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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

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Take-home messages

USERS' INSTRUCTIONS

Definition and target audience

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

STRUCTURE

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

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

AGREE evaluation

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

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

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

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

Additional notes

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

Examined documents: 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

Examined documents: 22 (12 CPGs, 10 OGDs)

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

Examined documents: 33 (24 CPGs, 9 OGDs)

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.

RENAL CANCER — Detailed summary tables

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**.

Examined documents: 12 (7 CPGs, 5 OGDs)

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.

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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.

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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.

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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

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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.

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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.

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Endometrial cancer

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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.

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