

# American Society of Clinical Oncology Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors

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## A B S T R A C T

### Purpose

To provide recommendations on appropriate uses for serum markers of germ cell tumors (GCTs).

### Methods

Searches of MEDLINE and EMBASE identified relevant studies published in English. Primary outcomes included marker accuracy to predict the impact of marker-based decisions on outcomes. Secondary outcomes included proportions with elevated markers and statistical tests of elevations as prognostic factors. An expert panel developed consensus guidelines based on data from 82 reports.

### Results

No studies directly compared outcomes of decisions with versus without marker assays. The search identified few prospective studies and no randomized controlled trials; most were retrospective series. Because data were lacking on primary outcomes, most Panel recommendations are based on secondary outcomes (relapse rates and time to relapse).

### Recommendations

The Panel recommended against using markers to screen for GCTs, to decide whether orchiectomy is indicated, or to select treatment for patients with cancer of unknown primary. To stage patients with testicular nonseminomas, the Panel recommended measuring three markers ( $\alpha$ -fetoprotein [AFP], human chorionic gonadotropin [hCG], and lactate dehydrogenase [LDH]) before and after orchiectomy and before chemotherapy for those with extragonadal nonseminomas. They also recommended measuring AFP and hCG shortly before retroperitoneal lymph node dissection and at the start of each chemotherapy cycle for nonseminoma, and periodically to monitor for relapse. The Panel recommended measuring postorchiectomy hCG and LDH for patients with seminoma and preorchiectomy elevations. They recommended against using markers to guide or monitor treatment for seminoma or to detect relapse in those treated for stage I. However, they recommended measuring hCG and AFP to monitor for relapse in patients treated for advanced seminoma.

## INTRODUCTION

The American Society of Clinical Oncology (ASCO) previously published evidence-based clinical practice guidelines on uses of tumor markers in breast<sup>1</sup> and GI<sup>2</sup> cancers. Increasing clinical research on biomarkers has led ASCO to initiate an expanded series of guidelines on markers for other malignancies. Each will involve a separate panel that combines expertise on the cancer of interest with expertise on tumor marker development and evaluation. Serum tumor markers (STMs) of germ cell tumors (GCTs) in adult patients was selected as this series' first new topic because of the large volume of publications and the long history of using serum concentrations of human

chorionic gonadotropin (hCG),  $\alpha$ -fetoprotein (AFP), and lactate dehydrogenase (LDH) to guide management decisions for patients with GCT. This systematic review and guideline focuses on these three STMs.

Most GCTs originate in the testes, and they account for approximately 95% of testicular cancers; however, GCTs occasionally originate in extragonadal sites such as the mediastinum or retroperitoneum.<sup>3-6</sup> Histologically, GCTs are divided into seminomas and nonseminomatous germ cell tumors (NSGCTs). Mixed GCTs with seminomatous and nonseminomatous components are considered NSGCTs. Treatment recommendations differ for NSGCTs and pure seminomas.<sup>5-9</sup> Since seminoma cells do not

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produce AFP, concentrations above the normal range may occur in patients with NSGCTs but not in those with pure seminoma. hCG or LDH concentrations above the normal range may occur with any GCT histology.

Although the tumor markers AFP and hCG play a large role in the management of GCTs, they are also produced by numerous other malignancies. Elevations in hCG are commonly seen in a wide variety of carcinomas, including neuroendocrine tumors and cancers of the bladder, kidney, lung, head and neck, GI tract (specifically gastric, pancreatic, biliary, and colorectal cancers), cervix, uterus, and vulva.<sup>10-12</sup> In addition, there are case reports of elevations in hCG in lymphoma and leukemia. Similarly, elevations of AFP are typical of hepatocellular carcinoma and certain benign liver diseases and may be seen in gastric and, rarely, in lung, colon, and pancreatic cancers.<sup>13-15</sup> Hereditary persistence of AFP elevations also has been reported but is rare.<sup>16-18</sup> Elevations in LDH are highly nonspecific and may be found in a vast number of benign and malignant conditions.

Manuals published by the American Joint Committee on Cancer (AJCC)<sup>19</sup> and the International Union Against Cancer (UICC)<sup>20</sup> uniformly incorporate hCG, AFP, and LDH assay results into GCT staging systems. Additionally, STM assay results are a key component of the most frequently used risk stratification system for GCT, developed by the International Germ Cell Cancer Collaborative Group (IGCCCG).<sup>21</sup> However, as with all tumor markers, potential uses of STMs for GCTs may include screening, diagnosis, monitoring during treatment, and surveillance after therapy is completed. This systematic review and guideline addresses each of these potential uses.

## GUIDELINE QUESTIONS

[Note: Questions 3 and 4 are addressed separately for NSGCT (Part I) and seminoma (Part II).]

1. Are STM assays indicated to screen asymptomatic adults without current or prior clinical findings suggestive of GCT?
2. In the following circumstances, are STM assays indicated to diagnose adults clinically suspected to have GCT:
  - A. To help determine need for orchiectomy in patients with a testis abnormality?
  - B. To evaluate cancers of unknown primary (CUP) possibly derived from GCT?
  - C. To evaluate patients presenting with metastatic disease and evidence of a testicular, retroperitoneal, or anterior mediastinal primary tumor?
3. In adult patients undergoing treatment (or observation), are STM assays indicated for the following uses:
  - A. To stage patients and predict prognosis before retroperitoneal lymph node dissection (RPLND), first-line chemotherapy, and/or radiation therapy?
  - B. To predict response to or benefit from treatment?
  - C. To monitor treatment response or progression during or immediately after therapy?
4. In adult patients, are STM assays indicated after presumably definitive therapy is completed for surveillance and routine monitoring to detect asymptomatic recurrence?

## CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, use of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where future research is needed.

ASCO's practice guidelines reflect expert consensus based on clinical evidence and literature available at the time they are written and are intended to assist physicians in clinical decision making and to identify questions and settings for further research. Because of the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline was submitted for publication. Guidelines are not continually updated and may not reflect the most recent evidence. Guidelines address only the topics specifically identified in the guideline and are not applicable to interventions, diseases, or stages of disease not specifically identified. Guidelines cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. ASCO guidelines describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO's guidelines, or for any errors or omissions.

## METHODS

### Panel Composition

The ASCO Clinical Practice Guidelines Committee convened an Expert Panel (hereafter referred to as the Panel) consisting of experts in clinical medicine and research methods relevant to STM use in diagnosis and management of patients with GCTs. The experts' fields included medical oncology, urology, development and use of tumor marker assays, health services research, epidemiology, and biostatistics. The Panel also included a patient representative. Panel members are listed in Appendix A.

## Overall Literature Review and Analysis

**Literature search strategy.** The systematic review for this guideline was conducted in collaboration with Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The MEDLINE and EMBASE databases were searched for relevant evidence published from 1990 through the end of 2008. Electronic searches were limited to articles published after 1990 since practice patterns (eg, risk stratification) and chemotherapy regimens changed substantially in the 1980s, making studies published before 1990 less relevant to current patient management and treatment decisions. Search terms included "germ cell tumors," "alpha-fetoprotein," "human chorionic gonadotropin," "lactate dehydrogenase," "cancer of unknown primary," and "testicular mass." Appendices B1 and B2 show the specific search strategy used with each database. Other GCT markers were omitted from the search since Panel members agreed early in their deliberations that evidence was unavailable to support routine use of any others. One reviewer selected articles for full-copy retrieval, and those sources' reference lists were searched for other relevant reports. Panel members provided additional references from personal files, particularly on points for which electronic searches failed to identify any relevant evidence. In these instances, studies published before 1990 were not excluded.

**Inclusion and exclusion criteria.** Articles were selected for inclusion in the systematic review if they were fully published English language reports of GCT marker assay results (AFP, hCG, and/or LDH) and outcomes for adult human patients from randomized controlled trials (RCTs), systematic reviews of RCTs, meta-analyses, clinical practice guidelines, prospective or retrospective cohort studies, case-control studies, or case series. Meeting abstracts, letters, commentaries, editorials, case reports, nonsystematic (narrative) reviews, studies with sample sizes smaller than 50 patients, and studies limited to pediatric GCTs were excluded. Studies also were excluded if marker assay results and outcomes for patients with seminoma were not reported separately from results and outcomes for those with NSGCT. Exclusion for sample sizes smaller than 50 patients did not apply to references provided by Panel members from personal files when electronic searches failed to identify any other relevant evidence.

**Data extraction.** Primary outcome measures of interest included overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), relapse-free survival (RFS), event-free survival (EFS), and progression-free survival (PFS), treatment-related toxicities, quality of life, and cost effectiveness of care. Secondary outcomes or data elements of interest included the proportion of patients with marker elevations, results of univariate and/or multivariate analyses of marker elevations as prognostic factors, rates of concordance and discordance between different markers in the same patients, and assay performance characteristics (sensitivity, specificity, and positive and negative predictive values). Data were extracted directly into evidence tables (Data Supplement Tables DS1-DS13) by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved by discussion and by consultation with Panel co-chairs if necessary.

## Consensus Development Based on Evidence

The entire Panel met once to review results of the systematic review and formulate guideline recommendations; additional work was completed by electronic review of drafts. All members of the Panel participated in preparation and review of the draft guideline docu-

ment. The guideline was submitted to *Journal of Clinical Oncology* for peer review. Feedback was also solicited from external reviewers. The content of the guideline and the manuscript were reviewed and approved by ASCO's Clinical Practice Guidelines Committee and by the Board of Directors before publication.

## Guideline and Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at [www.asco.org/guidelinescoi](http://www.asco.org/guidelinescoi)). Members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any of these relationships. Disclosure information for each member of the Panel is published adjunct to this guideline.

## Revision Dates

ASCO guidelines are normally updated every 3 years. At annual intervals, the Panel co-chairs and two Panel members designated by the co-chairs will determine the need for revisions to the guidelines on the basis of an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revised guidelines to the Clinical Practice Guidelines Committee and the ASCO Board for review and approval.

## RESULTS

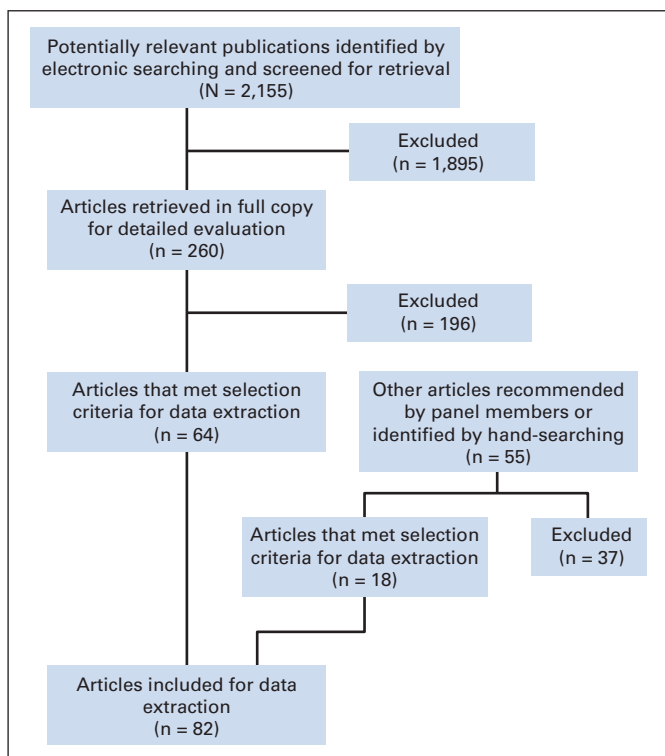
### Literature Search

Electronic searches of MEDLINE and EMBASE identified a total of 2,155 unique records. Review of titles and abstracts eliminated 1,895 as either not relevant to any of the guideline's clinical questions or not meeting study selection criteria (Fig 1). Of 260 articles selected for full-text retrieval, 64 met study selection criteria for data extraction. Hand-searching of reference lists from included articles and recommendations from Panel members identified 55 additional articles retrieved in full text, of which 18 met study selection criteria.

Of the 82 articles extracted, none addressed guideline question 1 (STM assays for screening), five addressed question 2 (STM assays for diagnosis, all on CUP), 58 addressed question 3 (STM assays during treatment; 42 on NSGCT, 15 on seminoma, and one with separate data on each), and 21 addressed question 4 (STM assays for surveillance after treatment; 11 on seminoma, eight on NSGCT, and two with separate data on each). Two articles reported data relevant to both questions 3 and 4. Evidence extracted from the 82 reports that met selection criteria is listed in Data Supplement Tables DS1-DS13.

### Study Quality and Limitations of the Literature

Evidence was unavailable from studies that directly compared outcomes of patient management decisions based on marker assay results with decisions made without knowledge of marker levels or



**Fig 1.** Exclusions and inclusions of publications identified for this systematic review.

their changes over time or with treatment. Consequently, it remains unknown whether measuring STM concentrations and using assay results to guide treatment decisions and management of patients with a GCT improves their survival. The literature search identified few prospective studies and no RCTs. Additionally, for many uses of STM assay results, few studies reported any of the primary outcomes specified for this systematic review. Pooled data analysis (meta-analysis) was not possible because of variability across studies with respect to outcomes reported and their definitions. Given these evidence gaps, most recommendations in this guideline were, of necessity, based on Panel members' consideration and judgment of secondary (surrogate) outcomes such as rates of relapse in subsets with versus without a marker elevation and/or the time to detection of relapse.

The Panel's rationale for using secondary (surrogate) outcomes as the basis for clinical recommendations rests largely on the following points. First, GCTs are relatively rare malignancies, with approximately 7,200 new cases per year in the United States.<sup>3,4,6</sup> Modern first-line therapy cures the overwhelming majority of patients (approximately 90% overall, > 95% of those diagnosed in stages I or II, and > 80% of those diagnosed in an advanced stage). Second-line therapies also cure many patients with relapsed disease, particularly those relapsing after treatment for early-stage disease. Thus, there are few deaths to power survival end points for studies of different surveillance strategies. Multivariate analyses (eg, the IGCCCG study<sup>21</sup>) show that high-magnitude STM elevations predict poor OS. There is also good evidence (see Background on STMs for GCTs) that in patients with an advanced GCT that is producing one or more STMs, high elevations reflect high disease burden. Although direct evidence is unavailable, it seems reasonable to assume that treatment for advanced or disseminated GCTs is most effective at the lowest possible

disease burden. Additionally, measuring STMs in serum samples from the small population of patients treated for GCT each year is noninvasive and relatively inexpensive. Given that there is no apparent harm from measuring STMs (other than the modest costs), and given that GCTs are rare and curable, it seems impractical to require randomized studies in which one arm has STMs checked less frequently or not at all.

### Other Guidelines and Consensus Statements

The European Association of Urology,<sup>22</sup> the European Society of Medical Oncology,<sup>8,9</sup> the National Comprehensive Cancer Network,<sup>6</sup> and the European Germ Cell Cancer Consensus Group<sup>5,7</sup> have published guidelines or consensus statements on managing testicular cancer and extragonadal GCTs. Additionally, the National Academy of Clinical Biochemistry (NACB) has published a laboratory medicine practice guideline on analytic methods for tumor markers and their use in testicular (and other) cancers<sup>23</sup>; PEBC of Cancer Care Ontario has published separate guidelines on management of stage I disease in patients with seminoma<sup>24</sup> or NSGCT,<sup>25</sup> and a group from the United Kingdom has published evidence-based pragmatic guidelines for follow-up of testicular cancer.<sup>26</sup> The Panel has evaluated these sources' recommendations on uses of STM assays and found them to be generally consistent with recommendations in this ASCO clinical practice guideline.

### Background on STMs for GCTs

Over the past three or more decades, many investigators have reported detecting elevated serum concentrations of hCG,<sup>27-34</sup> AFP,<sup>29-34</sup> and LDH<sup>35-39</sup> in patients with GCTs. Studies that used serial determinations to guide treatment decisions for patients with GCTs<sup>40,41</sup> and that evaluated STM elevations as prognostic factors for these tumors<sup>42-45</sup> also were reported 25 to 30 years ago. Multiple reviews<sup>11,12,23,46-50</sup> have been published that summarize contributions of basic and clinical scientists to knowledge of STMs for GCT. The brief summary included here draws on these sources to highlight key information for this guideline (Table 1). Additionally, Table 2 provides more detailed information on the causes, pathophysiology, and management of false-positive test results, operationally defined as marker elevations that are unrelated to recurrence or progression of GCTs.

**hCG.** hCG is a glycoprotein hormone secreted by the placenta during pregnancy; it has a molecular weight of 38 kDa and consists of two noncovalently bound subunits:  $\alpha$  (13 kDa) and  $\beta$  (28 kDa).<sup>11,12,23,46-49</sup> The  $\alpha$  subunit is common to three other glycoprotein hormones: luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. Although  $\beta$ -hCG shares substantial sequence homology (approximately 80%) with the  $\beta$  subunits of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone, the C-terminal 24 amino acids comprise a unique peptide sequence that has been used to generate antibodies specific to  $\beta$ -hCG. Multiple isoforms of  $\beta$ -hCG differing primarily in the extent of glycosylation have been identified,<sup>12,23</sup> and assays are available to measure these isoforms separately or in total.<sup>12</sup>

Immunohistology studies on tumor samples demonstrated that  $\beta$ -hCG is present in syncytiotrophoblastic cells of many testicular GCTs but is more common among patients with NSGCT than among those with seminoma.<sup>31,33,51-55</sup> Some of these studies also correlated tissue staining with serum elevations.<sup>31,33,53</sup> Production of  $\beta$ -hCG

**Table 1.** Summary of Key Information for Serum Tumor Markers of GCTs

Variable	AFP	hCG	LDH
Assay techniques (as recommended by NACB) <sup>23</sup>	2-site immunometric assays with mAbs ± polyclonal antisera	Double-antibody immunometric assays that measure total hCGβ (intact α/β dimer plus free β monomer)	Enzymatic activity assays measuring conversion of lactate to pyruvate or vice versa
ULN	10-15 μg/L (≈9 if < 40 years of age; ≈13 if > 40 years of age)	5-10 U/L (0.7 U/L in men < 50 years of age; 2.1 U/L if > 50 years of age)	Highly variable and laboratory-specific; depends on assay conditions; elevated if > 1.5 times lab-specific ULN
Units (and conversion factors, if applicable)	International units (kU/L) or mass units (μg/L); 1 U = 1.21 ng	International units (U/L); 5 U/L of hCG corresponds to 15 pmol/L	U/L and fold-increase over ULN
Detection limit (as recommended by NACB) <sup>23</sup>	< 1 μg/L (0.8 kU/L) of serum or plasma	< 1 U/L of serum or plasma (and < 2% cross-reactivity with LH)	Highly dependent on assay method and conditions
Approximate biologic half-life	5-7 days	1.5-3 days	Not reported
Seminomatous GCT (approximate proportion of patients with elevations)	Never elevated in pure seminoma	Yes (15%-20% in advanced disease)	Yes (in 40%-60% of patients)
Nonseminomatous GCT (approximate proportion of patients with elevations)	Yes (10%-20% in stage I, 20%-40% in low-volume stage II, 40%-60% in advanced disease)	Yes (10%-20% in stage I, 20%-30% in low-volume stage II, 40% in advanced disease)	Yes (in 40%-60% of patients)
Other malignancies sometimes associated with elevations	Hepatocellular carcinoma, gastric, lung,* colon,* and pancreatic cancer*	Neuroendocrine, bladder, kidney, lung, head, neck, GI, cervix, uterus and vulva, lymphoma,* and leukemia*	Lymphoma, small-cell lung cancer, Ewing sarcoma, osteogenic sarcoma
Nonmalignant conditions sometimes associated with elevations	Alcohol abuse, hepatitis, cirrhosis, biliary tract obstruction, hereditary persistence*	Marijuana, hypogonadism	Many (processes that involve cell or tissue damage, eg, myocardial infarction, liver or muscle disease), hemolysis of blood sample

Abbreviations: GCT, germ cell tumor; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NACB, National Academy of Clinical Biochemistry; mAb, monoclonal antibody; ULN, upper limit of normal; LH, luteinizing hormone.

\*Serum tumor marker elevation rarely seen.

resulting in elevated concentration in serum is not unique to GCTs; it has been observed with many other malignancies, including neuroendocrine tumors and cancers of the bladder, kidney, lung, head and neck, GI tract, cervix, uterus, and vulva.<sup>10-12</sup> GCTs (and other malignancies) typically produce the hyperglycosylated isoform of β-hCG, which reportedly inhibits apoptosis and acts as an autocrine factor.<sup>12</sup>

Moderate elevations unrelated to disease burden or progression can also occur as a result of hypogonadism,<sup>12,23,47</sup> but these levels usually return to normal with testosterone replacement.

Double-antibody immunometric assays, with high-sensitivity detection and quantitation using fluorescence or chemiluminescence, have been available for β-hCG since the early 1980s.<sup>11,12,23</sup> The NACB

**Table 2.** Causes of False-Positive Test Results for Serum Tumor Markers

Marker	Cause of False-Positive Result	Pathophysiology and Management
AFP	Benign liver disease	Hepatitis, hepatic toxicity from chemotherapy, and certain other benign liver disorders may elevate serum AFP.
	Constitutively elevated AFP	Some individuals have serum AFP levels that are chronically mildly elevated in the range of 15-30 ng/mL. Elevated AFP levels due to cancer will generally show a consistent pattern of increasing in value.
	Tumor lysis	Serum tumor marker levels may rise during the first week of chemotherapy because of tumor lysis. If tumor marker levels rise between day 1 of cycle 1 and day 1 of cycle 2, tumor marker level assays should be repeated midway through cycle 2 to determine whether levels have begun to decline.
hCG	Hepatocellular carcinoma and other cancers	Germ cell tumors are not the only cancers that produce AFP. Elevated serum AFP is thus not diagnostic for germ cell tumor in patients with poorly differentiated cancers.
	Pituitary hCG/hypogonadism	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. Administration of supplemental testosterone reduces the release of gonadotropin-releasing hormone and consequently suppresses pituitary production of LH and hCG.
	Tumor lysis	Serum tumor marker levels may rise during the first week of chemotherapy because of tumor lysis. If tumor marker levels rise between day 1 of cycle 1 and day 1 of cycle 2, tumor marker level assays should be repeated midway through cycle 2 to determine whether levels have begun to decline.
	Other cancers	Other cancers can produce moderately elevated levels of hCG, so elevations of hCG are not diagnostic of a germ cell tumor in patients with poorly differentiated cancers.
LDH	Heterophilic antibodies	Heterophilic antibodies have been reported to result in false-positive hCG results in women.
	Almost anything that results in cellular lysis or injury.	Strenuous exercise, liver disease, myocardial infarction, kidney disease, hemolysis, pneumonia, and countless other things can result in elevations of LDH. The only proven utility of LDH is for prognosis of chemotherapy-naïve patients with histopathologically diagnosed metastatic germ cell tumors.

Abbreviations: AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LH, luteinizing hormone; LDH, lactate dehydrogenase.

recommends measuring both hCG (the intact heterodimer) and free  $\beta$ -hCG by using assays that measure each separately or both together.<sup>23</sup> They also recommend carefully calibrating assays against an international reference standard and quantitating the heterodimer and free  $\beta$ -hCG on an equimolar basis, using an assay with a detection limit of  $\leq 1$  U/L (NACB Testicular Cancer Panel Recommendation 6), which corresponds to 3 pmol/L.<sup>23</sup>

Although the reference upper limit of normal (ULN) for most assays reportedly is 5 to 10 U/L, it is 0.7 U/L for healthy men younger than 50 years of age and approximately 2.1 U/L for those older than age 50 years and in good health.<sup>23</sup> Because assays differ with respect to detection and quantitation of different  $\beta$ -hCG isoforms and heterodimer versus free  $\beta$  subunit, it is probably best to confirm mild to moderate elevations ( $> 5$  to  $< 50$  U/L) by sending a duplicate sample to a second laboratory that uses a different assay. In patients with seminoma and increased  $\beta$ -hCG, the concentration usually is  $< 300$  U/L.<sup>11,12,23</sup> In contrast, many patients with NSGCT have concentrations ranging from  $> 1,000$  to  $> 10,000$  U/L,<sup>11,12,23</sup> but concentration can rise to  $> 50,000$  U/L in those with poor-prognosis NSGCT.<sup>21</sup> If orchiectomy leaves the patient free of residual disease, serum concentration of  $\beta$ -hCG declines, with a half-life of approximately 1.5 days.<sup>56</sup> Declines are typically slower during chemotherapy, and long half-lives ( $> 3.5$  days) have been studied as predictors of eventual recurrence or failure.<sup>57-62</sup> Since the concentration may surge during the first week of chemotherapy, rates of hCG decline should be estimated using two measurements (or preferably more, analyzed by linear regression) on sera obtained sequentially after week 1.<sup>23</sup>

**AFP.** AFP is a monomeric 70-kDa glycoprotein homologous with albumin.<sup>23,46-49</sup> It is produced during pregnancy, initially by the yolk sac and subsequently by fetal liver and GI tract.<sup>23,46,47</sup> AFP is thought to function as a carrier protein in the fetus.<sup>23</sup> AFP concentrations are high in fetal plasma, then decline after birth, with a half-life of 5 days<sup>23</sup>; they fall to adult levels ( $< 15$   $\mu$ g/L) before the end of the first year of life.<sup>23,46,47,49</sup>

Immunohistology studies on orchiectomy tissue samples have shown that AFP is produced by tumor cells in pure embryonal carcinomas, yolk sac tumors, and teratomas, as well as in mixed tumors with embryonal carcinoma, yolk sac, or teratoma components.<sup>51-54</sup> Although some mixed tumors included separate cells that stained for one or the other, no study reported observing one or more cells that stained simultaneously for  $\beta$ -hCG and AFP. Additionally, no studies reported AFP staining in tissue samples from pure seminomas or pure choriocarcinomas. Thus, neither of these tumors are associated with increased serum concentrations of AFP.<sup>23,46-49</sup>

Elevated serum concentrations of AFP may also occur in malignancies other than GCT, including most hepatocellular carcinomas,<sup>63,64</sup> some gastric cancer and, rarely, in lung, colon, and pancreatic cancers.<sup>13-15</sup> However, these cancers do not usually occur simultaneously with a GCT.<sup>23</sup> Benign liver disease (eg, hepatitis or cirrhosis), chemotherapy-induced liver damage, and ataxia telangiectasia can be accompanied by moderate increases of serum AFP concentration.<sup>23,47,49</sup> Hereditary persistence of AFP elevations despite complete responses to GCT treatment also has been reported but is rare.<sup>16-18</sup> These other causes must be ruled out before interpreting mildly elevated AFP concentrations (15-30  $\mu$ g/L) as evidence for presence, progression, or recurrence of a GCT.

AFP is measured by two-site immunometric assays that use monoclonal antibodies or a combination of monoclonal and poly-

clonal antibodies.<sup>23</sup> This method yields results similar to those obtained with radioimmunoassay and has replaced the older method in most laboratories. The NACB recommends (Testicular Cancer Panel Recommendation 5) that laboratories calibrate their assays against an international reference sample, report their results in either  $\mu$ g/L or kU/L, and use assays with detection limits  $\leq 1$   $\mu$ g/L ( $\leq 0.8$  kU/L).<sup>23</sup> Concentrations more than twice the ULN (ie,  $> 30$   $\mu$ g/L in most laboratories) may be considered elevated; however, they are between 1,000 and 10,000 in some intermediate-prognosis patients with NSGCT and can be  $> 10,000$   $\mu$ g/L in some poor-prognosis patients.<sup>21</sup> If orchiectomy leaves the patient free of residual disease, serum concentration of AFP declines, with a half-life of approximately 5 days.<sup>56</sup> As with hCG, declines are typically slower during chemotherapy, and long half-lives ( $> 7$  days) have been studied as predictors of eventual recurrence or failure.<sup>57-62</sup> Rates of AFP decline should be estimated using two measurements (or preferably more, analyzed by linear regression), again using sera obtained sequentially after week 1 to avoid surges during the first week of chemotherapy.<sup>23</sup>

**LDH.** LDH is an intracellular enzyme that catalyzes the oxidation of lactate to pyruvate and has a molecular mass of 138 kDa.<sup>49,50</sup> In serum, it exists as a tetramer, with five isoenzyme forms generated from two nonidentical subunits: LDH-A and LDH-B.<sup>23,36,38,39,47,49,50</sup> The LDH-1 isoenzyme consists of four identical LDH-B subunits, while the LDH-5 isoenzyme is composed of four identical LDH-A subunits. LDH-2 ( $B_3A_1$ ), LDH-3 ( $B_2A_2$ ), and LDH-4 ( $B_1A_3$ ) have varying mixtures of the two subunits. The gene encoding LDH-B has been localized to a region on the short arm of chromosome 12 shown to be present at elevated copy number in NSGCTs and seminomas.<sup>23,50</sup> LDH-1 can be measured separately from the other isoenzyme forms by zymography or by immunoprecipitation of the other isoenzymes before measuring catalytic activity,<sup>23,50</sup> and data have been reported showing that most of the elevated activity in sera from patients with GCT is LDH-1.<sup>49,50</sup> In practice, however, many laboratories report total LDH activity rather than LDH-1 only.<sup>47</sup>

Of the three STMs used to evaluate patients with GCTs, LDH is least specific but is also most frequently elevated.<sup>23,47,49,50</sup> It has been studied as a prognostic marker in lymphoma, small-cell lung carcinoma, Ewing sarcoma, and osteogenic sarcoma, as well as in all histologic subtypes of GCTs. Elevated LDH activity occurs in approximately 60% of patients with NSGCT and in 80% of those with seminoma. Rising concentrations are generally thought to reflect tumor burden and/or rapid cell proliferation. However, many nonmalignant diseases and disorders, particularly those involving cell and/or tissue damage, are also associated with elevations of circulating LDH because of its release from damaged cells. Additionally, hemolysis in the sample used for measuring serum LDH activity falsely increases the result.

LDH assays measure enzymatic activity in serum samples.<sup>23,47,49,50</sup> Assay results for LDH activity can vary with methodologic factors such as the physical conditions (pH, temperature) under which reactions are run and whether the reaction measures conversion of lactate to pyruvate or vice versa.<sup>47</sup> Because of this variability, results are usually reported relative to the ULN under the particular assay conditions used in the specific laboratory. In patients with GCTs, levels  $> 1.5$ -fold greater than the ULN are generally considered elevated, although patients with metastatic NSGCT are not considered to have a poor prognosis or high risk for relapse until levels are  $> 10$ -fold greater than the ULN.<sup>21</sup>

## GUIDELINE RECOMMENDATIONS

The recommendations are summarized in Table 3. Recommendations are organized as follows: those on markers for screening begin with “1,” those on markers for diagnosis begin with “2,” those labeled “3” address markers measured during treatment, and those labeled “4” address markers for surveillance after presumably definitive therapy. Additionally, Part I addresses questions 3 and 4 for NSGCT, while Part II addresses the same questions for seminoma.

### STMs to Screen for GCTs

1. Clinical question: Are STM assays indicated to screen asymptomatic adults without current or prior clinical findings suggestive of GCT?

*Recommendation 1.* The Panel recommends against the use of STM assays to screen asymptomatic adults for GCTs because there is no evidence to support screening for GCTs with any blood test.

*Literature review and analysis.* The literature search did not find any studies published between 1990 and the end of 2008 that met selection criteria and reported results of STM assays in asymptomatic adults. Because of the low incidence and low mortality of testis cancer and extragonadal GCTs (there are about 400 deaths in the United States annually from testis cancer and fewer from extragonadal GCTs<sup>65</sup>), it is highly unlikely that screening with STMs or any other tests could decrease mortality or be cost effective for these diseases.

### STMs to Diagnose GCTs

2. Clinical question: In the following circumstances, are STM assays indicated to diagnose adults clinically suspected to have GCTs:

2A. To help determine need for orchiectomy in patients with a testis abnormality?

*Recommendation 2A.* The Panel recommends that all patients suspected of having a testicular GCT have blood drawn for measurement of serum AFP and hCG before diagnostic orchiectomy to assist in establishing the diagnosis and to help interpret postorchiectomy tumor marker levels. However, the Panel recommends against using results of STM assays to guide decision making about whether or not to perform a diagnostic orchiectomy, since there is no evidence indicating that STM assay results predict or improve outcomes of these decisions. STM concentrations in the normal range do not rule out testicular neoplasm or the need for diagnostic orchiectomy.

A significantly elevated serum AFP can establish the diagnosis of a mixed GCT in a patient whose histopathologic diagnosis is pure seminoma because seminomas do not produce AFP. However, borderline elevated values should be interpreted cautiously.

*Literature review and analysis.* The literature search did not identify any studies published between 1990 and 2008 that met selection criteria and reported results of STM assays in patients with an undiagnosed testicular mass. Additionally, evidence is lacking to determine whether preorchiectomy measurement of AFP and hCG influences survival or other health outcomes. Nevertheless, the Panel's recommendation to measure STM concentrations in preorchiectomy samples is based on two considerations. First, significantly elevated AFP would generally preclude the diagnosis of pure seminoma regardless of histopathology.<sup>31,51-54</sup> The Panel recommends cautious interpretation of borderline AFP elevations since false-positives are possible (see Background on STMs for GCTs and Table 2 for more details). Although one report<sup>66</sup> suggested that minor elevations

( $\leq 16$  ng/mL) may not invariably reflect occult NSGCT cells, others<sup>34,67,68</sup> disagree.

Second, knowing the concentration of STMs before orchiectomy facilitates interpretation of postorchiectomy elevations. For staging purposes, it is relevant to know whether STMs are declining after orchiectomy and, if so, how quickly.<sup>19,20,69-71</sup> In addition, while risk stratification to guide further treatment uses postorchiectomy STM concentrations, preorchiectomy results are meaningful by themselves if they are within normal ranges.

2B. To evaluate CUP possibly derived from GCT?

*Recommendation 2B.* The Panel recommends against using serum AFP and hCG assay results to guide treatment for patients with CUP and indeterminate histology because evidence is lacking to support this use. Patients presenting with undifferentiated carcinoma in the midline should be considered for treatment with a chemotherapy regimen for disseminated GCTs, even if serum hCG and AFP concentrations are within the normal ranges.

*Literature review and analysis.* The literature search identified five retrospective analyses<sup>72-76</sup> that met selection criteria and reported results of pretreatment STM assays for a total of 1,513 patients with CUP (range, 85 to 997 per study; Data Supplement Table DS1). Two studies<sup>72,76</sup> limited their analyses to patients treated with cisplatin-based regimens. No studies reported that elevated levels of hCG, AFP, or of either marker was a statistically significant predictor of overall chemotherapy response, differential response to cisplatin-based versus other regimens, or treatment outcome. Three studies<sup>72,75,76</sup> reported that elevated LDH was a statistically significant predictor of shorter survival in univariate analyses. However, one study<sup>75</sup> was limited to patients presenting with hepatic metastases from unknown primaries, and in a second study,<sup>72</sup> LDH was not a statistically significant independent factor to predict OS in multivariate analysis.

2C. To evaluate patients presenting with metastatic disease and evidence of a testicular, retroperitoneal, or anterior mediastinal primary tumor?

*Recommendation 2C.* In rare patients who present 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 diagnosis of GCT. For such rare, medically unstable patients, treatment need not be delayed until histology results permit a tissue diagnosis.

*Literature review and analysis.* In the vast majority of cases, treatment decisions can wait for histopathologic diagnosis of GCT. However, in the rare patient with disease burden that demands urgent treatment, highly elevated AFP and/or hCG concentrations and either a testis mass plus metastatic disease or radiographic evidence of advanced-stage cancer with a midline dissemination pattern consistent with GCT can be adequate grounds to diagnose GCT and start chemotherapy. Although evidence is lacking to determine whether STM assays in these patients improve survival or other health outcomes, this recommendation stems from reports that while various carcinomas produce hCG and AFP, the elevations are typically mild or moderate and these other cancers are incurable when metastatic.<sup>11,77,78</sup> Nonetheless, histopathologic diagnosis should come first whenever treatment can wait for the results (nearly always). There are case reports of curable hematologic malignancies producing AFP or hCG.<sup>79-81</sup>

**Table 3.** Summary of Recommendations

Marker Use	Setting	Recommendation
1. Screening	Asymptomatic adults	Recommendation 1. The Panel recommends against use of STMs or any other blood tests to screen for GCTs.
2. Diagnosis	A. To determine need for orchiectomy	Recommendation 2A. The Panel recommends drawing blood to measure serum AFP and hCG before orchiectomy for all patients suspected of having a testicular GCT to help establish the diagnosis and interpret postorchiectomy levels. However, the Panel recommends against use of STM assay results to guide decision making on need for an orchiectomy. Concentrations in the normal range do not rule out testicular neoplasm or the need for diagnostic orchiectomy.
	B. To evaluate CUP possibly derived from GCT	Recommendation 2B. The Panel recommends against using serum AFP and hCG assay results to guide treatment of patients with CUP and indeterminate histology, because evidence is lacking to support this use. Consider treatment with a chemotherapy regimen for disseminated GCT in patients presenting with undifferentiated midline carcinoma even if serum hCG and AFP concentrations are within normal ranges.
	C. To evaluate patients presenting with metastasis and a primary tumor in testis, retroperitoneum, or anterior mediastinum	Recommendation 2C. In rare male patients presenting with 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 diagnosis of GCT. For such rare, medically unstable patients, treatment need not be delayed until after tissue diagnosis.
<b>Part I: NSGCT</b>		
I-3. Monitoring during treatment (or observation)	A. For staging and prognosis before chemotherapy and/or additional surgery	Recommendation I-3A-1. Although evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes for these patients, the Panel recommends measuring serum AFP, hCG, and LDH for all patients with testicular NSGCT shortly after orchiectomy and before any subsequent treatment. The magnitude of postorchiectomy STM elevations is used to stratify risk and select treatment but must be interpreted appropriately. Serial STM measurements may be needed to determine whether STM levels are rising or falling and, if falling, whether the decline approximates the marker's biologic half-life.  Recommendation I-3A-2. Although direct evidence is lacking to demonstrate that decisions based on STM assay results improve survival or other health outcomes for these patients when compared with decisions made without assay results, the Panel recommends measuring serum AFP, hCG, and LDH before chemotherapy begins for those with mediastinal or retroperitoneal NSGCTs to stratify risk and select treatment.
	B. To predict response to or benefit from treatment	Recommendation I-3B-1. The Panel recommends measuring AFP and hCG shortly before RPLND in patients with clinical stage I or II NSGCT; those with rising concentrations are beyond stages IA or IB and need systemic therapy similar to the regimens used for patients with stage III disease. Recommendation I-3B-2. Although direct evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes when compared with decisions made without assay results, the Panel recommends measuring hCG, AFP, and LDH immediately prior to chemotherapy for stage II/III testicular NSGCT. The magnitude of marker elevations guides chemotherapy regimen choice and treatment duration.
	C. To monitor response or progression during or soon after therapy	Recommendation I-3C. Although direct evidence is lacking to determine whether monitoring treatment response with STM assays during chemotherapy improves survival or other health outcomes of patients with NSGCT, the Panel recommends measuring serum AFP and hCG at the start of each chemotherapy cycle and again when chemotherapy concludes. However, the Panel sees no indication to delay the start of chemotherapy until after results of STM assays are known. Rising AFP and/or hCG levels during chemotherapy usually imply progressive disease and the need to change regimen. However, tumor lysis from chemotherapy, particularly during the first cycle, may result in a transient spike in STM levels, and such a spike does not represent treatment failure. Resect all residual disease for patients whose STM levels have normalized and who have resectable residual mass(es) following chemotherapy. Slow decline during treatment conveys higher risk of treatment failure but does not indicate need to change therapy. Persistently elevated but slowly declining postchemotherapy levels do not indicate immediate need for additional chemotherapy; resection of residual masses need not be delayed until STM levels normalize.
I-4. For surveillance	After presumably definitive therapy	Recommendation I-4. Although direct evidence is unavailable to determine whether monitoring STM concentrations during surveillance and following definitive therapy for NSGCT improves patients' survival or other health outcomes, the Panel recommends measuring AFP and hCG at each visit during surveillance after definitive therapy for NSGCT, regardless of stage. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used by the available uncontrolled series: every 1 to 2 months in the first year, every 2 to 4 months in the second year, every 3 to 6 months in the third and fourth years, every 6 months in the fifth year, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed.
<b>Part II: Seminoma</b>		
II-3. Monitoring during treatment (or observation)	A. For staging and prognosis before RPLND, radiation, or chemotherapy	Recommendation II-3A. Although direct evidence is lacking to determine whether measuring STM concentrations improves survival or other health outcomes of these patients, the Panel recommends measuring postorchiectomy serum concentrations of hCG and/or LDH for patients with testicular pure seminoma and preorchiectomy elevations. However, the Panel recommends against using postorchiectomy serum concentrations of either hCG or LDH to stage or predict prognosis of patients with involved nodes and/or metastasis.
	B. To predict response to or benefit from treatment	Recommendation II-3B. The panel recommends against using tumor marker levels to guide treatment decisions for seminoma. Evidence is lacking that selecting therapy based on tumor marker levels yields better outcomes.

(continued on following page)



**Table 3.** Summary of Recommendations (continued)

Marker Use	Setting	Recommendation
	C. To monitor response or progression during or soon after therapy	Recommendation II-3C. The Panel recommends against using tumor markers to monitor response or progression of seminomas 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).
II-4. For surveillance	After presumably definitive therapy	Recommendation II-4. Conclusive evidence is lacking for clinical utility of STMs in post-treatment surveillance for stage I seminoma, and the Panel recommends against this use. However, while direct evidence is unavailable to determine whether monitoring STM concentrations improves survival or other health outcomes of patients who have completed therapy for advanced seminoma, rising levels may be the earliest sign of relapse, and the Panel recommends measuring STMs at each visit for these patients. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: every 2 to 4 months in the first year, every 3 to 4 months in the second year, every 4 to 6 months in the third and fourth years, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed.

Abbreviations: STM, serum tumor marker; GCT, germ cell tumor; AFP,  $\alpha$ -fetoprotein; hCG, human chorionic gonadotropin; CUP, cancers of unknown primary; NSGCT, nonseminomatous germ cell tumor; LDH, lactate dehydrogenase; RPLND, retroperitoneal lymph node dissection.

## PART I: NSGCT

### STMs During Treatment

I-3. Clinical question: In adult patients undergoing treatment (or observation) for NSGCT (postorchietomy, for those with testicular tumors), are STM assays indicated for the following uses:

I-3A. To stage patients and predict prognosis before chemotherapy and/or additional surgery?

*Recommendation I-3A-1.* Although direct evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes for these patients when compared with decisions without assay results, the Panel recommends measuring serum AFP, hCG, and LDH after orchietomy and before any subsequent treatment for all patients with testicular NSGCT. The magnitude of STM elevations after orchietomy influences risk stratification and treatment decisions, but levels must be interpreted appropriately, paying particular attention to conditions that may cause false-positive elevations. Serial STM measurements may be needed to determine whether STM levels are rising or falling and, if falling, whether the decline approximates the marker's biologic half-life (24-36 hours for hCG and 7 days for AFP; see Background on STMs for GCTs and Tables 1 and 2).

*Literature review and analysis.* Four retrospective series<sup>71,82-84</sup> with a combined total of 823 patients diagnosed with low-stage or good-risk NSGCT reported STM concentrations in postorchietomy samples obtained before RPLND (Data Supplement Table DS3). The most convincing evidence is provided by the largest series ( $n = 453$ )<sup>71</sup>, which used Cox multivariate regression analysis to show that persistent AFP and/or hCG elevation after orchietomy was an independent, statistically significant predictor of progression after RPLND (HR [hazard ratio], 5.6; 95% CI, 2.4 to 12.8;  $P < .001$ ). Two other series<sup>82,83</sup> reported univariate analyses showing that persistent postorchietomy AFP and/or hCG elevations predict a higher likelihood of nodal involvement in RPLND specimens. One of the two series<sup>83</sup> also reported a smaller proportion of patients free of disease at 3 years among those with postorchietomy AFP and/or hCG elevations (86% v 100%). The fourth series<sup>84</sup> reported that univariate analysis showed a statistically significant increase in the post-RPLND relapse

rate among patients with postorchietomy AFP or hCG concentrations that remained elevated (80% v 16%; relative risk, 8.0; 95% CI, 2.3 to 27.8;  $P = .001$ ). Thus, while direct evidence is lacking to show that decisions based on STM assay results improve outcomes when compared with decisions made in their absence, the Panel finds available data on secondary outcomes in retrospective studies adequate to support using persistent postorchietomy AFP or hCG elevations to identify patients with low-stage NSGCT that is unlikely to be cured by RPLND but may benefit from systemic chemotherapy.

For advanced NSGCT, 21 retrospective series<sup>85-105</sup> with a combined total of up to 6,815 patients and two international, multicenter pooled analyses with 996<sup>106</sup> and 5,202<sup>21</sup> patients, respectively, reported STM concentrations in samples obtained postorchietomy but prechemotherapy (Data Supplement Table DS4). It is difficult to estimate accurately the total number of patients with advanced NSGCT included in these 23 articles, since several groups published multiple retrospective series, and some of these groups also contributed patients to the pooled multicenter analyses. In the Panel's opinion, the IGCCCG multicenter analysis<sup>21</sup> provides the strongest evidence to support including STM assay results in strategies to stratify risk of poor outcome in patients with advanced NSGCT.

Nineteen of the 21 retrospective series and both multicenter pooled analyses reported that univariate analyses showed statistically significant associations of marker elevations with poorer outcomes after chemotherapy (Data Supplement Table DS4). Reported outcomes included response rates, presence of residual tumor in lymph nodes (post-RPLND) or elsewhere (after resection), and time-to-event outcomes (OS, DFS, EFS, RFS, and/or PFS). However, studies varied considerably with respect to the outcomes they reported, the times after treatment at which outcomes were estimated, and the duration of follow-up available for estimating time-to-event outcomes. Only two series<sup>90,92</sup> reported that STM elevations were not significantly associated with poorer outcomes. Seven series<sup>88,89,93,96,101,102,105</sup> and the IGCCCG pooled analysis<sup>21</sup> reported multivariate analyses showing that STM elevations were statistically significant independent predictors of poor outcomes (OS and PFS in the IGCCCG multivariate analysis<sup>21</sup>). Each of seven studies<sup>21,89,93,95,96,100,102</sup> included prechemotherapy STM elevations as an

independent prognostic factor in the classification schemes or models they developed (or evaluated) for risk of relapse, progression, death, or other poor outcome in patients with advanced or metastatic NSGCT.

Although one study<sup>104</sup> unsuccessfully attempted to further subdivide the poor-risk subset, the IGCCCG categories<sup>21</sup> remain the most frequently used risk stratification scheme for patients with advanced or metastatic NSGCT. Table 4 lists the STM concentrations associated with the good-, intermediate-, and poor-risk categories; other factors used to stratify patients into these risk categories; and estimates of OS and PFS at 5 years for each risk group derived from their data set and regression models. These range from 92% and 89%, respectively, for the good-risk group to 48% and 41%, respectively, for the poor-risk group. Recommendations on chemotherapy regimen and duration (number of cycles) in most current NSGCT treatment guidelines for patients with advanced NSGCT<sup>5-8,22</sup> depend on IGCCCG risk categories. Thus, the magnitude of marker elevations contributes to management decisions for patients with advanced NSGCT.

The Panel recommends caution with interpreting marker results (see Background on STMs for GCTs and Table 2 for more complete information on possible causes and management of false-positive results). Mildly or moderately elevated STM levels may result from the primary tumor in the testis, and STM levels may decline to normal following orchiectomy, an event that can be ascertained only through serial STM measurements. False-positive AFP elevations (or persistently elevated concentrations) have occurred in association with liver damage from non-neoplastic conditions including hepatitis, cirrhosis, biliary tract obstruction, and alcoholism, or from certain drugs or viral infections.<sup>16,107,108</sup> Hereditary persistence of AFP elevations despite complete responses to GCT treatment also has been reported but is rare.<sup>16-18</sup> Moreover, marijuana use may cause a spurious rise of hCG

concentration in patients with testicular GCT.<sup>109</sup> Unexplained, stable, but small increases in serum AFP or hCG that do not reflect disease also have been reported in patients with GCT.<sup>110</sup> Additionally, given the myriad possible causes for elevated LDH concentrations (Table 2), the Panel particularly recommends caution when interpreting increased LDH unaccompanied by increased AFP or hCG or abnormal radiographic or physical examination findings as evidence of disease stage progression or relapse. Nevertheless, the IGCCCG analysis<sup>21</sup> showed that the magnitude of postorchiectomy LDH elevation is useful to stratify risk of patients with NSGCT.

*Recommendation I-3A-2.* Although direct evidence is lacking to demonstrate that decisions based on STM assay results improve survival or other health outcomes for these patients when compared with decisions made without assay results, the Panel recommends measuring serum AFP, hCG, and LDH before chemotherapy begins for patients with mediastinal or retroperitoneal NSGCTs to stratify risk and guide treatment.

*Literature review and analysis.* The strongest evidence supporting this recommendation is from subset (n = 524) analyses<sup>102,111-113</sup> on patients with extragonadal primary NSGCTs who were included in the IGCCCG multicenter pooled analysis.<sup>21</sup> Univariate and multivariate analyses found that STM elevations were statistically significant predictors of treatment outcome (including OS) for patients with extragonadal tumors (Data Supplement Table DS4). They also showed that IGCCCG risk categories<sup>21</sup> distinguished intermediate- from poor-risk patients with extragonadal NSGCTs (OS at 5 years, 75% v 48%). In both regression tree and Cox proportional hazards analyses, elevated prechemotherapy hCG concentration was an independent, statistically significant predictor for decreased survival (Cox

**Table 4.** IGCCCG Risk Categories for Patients With Metastatic GCTs

Variable	NSGCT Risk			Seminoma Risk		
	Good	Intermediate	Poor	Good	Intermediate	Poor
Marker (units)*						
AFP (μg/L)	< 1,000	≥ 1,000 but ≤ 10,000†	> 10,000‡	< ULN	< ULN	No seminoma patients classified in poor-risk category
hCG (U/L)	< 5,000	≥ 5,000 but ≤ 50,000†	> 50,000‡	Any	Any	
LDH (× ULN)§	< 1.5	≥ 1.5 but ≤ 10†	> 10‡	Any	Any	
Primary tumor site	Testis or retroperitoneum	Testis or retroperitoneum	Mediastinum, † testis, or retroperitoneum	Any	Any	
Sites of metastases	No nonpulmonary visceral	No nonpulmonary visceral	One or more nonpulmonary visceral‡	No nonpulmonary visceral	One or more nonpulmonary visceral¶	
Approximate proportion of patients in this risk group, %	56	28	16	90	10	
Predicted OS at 5 years, %	92	80	48	86	72	
Predicted PFS at 5 years, %	89	75	41	82	67	

Abbreviations: IGCCCG, International Germ Cell Cancer Collaborative Group; GCT, germ cell tumor; NSGCT, nonseminomatous germ cell tumor; AFP, α-fetoprotein; ULN, upper limit of normal; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

\*Concentrations of each marker must be in the ranges shown in patients assigned to each risk category. See original IGCCCG report<sup>12</sup> for other criteria associated with each risk group.

†Any one of these findings is sufficient by itself to classify a patient as intermediate risk.

‡Any one of these findings is sufficient by itself to classify a patient as poor risk.

§Fold increase over ULN.

¶This is the only factor distinguishing good-risk from intermediate-risk seminoma.

HR, 1.5; 95% CI, 1.1 to 2.1;  $P < .022$ ). Recommendations on chemotherapy regimen and duration in current treatment guidelines<sup>5-8,22</sup> also are based on IGCCCG risk groups<sup>21</sup> for extragonadal NSGCTs, which use the magnitude of STM elevations to stratify patients (Table 4).

I-3B. To predict response to or benefit from treatment?

*Recommendation I-3B-1.* The Panel recommends measuring serum AFP and hCG shortly before RPLND in patients with clinical stage I or II NSGCT. Those with rising or persistently elevated serum AFP or hCG are beyond stages IA or IB and require systemic therapy similar to the regimens used for patients with stage III disease.

*Literature review and analysis.* Direct evidence is lacking to demonstrate that decisions based on STM assay results improve survival or other health outcomes for patients with clinical stage I/II NSGCT when compared with decisions made without assay results. Nevertheless, rising or persistent elevation of AFP or hCG concentration shortly before RPLND is associated with an increased risk of relapse and decreased DSS, suggesting the surgical procedure is less likely to cure such patients. Indiana University reported on 30 patients with clinical stage I testicular NSGCT who had rising or persistently elevated STMs at RPLND (ie, clinical stage IS) and did not receive adjuvant chemotherapy afterward.<sup>70</sup> Relapses occurred in five (83%) of six patients with elevated AFP and six (25%) of 24 patients with elevated hCG. While the Indiana University report did not include data on likelihood of post-RPLND relapse in those without STM elevations, multivariate analysis on clinical stage I or II NSGCT patients treated at Memorial Sloan-Kettering Cancer Center<sup>71</sup> found that patients with persistently elevated postorchietomy STMs were 5.6 times more likely (95% CI, 2.4 to 12.8;  $P < .001$ ) to relapse after RPLND compared with patients with normal or appropriately declining STMs (Data Supplement Table DS3). Moreover, DSS at 5 years was 94% among patients with elevated STMs ( $n = 19$ ), clinical stage IIB disease ( $n = 16$ ), or both ( $n = 7$ ), compared with 99.7% among patients with stage I to IIA disease and normal STMs. The Panel finds this evidence sufficient to recommend measuring AFP and hCG shortly before RPLND in patients with clinical stage I or II NSGCT.

*Recommendation I-3B-2.* Although direct evidence is lacking to determine whether decisions based on STM assay results improve survival or other health outcomes when compared with decisions made without assay results, the Panel recommends measuring hCG, AFP, and LDH immediately before chemotherapy for stage II or III testicular NSGCTs. The magnitude of marker elevations guides choice of chemotherapy regimen and treatment duration.

*Literature review and analysis.* As described in literature review and analysis for Recommendation I-3A-1, the magnitude of hCG, AFP, and LDH elevations predicts prognosis and treatment outcomes. Different chemotherapy treatment plans have been studied for patients with intermediate- and poor-risk versus good-risk disease.<sup>114</sup> Initially, standard chemotherapy for all patients included four cycles, most often using either bleomycin, etoposide, and cisplatin (BEP) or etoposide, ifosfamide, and cisplatin (VIP) for patients with a contraindication to bleomycin.<sup>115-117</sup> Subsequently, two randomized controlled trials confirmed that in patients with good-risk disease, equivalent outcomes are achieved with either three or four cycles of BEP.<sup>118-120</sup> Thus, standard chemotherapy for good-risk patients now uses three cycles of BEP or else four cycles of etoposide and cisplatin (EP).<sup>6-8,22</sup> However, because outcomes are inferior and need improvement for patients with intermediate- or poor-risk disease, ran-

domized trials have not tested abbreviated courses of chemotherapy in these patients.<sup>121</sup>

I-3C. To monitor treatment response or progression during or soon after therapy?

*Recommendation I-3C.* Although direct evidence is lacking to determine whether monitoring treatment response with STM assays during chemotherapy for patients with NSGCTs improves their survival or other health outcomes, the Panel recommends measuring serum AFP and hCG at the start of each chemotherapy cycle and again when chemotherapy concludes. However, the Panel sees no indication to delay the start of chemotherapy until after results of STM assays are known. Rising levels of AFP and/or hCG during chemotherapy usually imply progressive disease, indicating failure of the treatment and the need to change regimens. However, tumor lysis from chemotherapy, particularly during the first cycle, may result in a transient spike in AFP and/or hCG levels, and such a spike does not represent treatment failure. Continuing increases after chemotherapy predict lack of benefit from RPLND and indicate the need for salvage therapy. However, the Panel also recommends that patients whose AFP and hCG levels have normalized and who have resectable residual mass(es) following chemotherapy should undergo resection of all residual disease. While slow marker decline during chemotherapy conveys a higher risk of treatment failure, it does not indicate a need to change therapy. Persistently elevated but slowly declining markers soon after chemotherapy do not indicate an immediate need for additional chemotherapy; resection of residual tumor need not be delayed until they normalize.

*Literature review and analysis.* The literature search did not find any evidence directly comparing outcomes of chemotherapy for NSGCT with versus without STM monitoring. Six retrospective series<sup>57-60,62,91</sup> with a combined total of 1,928 patients and a randomized trial ( $n = 217$ )<sup>122</sup> reported on AFP and hCG concentrations during first-line chemotherapy for disseminated NSGCT (Data Supplement Table DS5). The RCT<sup>122</sup> compared four cycles of BEP chemotherapy with two cycles of BEP followed by two cycles of high-dose chemotherapy. Prolonged marker half-life was a statistically significant predictor of poor response and shorter survival by both univariate and Cox regression analyses in the earliest of these reports.<sup>57</sup> Two other series also reported that prolonged STM half-life was statistically significant by univariate analysis to predict decreased likelihood of survival at 10 years<sup>60</sup> and that by multivariate analysis, longer time to normalization of STM concentrations was a statistically significant independent predictor for decreased likelihood of PFS and OS at 4 years.<sup>62</sup> However, two other series reported that prolonged marker half-life early in chemotherapy was not statistically significant to predict relapse, survival,<sup>58</sup> or treatment failure.<sup>59</sup> Since studies disagreed, the Panel deemed available evidence insufficient to recommend changing therapy solely on the basis of slow marker decline. Similarly, although it has been reported that some patients have a transient surge in AFP and/or hCG levels after the initiation of chemotherapy, there is no evidence to support changing therapy on the basis of the presence or absence of such a surge. Because marker levels may rise because of tumor lysis during the first week of treatment, interpreting levels at the beginning of cycle 2 must be done cautiously.<sup>123</sup> Patients whose marker levels do not decline from the first day of cycle 1 to the first day of cycle 2 should have repeat marker levels drawn during the second or third week of cycle 2 to determine whether the levels are rising, a finding that would generally be an indication to change the treatment plan.

The RCT<sup>122</sup> reported a subset analysis on patients treated for at least three cycles who also had data available for calculating the rate of marker decline over the first two cycles of BEP chemotherapy (n = 165, 75% of those randomized; Data Supplement Table DS5). Among patients with an unsatisfactory rate of marker decline ( $t_{1/2} > 7$  days for AFP or  $t_{1/2} > 3.5$  days for hCG), those receiving two subsequent cycles of high-dose chemotherapy (n = 38) had an increased rate of durable complete responses and a greater likelihood of being alive at 2 years compared with those (n = 31) receiving two more cycles of standard-dose chemotherapy (78% v 55%;  $P = .11$ ). In contrast, those with a satisfactory rate of marker decline experienced similar outcomes whether the final two cycles used high-dose (n = 33) or standard-dose (n = 63) chemotherapy (78% v 85%;  $P = .29$ ). The Panel found this evidence promising but insufficient to recommend selecting patients with NSGCT for intensified therapy based on an unsatisfactory rate of marker decline during initial cycles of standard-dose therapy; these results need to be validated in a subsequent trial.

Eight retrospective series<sup>97,103,124-129</sup> with a combined total of 1,242 patients reported on AFP and hCG concentrations after chemotherapy but before surgery (RPLND or residual tumor resection) for poor-risk, advanced, or metastatic NSGCT (Data Supplement Table DS6). Some patients may have been included in more than one of three reports from the same institution.<sup>103,125,129</sup> Six of the eight reports evaluated whether persistently elevated or rising marker concentrations predicted poor outcomes. Most of these reported univariate analyses<sup>97</sup> or multivariate analysis<sup>103,125,127</sup> showing that marker elevations were statistically significant predictors for shorter OS or DSS. One exception<sup>128</sup> reported that elevated marker concentration at postchemotherapy RPLND did not predict disease progression or relapse (HR, 1.30; 95% CI, 0.63 to 2.73;  $P = .5$ ). Additionally, a study on patients with primary mediastinal NSGCT<sup>129</sup> reported that elevated but stable postchemotherapy marker concentration did not predict shorter survival compared with those whose marker concentrations normalized (HR, 1.69; 95% CI, 0.9 to 3.2;  $P = .10$ ). However, this study also reported that rising postchemotherapy marker concentration did predict shorter survival (HR, 2.25; 95% CI, 1.1 to 4.6;  $P = .03$ ), as did persistent elevation of either AFP or hCG after postchemotherapy resection of residual tumor (HR, 4.65; 95% CI, 2.3 to 9.4;  $P < .001$ , by multivariate analysis). Thus, the Panel views rising AFP or hCG levels at the end of treatment as an indication for salvage therapy.

Two series<sup>97,125</sup> reported that failure to achieve marker normalization (ie, persistently elevated concentrations) after chemotherapy was a statistically significant predictor of increased likelihood for finding viable GCT cells at residual tumor resection. However, two series also reported finding viable tumor in 21%<sup>97</sup> or 65%<sup>124</sup> of residual tumor specimens resected from patients with STM concentrations that normalized after chemotherapy. Moreover, Ravi et al<sup>124</sup> reported finding no viable cancer in 27% of residual tumors resected from patients with elevated postchemotherapy marker concentrations, and Kobayashi et al<sup>126</sup> reported that mild persistent elevations of postchemotherapy AFP concentrations (10-30 ng/mL) did not predict for presence of malignant cells at resection of residual tumor. On the basis of these reports, the Panel recommends against using normalized AFP and hCG concentrations to select patients who might safely avoid postchemotherapy RPLND or residual tumor resection. The Panel also views data from these reports and those summarized in the preceding paragraph<sup>128,129</sup> as evidence that persistently elevated but

slowly declining postchemotherapy markers are neither an indication for additional chemotherapy nor a contraindication to resecting residual masses.

Additional evidence that persistently elevated AFP or hCG does not contraindicate resecting residual tumor comes from reports that in a substantial proportion of such patients, salvage surgery can be successful. The Indiana University series<sup>125</sup> reported that among 114 patients, the 5-year OS was 53.9%, and 46% had either fibrosis or teratoma found at surgery. Investigators at the University of Bonn<sup>130</sup> reported that 17 (57%) of 30 patients were long-term survivors, only 64% had residual cancer found at surgery, and a complete resection of residual disease was the best predictor of outcome. British investigators<sup>124</sup> similarly reported that 17 (57%) of 30 patients with elevated STMs undergoing resection of residual tumors became continuously disease-free. However, the Panel found no evidence of benefit from resecting residual tumor or from salvage surgery in patients with NSGCT and serum AFP or hCG concentrations that continue to rise during chemotherapy or soon after it concludes. Serial measurements must be obtained to determine whether levels are rising or falling.

### **STMs for Surveillance of Definitively Treated NSGCT**

I-4. Clinical question: In adult patients with NSGCT, are STM assays indicated after presumably definitive therapy for surveillance and routine monitoring to detect asymptomatic recurrence?

*Recommendation I-4.* Although direct evidence is unavailable to determine whether monitoring STM concentrations during surveillance and following definitive therapy for NSGCT improves patients' survival or other health outcomes, the Panel recommends measuring AFP and hCG at each visit regardless of stage. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: every 1 to 2 months in the first year, every 2 to 4 months in the second year, every 3 to 6 months in the third and fourth years, every 6 months in the fifth year, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed.

*Literature review and analysis.* The literature search found no studies that directly compared survival or other health outcomes of surveillance for relapse with versus without STM assays in patients who completed treatment for NSGCT and appeared free of detectable disease. The search also found no studies that directly compared outcomes of different surveillance intervals or durations for such patients and that used STM assays or other diagnostic interventions.

Three retrospective analyses with a combined total of 499 patients reported on STM concentrations at NSGCT relapse (Data Supplement Table DS7). In each of the three,<sup>113,131,132</sup> the majority of patients who required salvage therapy for relapsed NSGCT had elevated STM concentrations when treatment began. However, these studies did not report the proportion of patients whose relapses were detected by an initial finding of increased STM concentrations.

The literature search also identified 10 series (one prospective<sup>133</sup> and nine retrospective<sup>134-142</sup>) that reported STM concentrations during surveillance after presumably definitive therapy for NSGCT (Data Supplement Table DS8). Although monitoring schedules varied across these series, most measured STM concentrations monthly in the first year, every other month in the second year, and at longer intervals in subsequent years. Imaging with computed tomography

(CT) and/or x-ray was typically less frequent than STM assays in each study.

The prospective series<sup>133</sup> reported on 154 patients undergoing surveillance for recurrence after orchiectomy alone for stage I NSGCT. Relapses were detected by STM elevations alone in eight (19%) of 42 cases and simultaneously by STM elevations and CT findings in another 17 patients (40.5%).

Six of nine retrospective series reported the proportion of patients with relapsed NSGCT initially detected by STM elevations. Of 39 relapses among 230 patients followed in one series,<sup>136</sup> 19 (48.7%) were initially detected by STM elevations alone and 10 additional relapses (25.7%) were simultaneously detected by STM elevations and CT findings. Another series<sup>137</sup> included 123 patients and reported that STM elevations were the initial sign in 40% of relapses and occurred together with other findings in another 26% of relapses. A series<sup>139</sup> reporting on 86 relapses among 301 patients followed for a median of 60 months detected 28 (32.6%) of these relapses at stage IS. These investigators also reported that, at the time of relapse, hCG concentrations were above the normal range in 39 (45%) and AFP concentrations were above the normal range in 36 (42%) of the 86 patients with recurrent NSGCT. Of 65 relapses (31%) found in 211 patients managed by observation alone after orchiectomy for stage I NSGCT,<sup>140</sup> 28.8% were detected by STM elevations alone, and 66.7% were detected simultaneously by STM elevations and other findings. Another series<sup>141</sup> of 399 patients followed after orchiectomy alone for stage I NSGCT reported that 112 (89.6%) of 125 patients with increased LDH concentrations at relapse had concurrent increases in AFP and/or hCG concentrations. These investigators concluded that routine measurement of LDH in patients on surveillance does not improve early detection of relapse relative to measurement of only AFP and hCG. Similarly, increased LDH concentration was the initial finding in none of 14 cases of relapsed NSGCT among 449 patients followed from January 2004 through December 2005 in the final series.<sup>142</sup> These investigators also reported that increased LDH concentration was the first evidence of relapse in only two of 81 patients with recurrent NSGCT seen from January 1992 through December 2005.

Evidence from these studies demonstrates that increased serum concentrations of AFP and/or hCG is a relatively low sensitivity marker (20% to 49% as the earliest finding) to detect relapses after presumably definitive therapy for NSGCT. Thus, measuring AFP and hCG is not a sufficient tool by itself to monitor for relapse in these patients. Each of the studies reviewed for this guideline included regular imaging and clinical evaluation, particularly during the first two years. However, since relapses are relatively infrequent, low sensitivity may not imply an unacceptably low negative predictive value. Not surprisingly, data are lacking to estimate specificity and positive predictive value. Patients with findings that suggest relapsed NSGCT, particularly those with AFP or hCG concentrations that were normalized by treatment and then rose in the next 1 to 2 years, generally began chemotherapy without biopsy to confirm the relapse; hence, false-positive rates are unknown.

The rationale for long-term monitoring of STMs is based on multiple series<sup>143-146</sup> reporting that at least half of late-relapsing patients have elevated STMs at the time of relapse, and 40% to 70% are asymptomatic at relapse. Indiana University has reported that of 83 late-relapsing patients (80 with NSGCT), 67% had elevated STMs at relapse, including 52% with elevated AFP, 10% with elevated hCG,

and 5% with both markers elevated.<sup>143</sup> Relapse occurred after 5 years in 72% of this group and after 2 to 5 years in the remaining 28%. Notably, 40% of these patients were asymptomatic when relapse was detected by marker elevation and/or radiographic imaging. Eight percent had elevated markers prior to the development of detectable disease on imaging studies or physical examination. A large German series reported on 72 late-relapsing patients with NSGCT (median interval to relapse, 64.5 months).<sup>144</sup> Fifty-one (71%) were asymptomatic with late relapse detected at routine follow-up. AFP was elevated at relapse in 45 (76%) of 59 patients with available assay results, and hCG was elevated in 12 (27%) of 45 with available assay results. Three men had marker-only relapses. A small population-based series from Norway<sup>145</sup> included 15 patients with NSGCT. Five (33%) had AFP elevations at late relapse, and one had elevated hCG at late relapse. Seven (47%) were asymptomatic and had relapse detected at routine follow-up. Pooled analysis of 426 late-relapsing patients with GCTs reported in seven series from various countries (which included the three series described above) found that 49% had elevated AFP and 24% had elevated hCG at the time of late relapse.<sup>147</sup> However, results were not reported separately by tumor type (NSGCT versus seminoma).

In the series from Indiana<sup>143</sup> and Memorial Sloan-Kettering Cancer Center,<sup>146</sup> asymptomatic patients had better outcomes, but this was not the case in the German<sup>144</sup> or Norwegian<sup>145</sup> series. In each series, more than half of relapses occurred after tumor-free intervals longer than 5 years, and not uncommonly, some occurred long after 10 years. Thus, the Panel recommends that annual surveillance should continue for at least 10 years. Some experts and centers recommend that surveillance should continue indefinitely. It is worth noting that, because marker-only late relapses are not usually treated unless they are radiographically detectable or unless palpable lesions develop to confirm relapse, the objective of following STMs beyond year 5 is to trigger a search for the site of relapse in patients whose tumor markers begin to rise. In contrast to hCG and AFP, the utility of following LDH is less clear because of the high false-positive rate.

## PART II: SEMINOMA

### **STMs During Seminoma Treatment**

II-3. Clinical question: In adult patients with pure seminoma undergoing treatment (or observation), are STM assays indicated for the following uses?

II-3A. To stage patients and predict prognosis before RPLND, radiation therapy, or chemotherapy?

*Recommendation II-3A.* Although direct evidence is lacking to determine whether measuring STM concentrations improves survival or other health outcomes of these patients, the Panel recommends measuring postorchiectomy serum concentrations of hCG and LDH for patients with testicular pure seminoma and preorchiectomy elevations because persistently elevated or rising concentrations may indicate metastatic disease and warrant a thorough work-up. However, the Panel recommends against using postorchiectomy serum concentrations of either hCG or LDH to stage or predict prognosis of patients with seminoma and involved nodes and/or metastatic disease.

*Literature review and analysis.* The literature search found no evidence that addressed the clinical utility of measuring hCG and LDH after orchiectomy for patients with testicular pure seminoma and

preorchietomy elevations. Nevertheless, in the Panel's opinion, determining whether diagnostic orchietomy normalizes the serum marker elevations is informative and helps stage patients with no other signs or symptoms of seminoma that persist after orchietomy. Note that in AJCC<sup>19</sup> and UICC<sup>20</sup> staging of testicular seminoma, those with elevated markers postorchietomy but no nodal involvement or disseminated tumor are separated into stage IS.

Four retrospective series<sup>148-151</sup> and an international, multicenter pooled analysis<sup>21</sup> reported STM concentrations in samples obtained postorchietomy but prechemotherapy from patients with advanced seminoma (Data Supplement Table DS12). An unknown proportion of the four series' combined total of 677 patients were also included in the pooled analysis (n = 660).

Univariate analyses reported by two<sup>148,150</sup> of four retrospective series on patients with seminoma (Data Supplement Table DS12) suggested that elevated postorchietomy hCG concentration might be a statistically significant predictor of shorter PFS. However, elevated postorchietomy hCG concentration was not a statistically significant predictor of shorter OS in any of the four seminoma series. Elevated postorchietomy LDH concentration was a statistically significant predictor of shorter PFS in univariate analyses in two seminoma series<sup>148,149</sup> but predicted shorter OS in only one of these.<sup>148</sup> In the pooled multivariate analysis, LDH concentration > 2 × ULN was a statistically significant independent predictor of shorter PFS and OS.<sup>21</sup> Nevertheless, the IGCCCG prognostic classification scheme adequately separated patients with good-prognosis advanced seminoma (90% of the total) from those with intermediate-prognosis advanced seminoma (the remaining 10%) using a single factor: the absence or presence of metastasis to an organ other than the lung. No patients with pure seminoma are classified as poor-prognosis. Thus, neither hCG nor LDH concentrations affect prognostic classification for patients with seminoma.

II-3B. To predict response to or benefit from therapy?

*Recommendation II-3B.* The Panel recommends against using hCG or LDH concentrations to guide treatment decisions for patients with pure seminoma. Conclusive evidence is lacking that selecting therapy based on tumor marker levels yields better outcomes.

*Literature review and analysis.* The literature search did not identify any studies that reported treatment outcomes after selecting patients with seminoma for different therapies on the basis of concentrations of hCG or LDH.

II-3C. To monitor treatment response or progression during or immediately after therapy?

*Recommendation II-3C.* The Panel recommends against using STMs to monitor treatment response of seminomas. However, the Panel recommends measuring hCG and AFP when treatment concludes. Rising tumor markers soon after therapy usually indicate progressive disease and thus mandate a thorough work-up to confirm or rule out the need for salvage therapy (usually chemotherapy).

*Literature review and analysis.* The literature search did not identify any reports on changes in STM concentration during chemotherapy among patients being treated for advanced seminoma. The literature search also did not find any studies reporting on proportion of patients with pure seminoma that responded incompletely or briefly to primary therapy (radiation or chemotherapy) in whom progression was detected by rising marker concentrations versus other means of post-treatment evaluation. Nevertheless, in the Panel's opin-

ion, rising marker concentrations soon after therapy concludes usually signals progressive disease.

This opinion is based on reports that roughly half of patients with seminoma that relapses after chemotherapy for metastatic disease have elevated hCG. Investigators at Indiana University<sup>152</sup> reported that among patients receiving salvage chemotherapy for relapsed seminoma, 14 (58%) of 24 had elevated hCG and 15 (63%) of 24 had elevated LDH at salvage. Memorial Sloan-Kettering Cancer Center<sup>153</sup> reported that among 27 seminoma patients relapsing after chemotherapy, 12 (44%) had elevated hCG and 17 (65%) had elevated LDH. Patients who have been diagnosed with pure seminoma but who in fact have a mixed GCT may have elevated AFP at progression or relapse, and this is the rationale for also measuring AFP soon after treatment. Measuring AFP in these patients has a low yield but may result in earlier diagnosis of relapse. The Panel did not endorse routine monitoring of LDH because, unlike hCG and AFP, there is a high false-positive rate for LDH. If LDH is monitored, the Panel recommends against basing treatment decisions on elevations of LDH alone and in the absence of corroborating evidence of progression or relapse.

### ***STMs for Surveillance of Definitively Treated Seminoma***

II-4. Clinical question: In adult patients with seminoma, are STM assays indicated after presumably definitive therapy for surveillance and routine monitoring to detect asymptomatic recurrence?

*Recommendation II-4.* Conclusive evidence is lacking for clinical utility of STMs in post-treatment surveillance of stage I seminoma, and the Panel recommends against this use. However, while direct evidence is unavailable to determine whether monitoring STM concentrations improves survival or other health outcomes of patients who have completed therapy for advanced seminoma, rising tumor markers may be the earliest sign of relapse, and the Panel recommends measuring STMs at each visit for these patients. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: every 2 to 4 months in the first year, every 3 to 4 months in the second year, every 4 to 6 months in the third and fourth years, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed.

*Literature review and analysis.* The literature search found no studies that directly compared survival or other health outcomes of surveillance for relapse with versus without STM assays in patients who completed treatment for seminoma and appeared free of detectable disease. The search also found no studies using STM assays or other diagnostic interventions that directly compared outcomes of different surveillance intervals or durations for such patients.

The literature identified 15 studies (three RCTs,<sup>154-156</sup> four prospective series,<sup>157-161</sup> and eight retrospective series<sup>135,139,162-167</sup> that reported STM concentrations during post-treatment follow-up of patients with seminoma (Data Supplement Table DS12). Although monitoring schedules varied across these studies, most measured STM concentrations every 2 to 4 months in the first year, every 3 to 4 months in the second year, and at longer intervals in subsequent years. Since more than half of late relapses (ie, relapses > 2 years after treatment) occurred after tumor-free intervals longer than 5 years, the Panel recommends that, as with NSGCT, annual surveillance should continue for at least 10 years. Relapses have been documented more

than 10 years after treatment, and some experts and centers recommend that surveillance should continue indefinitely. Imaging with CT and/or x-ray was typically less frequent than STM assays but was included in each study. Thus, the Panel recommends against relying on STM assays as the only means of monitoring patients for relapse after therapy for advanced seminoma concludes. Patients who have been diagnosed with pure seminoma but who in fact have a mixed GCT may have an elevated AFP at relapse after chemotherapy for advanced disease; thus, the Panel recommends measuring AFP and hCG during surveillance. Measuring AFP in these patients is of low yield but may result in earlier diagnosis of relapse.

One RCT (n = 478) compared different radiation therapy fields after orchiectomy for stage I testicular seminoma.<sup>154</sup> Investigators reported that increased hCG concentration was the first indication of relapse for two (11%) of 18 recurrences, which represented only 0.4% of all patients randomized and followed. The second RCT (n = 625) compared different doses and schedules for postorchiectomy radiation therapy in a similar patient population.<sup>155</sup> Investigators reported that hCG concentrations were above normal at or before relapse in only three (14.3%) of 21 relapsing patients with seminoma (0.5% of randomly assigned patients) at a median follow-up of 61 months. STM elevation was the only evidence of relapse for only one of these three patients. Similarly, among 1,477 patients on a randomized trial comparing carboplatin with radiation therapy, only one of 65 relapses was manifested only by elevated markers.<sup>156</sup> These series did not report LDH results.

Each of the five prospective series<sup>157-161</sup> summarized in Data Supplement Table DS12 also focused on patients with stage I testicular seminoma. Investigators at Princess Margaret Hospital in Toronto<sup>157,158</sup> reported that among 364 clinical stage I patients treated with surveillance or radiation therapy, four (11%) of 38 relapses had elevated hCG at relapse and two (5%) of 38 had an elevated AFP level. Thus six (1.6%) of 364 patients had relapse with elevated STMs. Another Canadian series<sup>159</sup> reported that among 88 patients on surveillance, none of 17 relapsing patients had elevated concentrations of hCG (or AFP). In a Spanish trial,<sup>160</sup> four (16%) of 25 relapses were initially detected by increased serum concentrations of hCG among 203 patients followed for a median of 52 months. In contrast, a subsequent trial by these investigators<sup>161</sup> reported five (38.5%) of 13 relapses initially detected by increased serum concentrations of hCG among 314 patients followed for a median of 34 months. One explanation for this difference was a surveillance schedule in which STMs were measured more frequently than abdominal CT scans were performed, unlike the Canadian surveillance schedule by which scans were performed at each visit. These series did not report LDH results.

Only four<sup>139,162-164</sup> of eight retrospective series listed in Data Supplement Table DS12 reported the proportion of patients experiencing seminoma relapse that was initially detected by an increase in STM concentration. Each reported on patients initially treated for stage I seminoma. Two (15.4%) of 13 relapses were detected by rising hCG concentrations in a series of 72 patients.<sup>162</sup> Among 339 patients followed in another series, STM concentrations were increased at relapse in eight (61.5%) of 13 recurrences, but only three (23%) of these recurrences were initially detected by the STM increase.<sup>163</sup> Of 35 relapses observed among 203 patients treated for seminoma and followed for a median of 9.2 years in a subsequent report from the Princess Margaret Hospital investigators cited above, none were initially detected by STM elevations.<sup>164</sup> Finally, only four (5.8%) of 69

relapses occurred at stage IS (STM elevation as the only sign of disease) among 394 patients followed for a median of 60 months.<sup>139</sup>

As with NSGCT, the rationale for long-term monitoring of STMs in patients with seminoma is based on multiple series reporting that at least half of late-relapsing patients have elevated STMs at the time of relapse and 40% to 46% are asymptomatic.<sup>144,145</sup> Dieckmann et al<sup>144</sup> reported that among 50 patients with late-relapsing seminomas (median time to relapse, 42 months), 13 (52%) of 25 with available assay results had elevated LDH, 11 (33%) of 33 with available results had elevated hCG, and three (9%) of 33 with available results had elevated AFP. Twenty-three patients (46%) were asymptomatic and had relapse detected at routine follow-up.<sup>144</sup> Note also that a significant minority of late-relapsing seminomas relapse with nonseminomatous elements. The small series from Norway<sup>145</sup> included 10 patients with seminoma, three of whom relapsed with embryonal carcinoma or poorly differentiated carcinoma. Six (60%) had hCG elevations at late relapse, and two others had elevated AFP at late relapse. Four men (40%) were asymptomatic, with relapse detected at routine follow-up. As mentioned in the literature review and analysis for Recommendation I-4, the international pooled analysis of 426 late-relapsing patients with GCTs<sup>147</sup> did not report marker assay results at relapse separately by tumor type (NSGCT *v* seminoma). As for NSGCT, because marker-only late relapses are not usually treated unless they are radiographically detectable or unless palpable lesions develop to confirm relapse, the objective of following STMs beyond year 5 is to trigger a search for the site of relapse in patients whose tumor markers begin to rise. In contrast to hCG and AFP, the utility of following LDH is less clear because of the high false-positive rate.

## FUTURE RESEARCH DIRECTIONS

The literature search and systematic review conducted for this guideline identified many gaps in the available evidence relevant to the clinical questions addressed here. Major gaps included the lack of studies that directly compared outcomes of diagnosis, treatment monitoring, and surveillance for relapse of GCTs with versus without results of STM assays. Additionally, studies were lacking that directly compared outcomes of different STM monitoring or surveillance intervals or durations for patients with NSGCT or advanced seminoma. It is unlikely that randomized controlled trials could be completed to fill these evidence gaps since routine measurement of STM concentrations in patients with GCTs has been considered standard of care for the past several decades and because there appears to be little harm in measuring STMs frequently. However, it may be possible to apply methods of comparative effectiveness research using multi-institutional and multipractitioner databases (or registries) to compare outcomes of patients followed with different intervals between STM assays or different durations of monitoring or surveillance. In addition, further studies are needed to clarify whether the rate of STM decline during treatment can be used to improve outcomes by identifying and more aggressively treating patients who are at increased risk of treatment failure with standard regimens.

## PATIENT COMMUNICATION

Uses of STMs to inform treatment decisions for patients with GCTs is not a subject that is commonly understood by patients diagnosed with

this disease, their families or caregivers, or the general public. The meaning of the term “serum tumor marker” is not self-evident to a layperson and neither are the potential uses for results of these laboratory measurements. They may find it difficult to pronounce alpha-fetoprotein or human chorionic gonadotropin. Individuals diagnosed with GCTs may feel great distress over their disease and fear about their prognosis; people who are emotionally distressed generally have a harder time comprehending detailed medical information. For these reasons, it is essential to educate patients about tumor markers using easily understood language and at a pace that enables them to absorb the information. Information should be conveyed at an educational level that the patient can understand. Asking patients to repeat back key pieces of information can be helpful in determining their level of comprehension.

The following are key facts about STMs for GCTs that should be conveyed:

- What are serum tumor markers? (They are substances in the blood that may indicate the presence of a germ cell tumor or may signal whether it is growing or shrinking.)
- What else besides germ cell tumor can cause these serum tumor markers to rise? (Other diseases including liver disease [AFP], a rare hereditary condition [AFP], drug exposure such as marijuana [hCG], and exercise or other conditions [LDH].)
- Which tumor makers will be measured? (AFP, hCG, and sometimes LDH.)
- How are they measured? (With a blood test.)
- How will test results be used to make decisions about the specific patient’s care? (They may be used to determine whether the germ cell cancer has spread, whether it is responding to treatment, how much chemotherapy should be administered, or to watch for a return of germ cell cancer after treatment.)
- Why they are checked so frequently for nonseminomas? (They are often the earliest sign that the nonseminoma cancer has come back and requires additional treatment.)

A patient who understands what tests are being done, and why they are being done will feel less powerless and may be more compliant with the testing schedule. Patient satisfaction may also be improved by effective communication because lack of information is a common patient complaint.

Although not directly related to STM assays, most males undergoing treatment for a GCT are of an age that makes fertility preservation a relevant issue. It would be useful to refer to ASCO’s guideline and associated clinical tools (Patient Guide and Options and Discussion Table) on this topic (available at: <http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines/Survivorship>).

## HEALTH DISPARITIES

ASCO clinical practice guidelines represent expert recommendations derived from critical appraisal of the best available evidence relevant to prospectively formulated, well-focused clinical questions on optimal practices in management of oncologic diseases. However, racial, ethnic, and socioeconomic disparities in quality of health care exist and persist in the United States. Members of racial and ethnic minority groups and patients with fewer financial re-

sources tend to have a higher burden of comorbid illness, are more likely to be uninsured or underinsured, face more challenges in accessing care, and are at greater risk of receiving care of poor quality than other Americans.<sup>168-171</sup>

In the case of testis cancer, which represents the vast majority of GCTs, the incidence varies greatly by race and is five times higher among white males than black males. The mortality rate for testis cancer is only twice as high in whites compared with blacks because among men with testis cancer, blacks are more likely than whites to be diagnosed with regional or distant metastatic disease and because among men with metastatic disease, blacks have lower 5-year survival rates than whites. For instance, 5-year survival for blacks and whites is 85% and 96%, respectively, for regional disease and 56% and 72%, respectively, for distant metastatic disease. There are only limited data on the incidence and mortality of testis cancer in other racial groups in the United States. The incidence of testis cancer in Asian Americans and Pacific Islanders is slightly higher than that in blacks, while Native Americans and Hispanics have an incidence that is roughly 60% of that in whites.<sup>172</sup> Awareness of disparities in quality of care should be considered in the context of this clinical practice guideline.

## AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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### Appendix

**Table A1.** Appendix A. Germ Cell Tumor Markers Panel Members

Panel Member	Institution
Timothy Gilligan, MD, co-chair	Taussig Cancer Institute, Cleveland Clinic
Daniel F. Hayes, MD, co-chair	University of Michigan Medical Center
Timothy Fancher	Patient Representative
Lawrence H. Einhorn MD	Indiana Cancer Pavilion, Indiana University
David C. Smith	University of Michigan Medical Center
Andrew J Stephenson, MD	Glickman Urological and Kidney Institute, Cleveland Clinic
David J. Vaughn, MD	Abramson Cancer Center, University of Pennsylvania
Ethan M. Basch, MD, Clinical Practice Guidelines Committee Liaison	Memorial Sloan-Kettering Cancer Center

**Table A2.** Appendix B1. MEDLINE Search Strategy

1. germ cell tumors.mp. or "Neoplasms, Germ Cell and Embryonal"/
2. Testicular Neoplasms/or GCT.mp.
3. Seminoma/
4. nonseminoma.mp.
5. non seminoma.mp.
6. non-seminoma.mp.
7. Carcinoma, Embryonal/
8. Choriocarcinoma, Non-gestational/or Choriocarcinoma/
9. Endodermal Sinus Tumor/
10. Teratoma/
11. Testicular mass.mp.
12. Neoplasms, Unknown Primary/
13. or/1-12
14. Gestational Trophoblastic Neoplasms/
15. 13 not 14
16. alpha-Fetoproteins/
17. AFP.mp.
18. human chorionic gonadotropin.mp. or Chorionic Gonadotropin/
19. hCG.mp.
20. beta-hCG.mp.
21. Chorionic Gonadotropin, beta Subunit, Human/
22. lactate dehydrogenase.mp. or L-Lactate Dehydrogenase/
23. LDH.mp.
24. or/16-23
25. Meta-Analysis/
26. meta-analys\$.pt.
27. meta-analys\$.tw.
28. metaanalys\$.tw.
29. Practice Guidelines/
30. practice guideline.pt.
31. practice guideline\$.tw.
32. systematic review.pt.
33. systematic review\$.tw.
34. systematic overview.tw.
35. Randomized Controlled Trials/
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. Controlled Clinical Trials/
39. Clinical Trials/
40. Cohort Studies/
41. Retrospective Studies/
42. Prospective Studies/
43. Case-Control Studies/
44. Follow-Up Studies/
45. Longitudinal Studies/
46. or/25-45
47. (editorial or comment or letter or news or case-report).pt.
48. 46 not 47
49. 15 and 24 and 48
50. limit 49 to English language

**Table A3.** Appendix B2. EMBASE Search Strategy

1. Germ Cell Tumor/
2. GCT.mp.
3. Testis Tumor/
4. Testis Cancer/
5. SEMINOMA/
6. TESTIS NONSEMINOMA CANCER/
7. Non Seminomatous Germinoma/
8. CHORIOCARCINOMA/
9. Embryonal Carcinoma/
10. Yolk SAC Tumor/
11. TESTIS TERATOMA/or TERATOMA/or MALIGNANT TERATOMA/
12. Testicular mass.mp.
13. "Cancer of Unknown Primary Site"/
14. or/1-13
15. Trophoblastic Tumor/
16. 14 not 15
17. Alpha Fetoprotein/
18. AFP.mp.
19. human chorionic gonadotropin.mp. or Chorionic Gonadotropin/
20. hCG.mp.
21. beta-hCG.mp. or Chorionic Gonadotropin Beta Subunit/
22. Lactate Dehydrogenase/
23. LDH.mp.
24. or/17-23
25. Meta Analysis/
26. meta-analys\$.tw.
27. metaanalys\$.tw.
28. Practice Guideline/
29. practice guideline\$.tw.
30. systematic review\$.tw.
31. systematic overview.tw.
32. Randomized Controlled Trial/
33. Clinical Trial/
34. Cohort Analysis/
35. Retrospective Study/
36. Prospective Study/
37. Case Control Study/
38. Follow Up/
39. Longitudinal Study/
40. or/25-39
41. (book or editorial or conference paper or letter or note or short survey or review).mp.
42. 40 not 41
43. 16 and 24 and 42
44. limit 43 to English language