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Circulating tumor markers: a guide to their appropriate clinical use
Comparative summary of recommendations from clinical practice guidelines (PART 1)

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Contributions of panel members

(1) Search and selection of guidelines (WP2);
(2) Appraisal of guidelines through the AGREE II tool (WP3)
(3) Assessment of the rate of utilization of a subset of guidance documents in clinical practice (WP4)
(4) Synthesis of recommendations and other information concerning tumor markers into summary tables (WP5);
(5) Assessment of correctness and completeness of the information summarized in the tables (WP6)

External validation

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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 Message*s 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.

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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 pp. 1-2). 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 excluded. 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).

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TAKE-HOME MESSAGES

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TAKE-HOME MESSAGES - Users' instructions

Definition and target audience

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

Structure

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

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

AGREE evaluation

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

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

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

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

Additional notes

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

Biliary cancer

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**

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Colorectal cancer

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	∅	**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	∅	**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	∅	**2/6** (ASCRS 2012-C, ASCRS 2013-R)	**1/7** (AIOM 2015)
	Recommendations on TMs not available	∅	**3/6** (AGA 2010, NICE 2014, SIGN 2011)	**0/7**
Reassessment after initial curative treatment	Recommendations on TMs not available	∅	**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	∅	**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.
∅ 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
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**

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Esophageal cancer

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	∅	**3/3** (AHS 2014, mep 2012, NHMRC 2014)	**0/0**
Differential diagnosis	Recommendations on TMs not available	∅	**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	∅	**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	∅	**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	∅	**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.
∅ 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

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**

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Hepatocellular carcinoma (HCC)

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	∅	**1/3** (MCC 2011)	**5/6** (AIOM 2015, AIRO 2012, AISF 2013, EASL-EORTC 2012, ESMO 2012)
Differential diagnosis ⚠	Recommendations on TMs not available	∅	**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	∅	**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	∅	**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)
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**

Pancreatic cancer

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	∅	**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**	**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	∅	**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.

∅ 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**

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DETAILED SUMMARY TABLES

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DETAILED SUMMARY TABLES - Users' instructions

Definition and target audience

Detailed Summary Tables are tables prepared for every tumor type which report recommendations and supplementary information from different guidance documents with enough details to be useful for health care providers, policy makers (for potential adaptation to specific settings) and staff developing educational material informed by available evidence.

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

Biliary cancer

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)
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**.

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Colorectal cancer

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 diagnoses	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)

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)

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**.

Esophageal cancer

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**.

Gastric cancer

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**.

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Hepatocellular carcinoma (HCC)

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)
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**.

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Pancreatic cancer

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)
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**.

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