (**EAU 2015**, **NICE 2014**, AIOM 2015, AUA 2013, NCCN 2015)	To date, there has been no consensus definition of a threshold level of PSA below which PSA is truly "undetectable" (NCCN 2015) PSA should be measured with standard assay methods (ultrasensitive assays are not indicated) (AIOM 2015)
Reassessment after initial curative treatment (RT)	2	2	The PSA level falls slowly after external-beam RT or brachytherapy and does not normally reach zero **(NICE 2014, EAU 2015**, AIOM 2015, AUA 2013) The interval before the PSA nadir is reached may be very long, sometimes up to 3 years or more (**EAU 2015**, AIOM 2015, AUA 2013)	A PSA nadir <1.0 ng/mL after external-beam RT or brachytherapy is associated with a favorable prognosis **(EAU 2015**, AIOM 2015) PSA may rise temporarily after initial external-beam RT or brachytherapy (*PSA bounce*) (**NICE 2014**)

to be continued

Examined documents: 33 (24 CPGs, 9 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Early detection of recurrence or progression (RP)	6	5	Periodic PSA determination should be offered to detect disease recurrence (**ACS 2014**, **AHS 2013**, **ASCO 2014**, **ASCO 2015**, **EAU 2015**, **NICE 2014**, AIOM 2015, AUA 2013, ESMO 2013, NCCN 2015) After RP, biochemical recurrence is defined by 2 consecutive PSA values of >0.2 ng/mL (**AHS 2013**, **ASCO 2014**, **EAU 2015**, AIOM 2015, AUA-ASTRO 2013, NCCN 2015) It is recommended that the finding of a single elevated serum PSA level should be reconfirmed before starting therapy (**EAU 2015**, **NICE 2014**) Analyze serial PSA levels after radical treatment using the same assay technique (**NICE 2014**) Bone scan and abdominopelvic CT should only be considered in asymptomatic patients with biochemical failure after RP who have a high baseline PSA (>10 ng/mL) or high PSA kinetics (PSADT <6 months or PSA velocity >0.5 ng/mL/month (**EAU 2015**) PET/CT cannot be recommended in patients with biochemical recurrence and PSA levels <2 ng/mL (**EAU 2015**) Distress/depression/PSA anxiety should be periodically monitored (at least annually) using simple screening tools (**ACS 2014**, **ASCO 2015**)	Suggested periodicity of PSA monitoring: - low or intermediate risk: PSA measurement every 6 to 12 months for the first 5 years, then annually thereafter. High risk every 6 months (**AHS 2013**) - every 6 to 12 months for the first 5 years, then annually thereafter (**ACS 2014**, **ASCO 2015**) - 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually (**EAU 2015**) - every 6 months for the first 2 years and then at least once a year (**NICE 2014**) PSADT <3 months is a negative prognostic factor after biochemical relapse (**AHS 2013**, **EAU 2015**, NCCN 2015) Ultrasensitive PSA (US PSA) assay remains controversial for routine follow-up (**EAU 2015**)
Early detection of recurrence or progression (RT)	3	1	Periodic PSA determination should be offered to detect disease recurrence (**AHS 2013**, **EAU 2015**, **NICE 2014**, AIOM 2015) Following RT, biochemical recurrence is defined as a rise by 2 ng/mL or more above the PSA nadir (defined as the lowest PSA level reached) (**AHS 2013**, **EAU 2015**, **NICE 2014**, AIOM 2015)	After RT, PSADT <3 months is associated with high risk of clinical recurrence and PSADT >15 months with low risk (**EAU 2015**)

to be continued

Examined documents: 33 (24 CPGs, 9 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Monitoring of treatment response in advanced disease	6	3	Patients with stage M1 disease with a good treatment response should be evaluated at 3 and 6 months with PSA and testosterone measurement during hormonal treatment **(AHS 2013**, **ASCO-CCO 2014**, **AUA 2015**, **EAU 2015**, AIOM 2015, APC 2015, NCCN 2015) PSA should not be measured routinely, but only when it will affect management (**AHS 2013**) *Castration-resistant prostate cancer (CRPC)* is defined as serum testosterone <50 ng/dL (1.7 nmol/L) plus 3 consecutive rises in PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL (**AUA 2015, EAU 2015, SOGUG 2012,** APC 2015) In patients undergoing intermittent androgen deprivation, PSA and testosterone should be monitored at set intervals during the treatment pause (1 or 3 months) (**EAU 2015**, **NICE 2014**) Intermittent hormone therapy should be stopped if PSA is >10 ng/mL (**EAU 2015**, **NICE 2014)** Patients should not be started on second-line therapy unless their serum PSA level is >2 ng/mL and testosterone is <50 ng/dL (**EAU 2015**)	As long as PSA remains at the nadir values obtained with therapy, bone scan, CT or PET/CT are not necessary because the probability of clinical progression is very low (AIOM 2015) Response to therapy is defined as a confirmed decrease in PSA level >50% (AIOM 2015) Visceral metastases may develop in men without rising PSA (APC 2015) In the first 2-3 months after starting chemotherapy or newer hormonal therapies, 20% of men experience a PSA flare, with a significant drop in PSA after the initial rise (*PSA surge syndrome*). Imaging is not required in this circumstance (AIOM 2015, APC 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**.
BPH = benign prostatic hyperplasia; CT = computed tomography; DRE = digital rectal examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PSADT = PSA doubling time; RP = radical prostatectomy; RT = radiotherapy.

Examined documents: 10 (7 CPGs, 3 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	2	0	Clinical question considered, but TMs not addressed (**ACCC 2012**) Clinical question considered, no explicit recommendations on TMs provided (**ICUD-EAU 2011**)	
Differential diagnosis	5	3	LDH determination may also be performed at the moment of presentation for all nonmetastatic patients, given that it is not always immediately clear if a patient has metastatic disease (**ACCC 2012**) Clinical question considered, no explicit recommendations on TMs provided (**EAU 2015, ICUD-EAU 2011**, AIOM 2015) Clinical question considered, but TMs not addressed (**AHS 2012, NICE 2015**, NCCN 2015)	Suspicion of renal cell carcinoma should prompt laboratory examinations of LDH (ESMO 2014)
Preoperative workup	4	3	Clinical question considered, no explicit recommendations on TMs provided (**EAU 2015, ICUD-EAU 2011**, ESMO 2014) Clinical question considered, but TMs not addressed for nonmetastatic disease (**ACCC 2012, AHS 2012**, AIOM 2015, NCCN 2015)	
Reassessment after initial curative treatment	1	0	Clinical question considered, but TMs not addressed (**AUA 2013**)	
Early detection of recurrence or progression	5	3	LDH determination may be used at the discretion of the clinician (**AUA 2013**) Clinical question considered, but TMs not addressed (**ACCC 2012, AHS 2012, EAU 2015, ICUD-EAU 2011**)	There are no data demonstrating that regular LDH measurements in the nonmetastatic setting improve detection of metastatic disease (**AUA 2013**) TM determinations are discouraged in the absence of symptoms or clinical findings (AIOM 2015)
Monitoring of treatment response in advanced disease	5	3	LDH may be used as a prognostic factor (incorporated in the Memorial Sloan-Kettering Cancer Center [MSKCC] or Motzer score) in patients with advanced/metastatic disease treated with some types of systemic therapy (**ACCC 2012, EAU 2015, ICUD-EAU 2011**, AIOM 2015, ESMO 2014, NCCN 2015) Clinical question considered, but criteria to monitor treatment response (including TMs) not addressed (**AHS 2012, SOGUG 2014**)	LDH >1.5 times the upper limit of the laboratory range (if incorporated in the MSKCC score) has negative prognostic value (**EAU 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**.

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Screening	2	1	Serum TMs or any other blood tests are not recommended to screen for germ cell tumors in asymptomatic men (**ASCO 2010**) Clinical question considered, but TMs not addressed (**USPSTF 2011**, EAU 2015)	
Differential diagnosis	3	5	Serum TM measurements are recommended before orchiectomy for all patients suspected of having a testicular germ cell tumor to help establish the diagnosis and interpret postorchiectomy levels (**ASCO 2010**, **SIGN 2011**, AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015) Recommended TMs: AFP, βhCG and LDH (**SIGN 2011**, EAU 2015, EGCCCG 2013, NCCN 2015) AFP and βhCG (**ASCO 2010**, ESMO 2013) The use of serum TM results is not recommended to guide decision-making on the need for an orchiectomy, because concentrations in the normal range do not rule out testicular cancer or the need for diagnostic orchiectomy (**ASCO 2010**) A significantly elevated serum AFP level can establish the diagnosis of a mixed germ cell tumor in a patient whose histopathological diagnosis is pure seminoma, because seminomas do not produce AFP. However, borderline elevated values should be interpreted cautiously (**ASCO 2010**) Serum TMs are not recommended to guide treatment of patients with cancers of unknown primary and indeterminate histology, because evidence is lacking to support this use (**ASCO 2010**) In rare male patients presenting with a testicular, retroperitoneal or anterior mediastinal primary tumor and whose disease burden has resulted in an urgent need to start treatment, substantially elevated serum AFP and/or hCG may be considered sufficient for a diagnosis of germ cell tumor. For such rare, medically unstable patients, treatment need not be delayed until after tissue diagnosis (**ASCO 2010**, EAU 2015) For hCG determination the use of assay methods that measure total hCG (intact α/β dimer plus free β monomer) is recommended (**ASCO 2010**) Clinical question considered, but TMs not addressed (**NICE 2015**)	Factors other than germ cell tumor that may elevate serum markers (**ASCO 2010**) **AFP** - other malignancies: hepatocellular carcinoma, gastric, lung, colon and pancreatic cancer and other poorly differentiated cancers - benign liver disease: hepatitis, cirrhosis, hepatic toxicity from chemotherapy, alcohol abuse, biliary tract obstruction - constitutively elevated AFP: some individuals have serum AFP levels that are chronically mildly elevated in the range of 15-30 ng/mL **βhCG** - other malignancies: neuroendocrine tumors, carcinomas of bladder, kidney, lung, head, neck, gastrointestinal tract, cervix, uterus and vulva, lymphoma and leukemia - unilateral orchiectomy and chemotherapy can cause low testosterone levels, which in turn can lead to increased production of LH and hCG by the pituitary gland. LH can cross-react with some assays for hCG - heterophilic antibodies have been reported to result in false-positive hCG results in women **LDH** - other malignancies: lymphoma, small cell lung cancer, Ewing's sarcoma, osteogenic sarcoma, melanoma - almost anything that results in cell lysis or injury: strenuous exercise, liver disease, myocardial infarction, kidney disease, hemolysis, pneumonia, and countless other things Serum AFP, βhCG and LDH levels may rise during the first week of chemotherapy because of tumor lysis. If TM levels rise between day 1 of cycle 1 and day 1 of cycle 2, TM level assays should be repeated midway through cycle 2 to determine whether levels have begun to decline (**ASCO 2010**) The only proven utility of LDH is for prognosis of chemotherapy-naïve patients with histopathologically diagnosed metastatic germ cell tumors (**ASCO 2010**)

to be continued

Examined documents: 12 (7 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Preoperative workup (before and after orchiectomy, and before chemotherapy and/or additional surgery)	4	5	Serum AFP, βhCG and LDH are recommended for all patients with testicular NSGCT pre-orchiectomy, shortly after orchiectomy, and weekly thereafter until normalization or plateau development (**AHS 2013**, **ASCO 2010**, **SIGN 2011**, **SIU-ICUD-UICC 2011**, AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015) Serum TMs after orchiectomy should be determined before chemotherapy or radiotherapy (**AHS 2013**, **ASCO 2010**, **SIGN 2011**, AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015) Marker concentrations should be used along with imaging techniques to allocate patients to prognostic groups (**SIGN 2011**) The persistence of elevated serum TM levels after orchiectomy might indicate the presence of metastatic disease (macro- or microscopic) and classify patients into the substage S1 (**AHS 2013**, **ASCO 2012**, **SIU-ICUD-UICC 2011**, AIOM 2015, EAU 2015, ESMO 2013) TMs are not recommended to guide treatment decisions for seminoma because evidence is lacking that selecting therapy based on TM levels yields better outcomes (**ASCO 2010**) AFP, βhCG and LDH should be determined before chemotherapy begins for those patients with mediastinal or retroperitoneal NSGCTs to stratify risk and select treatment (**ASCO 2010**, EGCCCG 2013)	Suggested schedules of TM determination - Pre-orchiectomy, 24 hours after orchiectomy, and weekly thereafter until normalization or plateau development (**SIGN 2011**) - Pre-orchiectomy and 5-7 days after orchiectomy (EAU 2015) Slightly elevated and stable AFP and βhCG levels after orchiectomy should be interpreted with caution, because these might not necessarily stem from disseminated NSGCT (**SIU-ICUD-UICC 2011**) The mean serum half-life of AFP and βhCG is 5-7 days and 2-3 days, respectively. The persistence of elevated serum TM levels after orchiectomy might indicate the presence of metastatic disease (macro- or microscopic), while the normalization of marker levels after orchiectomy does not rule out the presence of tumor metastases (**ASCO 2010**, EAU 2015, EGCCCG 2013) TNM classification for testicular cancer (UICC, 2009, 7th ed.) (EAU 2015) Serum TMs: SX Serum marker studies not available or not performed S0 Serum marker study levels within normal limits S1 LDH (U/L) <1.5 × N and hCG (mIU/mL) <5,000 and AFP (ng/mL) <1,000 S2 LDH (U/L) 1.5-10 × N or hCG (mIU/mL) 5,000-50,000 or AFP (ng/mL) 1,000-10,000 S3 LDH (U/L) >10 × N or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000 (N: upper limit of the reference interval)

to be continued

Examined documents: 12 (7 CPGs, 5 OGDs)

<table>
<tr><th>Clinical question</th><th>CPG</th><th>OGD</th><th>Summary of recommendations [1]</th><th>Supplementary information [2]</th></tr>
<tr><td>Early detection of recurrence or progression</td><td>5</td><td>5</td><td>Periodic determination of TMs is recommended. Duration of follow-up after therapy is completed should be at least 10 years in NSGCTs and at least 5 years in seminomas; evaluations should be more frequent in the first 2 years and in patients under active surveillance (AHS 2013, ASCO 2010, SIGN 2011, SIU-ICUD-UICC 2011, AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015)

TMs are not reccomended for surveillance of stage I seminoma (ASCO 2010)

Clinical question considered, but TMs not addressed (CCO 2014)</td><td>LDH has not been shown to be helpful in the follow-up in patients with germ cell tumors (SIGN 2011)

The frequency of TM determination during follow-up should be scheduled with reference to initial stage, histological type and post-orchiectomy treatments. Different guidelines report partially different schemes, which are summarized in the following table (AHS 2013, ASCO 2010, EAU 2015, NCCN 2015)

<u>Seminoma</u>
<table>
<tr><th>Clinical stage</th><th>Years after therapy is completed</th><th>Suggested timing of TM determination (min-max)</th></tr>
<tr><td>Stage I</td><td></td><td></td></tr>
<tr><td></td><td>1</td><td>every 2-6 months</td></tr>
<tr><td></td><td>2</td><td>every 3-6 months</td></tr>
<tr><td></td><td>3</td><td>every 4-12 months</td></tr>
<tr><td></td><td>4</td><td>every 4-12 months</td></tr>
<tr><td></td><td>5</td><td>every 6-12 months</td></tr>
<tr><td></td><td>Thereafter</td><td>every 12 months</td></tr>
<tr><td>Stages IIA, IIB, IIC, IID, III</td><td></td><td></td></tr>
<tr><td></td><td>1</td><td>every 2-4 months</td></tr>
<tr><td></td><td>2</td><td>every 3-4 months</td></tr>
<tr><td></td><td>3</td><td>every 4-6 months</td></tr>
<tr><td></td><td>4</td><td>every 4-12 months</td></tr>
<tr><td></td><td>5</td><td>every 6-12 months</td></tr>
<tr><td></td><td>Thereafter</td><td>every 12 months</td></tr>
</table>
<u>NSGCT</u>
<table>
<tr><th>Clinical stage</th><th>Years after therapy is completed</th><th>Suggested timing of TM determination (min-max)</th></tr>
<tr><td>Stage I S0</td><td></td><td></td></tr>
<tr><td></td><td>1</td><td>every 1-3 months</td></tr>
<tr><td></td><td>2</td><td>every 2-6 months</td></tr>
<tr><td></td><td>3</td><td>every 3-6 months</td></tr>
<tr><td></td><td>4</td><td>every 3-12 months</td></tr>
<tr><td></td><td>5</td><td>every 6-12 months</td></tr>
<tr><td></td><td>Thereafter</td><td>every 12 months</td></tr>
<tr><td>Stages I S+, II, III</td><td></td><td></td></tr>
<tr><td></td><td>1</td><td>every 1-3 months</td></tr>
<tr><td></td><td>2</td><td>every 2-6 months</td></tr>
<tr><td></td><td>3</td><td>every 3-6 months</td></tr>
<tr><td></td><td>4</td><td>every 3-12 months</td></tr>
<tr><td></td><td>5</td><td>every 6-12 months</td></tr>
<tr><td></td><td>Thereafter</td><td>every 12 months</td></tr>
</table></td></tr>
</table>

to be continued

Examined documents: 12 (7 CPGs, 5 OGDs)

Clinical question	CPG	OGD	Summary of recommendations [1]	Supplementary information [2]
Monitoring of treatment response in advanced disease	2	5	In NSGCT determination of TMs is recommended at the start of each chemotherapy cycle and again when chemotherapy concludes (AHS 2013, ASCO 2010, AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015) In metastatic patients, these TM levels before the start of chemotherapy – and not those pre-orchiectomy – should be used for the correct allocation to the IGCCC prognostic category into good-, intermediate- or poor-risk groups (AHS 2013, ASCO 2010, AIOM 2015, EAU 2015, EGCCCG 2013, ESMO 2013, NCCN 2015) In NSGCT the start of chemotherapy should not be delayed until after the results of serum TM assays are known. (ASCO 2010) In seminomas TMs are not recommended during treatment. However, serum hCG and AFP should be measured when seminoma treatment concludes. Rising concentrations usually indicate progressive disease and the need for salvage therapy (usually chemotherapy) (ASCO 2010)	Rising AFP and/or βhCG levels during chemotherapy usually imply progressive disease and the need to change regimen (ASCO 2010) Tumor lysis from chemotherapy, particularly during the first cycle, may result in a transient spike in serum TM levels, and such a spike does not represent treatment failure (ASCO 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**.
IGCCC = International Germ Cell Consensus Classification; LH = luteotropic hormone; NSGCT = non-seminomatous germ cell tumor.

Selected guidelines (by cancer site)

Bladder cancer

AHS 2013-MI. Alberta Provincial Genitourinary Tumour Team. Muscle invasive and locally advanced/metastatic bladder cancer. Edmonton, Alberta: CancerControl Alberta; 2013.

AHS 2013-NM. Alberta Provincial Genitourinary Tumour Team. Nonmuscle invasive bladder cancer. Edmonton, Alberta: CancerControl Alberta; 2013. http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gu009-noninvasive-bladder.pdf.

AHS 2013-UT. Alberta Provincial Genitourinary Tumour Team. Upper tract urothelial tumours. Edmonton, Alberta: CancerControl Alberta; 2013. http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gu008-upper-tract.pdf.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Carcinoma della vescica. Milan: AIOM; 2015.

AURO 2010. Puppo P, Conti G, Francesca F, Mandressi A, Naselli A; AURO.it guideline committee. New Italian guidelines on bladder cancer, based on the World Health Organization 2004 classification. BJU Int. 2010; 106(2):168-79. doi: 10.1111/j.1464-410X.2010.09324.x.

CUA 2013. Kapoor A, Allard CB, Black P, Kassouf W, Morash C, Rendon R. Canadian guidelines for postoperative surveillance of upper urinary tract urothelial carcinoma. Can Urol Assoc J. 2013;7(9-10):306-11. doi: 10.5489/cuaj.1578.

EAU 2015-MI. Witjes LA, Compérat E, Cowan NC, et al. Guidelines on muscle-invasive and metastatic bladder cancer. Arnhem, Netherlands: European Association of Urology; 2015.

EAU 2015-NM. Babjuk M, Böhle A, Burger M, et al. Guidelines on non-muscle-invasive bladder Cancer (Ta, T1 and CIS). Arnhem, Netherlands: European Association of Urology; 2015.

EAU 2015-UR. Gakis G, Witjes JA, Compérat E, et al. Guidelines on primary urethral carcinoma. Arnhem, Netherlands: European Association of Urology; 2015.

EAU 2015-UT. Rouprêt M, Babjuk M, Böhle A, et al. Guidelines on urothelial carcinomas of the upper urinary tract. Arnhem, Netherlands: European Association of Urology; 2015.

ESMO 2014. Bellmunt J, Orsola A, Leow JJ, et al. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 (Suppl 3):iii40-8. doi: 10.1093/annonc/mdu223.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Bladder cancer, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015-SC. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

NICE 2015-BC. National Collaborating Centre for Cancer. Bladder cancer: diagnosis and management. NICE guideline NG2. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng2.

USPSTF 2011. Moyer VA; U.S. Preventive Services Task Force. Screening for bladder cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2011;155(4):246-51. doi: 10.7326/0003-4819-155-4-201108160-00008.

Breast cancer

AHS 2012-BB. Alberta Provincial Breast Tumour Team. Staging investigations for asymptomatic and newly diagnosed breast cancer. Edmonton, Alberta: Alberta Health Services, Cancer Care; 2012.

AHS 2013-FU. Alberta Provincial Breast Tumour Team. Follow-up care for early-stage breast cancer. Edmonton, Alberta: CancerControl Alberta; 2013.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Neoplasie della mammella. Milan, Italy: Associazione Italiana di Oncologia Medica (AIOM); 2015.

ASCO 2012-FU. Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013; 31(7):961-5. doi: 10.1200/JCO.2012.45.9859.

ASCO 2015-M+. Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2015; 33(24):2695-704. doi: 10.1200/JCO.2015.61.1459.

CECOG 2009. Beslija S, Bonneterre J, Burstein HJ, et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol. 2009; 20(11):1771-85. doi: 10.1093/annonc/mdp261.

ESMO 2013-EarlyBC. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi7-23. doi: 10.1093/annonc/mdt284.

ESMO 2014-ABC. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol. 2014;25(10):1871-88. doi: 10.1093/annonc/mdu385.

EUSOMA 2014-Young. Partridge AH, Pagani O, Abulkhair O, et al. First international consensus guidelines for breast cancer in young women (BCY1). Breast. 2014;23(3):209-20. doi: 10.1016/j.breast.2014.03.011.

NCCN 2014-Diagn. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast cancer screening and diagnosis, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast cancer, version 1.2016. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NHMRC 2010. National Breast and Ovarian Cancer Centre. Recommendations for follow-up of women with early breast cancer. Surry Hills, NSW: National Breast and Ovarian Cancer Centre; 2010. https://guidelines.canceraustralia.gov.au/guidelines/early_breast_cancer.

NICE 2012-EarlyBC. National Collaborating Centre for Cancer. Early and locally advanced breast cancer. Diagnosis and treatment. London, UK: National Institute for Health and Clinical Excellence (NICE); 2009. https://www.nice.org.uk/guidance/cg80. Validity verification: 2012.

NICE 2014-M+. National Collaborating Centre for Cancer. Advanced breast cancer: diagnosis and treatment. London, UK: National Institute for Health and Clinical Excellence (NICE); 2009. https://www.nice.org.uk/guidance/cg81. Validity verification: 2014.

NICE 2015-SC. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

Cervical cancer

AHS 2013. Alberta Provincial Gynecologic Oncology Team. Cancer of the uterine cervix. Edmonton, Alberta: CancerControl Alberta; 2013.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Neoplasie dell'utero: endometrio e cervice. Milan, Italy: Associazione Italiana di Oncologia Medica (AIOM); 2015.

CCO 2015. Elit L, Fyles A, Fung-Kee-Fung M, Oliver T; Gynecology Cancer Disease Site Group. Follow-up for women after treatment for cervical cancer. Toronto, ON: Cancer Care Ontario; 2009. Validity verification: 2015.

ESMO 2012. Colombo N, Carinelli S, Colombo A, Marini C, Rollo D, Sessa C; ESMO Guidelines Working Group. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 (Suppl 7):vii27-32.

NACB 2010. Sturgeon CM, Duffy MJ, Hofmann BR, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. Clin Chem. 2010; 56(6):e1-48. doi: 10.1373/clinchem.2009.133124.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Cervical cancer, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

Endometrial cancer

ACN 2011. Cancer Council Australia Endometrial Cancer Guidelines Working Party. Clinical practice guidelines for the treatment and management of endometrial cancer. Sydney: Cancer Council Australia; 2011. http://wiki.cancer.org.au/australia/Guidelines:Endometrial_cancer/Treatment/Early_stage.

AHS 2013. Alberta Provincial Gynecologic Oncology Tumour Team. Endometrial cancer. Edmonton, Alberta: Cancer Control Alberta; 2013.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Neoplasie dell'utero: endometrio e cervice. Milan, Italy: Associazione Italiana di Oncologia Medica (AIOM); 2015.

ESMO 2013. Colombo N, Preti E, Landoni F, et al. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi33-8. doi: 10.1093/annonc/mdt353.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

SGO 2014 (a). SGO Clinical Practice Endometrial Cancer Working Group, Burke WM, Orr J, Leitao M, et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol. 2014; 134(2):385-92. doi: 10.1016/j.ygyno.2014.05.018.

SGO 2014 (b). SGO Clinical Practice Endometrial Cancer Working Group, Burke WM, Orr J, Leitao M, et al. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol. 2014; 134(2):393-402. doi: 10.1016/j.ygyno.2014.06.003.

Ovarian cancer

ACOG 2009-HR. American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2009; 113(4):957-66. doi: 10.1097/AOG.0b013e3181a106d4.

ACOG 2011-EC. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. Obstet Gynecol. 2011; 117(3):742-6. doi: 10.1097/AOG.0b013e31821477db.

ACOG 2013-AM. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Management of adnexal masses. Obstet Gynecol. 2007; 110(1):201-14. Validity verification: 2013.

AHS 2011-HR. Alberta Provincial Breast Tumour Team. Risk reduction and surveillance strategies for individuals at high genetic risk for breast and ovarian cancer. Edmonton, Alberta: Alberta Health Services, Cancer Care; 2011.

AHS 2013-EC. Alberta Provincial Gynecologic Oncology Tumour Team. Epithelial ovarian, fallopian tube, and primary peritoneal cancer. Edmonton, Alberta: CancerControl Alberta; 2013.

AHS 2013-GCT. Alberta Provincial Gynecologic Oncology Tumour Team. Ovarian germ cell tumours. Edmonton, Alberta: CancerControl Alberta; 2013.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Tumori dell'ovaio. Milan, Italy: Associazione Italiana di Oncologia Medica (AIOM); 2015.

BSGE 2011. Royal College of Obstetricians and Gynaecologists (RCOG), British Society of Gynaecological Endoscopy (BSGE). Management of suspected ovarian masses in premenopausal women. London, UK: Royal College of Obstetricians and Gynaecologists; 2011. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg62/.

CCO 2011. Fung Kee Fung M, Kennedy E, Francis J, Mackay H; Gynecologic Cancer Disease Site Group. Optimal chemotherapy for recurrent ovarian cancer. Toronto, ON: Cancer Care Ontario; 2011.

CCO 2011-AM. Dodge J, Covens A, Lacchetti C, et al. Management of a suspicious adnexal mass. Toronto, ON: Cancer Care Ontario; 2011.

ESGO 2011. Morice P, Denschlag D, Rodolakis A, et al. Recommendations of the Fertility Task Force of the European Society of Gynecologic Oncology about the conservative management of ovarian malignant tumors. Int J Gynecol Cancer. 2011; 21(5):951-63. doi: 10.1097/IGC.0b013e31821bec6b.

ESGO 2012-FU. Verheijen RH, Cibula D, Zola P, Reed N; Council of the European Society of Gynaecologic Oncology. Cancer antigen 125: lost to follow-up?: a European Society of Gynaecological Oncology consensus statement. Int J Gynecol Cancer. 2012; 22(1):170-4. doi: 10.1097/IGC.0b013e318226c636.

ESMO 2012-GCT. Colombo N, Peiretti M, Garbi A, et al. Non-epithelial ovarian cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 (Suppl 7):vii20-6.

ESMO 2013-EC. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi24-32. doi: 10.1093/annonc/mdt333.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Ovarian cancer. Version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network (NCCN); 2015.

NCCN 2015-HR. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast and ovarian, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NHMRC 2011-HR. Cancer Australia. Recommendations for management of women at high risk of ovarian cancer. Surry Hills, NSW: Cancer Australia; 2011. https://canceraustralia.gov.au/publications-and-resources/clinical-practice-guidelines/recommendations-management-women-high-risk-ovarian-cancer.

NHMRC 2012. Cancer Australia. Follow-up of women with epithelial ovarian cancer. Surry Hills, NSW: Cancer Australia; 2012. https://www.clinicalguidelines.gov.au/portal/2172/follow-women-epithelial-ovarian-cancer.

NICE 2011-EC. National Collaborating Centre for Cancer. Ovarian cancer. The recognition and initial management of ovarian cancer. London, UK: National Institute for Health and Clinical Excellence (NICE); 2011. http://www.nice.org.uk/guidance/cg122.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

SIGN 2013-EC. Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer. A national clinical guideline. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network (SIGN); 2013.

USPSTF 2012. Moyer VA; U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2012; 157(12):900-4. doi:10.7326/0003-4819-157-11-201212040-00539.

Prostate cancer

ACS 2014. Skolarus TA, Wolf AM, Erb NL, et al. American Cancer Society prostate cancer survivorship care guidelines. CA Cancer J Clin. 2014; 64(4):225-49. doi: 10.3322/caac.21234.

AHS 2013. Alberta Provincial Genitourinary Tumour Team. Prostate cancer. Edmonton, Alberta: CancerControl Alberta; 2013.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Linee guida carcinoma della prostata. Milan: AIOM; 2015.

APC 2015. Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol. 2015; 26(8):1589-604. doi: 10.1093/annonc/mdv257.

ASCO 2012. Basch E, Oliver TK, Vickers A, et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology provisional clinical opinion. J Clin Oncol. 2012; 30(24):3020-5. doi: 10.1200/JCO.2012.43.3441.

ASCO 2014. Freedland SJ, Rumble RB, Finelli A, et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2014; 32(34):3892-8. doi: 10.1200/JCO.2014.58.8525.

ASCO 2015. Resnick MJ, Lacchetti C, Bergman J, et al. Prostate cancer survivorship care guideline: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2015; 33(9):1078-85. doi: 10.1200/JCO.2014.60.2557.

ASCO-CCO 2014. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014; 32(30):3436-48. doi: 10.1200/JCO.2013.54.8404.

AUA 2011. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. Linthicum, MD: American Urological Association Education and Research, Inc.; 2007. http://www.auanet.org/education/guidelines/prostate-cancer.cfm. Validity verification: 2011.

AUA 2013. Carroll P, Albertsen PC, Greene K, et al. PSA testing for the pretreatment staging and posttreatment management of prostate cancer: 2013 revision of 2009 best practice statement. Linthicum, MD: American Urological Associa-

tion Education and Research, Inc.; 2013.

AUA 2013-ED. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. Linthicum, MD: American Urological Association Education and Research, Inc.; 2013. http://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm.

AUA 2015. Cookson MS, Roth BJ, Dahm P, et al. Castration-resistant prostate cancer: AUA guideline. Linthicum, MD: American Urological Association Education and Research, Inc.; 2015. http://www.auanet.org/education/guidelines/castration-resistant-prostate-cancer.cfm.

AUA-ASTRO 2013. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol. 2013; 190(2):441-9. doi: 10.1016/j.juro.2013.05.032.

CCO 2010. Chin J, Srigley J, Mayhew LA, et al. Guideline for optimization of surgical and pathological quality performance for radical prostatectomy in prostate cancer management. Toronto, ON: Cancer Care Ontario; 2008. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13952. Validity verification: 2010.

CCO 2012-BT. Rodrigues G, Yao X, Loblaw A, Brundage M, Chin J, Genitourinary Cancer Disease Site Group. Low-dose rate brachytherapy for patients with low- or intermediate-risk prostate cancer. Toronto, ON: Cancer Care Ontario; 2012.

CCO 2014-AS. Morash C, Tey R, Agbassi C, et al. Active surveillance for the management of localized prostate cancer. Toronto, ON: Cancer Care Ontario; 2014.

CCO 2015. Young S, Bansal P, Vella E, et al. Referral of suspected prostate cancer by family physicians and other primary care providers. Program in Evidence-Based Care Evidence-Based Guideline No. 24-3. Toronto, ON: Cancer Care Ontario; 2012. Validity verification: 2015.

CTFPHC 2014. Canadian Task Force on Preventive Health Care, Bell N, Connor Gorber S, Shane A, et al. Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ. 2014; 186(16):1225-34. doi: 10.1503/cmaj.140703.

CUA 2011. Izawa JI, Klotz L, Siemens DR, et al. Prostate cancer screening: Canadian guidelines 2011. Can Urol Assoc J. 2011; 5(4):235-40. doi: 10.5489/cuaj.11134.

EAU 2015. Mottet N, Bellmunt J, Briers E, et al. Guidelines on prostate cancer. Arnhem, Netherlands: European Association of Urology; 2015.

EGAPP 2014. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: does PCA3 testing for the diagnosis and management of prostate cancer improve patient health outcomes? Genet Med. 2014; 16(4):338-46. doi: 10.1038/gim.2013.141.

ESMO 2013. Horwich A, Parker C, de Reijke T, Kataja V; ESMO Guidelines Working Group. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi106-14. doi: 10.1093/annonc/mdt208.

GEC-ESTRO 2013. Hoskin PJ, Colombo A, Henry A, et al. GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol. 2013; 107(3):325-32. doi: 10.1016/j.radonc.2013.05.002.

NCCN 2014. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate cancer early detection, version 1.2014. Fort Washington, PA: National Comprehensive Cancer Network; 2014.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate Cancer. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2014. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. London, UK: National Institute for Health and Care Excellence (NICE); 2014. http://www.nice.org.uk/guidance/cg175.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. NICE guideline NG12. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

NICE 2015-PCA3. National Institute for Health and Care Excellence (NICE). Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index. London, UK: National Institute for Health and Care Excellence (NICE); 2015. https://www.nice.org.uk/guidance/dg17.

SIOG 2014. Droz JP, Aapro M, Balducci L, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol. 2014; 15(9):e404-14. doi: 10.1016/S1470-2045(14)70018-X.

SIUrO 2013. Bertaccini A, Fandella A, Pappagallo GL, et al. Italian Prostate Biopsies Group: update guidelines' compendium. Bologna, Italy: Società Italiana Urologia Oncologica; 2013. http://www.siuro.it/it/eventi/italian-prostate-biopsies-group-update-guidelines-compendium.

SOGUG 2012. Climent MA, Piulats JM, Sánchez-Hernández A, et al. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. Crit Rev Oncol Hematol. 2012; 83(3):341-52. doi: 10.1016/j.critrevonc.2012.01.002.

UMHS 2012. University of Michigan Health System. Cancer screening. Ann Arbor, MI: University of Michigan Health System; 2012. http://www.med.umich.edu/1info/FHP/practiceguides/adult_cancer.html.

USPSTF 2012. Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012; 157(2):120-34. doi: 10.7326/0003-4819-157-2-201207170-00459.

Renal cancer

ACCC 2012. Urological Tumours National Working Group. Renal cell carcinoma - Version: 2.0. Utrecht, Netherlands: Association of Comprehensive Cancer Centres; 2010. http://www.oncoline.nl/renal-cell-carcinoma. Validity verification: 2012.

AHS 2012. Alberta Provincial Genitourinary Tumour Team. Renal cell carcinoma. Edmonton, Alberta: Alberta Health Services, Cancer Care; 2012.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Tumori del rene. Milan, Italy: Associazione Italiana di

Oncologia Medica (AIOM); 2015.

AUA 2013. Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. Linthicum, MD: American Urological Association Education and Research, Inc.; 2013.

EAU 2015. Ljungberg B, Bensalah K, Bex A, et al. Guidelines on renal cell carcinoma. Arnhem, Netherlands: European Association of Urology; 2015.

ESMO 2014. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 (Suppl 3):iii49-56. doi: 10.1093/annonc/mdu259.

ICUD-EAU 2011. Kirkali Z, Mulders P. Kidney Cancer Edition 2011: 1st EAU-ICUD International Consultation on Kidney Cancer Barcelona--2010. Paris, France: Edition 21; 2011. http://www.icud.info/kidneycancer.html.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Kidney cancer, version 3.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

SOGUG 2014. García Del Muro X, Gallardo E, García Carbonero I, et al. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with renal cell carcinoma. Cancer Chemother Pharmacol. 2014; 73(6):1095-107. doi: 10.1007/s00280-014-2413-0.

Testicular cancer

AHS 2013. Alberta Provincial Genitourinary Tumour Team. Testicular germ cell tumours. Edmonton, Alberta: CancerControl Alberta; 2013.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Tumore del testicolo. Milan, Italy: Associazione Italiana di Oncologia Medica (AIOM); 2015.

ASCO 2010. Gilligan TD, Seidenfeld J, Basch EM, et al. American Society of Clinical Oncology clinical practice guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol. 2010; 28(20):3388-404. doi: 10.1200/JCO.2009.26.4481.

CCO 2014. Chung P, Mayhew LA, Warde P, Winquist E, Lukka H; members of the Genitourinary Cancer Disease Site Group. Management of stage I seminoma. Lock M and Brown J, reviewers. Toronto, ON: Cancer Care Ontario; 2008. Validity verification: 2014.

EAU 2015. Albers P, Albrecht W, Algaba F, et al. Guidelines on testicular cancer. Arnhem, Netherlands: European Association of Urology; 2015.

EGCCCG 2013. Beyer J, Albers P, Altena R, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European Consensus Conference on Diagnosis and Treatment of Germ-Cell Cancer. Ann Oncol. 2013; 24(4):878-88. doi: 10.1093/annonc/mds579.

ESMO 2013. Oldenburg J, Fosså SD, Nuver J, et al. Testicular seminoma and non-seminoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 (Suppl 6):vi125-32. doi: 10.1093/annonc/mdt304.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Testicular cancer, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

SIGN 2011. Scottish Intercollegiate Guidelines Network. Management of adult testicular germ cell tumours. A national clinical guideline. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2011. http://www.sign.ac.uk/guidelines/fulltext/124/index.html.

SIU-ICUD-UICC 2011. Stephenson AJ, Aprikian AG, Gilligan TD, et al. Management of low-stage nonseminomatous germ cell tumors of testis: SIU/ICUD Consensus Meeting on Germ Cell Tumors (GCT), Shanghai 2009. Urology. 2011;78(4 Suppl):S444-55. doi: 10.1016/j.urology.2011.02.030.

USPSTF 2011. U.S. Preventive Services Task Force. Screening for testicular cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2011; 154(7):483-6. doi: 10.7326/0003-4819-154-7-201104050-00006.

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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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Contributions of panel members
[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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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.

References

1. Gion M, Trevisiol C, Rainato G, Fabricio ASC. Marcatori circolanti in oncologia: guida all'uso clinico appropriato. I Quaderni di Monitor. Roma: AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali 2016.
2. Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Circulating tumor markers: a guide to their appropriate clinical use. Comparative summary of recommendations from clinical practice guidelines (Part 1). Int J Biol Markers. 2016;31:e332-e367.
3. Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Circulating tumor markers: a guide to their appropriate clinical use. Comparative summary of recommendations from clinical practice guidelines (Part 2). Int J Biol Markers. 2017;32:e1-e52.
4. Gion M. Need for knowledge translation to improve tumor marker application. Int J Biol Markers. 2016;31:e331.
5. IOM (Institute of Medicine). Clinical practice guidelines we can trust. Washington, DC: The National Academies Press 2011.

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)

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)
	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)

Head and neck cancer

ADA 2010. Rethman MP, Carpenter W, Cohen EE, et al. Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. J Am Dent Assoc. 2010; 141(5):509-20.

AHS 2013. Alberta Provincial Head and Neck Tumour Team. Nasopharyngeal cancer treatment. Edmonton, Alberta: CancerControl Alberta; 2013.

AIOCC-AIRO-AIOM 2012. AIOCC, AIOM, Gruppo di Studio AIRO Testa-collo. Tumori della testa e collo: algoritmi diagnostico-terapeutici AIOCC-AIRO-AIOM – versione 2 (aprile) 2012. www.radioterapiaitalia.it.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Tumori della testa e del collo. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

CCO 2009. Gilbert R, Devries-Aboud M, Winquist E, Waldron J, McQuestion M; Head and Neck Disease Site Group. The management of head and neck cancer in Ontario. Toronto, ON: Cancer Care Ontario; 2009.

ESMO-EHNS-ESTRO 2010-SCC. Grégoire V, Lefebvre JL, Licitra L, Felip E; EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21(Suppl 5):v184-6. doi: 10.1093/annonc/mdq185.

ESMO-EHNS-ESTRO 2012-NPC. Chan AT, Grégoire V, Lefebvre JL, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 ;23(Suppl 7):vii83-5.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Head and neck cancers, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

USPSTF 2013. Moyer VA; U.S. Preventive Services Task Force. Screening for oral cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014 ;160(1):55-60. doi: 10.7326/M13-2568.

Lung cancer

ACCP 2013. American College of Chest Physicians. Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2013;143(5_suppl):e1S-e512S. http://journal.publications.chestnet.org/issue.aspx?journalid=99&issueid=926876&direction=P.

AHS 2012-NSCLC.s3. Alberta Provincial Thoracic Tumour Team. Non-small cell lung cancer stage III. Edmonton, Alberta: Alberta Health Services, Cancer Care; 2012.

AHS 2012-SCLC.es. Alberta Provincial Thoracic Tumour Team. Small cell lung cancer - extensive stage. Edmonton, Alberta: CancerControl Alberta; 2012.

AHS 2012-SCLC.ls. Alberta Provincial Thoracic Tumour Team. Small cell lung cancer - limited stage. Edmonton, Alberta: CancerControl Alberta; 2012.

AHS 2013-NSCLC.s4. Alberta Provincial Thoracic Tumour Team. Non-small cell lung cancer stage IV. Edmonton, Alberta: CancerControl Alberta; 2013.

AHS 2014-NSCLC.s1. Alberta Provincial Thoracic Tumour Team. Non small cell lung cancer stage I. Edmonton, Alberta: Alberta Health Services, Cancer Care; 2014.

AHS 2014-NSCLC.s2. Alberta Provincial Thoracic Tumour Team. Non-small cell lung cancer stage II. Edmonton, Alberta: Alberta Health Services, Cancer Care; 2014.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Neoplasie del polmone. Milano, IT: Associazione Italiana di Oncologia Medica (AIOM); 2015.

AIOT 2012-NSCLC. Gridelli C, de Marinis F, Di Maio M, et al. Maintenance treatment of advanced non-small-cell lung cancer: results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. Lung Cancer. 2012; 76(3):269-79. doi: 10.1016/j.lungcan.2011.12.011.

ASCO 2015-NSCLC.s4. Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015; 33(30):3488-515. doi: 10.1200/JCO.2015.62.1342.

ASCO 2015-SCLC. Rudin CM, Ismaila N, Hann CL, et al. Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline. J Clin Oncol. 2015; 33(34):4106-11. doi: 10.1200/JCO.2015.63.7918.

BTS-SCTS 2010. Lim E, Baldwin D, Beckles M, et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010;65(Suppl 3):iii1-27. doi: 10.1136/thx.2010.145938.

CCO 2014-dia. Del Giudice L, Young S, Vella E, et al. Referral of suspected lung cancer by family physicians and other primary care providers. Toronto, ON: Cancer Care Ontario; 2011. Validity verification: 2014.

CCO 2014-fu. Ung YC, Souter LH, Darling G, et al. Follow-up and surveillance of curatively treated lung cancer patients. Toronto, ON: Cancer Care Ontario (CCO); 2014.

CCO 2014-NSCLC.m+. Lung Cancer Disease Site Group (DSG). First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer. Goffin J, Poon R. Reviewers. Toronto, ON: Cancer Care Ontario; 2010. Validity verification: 2014.

CECOG 2012-NSCLC. Brodowicz T, Ciuleanu T, Crawford J, et al. Third CECOG consensus on the systemic treatment of

non-small-cell lung cancer. Ann Oncol. 2012; 23(5):1223-9. doi: 10.1093/annonc/mdr381.

ELCWP 2012. Berghmans T, Pasleau F, Paesmans M, et al. Surrogate markers predicting overall survival for lung cancer: ELCWP recommendations. Eur Respir J. 2012; 39(1):9-28. doi: 10.1183/09031936.00190310.

ESMO 2013-NSCLC. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24(Suppl 6):vi89-98. doi: 10.1093/annonc/mdt241.

ESMO 2014 (a). Vansteenkiste J, Crinò L, Dooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014; 25(8):1462-74. doi: 10.1093/annonc/mdu089.

ESMO 2014 (b). Eberhardt WE, De Ruysscher D, Weder W, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015;26(8):1573-88. doi: 10.1093/annonc/mdv187.

ESMO 2014 (c). Besse B, Adjei A, Baas P, Meldgaard P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol. 2014;25(8):1475-84. doi: 10.1093/annonc/mdu123.

ESMO 2014 (d). Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO Consensus Conference on Lung Cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol. 2014;25(9):1681-90. doi: 10.1093/annonc/mdu145.

ESMO 2014-NSCLC.m+. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25(Suppl 3):iii27-39. doi: 10.1093/annonc/mdu199.

ESMO-JSMO 2013-SCLC. Früh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24(Suppl 6):vi99-105. doi: 10.1093/annonc/mdt178.

FS 2013. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology. 2013; 266(1):304-17. doi: 10.1148/radiol.12120628.

NCCN 2015-NSCLC. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Non-small cell lung cancer, version 5.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NCCN 2015-SCLC. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Small cell lung cancer, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NCCN 2015-scr. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Lung cancer screening, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2011. National Collaborating Centre for Cancer. Lung cancer. The diagnosis and treatment of lung cancer. London, UK: National Institute for Health and Clinical Excellence (NICE); 2011. https://www.nice.org.uk/guidance/cg121.

NICE 2015-dia. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

SIGN 2014. Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer. A national clinical guideline. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network (SIGN); 2014. http://www.sign.ac.uk/guidelines/fulltext/137/index.html.

USPSTF 2014-scr. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 160(5):330-8. doi: 10.7326/M13-2771.

Melanoma

ACCC 2012. Dutch Working Group on Melanoma. Melanoma - version: 2.0. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres; 2012.

AHS 2013-FU. Alberta Provincial Cutaneous Tumour Team. Referral and follow-up surveillance of cutaneous melanoma. Edmonton, Alberta: CancerControl Alberta; 2013.

AHS 2013-IV. Alberta Provincial Cutaneous Tumour Team. Management of resectable stage IV primary cutaneous melanoma without nodal disease. Edmonton, Alberta: CancerControl Alberta; 2013. http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu009-resectable-stage-IV-disease.pdf.

AHS 2013-PROP. Alberta Provincial Cutaneous Tumour Team. Preoperative and pretreatment investigations for malignant melanoma. Edmonton, Alberta: CancerControl Alberta; 2013.

AHS 2015-URM. Alberta Provincial Cutaneous Tumour Team. Systemic therapy for unresectable stage III or metastatic cutaneous melanoma. Edmonton, AB: CancerControl Alberta; 2015.

AIOM 2015. Associazione Italiana di Oncologia Medica (AIOM). Melanoma. Milano, IT: AIOM; 2015.

BAD 2010. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised U.K. guidelines for the management of cutaneous melanoma 2010. Br J Dermatol. 2010; 163(2):238-56. doi: 10.1111/j.1365-2133.2010.09883.x.

EDF-EADO-EORTC 2012. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline--Update 2012. Eur J Cancer. 2012; 48(15):2375-90. doi: 10.1016/j.ejca.2012.06.013.

ESMO 2012. Dummer R, Hauschild A, Guggenheim M, et al. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23(Suppl 7):vii86-91.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Melanoma, version 3.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015-ME. National Collaborating Centre for Cancer. Melanoma: assessment and management. London, UK: National Institute for Health and Care Excellence (NICE); 2015. http://www.nice.org.uk/guidance/ng14.

NICE 2015-SC. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

SIDeMaST 2011. Società Italiana di Dermatologia Medica, Chirurgica, Estetica e delle Malattie Sessualmente Trasmesse. Linee guida e raccomandazioni SIDeMaST. Pisa: Pacini Editore; 2011.

USPSTF 2009. U.S. Preventive Services Task Force. Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009; 150(3):188-93. http://www.uspreventiveservicestaskforce.org/uspstf/uspsskca.htm.

Mesothelioma

AHS 2012. Alberta Provincial Thoracic Malignancies Tumour Team. Malignant pleural mesothelioma. Edmonton, Alberta: CancerControl Alberta; 2012.

AHS 2014-MPE. Alberta Provincial Lung Tumour Team. Malignant pleural effusion. Edmonton, Alberta: CancerControl Alberta; 2014.

BTS 2010-MPE. BTS Pleural Disease Guideline Group. British Thoracic Society pleural disease guideline 2010. Thorax. 2010; 65(Suppl 2):ii1-76.

ERS-ESTS 2010. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J. 2010; 35(3):479-95. doi: 10.1183/09031936.00063109.

ESMO 2010. Stahel RA, Weder W, Lievens Y, Felip E; ESMO Guidelines Working Group. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21(Suppl 5):v126-8. doi: 10.1093/annonc/mdq173.

imp 2013. Pinto C, Novello S, Torri V, et al. Second Italian consensus conference on malignant pleural mesothelioma: state of the art and recommendations. Cancer Treat Rev. 2013; 39(4):328-39. doi: 10.1016/j.ctrv.2012.11.004.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Malignant pleural mesothelioma, version 1.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NHMRC 2013. Organising Committee. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. Sydney: Asbestos Diseases Research Institute; 2013. http://asbestosresearch.org.au/files/Guidelines_for_the_diagnosis_and_treatment_of_malignant_pleural_mesothelioma.pdf.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

Thyroid cancer, differentiated

AACE-AME-ETAM 2010. Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2010; 16(Suppl 1):1-43. doi: 10.4158/10024.GL.

AIOCC-AIRO-AIOM 2012. AIOCC, AIOM, Gruppo di Studio AIRO Testa-collo. Tumori della testa e collo: algoritmi diagnostico-terapeutici AIOCC-AIRO-AIOM, versione 2 (aprile) 2012. www.radioterapiaitalia.it.

ATA 2009. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19(11):1167-214. doi: 10.1089/thy.2009.0110.

BTA 2014. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014; 81(Suppl 1):1-122. doi: 10.1111/cen.12515.

ESMO 2012. Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23(Suppl 7):vii110-9.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Thyroid carcinoma, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

Thyroid cancer, medullary

AACE-AME-ETAM 2010. Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2010; 16(Suppl 1):1-43. doi: 10.4158/10024.GL.

AIOCC-AIRO-AIOM 2012. AIOCC, AIOM, Gruppo di Studio AIRO Testa-collo. Tumori della testa e collo: algoritmi diagnostico-terapeutici AIOCC-AIRO-AIOM, versione 2 (aprile) 2012. www.radioterapiaitalia.it.

ATA 2015. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015; 25(6):567-610. doi: 10.1089/thy.2014.0335.

BTA 2014. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014; 81(Suppl 1):1-122. doi: 10.1111/cen.12515.

ESMO 2012. Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23(Suppl 7):vii110-9.

NCCN 2015. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Thyroid carcinoma, version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015.

NICE 2015. National Collaborating Centre for Cancer. Suspected cancer: recognition and referral. London, UK: National Institute for Health and Care Excellence; 2015. https://www.nice.org.uk/guidance/ng12.

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